SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym P 1, line 1
Trial registration	2a	Trial identifier and registry name. 04418115 NCT; P1, line 33 If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set Not relevant
Protocol version	3	Date and version identifier 12.06.2024; bmjopen-2023-077514.R2
Funding	4	Sources and types of financial, material, and other support P 15, line 407-409
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors P 13, line 394-395
	5b	Name and contact information for the trial sponsor P 1 and P 15, line 391-397
	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 P 15, line 408-409
	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) P14, line 374-378
Introduction		
Background and rationale	6a	Description of research question P5, line 93-99 and justification for undertaking the trial, including summary of relevant studies (published and unpublished) P4, line 64-92 examining benefits and harms for each intervention P 8, line 185-191
	6b	Explanation for choice of comparators P 4, line 75-88

Objectives	7	Specific objectives or hypotheses P 5, line 95-99
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) P 5, line 115-136

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 P 6, line 137-141
Eligibility criteria	10	Inclusion and exclusion criteria for participants .P 6, line 147-161 If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) P 6, line 166-174
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered P 7, line 174-184
	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) P 14, line 374-378
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not relevant
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial P 7, line 159 and P 8, line 193-196
Outcomes	12	Primary P 10, line 240-246, secondary P 10, line 248-281, and P 12, line 322-325 and other outcomes, P 9, line 214-225 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 P 4, line 86-92 and harm P 8, line 193-196, and P 8, line 189-191 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) P 7, line 11, P 4, line 14
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 P 13, line 337-360

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size P 6, line 119-126

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 P 6, line 127-132
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 P 6, line 131-136
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions P 6, line 129-131, and P 6, line 132-136
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how P 2, line 17-18
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not relevant

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 P 9-10, line 231-281, P 12, line 300-326. Reference to where data collection forms can be found, if not in the protocol P 9, line 228. Laboratory test will be described in its own protocol which is in supplementary materials
	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 P 11, 338-352
Data management	19	Plans for data entry, P 14, page 367 coding, security, and storage, P 14, line 367-369 including any related processes to promote data quality (eg, double data entry; range checks for data values) P 13, line 332-334, and 349-354. 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 P 13, line 337-354. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) P11, line 347-348. Qualitative data analysis, P 13-14, line 355-360
	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) P 13, line 349-354.
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. P 14, line 375-380, and P 15, line 410-411.
	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. P 14, line 375-380
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 P 2, line 10, P3, line 38, P 8, line 189-180, P 15, line 378
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor P 14, line 375-380,
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval. The study has got approval from the research ethics committee Page 1, line 28-29.
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) P 6, line 120-126, here we report necessary changes due to the impact of Covid-19 pandemic had on the recruitment process. Likewise, our sub-study on Biomarkers, P 9, line 210-228 needed to be approved by REC as a sub study under our main study (REC south-east ID number: 112285)

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) P 6, line 131 (the study coordinator will receive this)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable. Described in the Biomarker protocol, added on to, Supplementary Material
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 P14, line 362-369.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site P15, line 413
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 P 14, line 362-369
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. All participating acupuncturists have an insurance which covers any harm during the treatment period. This information is given in the information sheet to all participants.
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
	31b	Authorship eligibility guidelines and any intended use of professional writers Page 15, line 394-399
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code P15, line 386-392
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 This is described in the Protocol for the Biomarker study, which can be accessed via Supplementary Materials