SPIRIT 2013 and SPIRIT-PRO Extension Checklist: Recommended Items to Address in a Clinical Trial Protocol

Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for Inclusion of Patient-Reported Outcomes in Clinical Trial Protocols: The SPIRIT-PRO Extension. JAMA : the journal of the American Medical Association 2018;319(5):483-94 doi: 10.1001/jama.2017.21903[published Online First: Epub Date])

Section/item	ItemNo	Description	SPIRIT-PRO Item No.	SPIRIT-PRO Extension or Elaboration Item Description	Addressed on Page No.
Administrative information					
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym			Title page
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry			Abstract
	2b	All items from the World Health Organization Trial Registration Data Set			See below (pages 14-20)
Protocol version	3	Date and version identifier			Abstract
Funding	4	Sources and types of financial, material, and other support			27

Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors			27
	5b	Name and contact information for the trial sponsor	SPIRIT-5a-PRO Elaboration	Specify the individual(s) responsible for the PRO content of the trial protocol.	See Spirit Item 2B below
	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			See Spirit Item 2B below; 27
	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)			10 and 22
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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	SPIRIT-6a-PRO Extension	Describe the PRO-specific research question and rationale for PRO assessment and summarize PRO findings in relevant studies.	5-6
	6b	Explanation for choice of comparators			5-6
Objectives	7	Specific objectives or hypotheses	SPIRIT-7-PRO Extension	State specific PRO objectives or hypotheses (including relevant PRO concepts/domains).	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)			Title, Abstract, 4 and 7
Methods: Participants, interventions, and outcomes					
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained			6 and 10

Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	SPIRIT-10-PRO Extension	Specify any PRO-specific eligibility criteria (eg, language/reading requirements or prerandomization completion of PRO). If PROs will not be collected from the entire study sample, provide a rationale and describe the method for obtaining the PRO subsample.	7, Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered			10-11, Figure 1, Supplemental Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)			22, Table 2
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)			7, 11, 15, Figure 2, Supplemental File 3
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial			Tables 1 and 2 including legends

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	SPIRIT-12-PRO Extension	Specify the PRO concepts/domains used to evaluate the intervention (eg, overall health-related quality of life, specific domain, specific symptom) and, for each one, the analysis metric (eg, change from baseline, final value, time to event) and the principal time point or period of interest.	12-22, Table 2
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)	SPIRIT-13-PRO Extension	Include a schedule of PRO assessments, providing a rationale for the time points, and justifying if the initial assessment is not prerandomization. Specify time windows, whether PRO collection is prior to clinical assessments, and, if using multiple questionnaires, whether order of administration will be standardized.	10, Table 2
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	SPIRIT-14-PRO Extension	When a PRO is the primary end point, state the required sample size (and how it was determined) and recruitment target (accounting for expected loss to follow-up). If sample size is not established based on the PRO end point, then discuss the power of the principal PRO analyses.	7

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size			10
Methods: Assignment of interventions (for controlled trials)					
Allocation:					
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions			10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned			10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions			10

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how			10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial			10
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 (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, 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	SPIRIT-18a (i)-PRO Extension	Justify the PRO instrument to be used and describe domains, number of items, recall period, and instrument scaling and scoring (eg, range and direction of scores indicating a good or poor outcome). Evidence of PRO instrument measurement properties, interpretation guidelines, and patient acceptability and burden should be provided or cited if available, ideally in the population of interest. State whether the measure will be used in accordance with any user manual and specify and justify deviations if planned.	2, 12-22, Table 2, Figure 2
			SPIRIT-18a (ii)-PRO Extension	Include a data collection plan outlining the permitted mode(s) of administration (eg, paper, telephone, electronic, other) and setting (eg, clinic, home, other).	2, 4, 11, Table 2, Supplemental File 3

			SPIRIT-18a (iii)-PRO Extension	Specify whether more than 1 language version will be used and state whether translated versions have been developed using currently recommended methods.	8, 20-21, 26-27
			SPIRIT-18a (iv)-PRO Extension	When the trial context requires someone other than a trial participant to answer on his or her behalf (a proxy-reported outcome), state and justify the use of a proxy respondent. Provide or cite evidence of the validity of proxy assessment if available.	NA
	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	SPIRIT-18b (i)-PRO Extension	Specify PRO data collection and management strategies for minimizing avoidable missing data.	7, 11, 22, Table 2
			SPIRIT-18b (ii)-PRO Elaboration	Describe the process of PRO assessment for participants who discontinue or deviate from the assigned intervention protocol.	22-23
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol			22, 24-25

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	SPIRIT- 20a-PRO Elaboration	State PRO analysis methods, including any plans for addressing multiplicity/type I (α) error.	22-24
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)			24
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	SPIRIT- 20c-PRO Elaboration	State how missing data will be described and outline the methods for handling missing items or entire assessments (eg, approach to imputation and sensitivity analyses).	22-23
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			21, 27

	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			NA
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	SPIRIT- 22-PRO Extension	State whether or not PRO data will be monitored during the study to inform the clinical care of individual trial participants and, if so, how this will be managed in a standardized way. Describe how this process will be explained to participants; eg, in the participant information sheet and consent form.	Table 2, Figure 2, page 22
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor			NA
Ethics and dissemination					
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval			3, 26

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)			NA
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)			10, Supplemental File 2
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable			NA
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			27, Supplemental File 2
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site			27
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			22

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			22
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions			3, 27
	31b	Authorship eligibility guidelines and any intended use of professional writers			27
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code			27
Appendices					
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates			Supplemental File 2

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			NA

Abbreviations: SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; PRO, patient-reported outcome.
*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license and is reproduced with permission.

Spirit Item 2B WHO Trial Registration Dataset

Data Category	Information
Primary registry and trial identifying number	German Clinical Trials Register https://www.drks.de/drks_web/ Trial ID: DRKS00023978
Date of registration in primary registry	28.12.2020
Secondary identifying numbers	Universal Trials Number (UTN): U1111-1263-1856 Ethics approval reference number: 1347/2020

Source(s) of monetary or material support	This study is an independent academic study, which is conducted with the financial support of Celgene, a company of Bristol Myers Squibb (NA-CL-MS-PI-13909_Seebacher: Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study). The people involved in decision-marking about this funding have no influence on the planning, conduct and publication of the study.
Primary sponsor	Medical University of Innsbruck, Austria
Secondary sponsor(s)	N/A
Contact for public queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at
Contact for scientific queries	Dr Barbara Seebacher Phone: +435050482499 Email: barbara.seebacher@i-med.ac.at

Public Title	Effects of actual and imagined music-stimulated gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Scientific Title	Effects of actual and imagined music-cued gait training on motor functioning and brain activity in people with multiple sclerosis: a multicentre study
Countries of recruitment	Austria
Health condition(s) or problem(s) studied	Multiple sclerosis (MS)
Intervention(s)	Group 1: Motor imagery (MI) with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks Group 2: MI with music cueing (the music beat is accentuated using metronome cueing and intermittent verbal cueing) plus gait training with music cueing; 15 & 15 min, 4x per week, for 4 weeks Group 3: Gait training alone with music cueing; the music beat is accentuated using metronome cueing and intermittent verbal cueing; 30 min, 4x per week, for 4 weeks

Key inclusion and exclusion criteria	Inclusion criteria: people with any MS phenotype according to the revised McDonald's criteria; aged 18 years or over; any ethnicity; disability status score on the EDSS of 2.0 to 5.0; stable disease; no evidence of disease activity; and able to speak and understand German language. Exclusion criteria: people with MS with concomitant diseases (such as malignant diseases, other neurological or psychiatric disorders, musculoskeletal problems affecting walking, pain, uncorrected visual or hearing impairment); cognitive impairment as defined by a MoCA cut-off score of 26/30 (<26 = impaired cognition; ≥26 = intact cognition); anxiety or depression as signified by a HADS anxiety subscale score of 11/21 or a depression subscale score of 11/21 or suicidality as evaluated by a narrative screening; pregnancy; a relapse of MS within the last three months; any medication initiation or change (including corticosteroids) or any physiotherapy change within three months prior to the study; any change of symptomatic treatment affecting walking (medication or physiotherapy) or of

	disease modifying treatment (DMT) during the study will lead to an exclusion of the participant from the further analysis. Any MRI/fMRI contraindications, e.g. implanted ferrous metal, heart pacemaker or claustrophobia. Healthy controls for the fMRI scanning: 15 age- and gender matched healthy controls without any history of neurological, psychiatric, orthopaedic or other disorder.
Study type	Prospective double-blind randomised parallel multicentre trial Allocation: stratified blocked randomisation with allocation concealment Intervention model: parallel assignment (1:1:1) Masking: assessor-blinded; patients blinded to the study hypotheses Primary study aim: to investigate whether there is a difference between the effects of accentuated music- and verbally cued MI, accentuated music- and verbally cued MI combined with gait training and accentuated music- and verbally cued gait training alone on walking in people with MS.
Date of first enrolment	09.02.2021

Target sample size	132 people with MS and 15 healthy controls (fMRT)
Recruitment status	Recruiting
Primary outcome(s)	• Walking speed as assessed by the Timed 25-Foot Walk (T25FW) • Walking distance as assessed by the 2-Minute Walk Test (2MWT)
Secondary outcomes	• Brain activation patterns as assessed by fMRI (and structural MRI); in addition to patients, healthy controls will be scanned at baseline and 4 weeks later, corresponding with the intervention period of this study • MS related fatigue as assessed by the validated German version of the Neurological Fatigue Index (NFI-MS) • MS related health-related QoL, HRQoL as assessed by the validated German version of the Multiple Sclerosis International Quality of Life (MusiQol) questionnaire • MI ability as measured by the validated German version KVIQ-G-10 of the Kinaesthetic and Visual Imagery Questionnaire, short version (KVIQ-10)

	• MI ability as measured by a mental chronometry test comparing the duration of imagined and real walking on a 6-metre walkway • Anxiety and depression as assessed by the German version of the HADS, complemented by additional narrative screening for suicidality • Global cognitive impairment as assessed by the German version of the Montreal Cognitive Assessment (MoCA) • Psychomotor speed, attention, visual scanning and tracking and working memory as assessed by the Symbol Digit Modalities Test (SDMT) • Music-induced motivation / the motivational qualities of music as assessed by the Brunel Music Rating Inventory-2 (BMRI-2) • Music-induced pleasure and arousal as assessed by the Pictorial Self-Assessment Manikin (SAM) • MS specific self-efficacy as assessed by the validated German version of the Unidimensional Self-Efficacy Scale for MS (USE-MS)

	• Number of falls in the intervention and follow-up periods (falls log, telephone interviews) • Home-based training management and coping, barriers to, facilitators of and problems with the training, documentation of the training frequency and duration (support will be provided) (weekly semi-structured telephone interviews during the intervention period) • Feedback on the general health status, walking, fatigue, training content and suggestions for adaptations of the intervention in a potential follow-up study, falls and documentation of falls (semi-structured telephone interview at 4-weeks follow-up)