Reporting guidelines for clinical trial protocols and reports of implantable neurostimulation devices: protocol for the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions

Rui V Duarte, PhD[1] Rebecca Bresnahan, PhD[1] Sue Copley, MSc[2] Sam Eldabe, MD[2] Simon Thomson, MBBS[3] Richard B North, MD[4] Ganesan Baranidharan, MD[5] Robert M Levy, MD[6] Rod S Taylor, PhD[7,8] SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group

[1] Liverpool Reviews and Implementation Group, University of Liverpool, Liverpool, UK
[2] Department of Pain Medicine, The James Cook University Hospital, Middlesbrough, UK
[3] Department of Anaesthesia, Mid and South Essex University Hospitals NHSFT, Basildon, UK
[4] Neurosurgery, Anesthesiology and Critical Care Medicine (ret.), Johns Hopkins University School of Medicine, Baltimore, MD, US
[5] Leeds Neuromodulation Centre, Leeds Teaching Hospitals, Leeds, UK
[6] International Neuromodulation Society, San Francisco, USA
[7] Institute of Health and Well Being, University of Glasgow, Glasgow, UK
[8] College of Medicine and Health, University of Exeter, Exeter, UK

Address for correspondence: Rui V Duarte, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, Liverpool L69 3GB, UK. E-mail: rui.duarte@liverpool.ac.uk

Sources of financial support: The development of the guidelines will be funded by Abbott, Boston Scientific Corp., Mainstay Medical, Medtronic Ltd, Nevro Corp. and Saluda Medical. Representatives from the research divisions of the companies supporting the study will be invited to participate in the Delphi survey and to be part of the Consensus Group.

Conflict of interest statement: RVD has received consultancy fees from Boston Scientific Corp, Mainstay Medical, Medtronic Ltd and Saluda Medical. SE has received consultancy fees from Abbott, Boston Scientific Corp, Mainstay Medical and Medtronic Ltd. He has received Department Research funding from the National Institute of Health Research, Medtronic Ltd, and Nevro Corp. ST has received consultancy fees from Boston Scientific Corp. He has received department research funding from the National Institute of Health Research, Boston Scientific Corp and Mainstay Medical. RBN serves as an unpaid officer of the nonprofit Neuromodulation Foundation, Inc. to which (like his former employers Johns Hopkins University and Sinai Hospital) grants and support have been provided by Abbott, Boston Scientific Corp., Medtronic, Inc., Nevro Corp., Nuvectra, and Stimwave, Inc. He receives

royalties from Abbott and consulting fees and royalties from Nuvectra. His wife holds shares in Stimwave, Inc. GB has a consulting agreement and is on the advisory board for Nevro Corp, Nalu Medical Inc, Abbott and Boston Scientific Corp. RST has received consultancy fees from Medtronic Ltd, Nevro Corp and Saluda Medical. The other authors declare no competing interests.

Authorship statement: RVD, SE, ST, RBN and RST conceptualised the study. RVD, SE, ST, RBN and RST wrote the first draft of the manuscript. All authors contributed to drafts of the manuscript and approved the final version of the manuscript.

Abstract

Objectives: SPIRIT and CONSORT statements have been shown to improve the quality of reporting of trial protocols and randomised controlled trials. Extensions to the SPIRIT and CONSORT statements specific to certain interventions have the potential to address methodological considerations that would otherwise be overlooked. The aim of this protocol is to describe the methods to develop reporting guidelines for clinical trial protocols and reports of implantable neurostimulation devices.

Materials and Methods: The SPIRIT-iNeurostim and CONSORT-iNeurostim extensions will be developed through a staged consensus process involving literature review and expert consultation. The initial list of candidate items will be informed by findings from previous systematic reviews and published protocols and clinical trials of implantable neurostimulation devices. The candidate items will be included in a two-round Delphi survey. In the first round, participants will be invited to vote on the importance of each item and to suggest additional relevant items. In the second round, participants will be invited to re-score the items considering feedback received and the suggested additional items. A consensus meeting will then take place to discuss the results of the Delphi survey and reach consensus on the items to include in the extensions.

Discussion: Development of the SPIRIT-iNeurostim and CONSORT-iNeurostim extensions has the potential to lead to improvements and increase in transparency of the reporting of clinical trial protocols and reports of implantable neurostimulation devices.

Keywords: clinical trials; consensus statement; delphi survey; neurostimulation; reporting guidelines

Background

The Consolidated Standards of Reporting Trials (CONSORT) initiative was created with the objective of improving the reporting and consequently clarity and transparency of randomised controlled trials (RCTs).[1] The introduction and requirement to adhere to CONSORT has improved the quality of reporting.[2] Subsequently, to ensure trial protocols were complete and more likely to produce valid data, the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative was established.[3] SPIRIT and CONSORT statements are endorsed by most high impact peer-reviewed journals, research institutions, commissioning agencies and national ethics committees. In addition to the generic (i.e. minimal) SPIRIT and CONSORT statements, extensions of these statements are developed to improve the reporting of trials considering different design aspects, data or interventions. Examples include the CONSORT extension for acupuncture trials[4] and the recently published SPIRIT and CONSORT extensions for artificial intelligence trials.[5,6] Extensions include items specific to an intervention that should be routinely reported in addition to the core items.

Adherence to SPIRIT and CONSORT in trials of implantable neurostimulation devices

Adherence to SPIRIT and CONSORT can be ascertained if the authors mention in the manuscript that the recommendations have been followed and/or if it is a requirement of the journal that a SPIRIT or CONSORT checklist is uploaded at the time of submission for consideration by the editors and peer-reviewers. Many high impact general medical journals (e.g., BMJ, JAMA, Annals Internal Medicine, Lancet) have signed up to an editor's concordant requiring mandatory completion of these checklists by authors. A number of journals that have a remit to publish trial protocols for publication (e.g., Trials, BMJ Open) require completion and submission of a SPIRIT checklist.

For neuromodulation, the protocols for TRIAL-STIM and MODULATE-LBP trials have been published and have adhered to SPIRIT. Completion of a CONSORT checklist is required by several pain-related journals when submitting a clinical trial (e.g., Pain, Anesthesiology, Journal of Pain). Notable recent clinical trials of implantable neurostimulation devices that reported adherence to CONSORT recommendations include TRIAL-STIM, EVOKE, SENZA-RCT and ACCURATE.

Recent systematic reviews, show that methodological and reporting deficiencies in trials of spinal cord stimulation (SCS) are common.[7,8] Recommendations for reporting based on these publications are presented in Tables 1 and 2. IMMPACT/ION/INS have recently published their recommendations for research design for RCTs of SCS.[9] However, the IMMPACT/ION/INS recommendations are not required to be formally adopted and are not a requirement for authors when reporting the design or reporting clinical trials.

To date, SPIRIT and CONSORT extensions have not been specifically developed for clinical trials of implantable neurostimulation devices and have the potential to improve the reporting, clarity, and transparency of trials in this area. The development of such extensions would add to an increase in confidence in the results of clinical trials of implantable neurostimulation devices.

Examples of types of implantable neurostimulation devices and current indications are presented in Table 3.

Table 1. Items to include when reporting trials of neurostimulation including a placebo arm [7]

Item	Recommendation
Programming and management	Report programming parameters for the active and the sham arm
	Describe how the patient handheld programmer was managed
	State how blinding was ensured if the patient handheld programmer was provided to the patients
	For studies that utilise a subthreshold programming as a comparator:
	Identify the position that the threshold was measured in
	State if a feedback loop/ position adjustment was utilised to vary current with position
	Report the duration of daily device use and frequency of programmer interactions
	Describe what provision was made for subjects to switch off their device in an emergency if patient handheld programmer was withheld
Programming and management when the study includes patients with rechargeable devices	Describe how a similar recharging burden was ensured in the different arms (i.e., report the frequency and duration of recharging)
	Report how the patient handheld programmer/charger was managed (particularly if it contains a feedback screen that allows the subject to assess IPG charge)
Research team	State if the team was split into blinded and unblinded side with no intermixing
	Report if there was one or more unblinded programmers member of the team
	Clearly state which members of the research team were blinded
Effectiveness of blinding	Describe how effectiveness of blinding of patients and members of the research team was assessed
Sham sensations	Describe how sham sensations were managed

IPG=implantable pulse generator

Table 2. Reporting Recommendations for RCTs of neurostimulation Pain [8]

The following information should be clearly reported

Reporting
- Source of funding and specific role of funder in compensation, study design and analysis

Study design
- Parallel group, cross-over, other
- Posting of a protocol detailing a priori inclusion criteria, outcomes assessed (with clear delineation of primary and secondary endpoints, and if multiple endpoints are primary, methods for multiplicity adjustment) and statistical methods employed on a website such as www.clinicaltrials.gov

Study methodology
- Clinical eligibility criteria
- Duration of washout in cross-over trials
- Extent and methodology of blinding
- Methods of randomization and its concealment
- Role of screening phase in enrolment of participants
- Initial settings and adjustment parameters for devices
- Allowance of concurrent treatments
- Methods to ensure balanced expectation of benefit of both researchers and patients (equipoise) between groups, and also balance of non-intervention treatment between groups (e.g., programming time, psychological support, physical activity, rescue meds, etc.)

Outcomes
- Primary and secondary outcomes
- Assessment of adverse events, including what and how these were assessed

Statistical analysis
- Number of participants and reasons for withdrawing
- Similarity of groups at baseline and methods for accommodating differences
- Type of analysis (superiority, noninferiority, etc.)
- Sample size calculations, power analyses, and assumed effect size
- Methods for dealing with missing data

Interpretation
- Clinical significance of any statistically significant difference

Table 3. Implantable neurostimulation devices and indications

Technology	**Indication**
Deep brain stimulation	Parkinson's disease
	Tremor and dystonia (excluding Parkinson's disease)
	Refractory epilepsy
	Refractory chronic pain syndromes (excluding headache)
	Intractable trigeminal autonomic cephalalgias
Dorsal root ganglion stimulation	Chronic pain
Gastroelectrical stimulation	Gastroparesis
Peripheral nerve stimulation	
Occipital nerve stimulation	Intractable chronic migraine
	Chronic cluster headaches
Multifidus nerve stimulation	Chronic low back pain
Sacral nerve stimulation	Faecal incontinence
	Idiopathic chronic non-obstructive urinary retention
Sphenopalatine ganglion stimulation	Chronic cluster headache
Spinal cord stimulation	Chronic pain of neuropathic origin
	Chronic pain of ischaemic origin
Vagus nerve stimulation	Refractory epilepsy in adults and children
	Treatment-resistant depression

Aim

The aim of this project is to develop SPIRIT and CONSORT extensions for clinical trials of implantable neurostimulation devices considering their respective indications.

Methods

Both SPIRIT-iNeurostim and CONSORT-iNeurostim extensions will be developed for clinical trial protocols and reports. We will follow the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network's methodological framework.[10] The SPIRIT-iNeurostim and CONSORT-iNeurostim extensions have been registered as reporting guidelines under development on the EQUATOR library of reporting guidelines in February 2021.

Literature review and candidate item generation

An initial list of candidate items will be informed by findings from previous systematic reviews that assessed methods and reporting in RCTs of SCS (Table 1 and 2)[7-9] and through a rapid review of published protocols and clinical trials considering the implantable neurostimulation devices presented in Table 3. The Working Group (i.e., combination of trialists, methodologists and clinicians experienced in trials of implantable neurostimulation devices – see section "Membership of the SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group, Steering Group and Consensus Group" for further details) will identify commonly reported methodological details and results from the studies of implantable neurostimulation devices (beyond the items already included in the SPIRIT and CONSORT checklist) and reframe them as candidate reporting items. For example, candidate items could include methodological details that are important for replicability or potential sources of bias specific to studies of implantable neurostimulation devices. Decisions on candidate items to be included in subsequent Delphi surveys will be made following consultation with the Steering Group and additional international experts.

Delphi consensus process

The candidate items for each extension will be voted on by an international expert group in a two-round Delphi survey. Participants in the Delphi survey will have the possibility of suggesting additional items. Experts will be identified and contacted via the Steering Group. The decision on the number of individuals to invite to complete a Delphi survey is not based on statistical power and must often be a pragmatic choice.[11] We will try to maximise the number of participants who complete the Delphi survey. In the first round of recruitment, the experts contacted will be able to suggest additional experts. As we will be seeking individuals with expertise in implantable neurostimulation devices and their users, we will approach relevant societies to disseminate information on the survey to their members (e.g., INS and INS Regional Chapters, NANS, IoN, IASP and IASP Chapters). Stakeholders will include

healthcare professionals, statisticians, methodologists, journal editors, patients and industry representatives.

DelphiManager software, developed and maintained by the COMET (Core Outcome Measures in Effectiveness Trials) initiative, will be used to undertake a two-round e-Delphi survey. Participants will be asked to vote on each item using a 9-point scale to rate items as follows: 1–3, not important; 4–6, important but not critical; and 7–9, important and critical. In the second round of the Delphi, participants will be shown the number of respondents and distribution of scores for each item from the first round. Participants will also be reminded how they personally scored each item in the first round. Participants will be asked to consider the responses from other Delphi participants and to re-score the items. Respondents will provide separate ratings for SPIRIT-iNeurostim and CONSORT-iNeurostim. Inclusion criteria threshold for the Delphi exercise will be considered as a median score ≥4. Items with a median score <4 will be excluded.

The results of the Delphi survey will inform the consensus meeting. Items proposed by the Delphi study participants will be added for discussion at the consensus meeting.

Consensus meeting

A face-to-face or virtual two-day consensus meeting will take place to discuss the findings of the Delphi survey and reach consensus on the items to include in the extensions. Stakeholders will be invited to discuss the items and vote on their inclusion. Each item will be presented to the Consensus Group alongside its score from the Delphi exercise and any comments made by the participants. The Consensus Group will be invited to comment on the importance of each item and whether it should be included in the SPIRIT-iNeurostim and / or CONSORT-iNeurostim extensions. The Consensus Group will also be invited to comment on the wording of the explanatory text accompanying each item and the position of each item relative to the SPIRIT 2013 and CONSORT 2010 checklists. An electronic vote will take place, with the option to include or exclude each item. A level of agreement of at least 70% has been pre-specified and deemed reasonable to demonstrate majority consensus for inclusion by the Steering Group. Anything else will be considered as insufficient for inclusion in the extension. The initial SPIRIT-iNeurostim and CONSORT-iNeurostim extensions will be refined through a pilot of the checklist.

Membership of the SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group, Steering Group and Consensus Group

The SPIRIT-iNeurostim and CONSORT-iNeurostim Working Group will consist of RD, RB, SC, SE, ST, RN, GB and RT. The Working Group will be responsible for acquisition, analysis,

interpretation of data, drafting the explanation and elaboration document and manuscripts for publication. Members of the Working Group will be part of the SPIRIT-iNeurostim and CONSORT-iNeurostim Steering Group (to include SPIRIT, CONSORT, EQUATOR and NSUKI representatives, and Editor in Chief of Neuromodulation) who will be responsible for overseeing the consensus process guidelines development methodology and of the SPIRIT-iNeurostim and CONSORT-iNeurostim Consensus Group (to include in addition to working group and steering group - i. journal editors; ii. representatives of each clinical condition and expertise with the different neurostimulation devices; iii. representatives from patient groups; iv. representatives from societies - INS, NANS, IoN; and v. representatives from companies that funded the study) who will be responsible for reaching consensus on the content and wording of the items within the checklists.

References

1. http://www.consort-statement.org
2. Ranganathan P. The CONSORT statement and its impact on quality of reporting of trials. Perspect Clin Res 2019;10(4):145-147.
3. http://www.consort-statement.org/resources/spirit
4. MacPherson H, Altman DG, Hammerschlag R, Youping L, Taixiang W, White A, Moher D, STRICTA Revision Group. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med 2010;7(6):e1000261.
5. Liu X, Rivera SC, Moher D, Calvert MJ, Denniston AK, The SPIRIT-AI and CONSORT-AI Working Group. Reporting guidelines for clinical trial reports for interventions involving artificial intelligence: the CONSORT-AI extension. Nat Med 2020;26:1364–1374
6. Rivera SC, Liu X, Chan A, Denniston AK, Calvert MJ, The SPIRIT-AI and CONSORT-AI Working Group, SPIRIT-AI and CONSORT-AI Steering Group & SPIRIT-AI and CONSORT-AI Consensus Group. Guidelines for clinical trial protocols for interventions involving artificial intelligence: the SPIRIT-AI extension. Nat Med 2020;26:1351–1363.
7. 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.
8. McNicol E, Ferguson M, Bungay K, Rowe EL, Eldabe S, Gewandter JS, Hayek SM, Katz N, Kopell BH, Markman J, Rezai A, Taylor RS, Turk DC, Dworkin RH, North RB, Thomson S. 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.
9. Katz N, Dworkin RH, North R, Thomson S, Eldabe S, Hayek SM, Kopell BH, Markman J, Rezai A, Taylor RS, Turk DC, Buchser E, Fields H, Fiore G, Ferguson M, Gewandter J, Hilker C, Jain R, Leitner A, Loeser J, McNicol E, Nurmikko T, Shipley J, Singh R, Trescot A, van Dongen R, Venkatesan L. Research Design Considerations for Randomized Controlled Trials of Spinal Cord Stimulation for Pain: IMMPACT/ION/INS Recommendations. Pain 2021;162(7):1935-1956.
10. Moher D, Schulz KF, Simera I, Altman DG. Guidance for developers of health research reporting guidelines. PLoS Med 2010;7:e1000217.
11. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB, Young B The COMET Handbook: version 1.0. Trials 2017;18:280.