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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

JCAMD002 Assessment Report – EVOKE SPINAL CORD STIMULATION SYSTEM

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Document history and contributors

Version	Date	Description
0.1	12.04.2023	First draft report
0.2	17.05.2023	Second draft report
0.3	12.06.2023	Final draft report validated by CSCQ
0.4	27.06.2023	Input from medical editor and factual accuracy check by the HTD has been processed
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1.0	17.07.2023	Report publication
1.1	25.08.2023	Final report with updated EMDN codes upon request of the HTD

Disclaimer

This joint clinical assessment (JCA) report was a pilot produced while the JCA report and submission dossier templates were still in development, and it was used for further fine-tuning these templates.

Participants

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CEB	

The work in EUnetHTA 21 is a collaborative effort. While the agencies in the Assessment Team actively wrote the JCA report, the entire EUnetHTA 21 consortium was involved in its production throughout various stages. This means that the Committee for Scientific Consistency and Quality (CSCQ) reviewed and discussed several drafts of the deliverable. The Consortium Executive Board (CEB) subsequently endorsed the final deliverable before publication.

Conflicts of interest

All authors, co-authors, CSCQ members, CEB members and external experts involved in the production of this JCA have declared that they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA 21 declaration of interest form. Conflicts of interest were evaluated according to the EUnetHTA 21 Procedure Guidance for handling declarations of interest (https://eunethta.eu/doi).

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How to cite this assessment

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Please contact the EUnetHTA 21 Secretariat (EUnetHTA@zinl.nl) if you have enquiries about this JCA.

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
AU	Australia
AIHTA	Austrian Institute for Health Technology Assessment
CE	Conformité Européenne
CEB	Consortium Executive Board
CI	Confidence interval
CLS	Closed-loop stimulator
CMM	Conventional medical management
CRPS	Complex regional pain syndrome
CSCQ	Committee for Scientific Consistency and Quality
CSR	Clinical study report
CST	Clinical system transceiver
ECAP	Evoked compound action potential
eCLS	External closed-loop stimulator
EMDN	European Medical Device Nomenclature
EPC	Evoke pocket console
EQ-5D	EuroQol 5 dimensions questionnaire
EQ-5D-5L	EuroQol 5 dimensions, 5 levels questionnaire
EU	European Union
GPE	Global Perceived Effect
HAS	Haute Autorité de Santé
HCP	Healthcare professional
HRQoL	Health-related quality of life
HTD	Health technology developer
ICD-11	International Classification of Diseases, 11th revision
IDEA	Innovación y Desarrollo Asistencial
IPG	Implantable pulse generator
JCA	Joint clinical assessment
MCS	Mental Component Summary
MD	Mean difference
MDR	Medical Device Regulation
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NA	Not applicable
NC	Not controlled
ND	No data
NePIQoL	Neuropathic Pain Impact on Quality of Life
NO	Nominal p-value
NP	Not prespecified

Abbreviation	Meaning
NS	Nonsignificant
NVA	Nederlandse Vereniging voor Anesthesiologie
ODI	Oswestry Disability Index
PCS	Physical Component Summary
PGIC	Patient Global Impression of Change
PICO	Population, Intervention, Comparator, Outcome
PROM	Patient-reported outcome measure
PSPS	Persistent spinal pain syndrome
PSQI	Pittsburgh Sleep Quality Index
PT	Preferred term
RCT	Randomised controlled trial
RD	Rate difference
RoB	Risk of bias
SAE	Serious adverse event
SAP	Statistical analysis plan
SCS	Spinal cord stimulation
SD	Standard deviation
SF-12	12-item Short Form survey
SF-36	36-item Short Form survey
SOC	System organ class
SSCP	Summary of safety and clinical performance
UDI-DI	Unique Device Identification-Device Identifier
UEMO	European Union of General Practitioners/Family Doctors
UK	United Kingdom
VAS	Visual Analogue Scale

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GENERAL INFORMATION

The aim of this joint clinical assessment (JCA) is to assess the relative clinical effectiveness and safety of the Evoke spinal cord stimulation (SCS) system medical device in the target patient population against relevant comparators. In accordance with the requirements of EUnetHTA 21 members, the target patient population and relevant comparators were defined before the start of the assessment in the assessment scope according to a Population, Intervention, Comparator, Outcome (PICO) framework. The assessment scope is presented in Section 3.

The assessment was based on the submission dossier submitted by the health technology developer (HTD) of this medical device, Saluda Medical Pty Ltd.

1.1 Assessment team

The assessment team consists of an assessor from the Austrian Institute for Health Technology Assessment (AIHTA) and co-assessors from Haute Autorité de Santé (HAS).

1.2 Overview of procedural steps

The procedural steps and corresponding dates for the JCA are listed in **Table 1**.

Table 1. Procedural steps for the joint clinical assessment of the Evoke spinal cord stimulation system

	Start date	End date
Project duration	02/11/2022	17/7/2023
Receipt of the letter of intent from the HTD	10/11/2022	
Scoping phase	02/11/2022	18/12/2022
PICO survey	10/11/2022	23/11/2022
PICO consolidation	24/11/2022	06/12/2022
Sharing of the consolidated PICO with the HTD	19/12/2022	
Receipt of the submission dossier	16/02/2023	
Check for formal completeness of the submission dossier	17/02/2023	26/02/2023
Final submission dossier (completed with the missing elements)	07/03/2023	
Assessment phase	07/03/2023	10/07/2023
First draft assessment report	07/03/2023	12/04/2023
CSCQ review of the first draft assessment report	13/04/2023	21/04/2023
Second draft assessment report	22/04/2023	16/05/2023
CSCQ validation review of the second draft assessment report	17/05/2023	26/05/2023
Third draft assessment report	27/05/2023	16/06/2023
Medical editing and HTD fact-checking	19/06/2023	23/06/2023
Final assessment	24/06/2023	27/06/2023
CEB review	16/06/2023	27/06/2023
CEB endorsement	28/06/2023	
Publication of the assessment report	11/07/2023	17/07/2023

Source: EUnetHTA 21 Secretariat.
Abbreviations: CEB=Consortium Executive Board; CSCQ=Committee for Scientific Consistency and Quality; HTD=health technology developer; PICO=Population, Intervention, Comparator, Outcome.

1.3 Stakeholder and external expert involvement

Stakeholders were consulted early in the JCA scoping process to support the development of the PICO questions.

Table 2. Contributors to the joint clinical assessment

Contributor	Patient or HCP	Organisation or individual	Type and timing of involvement
Stakeholders	Patients and HCPs	Innovación y Desarrollo Asistencial, Spain Dutch Society of Anaesthesiologists (NVA), the Netherlands European Union of General Practitioners/Family Doctors, Belgium AZ Delta Hospital Roeselare, Belgium	Participated in the open call for input during the scoping process. Completed an online submission.

Source: EUnetHTA 21 Secretariat.
Abbreviations: HCP=healthcare professional; NVA=Nederlandse Vereniging voor Anesthesiologie.

Stakeholder organisations were invited to provide input via an online questionnaire during the scoping process. Four stakeholder organisations made submissions. Three stakeholder organisations represented healthcare professionals working in the area of anaesthesiology, pain management and general practice. One stakeholder organisation was an organisation that manages and promotes services for the elderly. One was a European umbrella organisation (European Union of General Practitioners/Family Doctors), two were national organisations (Innovación y Desarrollo Asistencial, Dutch Society of Anaesthesiologists) and one was a Belgian hospital.

Submissions from stakeholder organisations, including details of the organisations funding, are listed in Appendix A.

2 BACKGROUND

2.1 Overview of the health condition

The health condition considered for the scope of this JCA is chronic, intractable pain of the trunk and/or limbs, the indication from the Conformité Européenne (CE)-marking certificate of the Evoke SCS system. The target populations are the full adult patient population with chronic, intractable pain of the trunk and/or limbs, and a subpopulation of adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome (PSPS).

Chronic pain persists well after the initial injury or illness that produced the initial pain has resolved. The International Association for the Study of Pain has defined chronic pain as pain that persists or recurs for longer than 3 months. Chronic pain is characterised by multiple aspects, including its nature, its aetiology, its perceived anatomic location or a combination of these (1). The exact definition of intractable pain varies among sources and there is no general consensus. Some states[1] in the United States of America have passed intractable pain laws and have thus defined the term. The common feature in all definitions includes the following: pain whose cause cannot be removed, and for which the full range of pain management modalities has been used without an adequate result or with intolerable side effects (2).

PSPS is the term used in defining the subpopulation of interest for this JCA. PSPS is a type of chronic neuropathic pain.

Chronic neuropathic pain is caused by a lesion or diseases affecting the somatosensory nervous system. The pain may be spontaneous or evoked as an increased response to a painful stimulus or a painful response to a normally nonpainful stimulus (1). PSPS is also called failed back surgery syndrome, now referred to as chronic pain after spinal surgery, terminology that has been incorporated in the International Classification of Diseases 11th revision (ICD-11). PSPS has not been adopted in ICD-11 but is proposed as a replacement term, divided into two types: type 1 PSPS (no surgery performed) and type 2 PSPS (after surgery) (3, 4).

Chronic pain affects approximately 20% of the European population and is more common among women, older people, and individuals with relative deprivation (5). Chronic pain interferes with daily activities and impairs a person's ability to perform physical activities, reduces their ability to perform their work and meet family responsibilities, and is the cause of mental health issues (6). Persistent or recurrent pain and other symptoms following spinal surgery affect between approximately 20–40% of patients (3).

[1] For example, the states of Arizona, California, Colorado, Florida, New Jersey, Texas, Oklahoma, Rhode Island, Virginia, Minnesota and Washington.

2.2 Characterisation of the health technology

2.2.1 Characteristics of the health technology

The characteristics of the medical device under assessment are presented in **Table 3**.

Table 3. Characteristics of the health technology

<table>
<tr><td>Device trade name</td><td>Evoke spinal cord stimulation (SCS) system</td></tr>
<tr><td>Name of manufacturer</td><td>Saluda Medical Pty. Ltd.</td></tr>
<tr><td>Device description according to the EMDN</td><td>The Evoke SCS system has several components that fall under the following EMDN codes:
J02020201 - Fully Implantable Spinal Neurostimulators, Rechargeable
J020299 - Neurostimulators, Spine, Others
J020280 - Neurostimulators, Spine, Accessories
J020701 - Programming units for neurostimulators
J020792 - Neurostimulators Programmers - Medical Device Software
J020203 - Spinal Neurostimulation Leads</td></tr>
<tr><td>Risk class of the device</td><td>Class III</td></tr>
<tr><td>Function of the device</td><td>Therapeutic</td></tr>
<tr><td>Models of the device/ reference numbers/ software version</td><td>
<table>
<tr><th>Device name</th><th>Catalogue number</th></tr>
<tr><td>Evoke closed-loop stimulator</td><td>1002</td></tr>
<tr><td>Evoke external closed-loop stimulator</td><td>1020</td></tr>
<tr><td>Evoke 12C percutaneous lead kit – 60 cm (including active anchor)</td><td>1008, 1016</td></tr>
<tr><td>Evoke 12C percutaneous lead kit – 90 cm (including active anchor)</td><td>1009, 1017</td></tr>
<tr><td>Evoke 12C lead extension kit – 55 cm</td><td>1011</td></tr>
<tr><td>Evoke lead adapter</td><td>1028</td></tr>
<tr><td>Evoke tunnelling tool</td><td>1012</td></tr>
<tr><td>Evoke epidural needle, 6.5”</td><td>1014</td></tr>
<tr><td>Evoke spares kit</td><td>1015</td></tr>
<tr><td>Evoke pocket console (EPC)</td><td>1003</td></tr>
<tr><td>Evoke charger EU/UK/AU</td><td>1006, 4006, 5006</td></tr>
<tr><td>Evoke clinical interface system:
Tablet (Microsoft Surface Pro; off-the-shelf; not a medical device)
Saluda medical software applications:
Evoke clinical programming application
Evoke clinical data viewer
Evoke firmware upgrade application</td><td>Clinical interface system: 1024
Tablet: NA
Software:
000870, version 1.50.9
002581, version 1.11.1
000897, version 2.4.0.0</td></tr>
<tr><td>Evoke clinical system transceiver</td><td>1004</td></tr>
</table>
</td></tr>
<tr><td>Intended purpose of the device</td><td>The Evoke SCS system is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs.</td></tr>
<tr><td>Indication and target population</td><td>The Evoke SCS system is intended for use in patients with chronic intractable pain of the trunk and/or limbs for whom the system is not contraindicated.
The Evoke SCS system has not been tested for use in patients who are under 18 years, or in patients who are pregnant or nursing.</td></tr>
<tr><td>Contraindications and/or restrictions for use and/or limitations of the device</td><td>The Evoke SCS system should not be used in patients who:
• Are unable to operate the system,
• Are unsuitable surgical candidates,
• Are unsuitable candidates for SCS.</td></tr>
</table>

Description of the device including its constituents	The Evoke SCS system comprises several key parts (Figure 1): • eCLS: an external stimulator for the trial stimulation period that delivers automatic or manually controlled therapy. • CLS: a totally implanted SCS that connects to the leads and delivers automatic or manually controlled therapy. • Evoke CAP12 percutaneous leads placed in the epidural space overlying the spinal cord. The leads are connected to the eCLS for a trial period, or permanently implanted and connected to the CLS for long-term therapy (1 or 2 leads). There are 12 electrodes on each lead. • Evoke CAP12X lead extensions may be used during the trial period to connect the leads to the eCLS. • Evoke lead adapter kit (comprising an Evoke lead adapter, a lead adapter cable and a lead adapter extension): allows connection of the eCLS to the leads or lead extensions during the trial stimulation period. • EPC: allows control of the therapy and monitoring of the stimulator (either a CLS or eCLS). The EPC and the stimulator communicate with each other wirelessly. The EPC kit also includes a magnet. The magnet allows stimulation from the CLS or eCLS to be stopped without using the EPC. • Evoke charger: allows recharging of the battery in the CLS or eCLS. The charger coil is placed on clothing covering the skin over the implanted CLS. The charge is transferred wirelessly to the CLS. The eCLS is recharged by placing the charger coil directly over the eCLS case.
Mode of action	The Evoke system delivers an electrical stimulus to the spinal cord via electrodes implanted in the epidural space, which causes the activated fibres to generate action potentials, inducing an electrical ECAP. The Evoke system measures ECAPs, which are representative of the spinal cord fibre activation that generates pain inhibition for an individual. The Evoke system delivers either 1) open-loop stimulation; or 2) ECAP-controlled closed-loop stimulation, for which the stimulation amplitude is automatically adjusted in real time to minimise the difference between the measured ECAP and the target ECAP to deliver consistent spinal cord activation at the target level (Figure 2). The stimulator can be programmed using up to four programmes that can be in closed- or open-loop stimulation mode (i.e., the patient may have both closed- and open-loop programmes). The stimulation programme(s), and thus the stimulation mode, is determined by the treating clinician with the patient feedback. The patient can toggle between programmes and can adjust the stimulation within a programme. Only the treating clinician can enable or disable the loop in a programme.
If applicable, specific description for the connected technology	An overview of the interoperability of the devices of the Evoke system is provided in Figure 3.

Source: Submission dossier.
Abbreviations: AU=Australia; CLS=closed-loop stimulator; ECAP=evoked compound action potential; eCLS=external closed-loop stimulator; EMDN=European Medical Device Nomenclature; EPC=Evoke pocket console; EU=European Union; NA=not applicable; SCS=spinal cord stimulation.

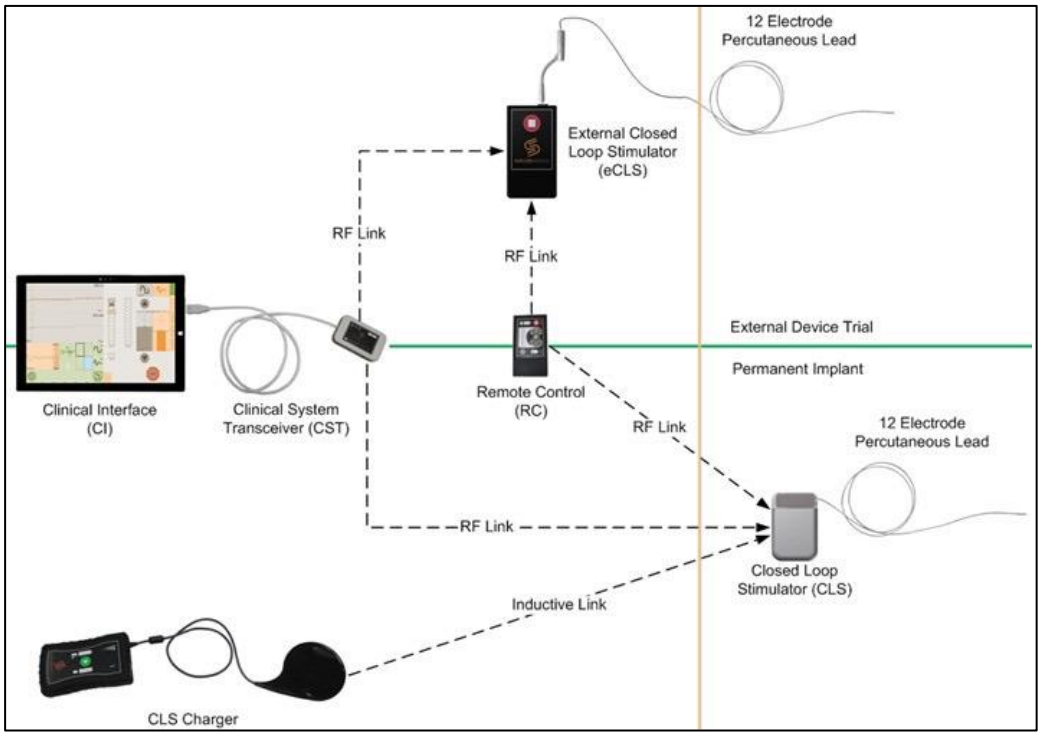

Figure 1. The Evoke closed-loop spinal cord stimulation system.
Source: Avalon study protocol.

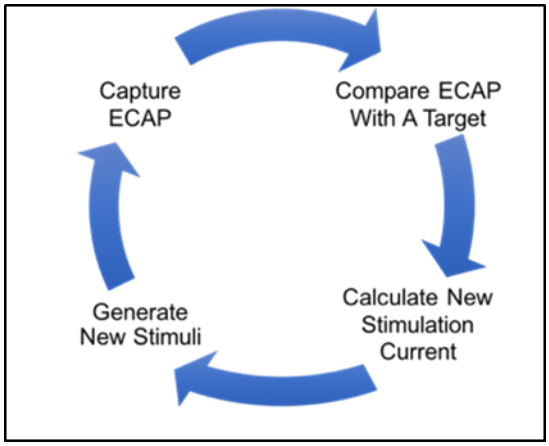

Figure 2. ECAP-controlled SCS mode of action.
Source: sumission dossier.
Abbreviations: ECAP-evoked compound action potential; SCS=spinal cord stimulation.

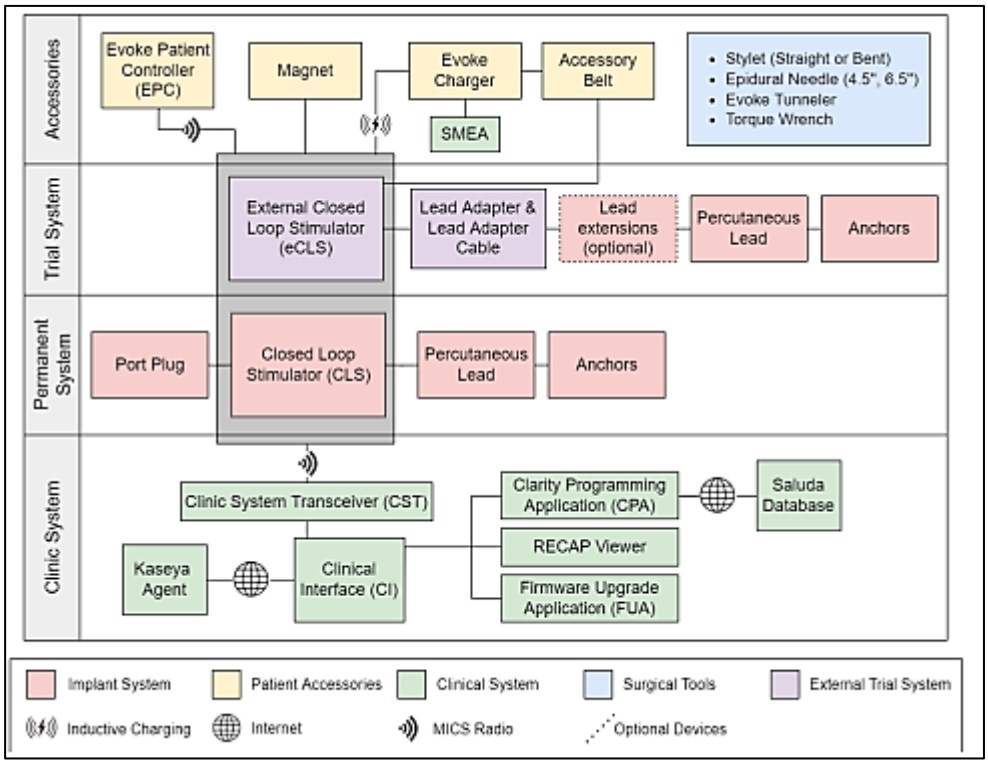

Figure 3. Interoperability of the devices of the Evoke spinal cord stimulation system.
Source: submission dossier.

2.2.2 Requirements/instructions for use

Table 4. Characteristics of use

Description of (surgical) procedures, services and organisational aspects associated with use of the device	The implantation procedure for the Evoke system is the same as for other SCS systems. The process for percutaneous lead implantation is described in the Evoke system surgical guide.
Suggested profile and training for users as outlined in the SSCP or the instructions for use	Intended users of the Evoke system include implanting physicians/surgeons, clinicians, patients, and Saluda medical representatives. Patients are users of the external accessories, for which the Evoke system user manual and Evoke system quick reference guide provide instructions. Clinicians explain the functioning of the device to patients and go through the Evoke system user manual with them. Implanting physicians are users of the closed-loop stimulators and accessories, leads and accessories, and surgical tools, for which the Evoke system surgical guide provides instructions. Clinicians/clinical users (including Saluda medical representatives) are users of the programming system, for which the Evoke system Clarity clinical manual and RECAP viewer user manual provide instructions. The implantation procedure for the Evoke system is the same as for other SCS systems; thus, implanting physicians should be trained in SCS procedures with minimal additional training for the Evoke system. Clinical staff using the clinical interface/CST to programme the Evoke system must be adequately trained in programming of SCS systems in general and the Evoke system specifically.
MRI compatibility	The Evoke SCS system is MR-conditional, which means that some configurations of the Evoke SCS system are suitable for use with MRI procedures under specific MRI settings. Patients must inform the clinical staff before their MRI examination that they have an implanted SCS and they should refer to the Evoke system MRI guidelines. All external components of the Evoke SCS system (e.g. Evoke pocket console, Evoke charger, magnet, and externalised leads and lead extensions) are MR-unsafe, meaning that the patient must remove all external components of their Evoke SCS system before entering a room in which an MRI scanner is located.

Source: submission dossier, instructions for use.
Abbreviations: CST=clinical system transceiver; MR=magnetic resonance; MRI=magnetic resonance imaging; SCS=spinal cord stimulation; SSCP=summary of safety and clinical performance.

2.2.3 Regulatory status of the technology

Regulatory information on the medical device under assessment is provided in **Table 5**.

Table 5. Regulatory information on the health technology

UDI-DI	Device name	Basic UDI-DI (MDR)
	Evoke closed-loop stimulator	935230701042AY
	Evoke external closed-loop stimulator	935230701020AN
	Evoke 12C percutaneous lead kit – 60 cm	935230701008AY 935230701016AX
	Evoke 12C percutaneous lead kit – 90 cm	935230701009B2 935230701017AZ
	Evoke 12C lead extension kit – 55 cm	935230701011AM
	Evoke lead adapter	935230701028B6
	Evoke tunnelling tool	935230701012AP
	Evoke epidural needle, 6.5”	935230701014AT
	Evoke spares kit	935230701015AV
	Evoke pocket console	935230701040AU
	Evoke charger EU	935230701006AU
	Evoke charger UK	935230704006BH
	Evoke charger AU	935230705006BQ
	Evoke clinical interface system: • Tablet (Microsoft Surface Pro; off-the-shelf; not a medical device) • Saluda medical software applications: Evoke clinical programming application Evoke clinical data viewer Evoke firmware upgrade application	Clinical interface system: 935230701024AW • Tablet: NA • Software: 935230701044B4 935230701045B6 935230701046B8
	Evoke clinical system transceiver	935230701004AQ
Name, identification number and country of the Notified Body	BSI Group, The Netherlands B.V. (Notified Body number: 2797)	
Date of initial CE marking	17 June 2019[a]	
Expiry date of current certificate	26 May 2024	
Date and reference of the expert panel opinion	NA	
[a] The conformity assessment according to the MDR (regulation (EU) 21017/745) for a newer generation of the Evoke SCS system is currently ongoing. BSI Group expects to complete the review of the MDR application by May 2024.		

Source: submission dossier.
Abbreviations: AU=Australia; CE=Conformité Européenne; EU=European Union; MDR=medical device regulation; NA=not applicable; UDI-DI=Unique Device Identification-Device Identifier; UK=United Kingdom.

Further regulatory information is included in the submission dossier (7).

3 RESEARCH QUESTION AND SCOPE

The JCA is performed against the parameters chosen after identification of the assessment scope via a survey of EUnetHTA 21 members, a consolidation process and subsequent endorsement by the CSCQ. The consolidated assessment scope including the PICO questions is presented in **Table 6**.

Table 6. Assessment scope including the consolidated PICO questions

Description of PICO elements	PICO 1	PICO 2	PICO 3
Population[a]	According to the intended use: adult patients with chronic intractable pain of the trunk and/or limbs	Subpopulation: adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome, with an insufficient effect from conventional pain management therapies	The same as for PICO 2
Intervention[b]	According to the intended use	The same as for PICO 1	The same as for PICO 1
Comparator	Latest generation of open-loop SCS systems (in addition to other pain management therapies)	The same as for PICO 1	Conventional nonsurgical pain management therapies (including pharmacotherapy with or without physiotherapy and/or psychotherapy, etc.)[c]
Outcome	The following outcomes are assessed across all PICO questions: **Time horizon for all outcomes**: preferably 24 months minimum, with an annual evaluation • Global pain, preferably measured using the VAS or Numeric Rating Scale • Responder rate, measured as global pain relief ≥50% vs. baseline at 6 months minimum • Healthcare consumption including pain medication consumption, other nonsurgical pain management therapies and number of outpatient visits • HRQoL: - Generic HRQoL, preferably measured using the SF-12 or SF-36 - Disease- or population-specific HRQoL (e.g. neuropathic pain impact on QoL measured using NePIQoL) • Health status, preferably measured using the EQ-5D • Functioning: - Exercise tolerance - Sleep quality - Body function • Disability measured using the ODI and the ability to perform activities of daily living • Participation restriction measured as the ability to return to work (or studies) • Patient satisfaction with treatment, preferably measured as GPE • Treatment discontinuation due to AEs • Sick leave episodes (number and duration) • All-cause mortality • Safety, including a description of each AE included in the following categories: - Any AEs related to the procedure and to the medical device, including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision and removal or replacement of the implanted components - Serious AEs		

[a] The type and duration of pain should be described in the "Patient baseline characteristics" section in the submission dossier presenting the studies included.
[b] Data on the conditions of use for the open- and closed-loop modes must be provided under the "Characteristics of the technology" and "Results" sections of the submission dossier.
[c] Placebo (sham-controlled) studies could be included under this PICO question.

Source: EUnetHTA 21 Committee for Scientific Consistency and Quality.

Abbreviations: AE=adverse event; EQ-5D=EuroQol 5 dimensions questionnaire; GPE=Global Perceived Effect; HRQoL=health-related quality of life; NePIQoL=Neuropathic Pain Impact on Quality of Life; ODI=Oswestry Disability Index; PICO=Population, Intervention, Comparator, Outcome; SCS=spinal cord stimulation; SF-12=12-item Short Form survey; SF-36=36-item Short Form survey; VAS=Visual Analogue Scale.

4 RESULTS

The results section describes findings from the systematic information retrieval, characterises the studies included and presents results on the relative effectiveness and relative safety of the health technology under assessment versus the comparators defined in the PICO questions. The assessment is based on the submission dossier, with the clinical study report (CSR) acting as the primary data source. Factors that may affect the degree of certainty of the relative effects are identified, taking into account the strengths and limitations of the evidence available.

4.1 Information retrieval

The studies included in the assessment were compiled using the following information:

Sources provided by the HTD in the dossier:

- List of HTD-sponsored studies on the Evoke SCS system (as of 02/03/2023),
- A bibliographic search for the Evoke SCS system (last search on 02/03/2023),
- A search in study registers/study result databases for the Evoke SCS system (last search on 02/03/2023).

The assessment team verified the completeness of the studies included by searching study registries and bibliographic databases for the Evoke SCS system (last search on 03/03/2023). An assessment of the appropriateness of the sources and the search strategies is provided in Appendix B.

No additional relevant study was identified via the supplementary searches conducted by the assessment team.

4.1.1 Resulting list of studies included: overall and by PICO question

Table 7 lists the studies used for the assessment, including the documentation available, and identifies which studies are relevant for the PICO questions of the assessment.

Table 7. Studies included: list of relevant studies used for the assessment of the relative effectiveness and relative safety

Study reference/ID Study type Study interventions	**Study for marketing authorisation/ CE marking of the technology under assessment**	**Sponsored[a] or third-party study of the technology under assessment**	**Documentation available from the submission dossier**
PICO 1			
Studies providing direct evidence: **Evoke *closed-loop* SCS system** vs. **Evoke *open-loop* SCS system**			
Evoke study[b] *RCT* Evoke closed-loop SCS vs. Evoke open-loop SCS	Yes[c]	Sponsored	• Study protocol: CLIN-PCL-002065, Rev4.00, 6 Aug 2018 (8) • SAP: Evoke SAP Rev5.00, 1 Feb 2018 (9) • CSR: CLIN-RPT-007480 (4 Dec 2019) (10) • Registry entry: NCT02924129 (11) • Publication or other reference: Mekhail 2020 (12), Mekhail 2022 (13), Costandi 2022 (14)
PICO 2			
No evidence provided by the HTD.			
PICO 3			
No evidence provided by the HTD.			
[a] Study sponsored by the HTD or in which the HTD participated financially in some other way. [b] In the following tables, the study is referred to with this name. [c] This is a pivotal study conducted to support a premarketing approval supplement for the feedback feature of the Evoke SCS system for the United States market.			

Source: Submission dossier.

Abbreviations: CE=Conformité Européenne; CSR=clinical study report; HTD=health technology developer; RCT=randomised controlled trial; SAP=statistical analysis plan; SCS=spinal cord stimulation.

One study (the Avalon study) from the clinical development programme for the intervention under assessment was provided by the HTD. As this is a noncomparative study, it was not included for the assessment of the relative effectiveness and safety of the Evoke SCS system. However, the Avalon study is presented for the safety outcomes in Section 4.4 as the study provides longer follow-up data on safety than the Evoke randomised controlled trial (RCT) and some safety endpoints not reported in the RCT[2].

Table 8 lists studies that were included by the HTD in the submission dossier, but that were not considered relevant for assessment of the relative effectiveness and relative safety of the medical device.

[2] Although 24-month follow-up data of the Evoke study is published in a journal article, it is not presented in this JCA because the corresponding CSR data was not provided by the HTD.

Table 8. List of studies excluded: studies included by the HTD but not used in the JCA report

Study reference/ID	Reason for exclusion
Duarte 2021 (15)	The aim of the study was to quantify the HRQoL utility values seen in a remission health state (defined as ≥80% pain reduction) which contrasts with more traditional health states of <50% and ≥50% pain relief. The study considered the Evoke and Avalon studies but the results for the populations of these two studies were not presented separately.
Taylor 2022 (16)	The study did not assess the efficacy or safety of the Evoke SCS system. The aims of the study were to 1) investigate the association between functional disability and HRQoL and 2) estimate the utility values associated with levels of functional disability in patients treated with ECAP SCS for chronic pain.

Source: Submission dossier.

Abbreviations: ECAP=evoked compound action potential; HRQoL=health-related quality of life; HTD=health technology developer; JCA=joint clinical assessment; SCS=spinal cord stimulation.

4.2 Characteristics of the studies included

4.2.1 Study design and study populations

Table 9 lists the characteristics of the study included in the assessment of the relative effectiveness and safety of the Evoke SCS system.

Table 9. Characteristics of the study included

Study reference/ID	Study type and design	Study population	Study arms (number of patients randomised/included)	Study duration, data cut off(s) and locations	Study endpoints
Evoke study	RCT Prospective, multicentre, randomised[a], double-blind[b] study with a noninferiority objective and, if met, a superiority objective	Patients aged ≥18 and ≤80 years Chronic, intractable pain of the trunk and/or limbs refractory to conservative therapy for a minimum of 6 months VAS leg pain score ≥6 cm VAS back pain score ≥6 cm VAS overall trunk and limb pain score ≥6 cm Pain medications stable for at least 30 days before baseline evaluation ODI score 41–80% (severely disabled or crippled) No prior experience with SCS	Evoke *closed-loop* SCS: N=67 Evoke *open-loop* SCS: N=67	Study duration: 3 years Data cutoff: 1 Apr 2019 (planned interim analysis) Planned study end: 9 Sept 2022 Number of centres: 16 US sites, including 13 that actively enrolled patients	Primary endpoint: ≥ 50% reduction in overall trunk and limb pain (VAS score) at the endpoint visit (at 3 months) AND no increase in baseline pain medication within 4 weeks of the endpoint visit Key secondary endpoints[c]: • % change in VAS leg pain at 3 months • % change in VAS back pain at 3 months • Incidence of ≥80% reduction in VAS overall trunk and limb pain at 3 months • Incidence of ≥50% reduction in VAS back pain at 3 months • % change in VAS overall trunk and limb pain at 12 months • % change in VAS leg pain at 12 months • % change in VAS back pain at 12 months • Incidence of ≥80% reduction in VAS overall trunk and limb pain at 12 months • Incidence of ≥50% reduction in VAS back pain at 12 months Other endpoints[d]: • AEs • Change, % change, incidence of 50% reduction in VAS pain scores at 12 months compared to baseline • Health status measured with EQ-5D-5L[e] • Disability measured with the ODI[e] • Patient satisfaction[f] at 12 months • Global improvement in overall status measured with the PGIC instrument at 12 months

					• Quality of sleep measured with the PSQI[e] • Health-related quality of life measured with the SF-12[e] • Pain medication use[g] • 24-month follow-up data[h] for VAS overall pain, ODI, SF-12, EQ-5D-5L, PSQI, PGIC and patient satisfaction with therapy

[a] Random assignment of subjects in a 1:1 fashion. Computer-generated randomisation with permuted blocks of size 4 and 6 in random order, stratified by study site.
[b] Neither the subjects nor the investigators or their staff were informed of the treatment group the subject was assigned to.
[c] Only secondary endpoints controlled for multiplicity.
[d] Only outcomes included in the PICO.
[e] Change from baseline to 12 months.
[f] See Table 15 for details on the measurement instrument.
[g] Not prespecified in the protocol but reported in the CSR.
[h] Not prespecified in the protocol but reported in the submission dossier. The CSR reported 24-month follow-up data for a lower number of patients than in the submission dossier. The reason for this being that the CSR reports the 12-month analysis, and only patients who had completed their 24-month visit at the time the report was produced were included in the CSR.

Source: Refer to Table 7.

Abbreviations: AE=adverse event; CSR=clinical study report; EQ-5D-5L=EuroQol 5 dimensions, 5 levels questionnaire; ODI=Oswestry Disability Index; PGIC=Patient Global Impression of Change; PSQI=Pittsburgh Sleep Quality Index; RCT=randomised controlled trial; SCS=spinal cord stimulation; SF-12=12-Item Short Form survey; VAS=Visual Analogue Scale.

Table 10 describes the interventions in the study included.

Table 10. Characterisation of the interventions in the study included

Study reference/ID	Study intervention	Study comparator
Evoke study	Evoke *closed-loop* SCS	Evoke *open-loop* SCS
	• Only patients with a ≥50% reduction in average overall trunk and limb pain on the VAS during a 2–11-day SCS trial period received a permanently implanted Evoke SCS system[a]. • Patients were asked not to change their baseline pain medications or increase/decrease their dosage or frequency until the 3-month follow-up visit, with the exception of taking pain medications for postoperative pain or AEs, and up to 2 g of Tylenol (paracetamol) daily as a rescue drug regimen, as needed.	
[a] Patients who provided informed consent and met the eligibility criteria were enrolled and randomised before the beginning of the SCS trial period.		

Source: Clinical study report.
Abbreviations: AE=adverse event; SCS=spinal cord stimulation; VAS=Visual Analogue Scale.

Table 11 provides information on the treatment duration and observation periods in the study included.

Table 11. Information on the course of the study included (including planned follow-up duration)

Study reference/ ID Outcome category	Planned follow-up	Study intervention	Study comparator
Evoke study		**N=67**	**N=67**
SCS trial period duration [days]			
Mean ± SD	–	5.5 ± 1.5	5.9 ± 1.7
Median	–	6.0	6.0
Range (min., max.)	–	2.0, 9.0	3.0, 11.0
Treatment duration [months]			
Mean ± SD	–	16.3 ± 3.8[a]	16.2 ± 4.8[a]
Observation period [months]			
All outcomes	• At 1, 3, 6, 9 and 12 months and biannually thereafter for up to 3 years. • For patients who crossed over after the 24-month visit: additional follow-up at 1 month and 3 months after crossover.		
[a] The median and range for the treatment duration were not reported in the clinical study report.			

Source: Clinical study report.
Abbreviations: N=number of patients randomised; SCS=spinal cord stimulation; SD=standard deviation.

4.3 Study results on relative effectiveness and relative safety

4.3.1 Results for the patient population "adult patients with chronic intractable pain of the trunk and/or limbs"

Table 12 describes the Evoke study included in the assessment for the patient population "adult patients with chronic intractable pain of the trunk and/or limbs" and specifies whether the complete study population or a relevant subpopulation is used.

Table 12. Studies included in the assessment for the patient population "adult patients with chronic intractable pain of the trunk and/or limbs", including the populations analysed

Study reference/ID Relevant study arms (number of patients randomised/included)	**Population analysed** **(number of patients randomised/included)**
PICO 1	
Direct comparison: Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS	
Evoke study Evoke *closed-loop* SCS (N=67) Evoke *open-loop* SCS (N=67)	Complete study population.

Source: Clinical study report.
Abbreviations: N=number of patients randomised; SCS=spinal cord stimulation.

The complete study population for the Evoke study matches the population for PICO 1.

The way in which the intervention was used in the Evoke study matches the intervention for PICO 1; however, in routine care the Evoke SCS system might be used in two modes by patients (they might have both closed- and open-loop programmes out of the four possible programmes, as determined by the treating physician according to the patient's feedback, and they can switch between their programmes freely). In addition, in routine care, various conservative therapeutic options may accompany SCS treatment. In the Evoke study, only pain medication was allowed for the participants.

The comparator used in the Evoke study may not strictly match the comparator for PICO 1. The HTD claims that the Evoke open-loop SCS system delivers stimulation that can be considered equivalent to the mechanism used by other commercially available SCS systems, but with an additional feature to measure ECAPs. However, the technical characteristics of the open-loop stimulation mode of Evoke SCS system are insufficiently described in the submission dossier to be able to conclude whether the stimulation mode is the same as for the latest generation of open-loop SCS systems. Owing to this uncertainty, health technology assessment bodies may need to make a judgement in the context of their own national setting as to whether or not the results of this study address PICO 1.

4.3.1.1 Patient characteristics

Table 13 lists the characteristics of the patients in the studies included in the assessment for "adult patients with chronic intractable pain of the trunk and/or limbs".

Table 13. Patient baseline characteristics including treatment/study discontinuations for the population "adult patients with chronic intractable pain of the trunk and/or limbs"

Study reference/ ID Characteristics Category	**Study intervention**	**Relevant comparator**
Evoke study	Evoke *closed-loop* SCS N=67	Evoke *open-loop* SCS N=67
Age [years]		
Mean ± SD	55 ± 10	56 ± 12
Median	56	57
Range (min., max.)	29, 80	25, 81
Sex [men], %	51	52
Body mass index [kg/m^2]		
Mean ± SD	31 ± 6	32 ± 7
Median	31	32
Range (min., max.)	18, 46	18, 49
Duration of pain [years]		
Mean ± SD	14 ± 10	11 ± 10
Median	11	9
Range (min., max.)	0.5, 41	0.7, 46
Pain location, n (%)		
Chronic intractable back pain	67 (100)	67 (100)
Chronic intractable leg pain	67 (100)	67 (100)
Unilateral	24 (36)	28 (42)
Bilateral	43 (64)	39 (58)
Pain aetiology (not mutually exclusive), n (%)		
Arachnoiditis	0 (0)	2 (3)
CRPS 1	0 (0)	1 (2)
Degenerative disc disease	33 (49)	42 (63)
Failed back surgery syndrome	38 (57)	41 (61)
Internal disc disruption or tear/discogenic pain	7 (10)	10 (15)
Lumbar facet-mediated pain	8 (12)	8 (12)
Mild–moderate spinal stenosis	26 (39)	27 (40)
Neuropathic pain	1 (2)	1 (2)
Radiculopathy	61 (91)	59 (88)
Sacroiliac joint-mediated pain	9 (13)	5 (8)
Spondylolisthesis	6 (9)	5 (8)
Spondylosis with myelopathy	2 (3)	3 (5)
Spondylosis without myelopathy	26 (39)	24 (36)
Other chronic pain	6 (9)	3 (5)
Baseline pain medication use, n (%)	63 (94)	59 (88)
Opioids	41 (61)	40 (60)
Nonopioids[1]	51 (76)	52 (78)
Previous noninvasive therapies[2], n (%)	65 (97)	64 (96)
Previous interventional procedure[3], n (%)	63 (94)	62 (93)
Previous back surgery[4]	39 (58)	41 (61)
Study discontinuation, n (%)		
At the end of the trial period (before the permanent implant)	8 (12)[a]	13 (20)[b]
After the implant, through 12-month follow-up	3 (4)[c]	5 (7)[d]

1: Nonopioid pain medication classes include: anticonvulsant, antidepressant, local anaesthetic, muscle relaxant, nonsteroidal anti-inflammatory drugs and other pain medications.
2: Noninvasive therapies include: acupuncture, aquatherapy, assistive device, biofeedback, chiropractic care, exercise therapy, massage therapy, psychotherapy, physical therapy and transcutaneous electrical nerve stimulator.
3: Interventional procedures include: ankle surgery, benign cyst removal, block/injection – other, epidural steroid injection, facet joint injection, intradiscal bilateral lumbar biacuplasty, intradiscal procedure (e.g.,

intradiscal electrothermal therapy), lumbar rhizotomy, lumbar surgical ablation, lumbar sympathetic block, medial branch block, radiofrequency denervation, sacroiliac joint injection and trigger point injection. 4: Back surgeries include: artificial disc replacement, discectomy or microdiscectomy, foraminotomy, kyphoplasty or vertebroplasty, laminectomy, nucleoplasty (e.g., disc decompression, laser surgery), spinal fusion, back surgery – not otherwise specified, and back surgery – other.
[a] Four patients withdrew and four failed the trial period. [b] Three patients withdrew and ten failed the trial period. [c] Two patients withdrew voluntarily, and one was lost to follow-up. [d] One patient withdrew voluntarily, two patients withdrew because of adverse events, one patient missed the follow-up at 3 months and one patient missed the follow-up at 12 months.

Source: Clinical study report.

Abbreviations: CRPS=complex regional pain syndrome; n=number of patients; N=number of patients randomised; SCS=spinal cord stimulation; SD=standard deviation.

There were no major differences between the treatment groups in the included study in terms of baseline characteristics.

4.3.1.2 Outcomes for PICO 1

Results are presented here for the relative effectiveness and relative safety of the medical device for PICO 1. The outcomes available in the study included in the assessment and their measurement instruments are presented in brief in **Table 14** and **Table 15**.

4.3.1.3 Outcomes available

Table 14 provides an overview of the outcomes available in the studies included in the assessment for PICO 1.

Table 14. Matrix of outcomes in the randomised controlled trial included for PICO 1 - direct comparison: Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS

Outcome	**Study ID** Evoke study
Global pain, preferably measured using the VAS or Numeric Rating Scale	Yes[a]
Responder rate, measured as global pain relief ≥50% vs. baseline at 6 months minimum	Yes[b]
Healthcare consumption including pain medication consumption, other nonsurgical pain management therapies and number of outpatient visits	Yes[c]
HRQoL: - Generic HRQoL, preferably measured with the SF-12 or SF-36 - Disease- or population-specific HRQoL (e.g. neuropathic pain impact on QoL measured with the NePIQoL)	 Yes[d] No[e]
Health status preferably measured by EQ-5D	Yes[f]
Functioning: - Exercise tolerance - Sleep quality - Body function	 No[e] Yes No[e]
Disability: - Disability measured using the Oswestry Disability Index - Ability to perform activities of daily living	 Yes No[e]
Participation restriction: - Ability to return to work (or studies)	 No[e]
Patient satisfaction with treatment, preferably measured as GPE	Yes[g]
Treatment discontinuation due to adverse events	Yes
Sick leave episodes (number and duration)	No[e]
All-cause mortality	Yes
Safety, including a description of each AE included in the following categories:	

- Any AEs related to the procedure and to the medical device including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision, removal or replacement of the implanted components	Yes
- Serious AEs	Yes

[a] VAS scores were reported.
[b] Part of the endpoint "≥50% reduction in overall trunk and limb pain (VAS score) **AND** no increase in baseline pain medication within 4 weeks of the endpoint visit".
[c] Only the pain medication use was reported in the study.
[d] SF-12 was used in the study (two components: physical and mental components).
[e] Outcome was not recorded in the study.
[f] Health status was measured by EQ-5D-5L.
[g] Measured by treatment satisfaction, satisfaction with pain relief and if the patient would recommend the therapy and by the Patient Global Impression of Change.

Source: Refer to Table 7.

Abbreviations: AE=adverse event; EQ-5D=EuroQol 5 dimensions questionnaire; GPE=Global Perceived Effect; HRQoL=health-related quality of life; NePIQoL=Neuropathic Pain Impact on Quality of Life; SF-12=12-item Short Form survey; SF-36=36-item Short Form survey; VAS=Visual Analogue Scale.

Not all outcomes requested for PICO 1 were reported in the study. Those not reported were: disease-specific HRQoL, ability to perform activities of daily living, exercise tolerance, ability to return to work (or studies), body function and sick leave episodes (number and duration). The HTD provided evidence for the rest of the outcomes requested.

The outcome "responder rate measured as global pain relief of ≥50% versus baseline at 6 months minimum" was reported as part of the primary endpoint of the study "≥50% reduction in overall trunk and limb pain at the endpoint visit AND no increase in baseline pain medication within 4 weeks of the endpoint visit", where the efficacy component was determined using the in-clinic, subject-completed VAS for overall trunk and limb pain. The definition of the endpoint is not clear regarding the pain-medication-use component. Assessment of the endpoint at 3 months and 12 months was planned. The definition of the endpoint for 3 months is: "within 4 weeks of the 3 month-visit". It is stated that the endpoint would also be assessed at 12 months. It is not clearly stated that the 12-month assessment would look at the 4-week window for the 3-month visit or the 4-week window for the 12-month visit. However, during the factual accuracy check, the HTD confirmed that the 12-month assessment considered the 4 weeks before that visit.

The outcomes reported are presented in brief in **Table 15**.

Table 15. Outcomes reported and their measurement instruments

Outcome (concept)	Outcome measurement instruments/ Type of outcome measurement instrument	Outcome measurement instrument definition/ Interpretation
Pain	VAS for pain/ PROM	Measure of pain rated by the patient on a 10-cm line scale ranging from 0 (no pain) to 10 (worst possible pain). • For the outcomes "≥50% reduction in overall trunk and limb pain at the endpoint visit AND no increase in baseline pain medication within 4 weeks of the endpoint visit" and "in-clinic VAS average overall trunk and limb pain", pain was assessed as the average trunk and limb pain in the last 24 hours.

Outcome (concept)	Outcome measurement instruments/ Type of outcome measurement instrument	Outcome measurement instrument definition/ Interpretation
		• For the outcome "7-day diary VAS overall average trunk and limb pain", pain was assessed using a pain diary (worst, least, and average pain each day over a 7-day time frame) completed by the patient at baseline and before each scheduled study visit.
Function	Pittsburgh Sleep Quality Index/PROM	Self-administered questionnaire measuring sleep quality over a 1-month time interval. 19 individual items generate seven "components" of the global score: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication and daytime dysfunction. The global score ranges from 0 (best sleep quality) to 21 (worst sleep quality).
Disability	Oswestry Disability Index/PROM	Self-administered questionnaire measuring how back or leg pain affects a patient's everyday life. 10 sections: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and travelling. Each section consists of 6 statements scored from 0 (no disability) to 5 (greatest disability). The total score is converted into a percentage or as a score out of 100, interpreted as follows: • 0 to 20: minimal disability • 21 to 40: moderate disability • 41 to 60: severe disability • 61 to 80: crippled • 81 to 100: bedridden or functional impairment
Health-related quality of life	SF-12/ PROM	Self-reported general health questionnaire measuring physical and mental health. 12 items relating to 8 health domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health) rated and combined to provide 2 summary scores ranging from 0 to 100, with higher scores indicating better health: • The Physical Component Summary, and • The Mental Component Summary Scores are standardised to population norms, with the mean score set at 50 (SD 10) in the USA.
Health status	EQ-5D-5L/ PROM	Instrument measuring health status consisting of the EQ-5D descriptive system and the EQ VAS. • EQ-5D-5L: self-administered questionnaire comprising 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with 5 levels (no problems, slight problems, moderate problems, severe problems and extreme problems) resulting in a 5-digit code that is converted to a single country-specific utility value ranging from 0 (equivalent to being dead) to 1 (full health). EQ-5D norm for the US population used in the Evoke study: 0.830 for responders aged 55–64 years and 0.867 for all age groups[1]. • EQ VAS: self-rated vertical VAS, ranging from 0 "the worst health state you can imagine" to 100 "the best health state you can imagine".

Outcome (concept)	Outcome measurement instruments/ Type of outcome measurement instrument	Outcome measurement instrument definition/ Interpretation
		EQ VAS norm for the US population used in the Evoke study: 76.9 for responders aged 55–64 years and 80.0 for all age groups[2].
	Patient Global Impression of Change/PROM	Single-item measure of the global improvement in overall status rated by participants on a 7-point scale: "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse" and "very much worse".
Satisfaction with treatment	Global Perceived Effect, 2 items/PROM	• Satisfaction with pain relief and satisfaction with therapy rated by participants in the Evoke study on a 5-point scale ranging from "very satisfied" to "very unsatisfied". • Likelihood of recommending therapy rated by participants on a 5-point scale ranging from "strongly recommend" to "definitely not recommend".

[1] EQ-5D index population norms (country-specific time-tradeoff value sets) table from Janssen and Szende, 2014 (17).
[2] EQ VAS ratings by age group and total population (not standardised) table from Janssen and Szende, 2014 (17).

Source: Clinical study report, Janssen and Szende, 2014 (17).
Abbreviations: EQ-5D-5L=EuroQol 5 dimensions, 5 levels questionnaire; PROM=patient-reported outcome measure; SF-12=12-item Short Form survey; SD=standard deviation; VAS=Visual Analogue Scale.

Assessment of the validity of outcome measurement instruments that were not specified in the consolidated PICO was beyond the scope of this JCA.

4.3.1.4 Risk of bias in the original clinical studies

Table 16 summarises the risk of bias (RoB) assessment for the Evoke study conducted by the assessment team at the outcome level using the Cochrane RoB 2.0 method.

These assessments were based on the Evoke publication (Mekhail 2020), the study protocol (CLIN-PCL-002065, Rev4.00, 6 Aug 2018), the statistical analysis plan (Evoke SAP Rev5.00, 1 Feb 2018) and the clinical study report (CLIN-RPT-007480, 4 Dec 2019).

Eight different outcomes were assessed, all of which were patient-reported outcome measures (PROMs). One was assessed as a single outcome (the overall endpoint success at 12 months) and six (ODI change from baseline, EQ-5D-5L change from baseline, patient satisfaction rate difference of very satisfied or satisfied, PGIC rate difference of very much improved or much improved, PSQI change from baseline and SF-12 change from baseline) were grouped, depending on their prespecified statistical analyses.

The corresponding detailed RoB tables are presented in Appendix D.

Table 16. Risk of bias: randomised controlled trial at study outcome level (Cochrane RoB 2.0)

Domain	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall RoB	Comments
Evoke study/ Overall endpoint success at 12 months (≥50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of the endpoint visit)	Low[a]	Low[b]	Low[c]	Low[d]	Low[e]	Low	The overall RoB for this outcome is rated as low, as the RoB for all domains was assessed as low.
Evoke study/ PROMs at 12 months (ODI change from baseline, EQ-5D-5L change from baseline, patient satisfaction rate difference of very satisfied or satisfied, PGIC rate difference of very much improved or much improved, PSQI change from baseline, SF-12 change from baseline)	Low[a]	Low[b]	High[f]	Low[g]	Low[e]	High	The overall RoB is rated as high as the domain for the missing outcome data is of high risk. High RoB for this domain was assigned because the protocol defines handling of missing data only for the primary and the hierarchical secondary endpoints. The endpoints assessed are neither of these.

[a] Random assignment of subjects in a 1:1 fashion at the time of the trial procedure. Computer-generated randomisation with permuted blocks of size 4 and 6 in random order, stratified by study site. Information on the concealment of the allocation sequence was not available.
[b] Both patients and investigators were blinded. An assessment of masking was completed to determine whether patients or investigators became unmasked to the treatment assignment.
[c] At 12 months: missing data for 8/67 patients (12%) from the Evoke closed-loop SCS group and 8/67 patients (12%) from the Evoke open-loop SCS group. A variety of prespecified sensitivity analyses were performed on the endpoint to assess the impact of missing data on the results (best case scenario, worst case scenario, tipping point analysis and multiple imputation).
[d] The responder rate was measured using the VAS (average pain in the last 24 hours). The second component of this endpoint was pain medication use; however the clinical study report does not mention a medication diary. Patients were asked about their pain medication during a follow-up call or visit.
[e] Data were analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis. It is unlikely that the numerical result assessed had been selected from multiple eligible outcome measurements within the outcome domain or multiple analyses of the data, on the basis of the results.
[f] Missing data for 12/67 patients (18%) from the Evoke *closed-loop* SCS group and 19/67 patients (28%) from the Evoke *open-loop* SCS group for all outcomes assessed in this RoB analysis.
[g] Outcome measurement (data collection) for each outcome was appropriate and the same measurement methods and thresholds were used in both the Intervention and the Comparator groups.

Source: Appendix D.

Abbreviations: EQ-5D=EuroQol 5 dimensions questionnaire; ODI=Oswestry Disability Index; PGIC=Patient Global Impression of Change; PROM=patient-reported outcome measure; PSQI=Pittsburgh Sleep Quality Index; RoB=risk of bias; SCS=spinal cord stimulation; SF-12=12-item Short-Form survey; VAS=Visual Analogue Scale.

4.3.1.5 Health outcome results

Table 17. Relative effectiveness results (dichotomous outcomes) – direct comparison: Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS

Time point	**Evoke *closed-loop* SCS**		**Evoke *open-loop* SCS**		**Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS**	
Outcome Study reference/ID	**N**	**Patients with event, n (%)**	**N**	**Patients with event, n (%)**	**RD[c] [95% CI] p-value**	**Hypothesis testing**
12 months **Evoke study**						
Overall endpoint success: ≥50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of the endpoint visit	59[a]	49 (83)	59[b]	36 (61)	22.0[d] [6.3, 37.7] 0.006	S-P-C
PGIC: overall status much or very much improved	55	45 (82)	48	36 (75)	6.8 [-9.1, 22.8] 0.473	NO-P-NC
Patient satisfaction: much or very much satisfied						
With pain relief	55	49 (89)	48	39 (81)	7.8 [-5.9, 21.6] 0.279	NO-P-NC
With therapy	55	50 (91)	48	41 (85)	5.5 [-7.1, 18.0] 0.540	NO-P-NC
Would strongly recommend or recommend therapy	55	52 (95)	48	42 (88)	7.0 [-4.1, 18.2] 0.298	NO-P-NC
Pain medication use	55	48 (87)	48	37 (77)	10.2 [-4.6, 25.0] 0.201	NO-P-NC
1		21 (44)		11 (30)	NR	
2		16 (33)		13 (35)	NR	
≥3		11 (23)		13 (35)	NR	
Opioid use	55	27 (49)	48	25 (52)	-3.0 [-22.3, 16.4] 0.844	NO-P-NC

Reading the "Hypothesis testing" columns:
1. Statistical significance: S=statistically significant against the α-level specified in the statistical analysis plan of the corresponding study; NS=nonsignificant; NO=nominal p-value.
2. Prespecification: P=statistical test was prespecified according to the statistical analysis plan of the corresponding study; NP=not prespecified.
3. Multiple hypothesis testing. C=appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study; NC=not controlled.

[a] Of the 69 patients randomised, 55 completed 12-month follow-up; 4 presumed nonresponders.
[b] Of the 69 patients randomised, 44 completed 12-month follow-up; 11 presumed nonresponders.

[c] Risk ratios were not reported in the clinical study report.
[d] Intention-to-treat analysis of the primary endpoint, with failures of the trial stimulation phase and withdrawals considered as failures. All the other missing data were classified as missing, and no data imputations were performed. As noninferiority was met, the results reported here are the superiority results. These were tested at a 2-sided significance level of 0.05. Noninferiority results are presented in Appendix C.2.

Source: Clinical study report.

Abbreviations: CI=confidence interval; n=patients with event; N=number of patients at the follow-up time point; NR=not reported in the CSR; PGIC=Patient Global Impression of Change; RD=rate difference; SCS=spinal cord stimulation; VAS=Visual Analogue Scale.

As prespecified in the Evoke study protocol and statistical analysis plan, a sensitivity analysis was conducted using different methods detailed in **Table 18** to assess the impact of the handling of missing data on the primary analysis of the overall endpoint success.

Table 18. Sensitivity analysis of the overall endpoint success

Attribute	Analysis method	Evoke *closed-loop* SCS N=67 n/N (%)	Evoke *open-loop* SCS N=67 n/N (%)	Rate difference [95% CI] p-value
Missing data	Best case scenario[a]	57/67 (85%)	36/67 (54%)	31.3% [16.7, 46.0] Noninferiority, δ = 10%: p<0.001 Superiority: p<0.001
Missing data	Worst case scenario[b]	49/67 (73%)	44/67 (66%)	7.5% [-8.1, 23.0] Noninferiority, δ = 10%: p=0.014 Superiority: p=0.347
Missing data	Multiple imputation[c]	NA[d]	NA[d]	21.8% [5.7, 37.9] Noninferiority, δ = 10%: p<0.001 Superiority: p=0.008
Missing data	Tipping point analysis[e]	100% of all conducted data imputations supported noninferiority of the Evoke closed-loop SCS group (p≤0.014). 75% of the missing data scenarios demonstrated that the Evoke closed-loop SCS group was superior to Evoke open-loop SCS group (p <0.05).		

[a] Including all patients randomised to the Evoke closed-loop SCS group with missing data as successes and all patients randomised to the Evoke open-loop SCS group with missing data as failures.
[b] Including all patients randomised to the Evoke closed-loop SCS group with missing data as failures and all patients randomised to the Evoke open-loop SCS group with missing data as successes.
[c] Multiple imputation via chained equations (fully conditional specification) was performed. Covariates that were considered for imputation of missing data were treatment group, age, sex, race/ethnicity and pain scores (baseline, end of trial and 1-month pain). 100 imputed data sets were generated and used to produce a pooled estimate of treatment effect (effect measure and p-value).
[d] Outcomes were imputed for 8 patients in the Evoke closed-loop SCS group and 8 patients in the Evoke open-loop SCS group.
[e] Determines the point between the best case and the worst case at which the significance threshold is met.

Source: Clinical study report.

Abbreviations: CI=confidence interval; NA=not applicable; n/N=number of patients with overall endpoint success/number of randomised patients.

For the noninferiority hypothesis, the results from the sensitivity analysis have the same directionality as for the results from the primary analysis.

For the superiority hypothesis, the results from the sensitivity analysis all have the same directionality as for the results from the primary analysis (although the worst-case scenario analysis is not statistically significant).

Table 19. Relative effectiveness results (quantitative outcomes) – direct comparison: Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS

Time point Outcome Study reference/ID	**Evoke *closed-loop* SCS**			**Evoke *open-loop* SCS**			**Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS**	
	N[a]	**Values at baseline** Mean ± SD Median Range (min., max.)	**Change[b] from baseline at 12 months** Mean ± SD Median Range (min., max.)	**N[a]**	**Values at baseline** Mean ± SD Median Range (min., max.)	**Change[b] from baseline at 12 months** Mean ± SD Median Range (min., max.)	**MD in change [95% CI]** **p-value**	**Hypothesis testing**
12 months **Evoke study**								
In-clinic average overall trunk and limb VAS pain [mm]	59	81.9 ± 10.6 82.5 60, 99	-58.1 ± 23.6 -63.0 -98, 0	59	82.3 ± 8.8 82.0 63, 99	-46.4 ± 32.3 -56.0 -92, 4	11.7[c] [1.4, 22.0] 0.027	NO-P-NC
7-day diary overall average trunk and limb VAS pain [mm]	59	78.1 ± 10.6 79.1 59.7, 96.3	-48.5 ± 26.3 -48.5 -85.4, 19.1	56	77.8 ± 9.6 79.4 60.0, 96.3	-42.3 ± 29.8 -49.1 -89.9, 5.7	6.1[c] [-4.3, 16.5] 0.245	NO-P-NC
ODI [points]	55	55.0 ± 9.4 52.0 42, 78	-28 ± 16.3 -30.0 -58, 2	48	55.9 ± 9.4 56.0 42, 78	-26.1 ± 14.5 -25.0 -60, 8	1.9[c] [-4.2, 8.0] 0.537	NO-P-NC
SF-12 PCS [points]	55	28.0 ± 6.9 27.1 14.1, 42.0	+11.7 ± 10.6 +11.2 -21.7, 43.3	48	26.7 ± 6.7 26.5 13.1, 45.5	+11.6 ± 9.6 +11.2 -15.1, 37.3	0.1[d] [-3.8, 4.1] 0.944	NO-P-NC
SF-12 MCS [points]	55	44.8 ± 10.6 43.2 24.7, 65.7	+7.4 ± 12.2 +8.0 -31.5, 25.7	48	51.5 ± 10.6 51.8 26.6, 74.3	-0.8 ± 10.0 -0.8 -22.2, 19.8	8.1[d] [3.7, 12.6] <0.001	NO-P-NC
EQ-5D-5L Index Score [points]	55	0.503 ± 0.153 0.500	+0.245 ± 0.194 +0.264	48	0.496 ± 0.120 0.499	+0.226 ± 0.170 +0.236	0.019[d] [-0.052, 0.091] 0.592	NO-P-NC

		0.152, 0.800	-0.501, 0.680		0.252, 0.778	-0.130, 0.661		
EQ-VAS [points]	55	52.1 ± 21.7 50.0 10, 95	+27.1 ± 23.4 +32.0 -15, 88	48	56.6 ± 23.5 60.0 10, 100	+20.3 ± 20.7 +16.5 -18, 70	6.9[d] [-1.8, 15.6] 0.120	NO-P-NC
PSQI [points]	55	14.0 ± 3.8 15.0 5, 21	-5.7 ± 4.2 -6.0 -15, 3	48	12.6 ± 4.2 13.0 3, 20	-4.5 ± 4.7 -5.0 -16, 3	1.2[c] [-0.6, 2.9] 0.184	NO-P-NC

Reading the "Hypothesis testing" columns:
1. Statistical significance: S=statistically significant against the α-level specified in the statistical analysis plan of the corresponding study; NS=nonsignificant; NO=nominal p-value.
2. Prespecification: P=statistical test was prespecified according to the statistical analysis plan of the corresponding study; NP=not prespecified.
3. Multiple hypothesis testing. C=appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study; NC=not controlled.

[a] The number of patients with an outcome at baseline is 62 in the closed-loop group and 63 in the open-loop group.
[b] The assessment team added + and - signs to indicate the direction of change from baseline.
[c] Greater decrease in the Evoke *closed-loop* SCS group.
[d] Greater increase in the Evoke *closed-loop* SCS group.

Source: Clinical study report.

Abbreviations: EQ-5D=EuroQol 5 dimensions questionnaire; CI=confidence interval; MCS=Mental Component Summary; MD=mean difference; n=patients with event; N=number of patients at the follow-up time point; ODI=Oswestry Disability Index; PCS=Physical Component Summary; PSQI=Pittsburgh Sleep Questionnaire Index; SCS=spinal cord stimulation; SD=standard deviation; SF-12=12-item Short Form survey.

Table 20. Safety outcomes – direct comparison: Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS

Time point Outcome Study reference/ID	**Evoke *closed-loop* SCS**		**Evoke *open-loop* SCS**	
	N	**Patients with event (n)/ number of patients randomised (%)**	**N**	**Patients with event (n)/ number of patients randomised (%)**
16 months (mean) **Evoke study**				
At least one AE	150[a]	45/67 (67)	104[a]	45/67 (67)
Serious AEs	16	10/67 (15)	11	8/67 (12)
Severe AEs (no specific scale used)[b]	22	14/67 (21)	13	9/67 (13)
Treatment discontinuation due to AEs	ND	2/67 (3)[c]	ND	4/67 (6)[c]
Treatment interruption due to AEs	ND	ND	ND	ND
Suspected unexpected serious adverse reaction[d]	0	0	0	0
All-cause mortality[e]	0	0/67 (0)	1[f]	1/67 (1)
Device-related AEs[e]	7[g]	7/67 (10)	5[g]	5/67 (7)
Procedure-related AEs[e]	17[g]	12/67 (18)	8[g]	8/67 (12)
Stimulation therapy-related AEs[e]	5[g]	4/67 (6)	3[g]	3/67 (4)
Device- or procedure-related AEs				
Premature battery depletion[e]	ND	ND	ND	ND
Lead migration[e]	7	6/67 (9)	3	3/67 (4)
Electrical dysfunction[e]	ND	ND	ND	ND
Wound infection[e,i]	1	1/67 (1)	1	1/67 (1)
IPG pocket pain	4	4/67 (6)	1	1/67 (1)
Dural puncture or tear	2	2/67 (3)	1	1/67 (1)
IPG malfunction due to electrocautery	2	2/67 (3)	0	0/67 (0)
Epidural abscess[h]	0	0/67 (0)	1	1/67 (1)
Inadequate lead placement	1	1/67 (1)	0	0/67 (0)
Lead breakage/fracture[i]	0	0/67 (0)	1	1/67 (1)
Muscle spasm or muscle cramp	0	0/67 (0)	1	1/67 (1)
Nausea and/or vomiting	1	1/67 (1)	0	0/67 (0)
Skin irritation or redness	0	0/67 (0)	1	1/67 (1)
Wound dehiscence	1	1/67 (1)	0	0/67 (0)
Surgical revision[e,h]	2	2/67 (3)	1	1/67 (1)
Replacement of the implanted components[e,h]	7	7/67 (10)	3	3/67 (4)
System explant[e,h]	4	4/67 (6)	5	5/67 (7)

[a] Total number of AEs.
[b] AEs were classified as mild (usually transient; does not interfere with the subject's usual activities), moderate (low-level inconvenience or concern to the subject; may interfere with usual activities) or severe (significantly limits the subject's ability to perform usual activities).
[c] Calculated by the assessment team from the clinical study report data.
[d] Defined as unanticipated adverse device effect.
[e] As requested by member state(s) in their PICOs.
[f] The primary cause of death was cardiac arrest; the secondary cause was uncontrolled hypertension. The event was adjudicated not to be related to the study.
[g] AEs adjudicated as definitely or possibly related to the device, procedure or stimulation therapy, respectively.
[h] During the implant phase.
[i] Adjudicated as serious procedure- or device-related AEs.

Source: Clinical study report.

Abbreviations: AE=adverse event; IPG=implantable pulse generator; N=number of events; n=number of patients with event; ND=no data; PICO=Population, Intervention, Comparator, Outcome.

The effect estimates for the safety outcomes are presented in Appendix C.1.1.

4.3.2 Results for the patient population "adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome, with an insufficient effect from conventional pain management therapies"

4.3.2.1 Outcomes for PICO 2

No evidence for PICO 2 was provided by the HTD. No study could be identified to address this PICO question in the search conducted by the assessment team.

4.3.2.2 Outcomes for PICO 3

No evidence for PICO 3 was provided by the HTD. No study could be identified to address this PICO question in the search conducted by the assessment team.

4.4 Safety results from the noncomparative study from the clinical development programme for the intervention under assessment

One single-arm study was also considered to assess the safety of the Evoke SCS system. The Avalon study is one of the studies from the clinical development programme for the Evoke SCS system and has 24-month follow-up.

Table 21. Studies considered for safety outcomes only: list of studies from the clinical development programme for the intervention under assessment

Study reference/ID Study type Study interventions	**Study for marketing authorisation/ CE marking of the technology under assessment**	**Sponsored[a] or third-party study of the technology under assessment**	**Documentation available from the submission dossier**
Studies providing noncomparative evidence: **Evoke *closed-loop* SCS system**			
Avalon study[b] *Single-arm study* Evoke *closed-loop* SCS	Yes[c]	Sponsored	• CSR: CLIN-RPT-002539 (24 Aug 2015) (18) • Clinical study protocol: SCLSH1502, Revision 5.0, 6 Sep 2016 (19) • Registry entry: ACTRN12615000713594 (20) • Publication or other reference: Russo 2020 (21), Brooker 2021 (22), Russo 2018 (23)

[a] Study sponsored by the HTD or in which the HTD participated financially in some other way.
[b] In the following tables, the study is referred to with this name.
[c] This is a pivotal study conducted to support premarketing approval for the Australian market.

Source: Clinical study report.
Abbreviations: CSR=clinical study report; HTD=health technology developer; SCS=spinal cord stimulation.

4.4.1 Study characteristics of the Avalon study

The main characteristics of the Avalon study, as well as characterisation of the study intervention and information on the course of the study, are presented in **Table 22**, **Table 23** and **Table 24**.

Table 22. Characteristics of the Avalon study considered for safety outcomes only

Study reference/ ID	Study type and design	Study population	Study arms (number of patients randomised/ included)	Study duration, data cutoff(s) and locations	Study endpoints
Avalon study	Prospective multicentre single-arm study	Males/females aged ≥18 years (if female, not pregnant). Chronic, intractable pain (VAS ≥6 cm for the past week) refractory to conservative therapy for a minimum of 3 months Pain medications stable for at least 4 weeks prior baseline evaluation. ODI score 41–80%	Evoke *closed-loop* SCS N=50	Study duration: 2 years (extended from 12 months mid-study; 3 subjects elected not to participate in the extension) Data cutoff: 14 Oct 2019 Number of centres: 4 sites in Australia	Primary endpoint: ability to successfully deliver neuromodulation in closed-loop stimulation mode at 1 month after implantation, rate of AEs (in particular, any AEs believed to be attributable specifically to use of closed-loop stimulation, over 24-month follow-up) Other endpoints[a]: • Change in VAS pain scores • Health status measured with the EQ-5D-5L • Disability measured with the ODI • Patient satisfaction • Sleep quality measured with the PSQI
[a] Only outcomes included in the PICO.					

Source: Clinical study report.

Abbreviations: AE=adverse event; EQ-5D-5L=EuroQol 5 dimensions, 5 levels questionnaire; N=number of patients included; ODI=Oswestry Disability Index; PSQI=Pittsburgh Sleep Quality Index; SCS=spinal cord stimulation; VAS=Visual Analogue Scale.

Table 23: Characterisation of the Avalon study intervention

Study reference/ID	Study intervention
Avalon study	*Evoke* closed-loop *SCS*
	• Only patients with a ≥40% reduction in VAS pain score during the trial period (length of the period at the discretion of the treating clinician) received a permanent Evoke closed-loop stimulator implant. • There were no restrictions or requirements for concomitant medication use for enrolled patients.

Source: Clinical study report.

Abbreviations: SCS=spinal cord stimulation; VAS=Visual Analogue Scale.

Table 24. Information on the course of the Avalon study considered from the clinical development programme (including planned follow-up duration)

Study reference/ ID Outcome category	Planned follow-up	Study intervention
Avalon study		**N=70**
Treatment duration [months] Mean ± SD	–	ND
Observation period [months] All outcomes	At 1, 3, 6, 12, 15, 18, 21 and 24 months	

Source: Clinical study report.

Abbreviations: N=number of patients randomised/included; ND=no data; SD=standard deviation.

4.4.2 Patient characteristics in the Avalon study

Table 25. Patient characteristics in the Avalon study

Study reference/ ID Characteristics Category	**Study intervention**
Avalon study	Evoke *closed-loop* SCS N=70
Age [years]	
Mean ± SD	56 ± 13
Median	57.5
Range (min., max.)	24, 77
Sex [m], %	50
Body mass index [kg/m^2]	
Mean ± SD	30.3 ± 5.7
Median	30.1
Range (min., max.)	18.9, 46.6
Duration of pain [years]	
Mean ± SD	14 ± 11
Median	12.5
Range (min., max.)	1, 43
Pain aetiology (not mutually exclusive), n (%)	
Arachnoiditis	0 (0)
Lumbar degenerative disease	1 (1)
Failed back surgery syndrome	38 (54)
Internal disc disruption/discogenic pain	7 (10)
Peripheral vascular disease	0 (0)
Radiculopathy	14 (20)
CRPS 1	0 (0)
CRPS 2	0 (0)
Angina	0 (0)
Lumbar spondylosis	5 (7)
Peripheral neuropathy	1 (1)
Neuropathic pain	2 (3)
Possible defect in the lumbar spine	1 (1)
Sciatica	1 (1)
Baseline pain medication use, n (%)	ND
Previous noninvasive therapies, n (%)	ND
Previous interventional procedure, n (%)	
Previous back surgery	47 (67)
Prior history of SCS	5 (7)
Study discontinuation, n (%)	
At the end of the trial period (before the permanent implant)	20 (29)[a]
After the implant, during 24-month follow-up	12 (17)[b]

[a] Of these 20 patients, 2 were withdrawn by the investigator, 1 discontinued because of an adverse event, 7 patients withdrew and 10 failed the trial period.
[b] Of these 12 patients, 3 discontinued because of an adverse event, 3 withdrew, 1 was withdrawn by the investigator, 1 discontinued because of device failure and 3 completed the study at 12 months and opted to stop.

Source: Clinical study report.
Abbreviations: CRPS=complex regional pain syndrome; SCS=spinal cord stimulation; SD=standard deviation.

4.4.3 Risk of bias

No formal RoB assessment was conducted for the Avalon study as the overall conclusion on the internal validity of single-arm studies is considered very limited, which is very unlikely to be changed by a formal RoB assessment.

4.4.4 Safety outcomes from the Avalon study

Table 26. Safety outcomes from the noncomparative evidence

Time point Outcome Study reference/ID		**Evoke *closed-loop* SCS**
	N	**Patients with event/number of randomised patients (%)**
24 months **Avalon study**		
At least one AE	215	55/70 (79)
Serious AEs	20	16/70 (23)
Severe AEs (no specific scale used)[a]	16	12/70 (17)
Treatment discontinuation due to AEs	ND	3/70 (4)[b]
Treatment interruption due to AEs	ND	ND
Suspected unexpected serious adverse reaction	0	0/70 (0)
All-cause mortality	1	1/70 (1)
Device- or procedure-related AEs[c]	77	38/70 (54)
Stimulation therapy-related AEs	0	0/70 (0)
All AEs (incidence >5%)		
Upper respiratory symptoms	23	16/70 (23)
Fall/trip/slip/twist	9	7/70 (10)
Lead migration	6	5/70 (7)
Dysaesthesia in a lower extremity	8	8/70 (11)
IPG pocket pain	9	9/70 (13)
Pain at the implant/incision site	7	7/70 (10)
Muscle spasm or muscle cramp	6	6/70 (8)
Nocturia	5	4/70 (6)
Unilateral leg pain	4	4/70 (6)
Urinary frequency increased	4	4/70 (6)
Surgical revision	ND	ND
Device- or procedure-related AEs (incidence >5%)		
Lead migration	6	5/70 (7)
Dysaesthesia in a lower extremity	7	7/70 (10)
IPG pocket pain	9	9/70 (13)
Pain at the implant/incision site	7	7/70 (10)
Stimulation-related AEs	0	0/70 (0)

[a] Aes were classified as mild, moderate, severe or life-threatening.
[b] Of these 3 patients, 1 discontinued because of allergy to an implanted component, 1 died and 1 had a brain tumour and opted to stop study participation.
[c] Defined as a study-related AE.

Source: Clinical study report.
Abbreviations: AE=adverse event; IPG=implantable pulse generator; ND=no data.

Only descriptive statistics were used to report the safety outcomes in the Avalon study.

4.5 Summary table addressing the uncertainty of the evidence

The uncertainty of the evidence is summarised in **Table 27** and **Table 28**.

Table 27. Uncertainty of the evidence for PICO 1

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p-value[a]
All outcomes	1 RCT	**Internal validity of individual studies** • The Evoke study was a prospective, multicentre RCT that included 134 patients (67 in both the intervention group and the comparator group) with 12-month follow-up. • Randomisation was performed in a 1:1 fashion using computer-generated small permuted blocks of two sizes and stratified by study site. • Information on the concealment of the allocation sequence was not available. • The patients and investigators were blinded to the treatment. • The study was designed with a primary objective of demonstrating noninferiority and, if met, superiority. • There were no major differences in baseline characteristics between the treatment groups in the study. **Applicability** • The study population is in line with the population for PICO 1. The study was conducted in the USA, not in Europe. • As is common practice for SCS, only patients with ≥50% pain reduction on the VAS (responder patients) at the end of the SCS trial period had a permanent device implanted. • There is uncertainty regarding whether the comparator used in the Evoke study is sufficient to address PICO 1. The HTD claims that the Evoke open-loop SCS system delivers stimulation that can be considered equivalent to the mechanism used in other commercially available SCS systems, but with an additional feature to measure ECAPs. However, the technical characteristics of the open-loop stimulation mode of the evoke SCS system are insufficiently described in the submission dossier to be able to conclude whether the stimulation mode is the same as in the latest generation of open-loop SCS systems. • It must be noted that the study used the HTD's own device, the Evoke SCS system, for both the investigational and the comparator arms. The Evoke SCS system can be operated as a closed-loop or an open-loop system, with up to four programme modes. During the study, neither the patients nor the treating physicians were able to switch between modes. • Not all outcomes requested in the PICO were recorded in the study. Those not recorded were: disease-specific HRQoL, ability to perform activities of daily living,	NA

		exercise tolerance, ability to return to work (or studies), body function and sick leave episodes (number and duration). The HTD provided evidence for the rest of the outcomes requested. **Heterogeneity and inconsistency** There was no heterogeneity or inconsistency, as only one RCT was available and included for assessment of the relative effectiveness and relative safety of the Evoke closed-loop SCS.	
Overall endpoint success: ≥50% reduction in overall trunk and limb pain (VAS score) **AND** no increase in baseline pain medication within 4 weeks of the endpoint visit	1 RCT	**Internal validity** • The overall risk of bias for this outcome was rated as low. • A variety of prespecified sensitivity analyses were performed for the endpoint to assess the impact of missing data on the results. All the sensitivity analysis results have the same directionality as the results from the primary analysis. • The responder rate was measured using the VAS (average pain in the last 24 hours). The second component of this endpoint was the change in pain medication use; however, the CSR does not mention a medication diary. Patients were asked about their pain medication during a follow-up call or visit. • Data were analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis. On the basis of the results, it is unlikely that the numerical result assessed was selected from multiple eligible outcome measurements within the outcome domain or from multiple analyses of the data. **Applicability** The outcome "responder rate measured as global pain relief of ≥50% versus baseline at 6 months minimum" requested in PICO 1 was reported as part of the primary endpoint of the study "≥50% reduction in overall trunk and limb pain at the endpoint visit AND no increase in baseline pain medication within 4 weeks of the endpoint visit". Although the overall endpoint is not the exact endpoint defined in PICO 1, it was considered equivalent to the outcome requested. Moreover, addition of the pain medication component might limit bias, as it ensures that pain medication is not increased within the month before measurement of the outcome.	Success rate difference at 12 months (%): 22.0 [6.3, 37.7] p=0.006 [*, #, $]
ODI change from baseline	1 RCT	**Internal validity** The overall risk of bias for this outcome was rated as high because of the "Missing data" domain. Missing data were not handled for this outcome. **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): 1.9[b] [-4.2, 8.0], p=0.537[#]

EQ-5D-5L change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): EQ-5D-5L Index Score: 0.019[c] [-0.052, 0.091] p=0.592[#] EQ-VAS: 6.9[c] [-1.8, 15.6] p=0.120[#]
Patient satisfaction (very satisfied or satisfied)	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	RD at 12 months (%): With pain relief: 7.8 [-5.9, 21.6] p=0.279 With therapy: 5.5 [-7.1, 18.0] p=0.540 Would strongly recommend or recommend therapy: 7.0 [-4.1, 18.2] p=0.298
PGIC (overall status very much improved or much improved)	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	RD at 12 months (%): 6.8 [-9.1,22.8] p=0.473[#]
PSQI change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): 1.2[b] [-0.6, 2.9] p=0.184[#]
SF-12 change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): Physical component: 0.1[c] [-3.8, 4.1] p=0.944 Mental component: 8.1[c] [3.7, 12.6] p<0.001

Change in overall average trunk and limb pain (VAS) from baseline	1 RCT	The statistical test for the analysis of this outcome was not prespecified in the SAP.	MD at 12 months (mm): In-clinic: 11.7[b] [1.4, 22.0] p=0.027 7-day diary average overall: 6.1[b] [-4.3, 16.5] p=0.245
All-cause mortality	1 RCT	Assessment of this outcome was not prespecified in the study protocol. Only descriptive statistics were used to report this outcome.	NA
Pain medication use Opioid use	1 RCT	Assessment of this outcome was not prespecified in the study protocol.	RD at 12 months (%): Pain medication: 10.2 [-4.6, 25.0] p=0.201 Opioids: -3.0 [-22.3, 16.4] p=0.844
Safety outcomes: each AE included in the following categories: - Any AEs related to the procedure and to the medical device - Serious AEs	1 RCT	**Internal validity** No hypothesis testing was performed for AEs. The incidence of all distinct AEs is presented, summarised by treatment group. All AEs requested in the PICO are reported, except for premature battery depletion and electrical dysfunction. **Applicability** The same device was used for both the intervention and the comparator groups, and it is only the programming that differs. Therefore, comparison of the two groups regarding device-and procedure-related safety outcomes is not meaningful. Only comparison of stimulation-related AEs might be meaningful. Safety data from the Evoke RCT are available up to 16 months (mean follow-up) in the CSR. Longer follow-up data are only available from the CSR of the Avalon single-arm study.	NA

[a] Use of * indicates statistical significance versus a prespecified α-level; use of # indicates a prespecified analysis according to the statistical analysis plan (for individual studies) or evidence synthesis protocol; use of $ indicates control for multiplicity. Alternatively, indicate if no formal hypothesis testing was carried out.
[b] Greater decrease in the Evoke *closed-loop* SCS group.
[c] Greater increase in the Evoke *closed-loop* SCS group.

Source: Clinical study report.

Abbreviations: AE=adverse event; CSR=clinical study report; EQ-5D-5L=EuroQol 5 dimensions, 5 levels questionnaire; HRQoL=health-related quality of life; HTD=health technology developer; MD=mean difference; NA=not applicable; ODI=Oswestry Disability Index; PGIC=patient global impression of change; PICO=population-intervention-comparator-outcomes; PSQI=Pittsburgh Sleep Quality Index; RD=rate difference; RCT=randomised controlled trial; SAP=statistical analysis plan; SCS=spinal cord stimulation; SF-12=12 Item Short Form Survey; VAS=visual analogue scale.

Table 28. Uncertainty of the evidence from the clinical development programme

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p-value
Safety outcomes	1 single-arm study	The Avalon study was a prospective, multicentre, single-arm pivotal study with 24-month follow-up. Published safety data are available up to 24 months. The planned follow-up for the Evoke RCT was also 24 months but the data were only available up to 16 months (mean follow-up) in the CSR. Only descriptive statistics were used to report the safety outcomes. Risk of bias was not assessed as this was a single-arm study, presented for the safety outcomes only.	NA

Source: Clinical study report.
Abbreviations: NA=not applicable; RCT=randomised controlled trial.

A version of this table using categories according to partial use of GRADE (24) is provided in Appendix E.

5 REFERENCES

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6 SUMMARY REPORT

The Evoke spinal cord stimulation (SCS) system is a spinal cord stimulator that has the ability to deliver either 1) open-loop stimulation; or 2) evoked compound action potential (ECAP)-controlled closed-loop stimulation, for which the stimulation amplitude is automatically adjusted in real time to minimise the difference between the measured ECAP and the target ECAP. The Evoke SCS system is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs.

Chronic pain persists well after the initial injury or illness that produced the initial pain has resolved. The International Association for the Study of Pain has defined chronic pain as pain that persists or recurs for longer than 3 months. Intractable pain is generally defined as pain whose cause cannot be removed, and for which the full range of pain management modalities has been used without an adequate result or with intolerable side effects. Persistent spinal pain syndrome is a type of chronic neuropathic pain that was used to define one subpopulation of interest in this joint clinical assessment (JCA). Chronic neuropathic pain is caused by a lesion or diseases affecting the somatosensory nervous system.

The aim of this JCA is to assess the relative clinical effectiveness and safety of the Evoke SCS system medical device in the target patient population against relevant comparators defined before the start of the assessment in the assessment scoping phase and based on the requirements of EUnetHTA 21 members.

Stakeholders were consulted early in the JCA scoping process to support the development of the assessment scope. Input was received from three healthcare professional organisations and from one organisation providing services to the elderly.

The consolidated assessment scope, including the Population, Intervention, Comparator, Outcome (PICO) questions, is presented in **Table 29**.

Table 29. Consolidated assessment scope

Description of PICO elements	PICO 1	PICO 2	PICO 3
Population[a]	According to the intended use: adult patients with chronic intractable pain of the trunk and/or limbs	Subpopulation: adult patients with chronic intractable back and leg pain (including radiating pain) associated with persistent spinal pain syndrome, with insufficient effect from conventional pain management therapies	Same as for PICO 2
Intervention[b]	According to the intended use	Same as for PICO 1	Same as for PICO 1
Comparator	Latest generation of open-loop SCS systems (in addition to other pain management therapies)	Same as for PICO 1	Conventional nonsurgical pain management therapies (including pharmacotherapy with or without physiotherapy and/or psychotherapy, etc.)[c]
Outcome	The following outcomes are assessed across all PICO question(s):		

	Time horizon for all outcomes: preferably 24 months minimum, with an annual evaluation • Global pain, preferably measured using the VAS or Numeric Rating Scale • Responder rate, measured as global pain relief ≥50% vs. baseline at 6 months minimum • Healthcare consumption including pain medication consumption, other nonsurgical pain management therapies and number of outpatient visits • HRQoL: - Generic HRQoL, preferably measured using the SF-12 or SF-36 - Disease- or population-specific HRQoL (e.g. neuropathic pain impact on QoL measured using NePIQoL) • Health status, preferably measured using the EQ-5D • Functioning: - Exercise tolerance - Sleep quality - Body function • Disability measured using the ODI and the ability to perform activities of daily living • Participation restriction measured as the ability to return to work (or studies) • Patient satisfaction with treatment, preferably measured as GPE • Treatment discontinuation due to AEs • Sick leave episodes (number and duration) • All-cause mortality • Safety, including a description of each AE included in the following categories: - Any AEs related to the procedure and to the medical device, including but not limited to premature battery depletion, lead migration, electrical dysfunction, infection, surgical revision and removal or replacement of the implanted components - Serious AEs
[a] The type and duration of pain should be described in the "Patient baseline characteristics" section in the submission dossier presenting the studies included. [b] Data on the conditions of use of the open- and closed-loop modes must be provided in the "Characteristics of the technology" and "Results" sections of the submission dossier. [c] Placebo (sham-controlled) studies could be included under this PICO.	

Source: EUnetHTA 21 Committee for Scientific Consistency and Quality.
Abbreviations: AE=adverse event; EQ-5D=EuroQol 5 dimensions questionnaire; GPE=Global Perceived Effect; HRQoL=health-related quality of life; NePIQoL=Neuropathic Pain Impact on Quality of Life; ODI=Oswestry Disability Index; PICO=Population, Intervention, Comparator, Outcome; SCS=spinal cord stimulation; VAS=Visual Analogue Scale.

The health technology developer (HTD) provided evidence to address PICO 1: the Evoke RCT study.

For assessment of PICO 2 and PICO 3, no evidence was provided by the HTD.

In addition, one single-arm study (Avalon study) with longer follow-up was included in the assessment of safety outcomes.

An evidence summary table, including the uncertainty of the evidence, is presented in **Table 30** and **Table 31**.

Table 30. Uncertainty of the evidence for PICO 1

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p-value[a]
All outcomes	1 RCT	**Internal validity of individual studies** • The Evoke study was a prospective, multicentre RCT that included 134 patients (67 in both the intervention and the comparator group) with 12-month follow-up. • Randomisation was performed in a 1:1 fashion using computer-generated small permuted blocks of two sizes and stratified by study site. • Information on the concealment of the allocation sequence was not available. • The patients and investigators were blinded to the treatment. • The study was designed with a primary objective of demonstrating noninferiority and, if met, superiority. • There were no major differences in baseline characteristics between the treatment groups in the study. **Applicability** • The study population is in line with the population for PICO 1. The study was conducted in the USA, not in Europe. • As is common practice for SCS, only patients with pain reduction ≥50% on the VAS (responder patients) at the end of the SCS trial period had a permanent device implanted. • There is uncertainty regarding whether the comparator used in the Evoke study is sufficient to address PICO 1. The HTD claims that the Evoke open-loop SCS system delivers stimulation that can be considered equivalent to the mechanism used in other commercially available SCS systems, but with an additional feature to measure ECAPs. However, the technical characteristics of the open-loop stimulation mode of the evoke SCS system are insufficiently described in the submission dossier to be able to conclude whether the stimulation mode is the same as in the latest generation of open-loop SCS systems. • It must be noted that the study used the HTD's own device, the Evoke SCS system, for both the investigational and the comparator arms. The Evoke SCS system can be operated as a closed-loop or an open-loop system, with up to four programme modes. During the study, neither the patients nor the treating physicians were able to switch between modes. • Not all outcomes requested in the PICO were recorded in the study. Those not recorded were disease-specific HRQoL, ability to perform activities of daily living,	NA

		exercise tolerance, ability to return to work (or studies), body function and sick leave episodes (number and duration). The HTD provided evidence for the rest of the outcomes requested. **Heterogeneity and inconsistency** There was no heterogeneity or inconsistency, as only one RCT was available and included for assessment of the relative effectiveness and relative safety of the Evoke closed-loop SCS system.	
Overall endpoint success: ≥50% reduction in overall trunk and limb pain (VAS score) **AND** no increase in baseline pain medication within 4 weeks of endpoint visit	1 RCT	**Internal validity** • The overall risk of bias for this outcome was rated as low. • A variety of prespecified sensitivity analyses were performed for the endpoint to assess the impact of missing data on the results. All the sensitivity analysis results have the same directionality as the results from the primary analysis. • The responder rate was measured using the VAS (average pain in the last 24 hours). The second component of this endpoint was the change in pain medication use; however, the CSR does not mention a medication diary. Patients were asked about their pain medication during a follow-up call or visit. • Data were analysed in accordance with a prespecified analysis plan that was finalised before unblinded outcome data were available for analysis. On the basis of the results, it is unlikely that the numerical result assessed was selected from multiple eligible outcome measurements within the outcome domain or from multiple analyses of the data. **Applicability** The outcome "responder rate measured as global pain relief of ≥50% versus baseline at 6 months minimum" requested in PICO 1 was reported as part of the primary endpoint of the study "≥50% reduction in overall trunk and limb pain at the endpoint visit AND no increase in baseline pain medication within 4 weeks of the endpoint visit". Although the overall endpoint is not the exact endpoint defined in PICO 1, it was considered equivalent to the outcome requested. Moreover, addition of the pain medication component might limit bias, as it ensures that pain medication is not increased within the month before measurement of the outcome.	Success rate difference at 12 months (%): 22.0 [6.3, 37.7] p=0.006 [*, #, $]
ODI change from baseline	1 RCT	**Internal validity** The overall risk of bias for this outcome was rated as high because of the "Missing data" domain. Missing data were not handled for this outcome. **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): 1.9[b] [-4.2, 8.0], p=0.537[#]

EQ-5D-5L change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): EQ-5D-5L Index Score: 0.019[c] [-0.052, 0.091] p=0.592[#] EQ-VAS: 6.9[c] [-1.8, 15.6] p=0.120[#]
Patient satisfaction (very satisfied or satisfied)	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	RD at 12 months (%): With pain relief: 7.8 [-5.9, 21.6] p=0.279 With therapy: 5.5 [-7.1, 18.0] p=0.540 Would strongly recommend or recommend therapy: 7.0 [-4.1, 18.2] p=0.298
PGIC (overall status very much improved or much improved)	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	RD at 12 months (%): 6.8 [-9.1,22.8] p=0.473[#]
PSQI change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): 1.2[b] [-0.6, 2.9] p=0.184[#]
SF-12 change from baseline	1 RCT	**Internal validity** See the details in the line for "ODI change from baseline". **Applicability** See the details in the line for "All outcomes".	MD at 12 months (points): Physical component: 0.1[c] [-3.8, 4.1] p=0.944 Mental component: 8.1[c] [3.7, 12.6] p<0.001

VAS overall average trunk and limb pain change from baseline	1 RCT	The statistical test for the analysis of this outcome was not prespecified in the SAP.	MD at 12 months (mm): In-clinic: 11.7[b] [1.4, 22.0] p=0.027 7-day diary average overall: 6.1[b] [-4.3, 16.5] p=0.245
All-cause mortality	1 RCT	Assessment of this outcome was not prespecified in the study protocol. Only descriptive statistics were used to report this outcome.	NA
Pain medication usage Opioid usage	1 RCT	Assessment of this outcome was not prespecified in the study protocol.	RD at 12 months (%): Pain medication: 10.2 [-4.6, 25.0] p=0.201 Opioids: -3.0 [-22.3, 16.4] p=0.844
Safety outcomes: each AE included in the following categories: - Any AEs related to the procedure and to the medical device - Serious AEs	1 RCT	**Internal validity** No hypothesis testing was performed for AEs. The incidence of all distinct AEs is presented, summarised by treatment group. All AEs requested in the PICO are reported, except for premature battery depletion and electrical dysfunction. **Applicability** The same device was used for both the intervention and the comparator groups, and it is only the programming that differs. Therefore, comparison of the two groups regarding device- and procedure-related safety outcomes is not meaningful. Only comparison of stimulation-related AEs might be meaningful. Safety data from the Evoke RCT are available up to 16 months (mean follow-up) in the CSR. Longer follow-up data are only available from the CSR of the Avalon single-arm study.	NA

[a] Use of * indicates statistical significance versus a prespecified α-level; use of # indicates a prespecified analysis according to the statistical analysis plan (for individual studies) or evidence synthesis protocol; use of $ indicates control for multiplicity. Alternatively, indicate if no formal hypothesis testing was carried out.
[b] Greater decrease in the Evoke *closed-loop* SCS group.
[c] Greater increase in the Evoke *closed-loop* SCS group.

Source: Clinical study report.

Abbreviations: AE=adverse event; CSR=clinical study report; EQ-5D-5L=EuroQol 5 dimensions, 5 levels questionnaire; HRQoL=health-related quality of life; HTD=health technology developer; MD=mean difference; NA=not applicable; ODI=Oswestry Disability Index; PGIC=patient global impression of change; PICO=population-intervention-comparator-outcomes; PSQI=Pittsburgh Sleep Quality Index; RD=rate difference; RCT=randomised controlled trial; SAP=statistical analysis plan; SCS=spinal cord stimulation; SF-12=12 Item Short Form Survey; VAS=Visual Analogue Scale.

Table 31. Uncertainty of the evidence from the clinical development programme

Outcome	Design	Factors that may affect the certainty of evidence	Effect estimate p-value
Safety outcomes	1 single-arm study	The Avalon study was a prospective, multicentre, single-arm pivotal study with 24-month follow-up. Published safety data are available for 24 months. The planned follow-up for the Evoke RCT was also 24 months, but the data were only available up to 16 months (mean follow-up) in the CSR. Only descriptive statistics were used to report the safety outcomes. Risk of bias was not assessed as this was a single-arm study, presented for the safety outcomes only.	NA

Source: Clinical study report.
Abbreviations: NA=not applicable; RCT=randomised controlled trial.

Appendix A Submissions from stakeholder organisations

Input from stakeholder organisations obtained via the open call for input are presented in this appendix.

Question	1.	2.	3.	4.
Please state the country where the HCP organisation/clinical society that you are representing is based	Spain	The Netherlands	Belgium	Belgium
Please name the HCP organisation/clinical society you are representing	IDEA (Innovación y Desarrollo Asistencial)	The Dutch Society of Anaesthesiologists	European Union of General Practitioners/Family Doctors UEMO	AZ Delta Hospital Roeselare
What role do you have in the organisation?	Member with mandate to speak on behalf of organisation	Member with mandate to speak on behalf of organisation	Member with mandate to speak on behalf of organisation	Office staff
How many members does your organisation have?	284	1800	24 national medical organisations	7 pain physicians
How is your organisation funded?	Idea is a private company that manages and promotes services for the elderly. Income is primarily generated by the management of centres for elderly, in the R + D + I Department, whose percentage of Idea's annual budget is 15%, we have participated in projects such as: ehcoBUTLER, H2020, PHC-20-2014 – Advancing active and healthy ageing with ICT. EU Contribution € 2.980.347. Funding to Idea: 156.000 euros. Erreka. Budget: 56.00 euros. E-Care project Phase 1: budget to Idea: 5.620 euros.	By members fees.	Funding by annual cotisations coming from national medical organisations according to the number of GPs/Family doctors in each country. No industry funding. Ireland, United Kingdom, Belgium, Holland, Luxemburg, Portugal, Spain, France, Italy, Switzerland, Germany, Czech Republic, Slovenia, Slovakia, Croatia, Hungary, Austria, Romania, Lithuania, Norway, Sweden, Finland, Serbia, and Turkey. Budget provisional 2023: for information see secretariat@uemo.eu.	AZ Delta is a public non university hospital
Please state the geographical spread of the organisation's membership	European	National	European	European

Please state the health condition(s) represented by the organisation and/or the remit of the organisation	Normal and pathological aging – elderly	Anaesthesiology, intensive care, and pain management	General practice/family medicine	Chronic pain at chronic pain clinic
Population Please state relevant patient sociodemographic (e.g., age, ethnicity, socioeconomic status) and clinical baseline characteristics (e.g., severity of condition, comorbidities) which may contribute to differences in treatment outcomes or treatment preferences. What are the relevant eligibility criteria for treatment decisions made by HCPs?	We have a sample of 500 people over 60 years old. 70% suffer from chronic pain. We do not know the criteria for inclusion of the sample of the study. Our sample focuses on 7 centres throughout the Spanish geography. 25% of the sample are patients considered fragile.	Sociodemographic: treatment available for everyone. Eligibility criteria: severe invalidating pain.	Chronic pain in trunk and limbs is very frequent in family medicine. Usually treated by a multimodal approach: counselling, physiotherapy, medication, psychological support. Sometimes specialized consultations are necessary: rheumatologist, neurologist, or pain clinic. More rarely surgical approach. The device concerns very rare patients who are resistant to usual therapy and were it is a contra-indication to surgery. In a GP patient's population, the number of patients, candidate for the device is less than 10 or 5 patients depending on the structure of the patient's population (age, multi-morbidity).	Typical eligibility criteria consist of candidates aged 18 years or older with chronic, intractable back and / or leg pain for more than six months, with a minimum visual analogue scale (VAS) score of 50mm to 60mm or higher (where 100mm indicates the worst imaginable pain) refractory to conservative therapy. A trial phase prior to implantation of the device is usually required for 21 days in Belgium. International recommendations define a successful trial as a patient obtaining at least 50% reduction in pain. The only reimbursement in Belgium is for residual neuropathic pain after spine surgery (persistent spinal pain syndrome type II).

Intervention Are there contextual factors, (e.g., prior, concurrent or subsequent treatments, training on administration, etc.) which may affect the safety and/or effectiveness of the intervention? Does the specific (professional) experience of the treating HCP or medical staff play a relevant role in the decision to use the intervention? Would the decision to use the intervention in clinical practice be affected by its route and/or frequency of administration? What would be relevant criteria for treatment discontinuation? Is there a specific time point at which you check the therapeutic effect? Where does the intervention fit in the current treatment landscape?	For chronic pain the treatment of choice is pharmacological treatment and physiotherapy. Based on the criteria of inclusion and exclusion of the sample, the research methodology would be described, taking into account the frequency and procedure of the sessions scheduled based on a study of the art previously carried out, or beta test previously carried out by the organization. For the assessment of the effect, the scheduled "treatment" should be carried out for three months. We would therefore select the sample based on the inclusion criteria, under the supervision of our ethics committee. The possible causes of interruption of participation in the particular study will be described in the informed consent.	Contextual factors: when all other treatments fail. Specific role: specialized neuromodulation physician. The decision to use the intervention in clinical practice would not be affected by its route and frequency of administration. Criteria for treatment discontinuation and specific timepoint to check the therapeutic effect: always test trial needing a minimum of 50% pain reduction. The place of the intervention in the current treatment landscape: last resort treatment.	According to different European country the intervention depends from the presence and the proximity of a center able to do this intervention and to assume the follow-up. Of course, the GP and his/her medical staff need to be trained to explain the intervention and to manage some technical problems (adjustments of stimulation) after the implantation. If the specialized centre is remote as in rural or deprived areas, a good contact between the specialist and the GP is necessary. A good information about the possible side effects is also necessary. Discontinuation of treatment must be discussed if inefficiency and/or side effects.	Contextual factors: SCS is usually considered as a treatment option after patients tried more conservative therapies without obtaining satisfactory pain relief. Patients are not usually considered for SCS if there is evidence of an active disruptive psychological or psychiatric disorder or other known condition significant enough to impact perception of pain or compliance of the intervention; ongoing coagulation therapy or uncontrolled coagulation disorder; have an existing drug pump and/or SCS system or another active implantable device such as a pacemaker, deep brain stimulator, or sacral nerve stimulator; active systemic infection or local infection in the area of the surgical site; allergic, or have shown hypersensitivity to any materials of the neurostimulation system, which come in contact with the body; documented history of substance abuse (narcotics, alcohol, etc.) or substance dependency; and poor cognitive ability or lack of capacity. The possibility of using the device in closed-loop mode, together with potential improvements in response may also influence the decision to use this intervention.

				Professional experience: Healthcare practitioners or medical staff experience should not play a role in the decision to use Evoke SCS. The implantation procedure for Evoke System is equivalent to that of other SCS systems; as such, minimal additional training is required for experienced physicians. Implanting physicians should be trained in SCS procedures. Decision to use the intervention: The route is similar to that for other SCS devices. Therapy administration may be improved with Evoke SCS due to the programming of the device being guided by ECAPs. Therefore, programming sessions required could be fewer in the long-term with Evoke SCS, which could influence the decision to use this system instead of other devices. Criteria for treatment discontinuation: The main reasons would be AEs or loss of efficacy despite adequate adherence. The definition of loss of efficacy may vary between healthcare practitioners and European settings. Therapeutic effect is usually evaluated at 3 and/or 6 months, 12 months and then on an annual basis. Where does the intervention fit in the current treatment landscape: Treatment option for patients with chronic neuropathic pain

				refractory to more conservative therapy.
Comparator(s) What is the standard of care in your country? Are you aware of the standard of care most commonly used in Europe? Are there different treatment options for different patient groups depending on severity, previous treatment, biomarker levels, etc.? What are the goals of current treatments? Are there contextual factors (e.g., prior, concurrent, or subsequent treatments) which may affect the safety and/or effectiveness of the comparators? Would the decision to use comparators in clinical practice be affected by their route and/or frequency of administration?	The treatment of chronic pain in Spain is managed under the quality standards of the Ministry of Health of the Government of Spain (https://www.sanidad.gob.es/organizacion/sns/planCalidadSNS/docs/EERR/Unidad_de_tratamiento_del_dolor.pdf). The treatment of chronic pain is managed by the Pain Units. These units are located in all the hospitals of the public network throughout the Spain. All those classified by chronic pain are referred to these units. The unit is composed of medical staff, who based on the type of pain (oncogenic, non-oncogenic, acute, or chronic), determine the personalized treatment. Once the inclusion criteria of the sample have been described, and this selection has been made, people with chronic pain in both locations described for piloting, will be able to participate in the study. It will be determined between our staff, and those responsible for the pain unit, whether participation in the study is safe and complies with the principle of beneficence.	CMM medication, physiotherapy, rehabilitation, minimal invasive pain treatments. The goals of current treatments are CMM goal, pain reduction, better quality of life, no medication, return to work, cost saving. There are no contextual factors which may affect safety and/or effectiveness of the comparators. No, the decision to use comparators in clinical practice would not be affected by their route and frequency of administration.	Chronic pain is a true bio-psycho-social problem. We have to compare a purely technical intervention with a more comprehensive attitude including psychosocial support and medication. A particular attention has to be done to patients with co-morbidities for example depression.	Standard of care for patients with chronic intractable back and / or leg pain is SCS with fixed-output, open-loop SCS. This is the standard of care most commonly used in Europe. Different treatment options are not necessarily available as patients considered for this intervention would not have obtained satisfactory results with more conservative treatment options. The goals of current treatments are to provide a reduction in pain intensity, reduction in oral medications including opioids and improvements in other important aspects affected by the chronic pain experience (e.g., sleep, function, quality of life). The decision to use comparators in clinical practice may be affected by the need to have more programming sessions in the long-term.

Outcome(s) Please define relevant safety, efficacy, and patient-centred outcomes (e.g., quality of life) which should be assessed. What safety and efficacy outcomes are used in clinical practice to inform clinical decisions regarding treatment and how are they measured? If surrogate outcomes (e.g., laboratory parameters) are relevant to the indication given, do you consider them to be clinically meaningful?	The safety and efficacy guidelines for the treatment of chronic pain are described by the Ministry of Health of Spain. The assessment of the effectiveness of the intervention would be described in the research methodology document. We would include pre-post intervention scales to determine the effectiveness of the intervention based on correlations and comparisons with a control group. We would include McGill Pain Questionnaire (MPQ) pain scale, and Subjective Well-being Scale (EBS-20). In addition, the analysis of technological parameters that the technology company determines, such as accessibility and usability, will be included. Prior to piloting we would perform a beta test. It is also essential for us that end users are involved in identifying explicit needs through co-design and co-creation groups.	Quality of life, objective measures, sleep, medication, return to work. Usual safety measures are not relevant.	The interest of a medullar stimulator is to give the patient a possible empowerment on the regulation of the device according to intensity of pain. Should the GP be integrated in the counselling for regulating the device or is there competent staff to do that (e.g. nurses)? Resources can be different according to countries. How to manage complications like pain around the stimulating box, local infections, electronical disconnections, control of effectiveness, management when cognitive impairment and when appropriate, decision for withdrawal. GPs consider important to evaluate the device itself (practicability, simplicity of use, side effects) but also all the context around its use (indication, accessibility, training, follow-up).	Pain intensity, physical function, emotional function, sleep, quality of life, medication use, satisfaction, serious adverse events, adverse events, explants due to loss of efficacy. Clinical decisions regarding treatment are guided by patient reported improvements in the outcomes mentioned or safety events that may require device explant. Evoked compound action potentials may be a clinically meaningful surrogate outcome by representing the number of spinal cord fibres activated by the stimulation provided by the SCS device. Patient adherence with therapy may also be a useful outcome.
If you have any further comments or remarks, please add them here	We would need to know the sample inclusion and exclusion criteria to determine if our sample meets the criteria needed for piloting.	None.	To answer such questionnaires, UEMO created a staff for discussing answers with 4 countries: Spain, Italy, France, and Switzerland. If this group considers that there are very different contexts across Europe, we have the possibility to send some questions to all delegations (collecting answers is one month)	None.

Source: EUnetHTA 21.

Abbreviations: CMM=conventional medical management; GP=general practitioner; EBS-20=subjective well-being scale; H2020=Horizon 2020; HCP=healthcare professional; ICT=information and communication technology; IDEA=Innovación y Desarrollo Asistencial, mm=millimetre; MPQ=McGill Pain Questionnaire; UEMO=European Union of General Practitioners/Family Doctors; R+D+I=research – development – innovation; SCS=spinal cord stimulation; VAS=visual analogue scale.

Appendix B Assessment of information retrieval

The evidence base provided by the HTD regarding the health technology under assessment was reviewed and checked for completeness by the assessment team. Search strategies were checked for appropriateness, and the results of information retrieval included in the HTD submission dossier were checked for completeness of studies against a systematic search in study registries, in Medline, Embase and in CENTRAL (Cochrane) bibliographic databases.

The documentation of searches conducted by the assessment team for the verification of the completeness of studies included in the assessment is provided below.

Some concerns regarding the information retrieval in the submission dossier were raised during this completeness check. Firstly, the HTD limited their search to references from 2017 onwards without any justifications. Although the date of CE marking is 2019, it could be possible that studies had been published before 2017. Secondly, there is no search in CENTRAL, although RCTs were included in the study pool. For a comprehensive search at least in Medline, Embase and CENTRAL is essential.

Search strategy of the search conducted in study registries and in bibliographic databases by the assessment team for study completeness check are presented below.

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: https://www.clinicaltrials.gov
- Interface: Expert Search

Search syntax
Evoke AND chronic pain

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int/
- Interface: Standard Search

Search syntax
Evoke AND chronic pain

3. Medline

Provider: National Library of Medicine

- Ovid MEDLINE(R) and In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to January 30, 2023>, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <2018 to January 30, 2023>

Search	Query
#1	closed-loop* spin* cord stimul*.mp.
#2	remove duplicates from 1

4. Embase

Provider: Elsevier

- Date of search: 31 Jan 2023

Search	Query
#1	'closed-loop* spin* cord stimul*'
#2	evoke:dn
#3	saluda:df
#4	#1 OR #2 OR #3

5. Cochrane

Provider: Wiley

- Date of search: 31 Jan 2023

Search	Query
#1	(closed-loop* spin* cord stimul*) (Word variations have been searched)

Appendix C Additional study information and data

C.1 Safety

C.1.1 Safety outcomes including effect estimates

Table 32 Safety outcomes including effect estimates

Time point Outcome Study reference/ID	**Evoke *closed-loop* SCS**		**Evoke *open-loop* SCS**		**Evoke *closed-loop* SCS vs.Evoke *open-loop* SCS**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RD [95 %-CI]**
16 months (mean) **Evoke study**					
At least one adverse event	150	45/67 (67)	104	45/67 (67)	0.0 [-15.9, 15.9]
Serious adverse events	16	10/67 (15)	11	8/67 (12)	3.0 [-8.6, 14.5]
Severe adverse events [no specific scale used][a]	22	14/67 (21)	13	9/67 (13)	ND
Treatment discontinuation due to adverse events	ND	2/67 (3)[b]	ND	4/67 (6)[b]	ND
Treatment interruption due to adverse events	ND	ND	ND	ND	ND
Suspected unexpected serious adverse reaction[c]	0	0/67 (0)	0	0/67 (0)	ND
All-cause mortality[d]	0	0/67 (0)	1	1/67 (1)	ND
Device-related adverse events	7	7/67 (10)	5	5/67 (7)	4.5 [-6.8, 15.7]
Procedure-related adverse events	17[e]	12/67 (18)	8[e]	8/67 (12)	4.5 [-7.8, 16.8]
Stimulation therapy-related adverse events	5[e]	4/67 (6)	3[e]	3/67 (4)	3.0 [-5.0, 11.0]
Device- or procedure-related adverse events					
Premature battery depletion	ND	ND	ND	ND	ND
Lead migration	7	6/67 (9)	3	3/67 (4)	4.5 [-4.0, 12.9]
Electrical dysfunction	ND	ND	ND	ND	ND
Wound infection[f]	1	1/67 (1)	1	1/67 (1)	0.0 [-4.1, 4.1]
IPG pocket pain	4	4/67 (6)	1	1/67 (1)	4.5 [-1.9, 10.9]
Dural puncture or tear	2	2/67 (3)	1	1/67 (1)	3.0 [-1.1, 7.1]
IPG malfunction due to electrocautery	2	2/67 (3)	0	0/67 (0)	3.0 [-1.1, 7.1]
Epidural abscess[f]	0	0/67 (0)	1	1/67 (1)	-1.5 [-4.4, 1.4]
Inadequate lead placement	1	1/67 (1)	0	0/67 (0)	1.5 [-1.4, 4.4]
Lead breakage/ fracture[f]	0	0/67 (0)	1	1/67 (1)	-1.5 [-4.4, 1.4]
Muscle spasm or muscle cramp	0	0/67 (0)	1	1/67 (1)	1.5 [-3.5, 6.5]
Nausea and/or vomiting	1	1/67 (1)	0	0/67 (0)	1.5 [-3.5, 6.5]
Skin irritation or redness	0	0/67 (0)	1	1/67 (1)	-1.5 [-4.4, 1.4]
Wound dehiscence	1	1/67 (1)	0	0/67 (0)	1.5 [-1.4, 4.4]
Surgical revision[g]	2	2/67 (3)	1	1/67 (1)	ND
Replacement of the implanted components[g]	7	7/67 (10)	3	3/67 (4)	ND
System explant[g]	4	4/67 (6)	5	5/67 (7)	Nd

Time point Outcome Study reference/ID	**Evoke *closed-loop* SCS**		**Evoke *open-loop* SCS**		**Evoke *closed-loop* SCS vs.Evoke *open-loop* SCS**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RD [95 %-CI]**
[a] AEs were classified as mild (usually transient; does not interfere with the subject's usual activities), moderate (low-level inconvenience or concern to the subject; may interfere with usual activities) or severe (significantly limits the subject's ability to perform usual activities). [b] Calculated by the assessment team from the CSR data. [c] Defined as unanticipated adverse device effect. [d] The primary cause of death was cardiac arrest, the secondary cause was uncontrolled hypertension. The event was adjudicated not to be related to the study. [e] AEs adjudicated as definitely or possibly related to the device, procedure or stimulation therapy. [f] Adjudicated as serious procedure- or device-related adverse events. [g] During the implant phase.					

Source: Clinical study report.

Abbreviations: AE=adverse event; CSR=clinical study report; IPG=implantable pulse generator; N=number of events; n=number of patients with event; ND=no data; PICO=population – intervention – comparator – outcome; RD=rate difference; SAE=serious adverse event.

C.1.2 Safety outcomes – disaggregated, by system organ class and by preferred term

No evidence was provided by the HTD on adverse events (serious, as well as non-serious) by system organ class (SOC) and preferred term (PT). Evidence on discontinuation due to adverse events by SOC and PT was also not provided.

C.2 Per protocol analysis results for the overall endpoint in the Evoke study

According to the CSR, the per protocol (PP) analysis population corresponds to the permanent implant subset (PIS) population. The statistical analysis plan of the Evoke study defined PIS as a subset of the intention-to-treat population "including all subjects who received a permanent implant, and the PP analysis population, which is a subset of PIS including subjects with no major deviations. Major protocol deviations (PDs) were defined as those that have the potential to affect the outcome of the primary endpoint. No subjects in either treatment group were determined to have a major PD. Therefore, there was not a separate PP population, and consequently not a separate PP analysis performed for this clinical study report." The results presented in **Table 33** are the results from the PIS analysis.

Table 33: Per protocol analysis results for the overall endpoint in the Evoke study

Time point Outcome Study reference/ID	**Evoke *closed-loop* SCS**		**Evoke *open-loop* SCS**		**Evoke *closed-loop* SCS vs. Evoke *open-loop* SCS**	
	N	**Patients with event n (%)**	**N**	**Patients with events n (%)**	**RD [95 %-CI] p-value**	**Hypothesis testing**
12 months **Evoke study**						
Overall endpoint success: ≥50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of endpoint visit	55	49 (89)	49	36 (74)	15.6 [0.8, 30.5] <0.001	S-P-C
Reading the "Hypothesis testing" columns: 1. Statistical significance: S = Statistically significant against the alpha level specified in the statistical analysis plan of the corresponding study, NS = Non-significant, NO = Nominal p-value 2. Prespecification: P = Statistical test was prespecified according to the statistical analysis plan of the corresponding study, NP = Not prespecified 3. Multiple hypothesis testing. C = Appropriate control for multiplicity according to the statistical analysis plan and clinical study report of the corresponding study, NC = Not controlled						

Source: Clinical study report.

Abbreviations: CI=confidence interval; n=patients with event; N=number of patients at follow-up; RD=rate difference; SCS=spinal cord stimulation; VAS=visual analogue scale.

Appendix D Risk of bias 2.0 tables

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) template for completion was used to present the risk of bias of the outcomes. The template was edited by Julian PT Higgins, Jelena Savović, Matthew J Page, and Jonathan AC Sterne on behalf of the RoB2 Development Group. The template version of 22 August 2019 was used. The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials in Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

D.1 Overall success endpoint at 12 months follow-up: 50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of the primary endpoint visit

Study details

Reference	Mekhail N, Levy RM, Deer TR, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. Lancet neurol 2020;19:123-134.

Study design

- X Individually-randomized parallel-group trial
- ☐ Cluster-randomized parallel-group trial
- ☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Evoke closed-loop SCS Comparator: Evoke open-loop SCS

Specify which outcome is being assessed for risk of bias	Overall success endpoint at 12 months follow-up: 50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of the primary endpoint visit
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	At 12 months: 22% difference (95% CI 6.3 to 37.7) (Table 2)

Is the review team's aim for this result…?

- X to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
- ☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

- ☐ occurrence of non-protocol interventions
- ☐ failures in implementing the intervention that could have affected the outcome
- ☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- X Journal article(s) with results of the trial
- X Trial protocol
- X Statistical analysis plan (SAP)
- X Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- X Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist

☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Subjects who provide informed consent and meet the study eligibility criteria were randomly assigned in a 1:1 fashion to receive either Investigational or Control stimulation at the time of the trial procedure. The randomization was computer generated utilizing permuted blocks of size 4 and 6, stratified by study site.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	According to the study protocol, "subjects, investigators and their staff will not have access to the randomization assignment. […] The Field Clinical Engineer (FCE) will allocate the treatment assignment. […] The study will be double-blind in that the treatment allocation will be concealed from the study subjects and the Investigators and their staff."	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	According to the study protocol, "the study will be double-blind in that the treatment allocation will be concealed from the study subjects and the Investigators and their staff."	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	At 12 months: 8/67 (12%) missing in the Evoke closed-loop SCS group; 8/67 (12%) missing in the Evoke open-loop SCS group.	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Sensitivity analysis and multiple imputation carried out.	Y
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to missing outcome data?		NA

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	The responder rate was measured by the VAS. The second component of this endpoint was the pain medication, however the CSR does not mention medication diary; patients were asked about their pain medication during a follow-up call or visit.	PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Data were analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis.	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	It is unlikely that the assessed numerical result has been selected from multiple eligible outcome measurements within the outcome domain or multiple analysis of the data, on the basis of the results.	N
5.3 ... multiple eligible analyses of the data?	It is unlikely that the assessed numerical result has been selected from multiple eligible outcome measurements within the outcome domain or multiple analysis of the data, on the basis of the results.	N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement		**Low**
Optional: What is the overall predicted direction of bias for this outcome?		NA

D.2 Patient-reported outcome measures (PROMS) at 12 months

Study details

Reference	Mekhail N, Levy RM, Deer TR, et al. Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. Lancet neurol 2020;19:123-134.

Study design

X Individually-randomized parallel-group trial
☐ Cluster-randomized parallel-group trial
☐ Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: Evoke closed-loop SCS Comparator: Evoke open-loop SCS

Specify which outcome is being assessed for risk of bias	At 12 months: • Oswestry Disability Index (ODI): change from baseline at 12 months • EQ-5D-5L: change from baseline at 12 months • patient satisfaction at 12 months: a, with pain relief: rate difference of very satisfied or satisfied; b, with therapy: rate difference of very satisfied or satisfied; c, likelihood of recommending therapy: rate difference of strongly recommend or recommend • Patient Global Impression of Change (PGIC): rate difference of very much improved or much improved at 12 months • Pittsburgh Sleep Quality Index (PSQI): change from baseline at 12 months • 12 Item Short Form Survey (SF-12) change from baseline at 12 months: a, physical component summary score; b, mental component summary score
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	• Oswestry Disability Index (ODI) change from baseline RD=1.9 (-4.2, 8.0), p= 0.537 • EQ-5D-5L change from baseline RD=0.019 (-0.052,0.091), p= 0.592 • patient satisfaction: a, with pain relief: rate difference of very satisfied or satisfied 7.8 (-5.9,21.6), p=0.279; b, with therapy: rate difference of very satisfied or satisfied 5.5 (-7.1,18.0), p= 0.540; c, likelihood of recommending therapy: rate difference of strongly recommend or recommend 7.0 (-4.1,18.2), p= 0.298 • Patient Global Impression of Change (PGIC) rate difference of very much improved or much improved 6.8 (-9.1,22.8), p= 0.473 • Pittsburgh Sleep Quality Index (PSQI) change from baseline RD=1.2 (-0.6,2.9), 0.184 • 12 Item Short Form Survey (SF-12) change from baseline: a, physical component summary score RD= 0.1 (-3.8,4.1), p= 0.944; b, mental component summary score RD= 8.1(3.7,12.6), p <.001

Is the review team's aim for this result…?

✖ to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)
☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions
☐ failures in implementing the intervention that could have affected the outcome
☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

- ✖ Journal article(s) with results of the trial
- ✖ Trial protocol
- ✖ Statistical analysis plan (SAP)
- ✖ Non-commercial trial registry record (e.g. ClinicalTrials.gov record)
- ☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)
- ☐ "Grey literature" (e.g. unpublished thesis)
- ☐ Conference abstract(s) about the trial
- ✖ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
- ☐ Research ethics application
- ☐ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
- ☐ Personal communication with trialist
- ☐ Personal communication with the sponsor

Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	Subjects who provide informed consent and meet the study eligibility criteria were randomly assigned in a 1:1 fashion to receive either Investigational or Control stimulation at the time of the trial procedure. The randomization was computer generated utilizing permuted blocks of size 4 and 6, stratified by study site.	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	According to the study protocol, "subjects, investigators and their staff will not have access to the randomization assignment. […] The Field Clinical Engineer (FCE) will allocate the treatment assignment. […] The study will be double-blind in that the treatment allocation will be concealed from the study subjects and the Investigators and their staff."	PY
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias arising from the randomization process?		NA

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	According to the study protocol, "the study will be double-blind in that the treatment allocation will be concealed from the study subjects and the Investigators and their staff."	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	12/67 (18%) in the closed-loop and 19/67 (28%) in the open-loop missing data for all outcomes assessed in this RoB.	N
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	The protocol defines handling of missing data only for the primary and the hierarchical secondary endpoints. The assessed endpoints are neither of these.	N
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		Y
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		PY
Risk-of-bias judgement		**High**
Optional: What is the predicted direction of bias due to missing outcome data?		Favours experimental

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?	Outcome measurement (data collection) for each outcome was appropriate, the same measurement methods and thresholds were used in both the Intervention and in the Control groups.	N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias in measurement of the outcome?		NA

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Data were analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis.	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	It is unlikely that the assessed numerical result has been selected from multiple eligible outcome measurements within the outcome domain or multiple analysis of the data, on the basis of the results.	N
5.3 ... multiple eligible analyses of the data?	It is unlikely that the assessed numerical result has been selected from multiple eligible outcome measurements within the outcome domain or multiple analysis of the data, on the basis of the results.	N
Risk-of-bias judgement		**Low**
Optional: What is the predicted direction of bias due to selection of the reported result?		NA

Overall risk of bias

Risk-of-bias judgement	Due to the missing outcome data.	**High risk**
Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental

Appendix E Partial use of GRADE table

Table 34: Uncertainties of the evidence categorised according to the partial use of GRADE for PICO 1

Outcome	Design	Factors that may affect certainty of evidence					Number of patients		Effect estimate p-value[a]
		Risk of bias	Indirectness	Inconsistency	Imprecision	Other	Intervention A	Intervention B	
Overall endpoint success (≥50% reduction in overall trunk and limb pain (VAS score) AND no increase in baseline pain medication within 4 weeks of endpoint visit)	1 RCT	Low	Issues are flagged[b,c,d,e]	1 study	No issues are flagged	None	67	67	Success rate difference at 12 months (%): 22.0 [6.3, 37.7] p=0.006[*, #, $]
ODI change from baseline	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	MD at 12 months (points): 1.9[l] [-4.2, 8.0], p=0.537[#]
EQ-5D-5L change from baseline	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	MD at 12 months (points): EQ-5D-5L Index Score: 0.019[m] [-0.052, 0.091] p=0.592[#] EQ-VAS: 6.9[m] [-1.8, 15.6] p=0.120[#]
Patient satisfaction rate difference of very satisfied or satisfied	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	RD at 12 months (%): With pain relief: 7.8 [-5.9, 21.6] p=0.279 With therapy: 5.5 [-7.1, 18.0] p=0.540 Would strongly recommend or recommend therapy: 7.0 [-4.1, 18.2] p=0.298
PGIC rate difference of very much improved or much improved	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	RD at 12 months (%): 6.8 [-9.1, 22.8] p=0.473[#]

PSQI change from baseline	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	MD at 12 months (points): 1.2[l] [-0.6, 2.9] p=0.184[#]
SF-12 change from baseline	1 RCT	High[f]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	MD at 12 months (points): Physical component: 0.1[m] [-3.8, 4.1] p=0.944 Mental component: 8.1[m] [3.7, 12.6] p<.001
VAS overall average trunk and limb pain change from baseline	1 RCT	NA[h]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	MD at 12 months (mm): In-clinic: 11.7[l] [1.4, 22.0] p=0.027 7-day diary average overall: 6.1[l] [-4.3, 16.5] p=0.245
All-cause mortality	1 RCT	NA[h]	Issues are flagged[b,c,d]	1 study	Issues are flagged[i]	None	67	67	NA
Pain medication use, opioid use	1 RCT	NA[h]	Issues are flagged[b,c,d]	1 study	Issues are flagged[g]	None	67	67	RD at 12 months (%): Pain medication: 10.2 [-4.6, 25.0] p=0.201 Opioids: -3.0 [-22.3, 16.4] p=0.844
Safety outcomes: each AE included in the following categories: - any AEs related to the procedure and to the medical device - SAEs 1 RCT Internal validity	1 RCT	NA[j]	Issues are flagged[b,c,d,k]	1 study	Issues are flagged[i]	None	67	67	NA

[a] Use of an * indicates statistical significance versus a pre-specified alpha-level, use of a # indicates a pre-specified analysis according to the SAP (for individual studies) or evidence synthesis protocol, use of a $ indicates control for multiplicity. Alternatively indicate if no formal hypothesis testing was carried out.
[b] The study was conducted in the U.S.
[c] There is uncertainty whether the comparator used in the Evoke study is sufficient to address PICO 1. The HTD claims that the Evoke open-loop SCS System delivers stimulation that can be considered equivalent to the mechanism used by other commercially available SCS systems but with the additional feature to measure ECAPs.

However, the technical characteristics of the open-loop stimulation mode of Evoke SCS System are insufficiently described in the submission dossier to be able to conclude if the stimulation mode belongs to the latest generation of open-loop SCS systems.

[d] It must be noted that the study used their own device, the Evoke SCS system, both for the investigational and comparator arms. The Evoke SCS system has the ability to be operated as a closed-loop or as an open-loop system with up to four program modes. During the study, the patients were not able to switch between modes, nor the treating physicians.

[e] The outcome "responder rate measured as global pain relief of ≥50% versus baseline at 6 months minimum" requested in PICO 1 was reported as part of the primary endpoint of the study "≥50% reduction in overall trunk and limb pain at the endpoint visit AND no increase in baseline pain medication within 4 weeks of the endpoint visit". Although the overall endpoint is not the exact endpoint defined in PICO 1, it was considered equivalent to the outcome requested. Moreover, addition of the pain medication component might limit bias, as it ensures that pain medication is not increased within the month before measurement of the outcome.

[f] Missing data in 12/67 (18%) patients from the Evoke *closed-loop* SCS group and in 19/67 (28%) patients from the Evoke *open-loop* SCS group for all outcomes assessed in this RoB analysis. Missing data was not handled for this outcome.

[g] Nominal p-value.

[h] The assessment of this outcome was not pre-specified in the study protocol.

[i] No p-value and CI reported.

[j] No hypothesis testing was performed for AEs. The incidence of all distinct AEs is presented, summarised by treatment group.

[k] All AEs requested in the PICO are reported, except for premature battery depletion and electrical dysfunction. The same device is used for both Intervention and Comparator groups, it is the programming, which differs. Therefore, the comparison of the two groups regarding device-and procedure-related safety outcomes is not meaningful. Only the comparison of the stimulation-related adverse events might be meaningful.

[l] Greater decrease in the Evoke *closed-loop* SCS group.

[m] Greater increase in the Evoke *closed-loop* SCS group.

Abbreviations: AE=adverse event; EQ-5D=EUROQOL 5 dimensions; MD=mean difference; NA=not applicable; ODI=Oswestry Disability Index; PGIC=patient global impression of change; PICO=population-intervention-comparator-outcomes; PSQI=Pittsburgh Sleep Quality Index; RD=rate difference; RCT=randomised controlled trial; SAE=serious adverse event; SCS=spinal cord stimulation; SF-12=12 Item Short Form Survey; VAS=visual analogue scale.