SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

Your manuscript may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please state "n/a" and provide a short explanation. **Leaving an item blank or stating "n/a" without an explanation will lead to your manuscript being returned before review.**

Upload your completed checklist as an additional file when you submit to *Trials*. You must reference this additional file in the main text of your protocol submission. The completed SPIRIT figure must be included within the main body of the protocol text and can be downloaded here: http://www.spirit-statement.org/schedule-of-enrolment-interventions-and-assessments/

In your methods section, please state that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1, Lines 1-3	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 4, Lines 54-56	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set		N/a. This information was not written in the manuscript because the data set is available on ClinicalTrials.gov with all information required. The ClinicalTrials.gov protocol number is

				registration number is cited in the protocol (Lines 54-56).
Protocol version	#3	Date and version identifier	Page 30, Line 647-650	
Funding	#4	Sources and types of financial, material, and other support	Page 33, Lines 717-718	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	Page 1, Lines 5-16, Page 33, Lines 720-723	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor		N/a, the study was funded by the National Institutes of Health (NIH), which is discussed on line 718. The NIH's contact information is considered standard and easily available. The contact information for the NIH is provided below. National Institutes of Health (NIH) 9000 Rockville Pike Bethesda, Maryland 20892 301-496-4000 TTY 301-402-9612
Roles and responsibilities: sponsor and funder	#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		N/a, the only funding is from the National Institutes of Health. They had no role in the study design, collection, analysis, interpretation, or writing.

Roles and responsibilities: committees	#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)		N/a, this trial did not have committees.
Introduction			Pages 4-8, Lines 60-150	
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	Page 5-7, Lines 81-121	
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	Pages 6-7, Lines 97-121	
Objectives	#7	Specific objectives or hypotheses	Pages 7-8, Lines 123-150	
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, non-inferiority, exploratory)	Page 9, Lines 153-163	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	Page 9, Lines 163-165	

		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 (eg, surgeons, psychotherapists)	Page 13-15, Lines 276-301	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Pages 12-13, Lines 248-261, Pages 19-21, Lines 408-457	
Interventions: modifications	#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)	Pages 16-17, Lines 334-352, Page 22, Lines 465-471	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	Page 18, Lines 379-381	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 18, Lines 383-385,	
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	Pages 22-23, Lines 473-496	

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)	Pages 19-21, Lines 393-457, Page 44, Lines 944-946	
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	Pages 23-24, Lines 499-508	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	Page 9, Lines 163-181, Page 13, Lines 270-274, Page 15, Lines 303-306	
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	Page 15, Lines 313-319	
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	Page 15, Lines 313-319	

Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 15, Lines 313-319	
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how		N/a, this is a pragmatic real-world study, therefore neither the study team nor the participants were blinded.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial		N/a, there is no blinding in this study because it is a pragmatic real-world study.
Methods: Data collection, management, and analysis				
Data collection plan	#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	Pages 19-21, Lines 408-457, Pages 22-23, Lines 473-496	
Data collection plan: retention	#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	Pages 17-18, Lines 364-370, Page 21, Lines 435-457	

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	Page 16, Lines 325-332, Page 25, Lines 534-542	
Statistics: outcomes	#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	Page 24, Lines 510-524	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)		N/a, there are no additional analyses (subgroup or adjusted) that are planned for this trial.
Statistics: analysis population and missing data	#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)	Pages 24-25, Lines 526-532	
Methods: Monitoring				
Data monitoring: formal committee	#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		N/a, there is no DMC in this trial.

Data monitoring: interim analysis	#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		N/a, no interim analyses are planned.
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	Pages 16-17, Lines 334-347, Page 22, Lines 465-471	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor		N/a, there are currently no procedures for auditing trial conduct other than standard annual IRB review. This is discussed on line 466.
Ethics and dissemination				
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	Pages 31-32, Lines 669-701	
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)	Page 32, Lines 703-704	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13, Lines 270-274, Page 32, Lines 684-687	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable		N/a, no ancillary studies are planned.

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	Page 16, Lines 325-332, Page 25, Lines 534-542	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 33, Lines 714-715	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 33, Lines 709-712	
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		N/a, no ancillary studies or post-trial care are planned.
Dissemination policy: trial results	#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	Pages 32-33, Lines 706-707	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers		N/a, no use of professional writers is intended.
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Pages 33, Lines 709-712	

Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates		N/a, the model consent form was not included in the manuscript. The informed consent materials can be obtained from the study team upon request.
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		N/a, this study does not collect any biological specimens for genetic or molecular analysis in this current trial or for future use in ancillary studies.