

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

| Section/item                      | Item No | Description                                                                                                  | Addressed on page number                                                                                              |
|-----------------------------------|---------|--------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Administrative information</b> |         |                                                                                                              |                                                                                                                       |
| Title                             | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | Page 1.                                                                                                               |
| Trial registration                | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                         | Page 3.                                                                                                               |
|                                   | 2b      | All items from the World Health Organization Trial Registration Data Set                                     | <a href="https://doi.org/10.1186/ISRCTN12418153">https://doi.org/10.1186/ISRCTN12418153</a>                           |
| Protocol version                  | 3       | Date and version identifier                                                                                  | Current protocol date/version page 8.<br>Table 1.                                                                     |
| Funding                           | 4       | Sources and types of financial, material, and other support                                                  | Award Information section, page 52.                                                                                   |
| Roles and responsibilities        | 5a      | Names, affiliations, and roles of protocol contributors                                                      | Author, affiliations Page 1. Role of protocol contributors provided during upload as per NIHR Open Research guidance. |
|                                   | 5b      | Name and contact information for the trial sponsor                                                           | Page 1, Indemnity section, page 48.                                                                                   |

|    |                                                                                                                                                                                                                                                                                          |                                                                                                                                                         |
|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 | Award Information section, page 52.                                                                                                                     |
| 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)                         | TSC, pages 10, 12, 35, 38, 40, 45, 47, 53.<br>DMC, pages 10, 35, 36, 39, 40, 45, 53.<br>Patient and Public Involvement and Engagement section, page 11. |

## 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        | Introduction section, pages 4-8.                             |
|                          | 6b | Explanation for choice of comparators                                                                                                                                                                     | Introduction section, pages 5-8.                             |
| Objectives               | 7  | Specific objectives or hypotheses                                                                                                                                                                         | Objectives section, pages 8-9.                               |
| 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) | Trial design section, page 12.<br>Allocation ratio, page 30. |

## 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           | Trial setting section, page 20.              |
| 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) | Table 3.<br>Trial training section, page 18. |
| Interventions        | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered                                                                   | Interventions section, pages 12-18.          |

|                      |     |                                                                                                                                                                                                                                                                                                                                                                                |                                                                            |
|----------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
|                      | 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)                                                                                                                                                                                 | Exercise modification, pages 13-14.<br>Orthoses modification, pages 15-16. |
|                      | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)                                                                                                                                                                                                                              | Pages 12,14,17, 19, 20, 33.                                                |
|                      | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial                                                                                                                                                                                                                                                                                  | Interventions section, page 12.                                            |
| 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 8-10.                                                                |
| 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)                                                                                                                                                                                               | Extended data Table 1.                                                     |
| 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                                                                                                                                                                                          | Sample size calculation section, pages 34-35.                              |
| Recruitment          | 15  | Strategies for achieving adequate participant enrolment to reach target sample size                                                                                                                                                                                                                                                                                            | Recruitment section, pages 21-26.                                          |

## **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 | Randomisation section, pages 29-30. |
| 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                                                                                                                                                | Randomisation section pages 29-30.  |
| Implementation                   | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions                                                                                                                                                                                                                                | Page 30.                            |
| Blinding (masking)               | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how                                                                                                                                                                                                                | Blinding section, page 31.          |
|                                  | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial                                                                                                                                                                                                     | Blinding section, page 31.          |

### **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 | Primary endpoint/outcome section, page 9.<br>Secondary endpoints/outcomes section, pages 9-10.<br>Interventions section, page 12.<br>Trial training section, page 18.<br>Extended data Table 1: schedule of enrolment, interventions, assessments. |
|                         | 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 33.                                                                                                                                                                                                                                          |

|                     |     |                                                                                                                                                                                                                                                                   |                                                                                                                         |
|---------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------|
| 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 | Data entry, pages 31, 44.<br>Coding, pages 23, 44.<br>Security, pages 44, 45, 46, 48.<br>Storage, pages 44, 45, 46, 48. |
| 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                                                                                          | Data analysis plan section, page 35.                                                                                    |
|                     | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses)                                                                                                                                                                                          | Subgroup analyses section, page 38.<br>Adjusted analysis section, page 38.                                              |
|                     | 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)                                                                                   | Participant population section, page 39.<br>Procedure(s) to account for missing or spurious data section, page 39.      |

## 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 | Composition of DMC, page 53.<br>Role summary, page 10, 35, 36, 39, 40, 45.<br>Reporting structure and Independence, page 10. |
|                 | 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                                                                                                                                                               | Interim analysis and criteria for the premature termination of the trial section, pages 38-39.                               |
| 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                                                                                                                                                     | Adverse events, pages 10, 19, 33, 36, 45.                                                                                    |
| Auditing        | 23  | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor                                                                                                                                                                                           | Pages 20, 46.                                                                                                                |

## Ethics and dissemination

|                               |     |                                                                                                                                                                                                                                                                                     |                                                                                                                              |
|-------------------------------|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|
| Research ethics approval      | 24  | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval                                                                                                                                                                                           | Ethics section, page 12.                                                                                                     |
| 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)                                                    | Amendments section, page 46.                                                                                                 |
| Consent or assent             | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)                                                                                                                                                        | Consent to full trial participation section, pages 28-29.                                                                    |
|                               | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable                                                                                                                                               | Not 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                                                                                                | Data protection and patient confidentiality section, pages 47-48.                                                            |
| Declaration of interests      | 28  | Financial and other competing interests for principal investigators for the overall trial and each study site                                                                                                                                                                       | Competing interests section, page 52.                                                                                        |
| 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                                                                                                                                     | Data protection and patient confidentiality section, pages 47-48.<br>Access to the final trial dataset section, pages 49-50. |
| 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                                                                                                                                                       | Indemnity section, pages 48-49.<br>Post-trial care section, page 49.                                                         |
| 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 | Dissemination section, page 50.                                                                                              |
|                               | 31b | Authorship eligibility guidelines and any intended use of professional writers                                                                                                                                                                                                      | Not applicable. Author contributions provided as part of submission process for NIHR Open Research.                          |

|     |                                                                                                                 |                                                         |
|-----|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | Access to the final trial dataset section, pages 49-50. |
|-----|-----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|

## Appendices

|                            |    |                                                                                                                                                                                                |                                                             |
|----------------------------|----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates                                                                                             | Not applicable. To be provided with main trial publication. |
| 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 | Not applicable.                                             |

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\*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.