Reporting guidelines for protocols of randomised controlled trials of implantable neurostimulation devices: the SPIRIT-iNeurostim extension

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Summary

Background The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement has improved the quality of reporting of randomised trial protocols. Extensions to the SPIRIT statement are needed to address specific issues of trial protocol reporting, including those relevant to particular types of interventions. Methodological and reporting deficiencies in protocols of clinical trials of implantable neurostimulation devices are common. The SPIRIT-iNeurostim extension is a new reporting guideline for randomised controlled trial protocols evaluating implantable neurostimulation devices.

Methods SPIRIT-iNeurostim was developed using the EQUATOR methodological framework including a literature review and expert consultation to generate an initial list of candidate items. The candidate items were included in a two-round Delphi survey, discussed at an international consensus meeting (42 stakeholders including healthcare professionals, methodologists, journal editors and industry representatives from the United States, United Kingdom, Netherlands and other countries), and refined through a checklist pilot (18 stakeholders).

Findings The initial extension item list included 42 candidate items relevant to SPIRIT-iNeurostim. We received 132 responses in the first round of the Delphi survey and 99 responses in the second round. Participants suggested an additional 14 candidate items for SPIRIT-iNeurostim during the first round of the survey, and those achieving initial consensus were discussed at the consensus meeting. The SPIRIT-iNeurostim extension includes 5 new checklist items, including one item for reporting the neurostimulation intervention comprising a separate checklist of 14 items.

Interpretation The SPIRIT-iNeurostim extension will help to promote increased transparency, clarity, and completeness of reporting trial protocols evaluating implantable neurostimulation devices. It will assist journal editors, peer-reviewers, and readers to better interpret the appropriateness and generalisability of the methods used for a planned clinical trial.

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Introduction

The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative was created to improve the reporting of protocols for randomised

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controlled trials.[1] The items described in the SPIRIT statement and included in the checklist represent the minimum reporting requirements for clinical trial protocols. The SPIRIT statement is endorsed or mandated by numerous high impact peer-reviewed journals, research institutions, research funding agencies and national ethics committees. Launched in 2007 and first published in 2013,[1] the SPIRIT initiative has improved the reporting quality of clinical trial protocols.[2–4] Extensions of the SPIRIT statement[5–7] are often developed to address specific study designs, data or interventions and include items that should be reported alongside the core items.

Neurostimulation refers to the use of electric current to stimulate the nervous system and to modulate nervous system activity. Neurostimulation interventions are used to manage various chronic health conditions including Parkinson's disease, treatment-resistant depression and chronic pain (detailed information on different neurostimulation interventions and indications are presented in the protocol for these extensions).[8] Currently, there are no SPIRIT extensions such as for non-pharmacologic treatments that could be implemented for protocols of trials of implantable neurostimulation devices. Further, there are common methodological and reporting deficiencies for trials of neurostimulation interventions. For example, the methodological and reporting deficiencies highlighted in systematic reviews of spinal cord stimulation (SCS) trial reporting[9,10] included lack of information on source of funding, extent and method of blinding, role of temporary trial phase in enrolment of participants, programming parameters and adequate reporting of participant withdrawals.[8] Recently, the evidence base in support of SCS has been strongly questioned.[11,12] In Australia, for example, there have been repercussions in the availability of the therapy.[13] Consideration of relevant details specific to implantable neurostimulation interventions at the protocol stage is paramount to improve study design and consequently improve the replicability of implantable neurostimulation studies.[14,15]

A SPIRIT extension specifically developed for protocols of trials of implantable neurostimulation devices (SPIRIT-iNeurostim extension) will enhance the reporting, clarity, and transparency of trials of implantable neurostimulation devices and thereby increase confidence in their results. The SPIRIT-iNeurostim extension, supported by the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network, is an international initiative to extend or elaborate current guidance, specifically for trial protocols of implantable neurostimulation devices.[8] It is complementary to the CONSORT-iNeurostim extension which aims to promote high-quality reporting of implantable neurostimulation devices trials.[16] This article describes the methods and processes used to develop the SPIRIT-iNeurostim extension guidelines and presents the checklist and explanations for the new extension items.

Methods

The SPIRIT-iNeurostim and CONSORT-iNeurostim extensions were developed concurrently for randomised trial protocols and reports to harmonise the recommendations and facilitate uptake. The development of the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions were registered on the EQUATOR library of reporting guidelines in February 2021 and the protocol published describing the methods.[8] Development of the guidelines followed the EQUATOR Network methodological framework.[17] The SPIRIT-iNeurostim and CONSORT-iNeurostim extensions adhere to the ACcurate COnsensus Reporting Document (ACCORD) recommendations for reporting consensus based studies.[18] Membership of the SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group, Steering Group, Consensus Group and participants in the checklist pilot are presented in Supplementary Material S1.

Ethical approval

The Institute of Population Health Research Ethics Committee (University of Liverpool) approved the research ethics application (Ref. 9755) for this study. The Participant Information Sheet was included as an attachment to the invitation email sent to potential Delphi participants and potential Consensus Group members. For the Delphi Survey, participants were required to consent to their anonymised data being used before they could complete the survey. The Consensus Group members were required to complete an electronic consent form before participating in the consensus meeting.

Literature review and candidate item generation

Candidate items informed by the findings of previous systematic reviews that assessed methods and reporting in RCTs of SCS,[9,10] and through a rapid review of published protocols and trials considering the implantable neurostimulation devices were included in Delphi surveys. Full details on the literature review and candidate item generation are provided in the companion CONSORT-iNeurostim manuscript.[16]

Delphi consensus process

A two-round Delphi survey was conducted including candidate items for the SPIRIT-iNeurostim extension using the DelphiManager software (version 5.0), developed and maintained by the Core Outcome Measures in Effectiveness Trials (COMET) initiative.

An international group of stakeholders with expertise in implantable neurostimulation devices were identified and invited via email by the Steering Group to participate

in the two-round Delphi survey (participant characteristics are presented in Supplementary Material S2).

In the first round of the Delphi survey, 42 candidate items were presented for consideration. The first round was open from 1st November to 30th November 2021. Fourteen new candidate items were proposed by participants and included in the second round of the Delphi survey.

The second round took place from 10th January to 15th February 2021. Full details on the Delphi consensus process, Consensus meeting and pilot of the checklist are provided in the companion CONSORT-iNeurostim manuscript.[16]

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Authors had full access to the data in the study. All authors were responsible for the decision to submit the manuscript.

Consensus recommendations

Two items were included as presented during the consensus meeting (i.e., as singular items) whereas 18 items were merged and combined into three items [two candidate items merged for Item 1(i); two candidate items merged for Item 10(i) and 14 candidate items merged for Item 11a(i)].

Twenty-one candidate items were excluded at the consensus meeting; <70% of the Consensus Group voted in favour of their inclusion. A further 16 items were excluded by the Working Group after the consensus meeting (despite that ≥70% of the Consensus Group voted in favour of their inclusion) because the Working Group considered that 13 items were covered by the current SPIRIT statement and three items were beyond the scope of the SPIRIT-iNeurostim extension (Supplementary Material S3).

The final SPIRIT-iNeurostim extension recommends five new checklist items that should be reported by authors in addition to the current SPIRIT statement for protocols of trials of implantable neurostimulation devices (Table 1). One of the items (11a (i)) consists of an intervention checklist, developed to include 14 recommended checklist items specific to the neurostimulation procedure as the intervention under evaluation, control, or comparator (Table 2).

Administrative information

SPIRIT-iNeurostim item 1(i)

In the title and/or abstract, state: the type of neurostimulation that will be investigated; and the neurological structure or nerve that will be stimulated.

Explanation. Stating the key aspects of a trial (i.e., the type of neurostimulation and the neurological structure to be investigated) facilitates database indexing. Appropriate indexing of a trial protocol enables a publication to be identified by search strategies and improves its visibility to electronic database users. Ideally, authors should state this information in the title, however, this may not be possible if the journal imposes a word limit on the title.

Examples.

"Pathway Of Low Anterior Resection syndrome relief after Surgery (POLARiS) feasibility trial protocol: a multicentre, feasibility cohort study with embedded randomised control trial to compare sacral neuromodulation and transanal irrigation to optimised conservative management in the management of major low anterior resection syndrome following rectal cancer treatment."[19]

"Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high- frequency spinal cord stimulation for chronic neuropathic low back pain (MODULATE-LBP): a trial protocol"[20]

"Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for disabling motor symptoms of Parkinson's disease (PD) that persist despite optimal pharmacological treatment."[21]

SPIRIT-iNeurostim item 4(i)

State the source(s) of funding for device costs.

Explanation. Information regarding the funding source(s) for device costs is required for determining risk of bias and for quality assessing trials. It is especially important that authors explicitly state the funding source(s) for device costs if a different funding source(s) is (are) sponsoring the general conduct of the trial. A systematic review[10] of 46 RCTs assessing SCS for adults and adolescents with pain reported that while most (82%) RCTs reported the source(s) of funding, less than half (41.2%) of RCTs specified the role of the sponsor (e.g., involvement in data collection and analysis, overseeing manuscript preparation or supplying devices). A Cochrane systematic review[22] of studies of medicines and medical devices (including RCTs, observational studies and cohort studies) found that studies that were funded by the manufacturing company of the medicine/device being investigated more often reported statistically significant efficacy results (i.e., p-value less than the pre-defined significance level; typically $p < 0.05$) and conclusions that favoured the manufacturer's medicine or device compared to non-industry sponsored studies. Further, patients may be denied access to implantable neurostimulation devices for insurance reasons, for example, and accept participation in Investigational Device Exemption trials to access the device for free which may potentially result in inflated treatment

Section/Item	Item No.	Description	Ext. No.	Extension description
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1 (i)	In the title and/or abstract, state: • the type of neurostimulation that will be investigated • the neurological structure or nerve that will be stimulated
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry		
	2b	All items from the World Health Organization Trial Registration Data Set		
Protocol version	3	Date and version identifier		
Funding	4	Sources and types of financial, material, and other support	4 (i)	State the source(s) of funding for device costs
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors		
	5b	Name and contact information for the trial sponsor		
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities		
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)		
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6a (i)	Describe the intended position of the neurostimulation intervention in the treatment pathway for the clinical indication
	6b	Explanation for choice of comparators		
Objectives	7	Specific objectives or hypotheses		
Trial design	8	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)		
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained		
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	10 (i)	Specify whether the study design will include a neurostimulation trial phase prior to permanent device implantation and, if so, describe the trial phase methods and the eligibility criteria required for patients to proceed to permanent device implantation
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11a (i)	See Table 2 Intervention checklist
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)		

(Table 1 continues on next page)

Section/Item	Item No.	Description	Ext. No.	Extension description
(Continued from previous page)				
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)		
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial		
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended		
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)		
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations		
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size		
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions		
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned		
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions		
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how		
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol		

(Table 1 continues on next page)

Section/Item	Item No.	Description	Ext. No.	Extension description
(Continued from previous page)				
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols		
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol		
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol		
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)		
	20c	Definition of analysis population relating to protocol non-adherence (e.g., as randomised analysis), and any statistical methods to handle missing data (e.g., multiple imputation)		
Methods: monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial		
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct		
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/ institutional review board (REC/IRB) approval		
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)		
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)		
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial		
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site		

(Table 1 continues on next page)

Section/Item	Item No.	Description	Ext. No.	Extension description
(Continued from previous page)				
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators		
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation		
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions		
	31b	Authorship eligibility guidelines and any intended use of professional writers		
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code		
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates		
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable		

Table 1: **SPIRIT-iNeurostim checklist.**

effects. Similar effects may occur for patients with free healthcare access to implantable neurostimulation devices (e.g., in the UK NHS).

Examples.

"After insurance authorization, subjects will first undergo a temporary trial stimulation phase during which an external stimulator (Evoke Trial System, Saluda Medical, Sydney, Australia) will be connected to one or two percutaneous Evoke leads (12-contact leads, all capable of stimulation and ECAP measurement) placed in the dorsal epidural space of the spinal canal."[23]

"Costs for devices, procedures, and medical visits related to the trial were covered by the sponsor for all participants; therefore, no risk of unblinding by insurance billing existed."[24]

Introduction

SPIRIT-iNeurostim item 6a(i)

Describe the intended position of the neurostimulation intervention in the treatment pathway for the clinical indication.

Explanation. Surgery is required to implant the electrode contacts, leads and pulse generator of implantable neurostimulation devices. Common adverse events include infection and pain at the implantation site[25–30] and lead migration and breakage.[25–28,30] Less common adverse events include haematoma and haemorrhage[25,26,28,29] which can, although very rarely, result in death.[28] For this reason, invasive neurostimulation is generally considered a treatment option for people for whom conventional medical management has failed, i.e., people with drug-resistant conditions.[31] It is therefore insightful to the reader that the authors describe the position of the neurostimulation intervention in the treatment pathway for the clinical indication in the study protocol. This should be based on the most recent national or international guidelines for the condition. It may include information about the type and number of failed interventions required for a patient to be eligible for implantation.

Examples.

"Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established treatment for disabling motor response fluctuations and dyskinesia that persist despite optimal pharmacological treatment."[21]

"The National Institute for Health and Care Excellence (NICE) recommends spinal cord stimulation (SCS) for refractory neuropathic pain. SCS is routinely used for people with predominantly neuropathic radicular pain that typically results from,

Item	Description
1. Neurostimulation device	1a) State the model and manufacturer of the neurostimulation device and all other hardware components
	1b) Specify the number and type of leads and electrode contacts required
	1c) Specify the distance between electrode contacts
2. Implant procedure	2a) Describe the surgical approach to implant the device including the use of anaesthesia
	2b) Specify the neurological structure or nerve to be targeted
	2c) Where applicable, describe how the correct positioning of leads will be confirmed
3. Programming	3a) Describe the stimulation parameters including pulse width (duration), frequency, amplitude and waveform programme
	3b) Specify whether stimulation will be adjustable or pre-set
	3c) For personalised stimulation, describe how optimal stimulation parameters will be achieved and state whether any additional hardware will be required
	3d) State the number and duration of stimulation sessions per day when the stimulation will not be used continuously during the entire day
4. Neurostimulation control or comparator (where applicable)	4a) If active, subtherapeutic, subthreshold or sham stimulation will be used as a comparator, provide details for items 1–3 if dissimilar from the intervention
	4b) If subtherapeutic, subthreshold or sham stimulation will be used, justify and describe how it will be achieved
5. Management	5a) Describe how the patient handheld programmer will be managed
	5b) If sham stimulation will be used as the control, describe how sham sensations will be managed

[a]The SPIRIT-iNeurostim intervention checklist is designed to replace item 11a of SPIRIT for reporting of trial protocols. This intervention checklist should be read in conjunction with the explanations of the SPIRIT-iNeurostim items provided in the main text.

Table 2: **SPIRIT-iNeurostim intervention checklist.**[a]

or persists after, spinal surgery (so-called failed back surgery syndrome [FBSS])."[20]

Methods: participants, interventions, and outcomes

SPIRIT-iNeurostim item 10a(i)

Specify whether the study design will include a neurostimulation trial phase prior to permanent device implantation and, if so, describe the trial phase methods and the eligibility criteria required for patients to proceed to permanent device implantation.

Explanation. This item may not be applicable to all types of implantable neurostimulation devices. A neurostimulation trial phase aims to identify people who may benefit from implantable neurostimulation devices in the long-term and enables patients to experience neurostimulation prior to permanent device implantation. CONSORT flow diagrams adapted for clinical trials that compare two different implantable neurostimulation interventions and adapted for clinical trials that compare an implantable neurostimulation intervention to an alternative non-neurostimulation intervention are provided in the companion CONSORT-iNeurostim manuscript.[16] Trials of SCS and peripheral nerve stimulation typically include a neurostimulation trial phase[32] and there is an increasing trend for trials of DBS to include a neurostimulation trial phase as new applications are investigated.[33] Specifically, in the NICE technology appraisal guidance for SCS for patients with chronic pain of neuropathic or ischaemic origin,[31] NICE recommends that only patients who have a successful trial phase should undergo permanent SCS device implantation. Evidence-based consensus recommendations on patient selection and temporary trial phase for SCS have been published.[34,35]

The duration of neurostimulation trial periods can vary from several minutes during surgery, referred to as "on-table" trials, to several days or weeks, referred to as "home" trials.[36] For "home" trials, implanters may use permanent anchored leads ("definitive" trials) or temporary percutaneous leads ("temporary" trials).[37] A trial phase may also be used to confirm appropriate lead location and/or to optimise stimulation parameters. It is important to report whether the trial parameters will match exactly what will be offered in the permanent implant, and rationale presented if the parameters will be different.

If the trial will include a neurostimulation trial phase, it is important that the authors describe the methods for the trial phase in sufficient detail to enable replication, including the reasons for the stimulation trial phase and the eligibility criteria required for patients to proceed to full implantation. This information may be based on the most recent national or international guidelines for the condition of interest. For example, for SCS for chronic pain, multi-specialty, multi-society guidelines on patient selection and SCS trial recommend that improved pain relief of ≥50% must be demonstrated using a validated outcome instrument, during or at the end of trial, to be considered successful.[34] It is also recommended that therapeutic efficacy should be evaluated multidimensionally, using validated measures for functional improvement, stable or decreased analgesic use, overall satisfaction, in addition to pain relief.[34]

Examples.

"… a successful screening trial will be defined as ≥ 50% pain relief and satisfactory on-table paraesthesia coverage (i.e., ≥80%) of the pain area, reduction in pain medications or improved quality of life and function, and successful location of leads at the anatomical target for paraesthesia-free therapies."[36]

SPIRIT-iNeurostim item 11a(i)
Intervention checklist.

Explanation. Well-described methods of interventions are essential for research replicability and enable readers to assess the external validity of research findings. In the SPIRIT statement,[1] it is acknowledged that the methodology for medical devices is generally more complex than the methodology of pharmacological interventions. Table 2 lists the additional methodological details that authors must report to comprehensively describe the methods for implantable neurostimulation devices.

Neurostimulation device. It is important that authors state the model and manufacturer of all hardware components of the neurostimulation device, including the leads and number of electrode contacts, especially if any of the hardware components are non-standard. Other clinical and research groups should be able to replicate the device setup exactly. Where applicable contact layouts should be added (e.g., for a 5-6-5 lead vs percutaneous lead) and number of columns.

Implant procedure. Authors should describe the approach to implant the neurostimulation device and include details about the implanter, their level of expertise and any specific training received. Where applicable, authors should describe how lead positioning will be confirmed, e.g., by imaging technology or by adequate paraesthesia coverage (≥80%) of a target area.

Programming. Neurostimulation waveforms are well-described in the literature.[38–43] Authors may prefer to reference publications rather than provide in-depth description of the waveforms in the trial protocol. Authors should mention whether the type of stimulation to be used is experimental or used in routine clinical practice. If "cycling" of stimulation will be used (i.e., a period of active, therapeutic stimulation followed by a pause in stimulation), describe the length of both the active and passive cycles. As a minimum, authors should provide the stimulation parameters to be used including pulse width, frequency and amplitude or a range for each parameter. Authors should also consider data collection to present neural dosing expressed as charge per pulse (amplitude [mA] x pulse width [ms]) or charge per second (amplitude [mA] x frequency [Hz] x pulse width [ms]),[44] consequent evidence of neural response (measured through evoked compound action potentials [ECAPs, mV][45] or other mechanisms).

Neurostimulation control or comparator (where applicable). The same level of detail provided for the active intervention should also be provided when describing the control arm. In parallel RCTs that use an inactive or sham comparator, authors should explain if and how the stimulation provided will be subtherapeutic, subthreshold or sham.

Management. In trials where participants are blind to stimulation received or in trials that include sham stimulation, the handheld programmer is often withheld from patients to avoid breaking the blind (because the implantable pulse generator [IPG] battery will not deplete, and most programmers show IPG charge level). From a safety perspective, if the handheld programmer is withheld from patients, safety provisions must be made to ensure that patients are able to switch off the neurostimulation device in an emergency. Authors should state how the patient handheld programmer will be managed, and if it is withheld, provide justification. When sham is used as the control, authors should clarify how unwanted stimulation sensations will be managed to prevent unblinding of participants.

Examples.

"The neuromodulation system (Evoke System, Saluda Medical, Sydney, Australia) offers both closed-loop and open-loop stimulation modes and is capable of measuring the SC activation produced by stimulation regardless of the stimulation mode by recording the neural response (i.e., ECAPs) after each stimulation pulse on the same leads used for stimulation."[40]

"The IPG is implanted in a subcutaneous pocket and is capable of stimulating the spinal cord nerves when used with one or two 8-contact percutaneous leads. The IPG is controlled by a patient remote and/or a clinician programmer. Lead(s): The percutaneous lead has eight contacts. Extension(s): An extension may be used during the permanent implantation procedure, to connect the lead to the IPG. IPG: The IPG is a rechargeable stimulator with 16 output terminals. Each of the 16 outputs can be programmed as a cathode or an anode."[20]

"All participants followed the same visit schedule and were instructed and trained to deliver two 30-minute stimulation sessions per day while in prone or side-laying position using their wireless activator; all were told that during the session, they "may or may not perceive stimulation"; all questionnaires were completed before any interaction with the participant; devices were programmed according to the group assignment but simulated parameter changes were done on the sham-control group to avoid bias by the length of the visit or the type of interaction during programming."[24]

"Programming placebo was performed with a 100-Hz stimulus to maintain an equal programming paradigm and sensation for the patient."[46]

"During these visits, all participants will be asked to complete the following questionnaires in addition to bringing their multi-day pain diary: … sensation map."[20]

"The sham lead positioned outside the epidural space ensures energy consumption without neurostimulation, requiring the patient to recharge the device. None of these participants will have had

exposure to SCS prior to the trial, so the experience of the therapy will be novel."[20]

Discussion

The SPIRIT-iNeurostim extension provides international consensus-based recommendations about the specific information that should be considered in the planning of randomised trials of implantable neurostimulation devices and should be reported in the respective trial protocols. The SPIRIT-iNeurostim extension items should be considered alongside the broader SPIRIT statement and other relevant guidelines for trial protocols.[1,47]

The SPIRIT-iNeurostim extension includes five checklist items, one of which is an intervention checklist that includes 14 items. Protocols for trials of implantable neurostimulation devices have not been published often. This can result in non-replicable trial protocols with minimum information and an absence of detail for the parameters of the intervention being evaluated. It has been observed that adherence to SPIRIT, and therefore comprehensive reporting of trial protocols, was better for industry-sponsored research than for non-industry sponsored research.[3,4] The items in the SPIRIT-iNeurostim extension are essential to ensure that interventions are replicable to aid future research studies planning and also for patient benefit in clinical practice.

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), the Institute of Neuromodulation (ION) and the International Neuromodulation Society (INS) collaborated and published recommendations for research design for RCTs of SCS.[48] However, the IMMPACT/ION/INS recommendations are not mandatory and are not applicable to all implantable neurostimulation devices. In contrast, the SPIRIT-iNeurostim extension was designed to be applicable to all implantable neurostimulation devices. The recommendations in the current SPIRIT-iNeurostim extension are consistent with previous recommendations.[9,48]

At the Consensus meeting, many initial candidate items and items suggested during the Delphi survey did not meet the threshold for inclusion in the SPIRIT-iNeurostim extension (Supplementary Material S4) and some items were excluded because they are only applicable to specific neurostimulation interventions. We therefore encourage researchers to review the full list of candidate items in the Supplementary material when planning their trial protocol as some excluded items may be relevant to their implantable neurostimulation device of interest. It is also important that the correct terminology is employed when describing the neurostimulation intervention.[49]

During the development of the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions, the Working Group collaborated with and acquired input from international stakeholders including methods groups (ACTTION, CONSORT, EQUATOR), neuromodulation societies (IASP SIG neuromodulation, ION, INS, NSUKI), journal editors and industry representatives. These collaborations ensure that the extensions reflect a range of experience covering all currently available implantable neurostimulation devices. Nevertheless, there was limited representation of gastroelectrical stimulation expertise during the consensus group. Further, the current study was set in the current context of neurostimulation interventions. As new implantable neurostimulation devices emerge, the SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group will assess the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions to ensure that the extensions are adapted appropriately and remain relevant to newer technologies.

The SPIRIT-iNeurostim extension aims to enhance transparency, clarity, and completeness of trial protocols for evaluations of implantable neurostimulation devices. We encourage journals that publish trial protocols of implantable neurostimulation devices to endorse the SPIRIT-iNeurostim extension and mandate its completion and submission alongside trial protocol submissions. This will encourage authors to consider these details in the trial planning and to provide all essential information in trial protocols, thereby facilitating journal editors' and peer-reviewers' assessment of the manuscripts and improving trial replicability and confidence in trial results.

Contributors

RVD, SE, ST, RBN and RST conceptualised the study. RVD, SE, ST and RST obtained the funding for the study. All authors contributed to the study design. RB and RVD contributed to data acquisition and analysis. All authors contributed to interpretation of the data. RB and RVD wrote the first draft of the manuscript. All authors contributed to drafts of the manuscript and approved the final version of the manuscript. RVD and RB have accessed and verified the data. All authors were responsible for the decision to submit the manuscript.

Data sharing statement

Data supporting this study are included within the article and/or supporting materials. After publication of all project's manuscripts, additional data are available through request from the corresponding author.

Declaration of interests

RVD reports consultancy fees from Mainstay Medical, Medtronic Ltd and Saluda Medical outside the submitted work. He is an employee of Saluda Medical; the employer had no role in the submitted work besides its contribution as a stakeholder. SE reports consultancy fees from Mainstay Medical, Medtronic Ltd, and Saluda Medical outside the submitted work. He has received Department Research funding from Saluda Medical, and Boston Scientific. ST reports consultancy fees from Boston Scientific Corp, Mainstay Medical and Saluda Medical outside the submitted work. He has received department research funding from the National Institute of Health Research. RBN serves as an unpaid officer of the nonprofit Neuromodulation Foundation, Inc., to which grants and support have been provided by Abbott, Boston Scientific Corp, Medtronic Ltd, Nevro Corp, Nuvectra, and Stimwave Inc outside the submitted work. He receives royalties from Abbott. GB has a consulting agreement with Nevro Corp, Mainstay Medical, Boston Scientific and Abbott. He has received department research funding from

Mainstay Medical and Saluda Medical. RML is an uncompensated consultant for Biotronik, Abbott, Nalu, and Saluda Medical, and has stock options from Nalu and Saluda Medical. RST reports consultancy fees from Medtronic Ltd, Nevro Corp and Saluda Medical outside the submitted work. The views expressed in this article are those of the author(s) and not necessarily those of the NIHR, or the Department of Health and Social Care. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102933.

References

1 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
2 Tan ZW, Tan AC, Li T, et al. Has the reporting quality of published randomised controlled trial protocols improved since the SPIRIT statement? A methodological study. *BMJ Open*. 2020;10(8):e038283.
3 Gryaznov D, von Niederhäusern B, Speich B, et al. Reporting quality of clinical trial protocols: a repeated cross-sectional study about the Adherence to SPIrit Recommendations in Switzerland, Canada and Germany (ASPIRE-SCAGE). *BMJ Open*. 2022;12(5):e053417.
4 Speich B, Odutayo A, Peckham N, et al. A longitudinal assessment of trial protocols approved by research ethics committees: the Adherance to SPIrit REcommendations in the UK (ASPIRE-UK) study. *Trials*. 2022;23(1):601.
5 Calvert M, King M, Mercieca-Bebber R, et al. SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials. *BMJ Open*. 2021;11(6):e045105.
6 Cruz Rivera S, Liu X, Chan AW, Denniston AK, Calvert MJ. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. *Nat Med*. 2020;26(9):1351–1363.
7 Porcino AJ, Shamseer L, Chan AW, et al. SPIRIT extension and elaboration for n-of-1 trials: SPENT 2019 checklist. *BMJ*. 2020;368:m122.
8 Duarte RV, Bresnahan R, Copley S, et al. Reporting guidelines for clinical trial protocols and reports of implantable neurostimulation devices: protocol for the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions. *Neuromodulation*. 2022;25(7):1045–1049.
9 Duarte RV, McNicol E, Colloca L, Taylor RS, North RB, Eldabe S. Randomized placebo-/sham-controlled trials of spinal cord stimulation: a systematic review and methodological appraisal. *Neuromodulation*. 2020;23(1):10–18.
10 McNicol E, Ferguson M, Bungay K, et al. Systematic review of research methods and reporting quality of randomized clinical trials of spinal cord stimulation for pain. *J Pain*. 2021;22(2):127–142.
11 Traeger A. Competing Narratives: moving the field forward on spinal cord stimulation. *Clin J Pain*. 2024;40(9):518–519.
12 Traeger AC, Bero LA. Corporate influences on science and health-the case of spinal cord stimulation. *JAMA Intern Med*. 2024;184(2):129–130.
13 David R. Poor policy and inadequate regulation of medical technology is driving low-value care in Australia's private health system. *Aust Health Rev*. 2024;48:119–122.
14 Zhang TC, Janik JJ, Grill WM. Mechanisms and models of spinal cord stimulation for the treatment of neuropathic pain. *Brain Res*. 2014;1569:19–31.
15 Levy RM, Mekhail NA, Kapural L, et al. Maximal analgesic effect attained by the use of objective neurophysiological measurements with closed-loop spinal cord stimulation. *Neuromodulation*. 2024. https://doi.org/10.1016/j.neurom.2024.07.003.
16 Duarte RV, Bresnahan R, Copley S, et al. Reporting guidelines for randomised controlled trial reports of implantable neurostimulation devices: the CONSORT-iNeurostim extension. *EClinicalMedicine*. 2024:102932. https://doi.org/10.1016/j.eclinm.2024.102932.
17 Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. *PLoS Med*. 2010;7(2):e1000217.
18 Gattrell WT, Logullo P, van Zuuren EJ, et al. ACCORD (ACcurate COnsensus Reporting Document): a reporting guideline for consensus methods in biomedicine developed via a modified Delphi. *PLoS Med*. 2024;21(1):e1004326.
19 Coxon-Meggy AH, Vogel I, White J, et al. Pathway of Low Anterior Resection syndrome relief after Surgery (POLARiS) feasibility trial protocol: a multicentre, feasibility cohort study with embedded randomised control trial to compare sacral neuromodulation and transanal irrigation to optimised conservative management in the management of major low anterior resection syndrome following rectal cancer treatment. *BMJ Open*. 2023;13(1):e064248.
20 Al-Kaisy A, Royds J, Palmisani S, et al. Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high-frequency spinal cord stimulation for chronic neuropathic low back pain (MODULATE-LBP): a trial protocol. *Trials*. 2020;21(1):111.
21 Sisodia V, Swinnen B, Dijk JM, et al. Protocol of a randomized controlled trial investigating Deep Brain Stimulation for MOtor symptoms in patients with Parkinson's disease DEmentia (DBS-MODE). *BMC Neurol*. 2023;23(1):160.
22 Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2(2):Mr000033.
23 Leitner A, Hanson E, Soliday N, et al. Real world clinical utility of neurophysiological measurement utilizing closed-loop spinal cord stimulation in a chronic pain population: the ECAP study protocol. *J Pain Res*. 2023;16:2497–2507.
24 Gilligan C, Volschenk W, Russo M, et al. An implantable restorative-neurostimulator for refractory mechanical chronic low back pain: a randomized sham-controlled clinical trial. *Pain*. 2021;162(10):2486–2498.
25 Sterman J, Cunqueiro A, Dym RJ, et al. Implantable electronic stimulation devices from head to sacrum: imaging features and functions. *Radiographics*. 2019;39(4):1056–1074.
26 Bennett J, MacGuire J, Novakovic E, et al. Characterizing complications of deep brain stimulation devices for the treatment of parkinsonian symptoms without tremor: a federal MAUDE database analysis. *Cureus*. 2021;13(6):e15539.
27 Thaha MA, Abukar AA, Thin NN, Ramsanahie A, Knowles CH. Sacral nerve stimulation for faecal incontinence and constipation in adults. *Cochrane Database Syst Rev*. 2015;2015(8):CD004464.
28 O'Connell NE, Ferraro MC, Gibson W, et al. Implanted spinal neuromodulation interventions for chronic pain in adults. *Cochrane Database Syst Rev*. 2021;12:CD013756.
29 Sprengers M, Vonck K, Carrette E, Marson AG, Boon P. Deep brain and cortical stimulation for epilepsy. *Cochrane Database Syst Rev*. 2017;7:CD008497.
30 Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. *Pain Med*. 2016;17(2):325–336.
31 National Institute for Health and Care Excellence. Technology appraisal guidance [TA159] Spinal cord stimulation for chronic pain of neuropathic or ischaemic origin. https://www.nice.org.uk/guidance/ta159/chapter/2-Clinical-need-and-practice. Accessed August 3, 2023.
32 Deer TR, Mekhail N, Provenzano D, et al. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: the

Neuromodulation Appropriateness Consensus Committee. *Neuromodulation*. 2014;17(6):515–550. discussion 50.
33 Shirvalkar P, Sellers KK, Schmitgen A, et al. A deep brain stimulation trial period for treating chronic pain. *J Clin Med*. 2020;9(10):3155.
34 Shanthanna H, Eldabe S, Provenzano DA, et al. Evidence-based consensus guidelines on patient selection and trial stimulation for spinal cord stimulation therapy for chronic non-cancer pain. *Reg Anesth Pain Med*. 2023;48(6):273–287.
35 Goudman L, Rigoard P, Billot M, Duarte RV, Eldabe S, Moens M. Patient selection for spinal cord stimulation in treatment of pain: sequential decision-making model - a narrative review. *J Pain Res*. 2022;15:1163–1171.
36 Eldabe S, Gulve A, Thomson S, et al. Does a screening trial for spinal cord stimulation in patients with chronic pain of neuropathic origin have clinical utility and cost-effectiveness? (TRIAL-STIM study): study protocol for a randomised controlled trial. *Trials*. 2018;19(1):633.
37 Simopoulos T, Sharma S, Aner M, Gill JS. A temporary vs. permanent anchored percutaneous lead trial of spinal cord stimulation: a comparison of patient outcomes and adverse events. *Neuromodulation*. 2018;21(5):508–512.
38 Foutz TJ, McIntyre CC. Evaluation of novel stimulus waveforms for deep brain stimulation. *J Neural Eng*. 2010;7(6):066008.
39 Krauss JK, Lipsman N, Aziz T, et al. Technology of deep brain stimulation: current status and future directions. *Nat Rev Neurol*. 2021;17(2):75–87.
40 Levy R, Deer TR, Poree L, et al. Multicenter, randomized, double-blind study protocol using human spinal cord recording comparing safety, efficacy, and neurophysiological responses between patients being treated with evoked compound action potential-controlled closed-loop spinal cord stimulation or open-loop spinal cord stimulation (the Evoke study). *Neuromodulation*. 2019;22(3):317–326.
41 Kapural L, Yu C, Doust MW, et al. Novel 10-kHz high-frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: the SENZA-RCT randomized controlled trial. *Anesthesiology*. 2015;123(4):851–860.
42 De Ridder D, Vancamp T, Falowski SM, Vanneste S. All bursts are equal, but some are more equal (to burst firing): burstDR stimulation versus Boston burst stimulation. *Expert Rev Med Devices*. 2020;17(4):289–295.
43 Thompson SL, O'Leary GH, Austelle CW, et al. A review of parameter settings for invasive and non-invasive vagus nerve stimulation (VNS) applied in neurological and psychiatric disorders. *Front Neurosci*. 2021;15:709436.
44 Miller JP, Eldabe S, Buchser E, Johanek LM, Guan Y, Linderoth B. Parameters of spinal cord stimulation and their role in electrical charge delivery: a review. *Neuromodulation*. 2016;19(4):373–384.
45 Parker JL, Karantonis DM, Single PS, Obradovic M, Cousins MJ. Compound action potentials recorded in the human spinal cord during neurostimulation for pain relief. *Pain*. 2012;153(3):593–601.
46 Kriek N, Groeneweg JG, Stronks DL, de Ridder D, Huygen FJ. Preferred frequencies and waveforms for spinal cord stimulation in patients with complex regional pain syndrome: a multicentre, double-blind, randomized and placebo-controlled crossover trial. *Eur J Pain*. 2017;21(3):507–519.
47 Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ*. 2014;348:g1687.
48 Katz N, Dworkin RH, North R, et al. Research design considerations for randomized controlled trials of spinal cord stimulation for pain: initiative on methods, measurement, and pain assessment in clinical trials/institute of neuromodulation/international neuromodulation society recommendations. *Pain*. 2021;162(7):1935–1956.
49 North RB, Lempka SF, Guan Y, et al. Glossary of neurostimulation terminology: a collaborative neuromodulation foundation, Institute of neuromodulation, and international neuromodulation society project. *Neuromodulation*. 2022;25(7):1050–1058.