

# SPIRIT 2025 checklist of items to address in a randomized trial protocol\*

| Section / Topic                        | No | SPIRIT 2025 checklist item description                                                                                                                                                                            | Reported on page no.                                                                       |
|----------------------------------------|----|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>Administrative information</b>      |    |                                                                                                                                                                                                                   |                                                                                            |
| Title and structured summary           | 1a | Title stating the trial design, population, and interventions, with identification as a protocol                                                                                                                  | Page 1 (Title: includes design and intervention)                                           |
|                                        | 1b | Structured summary of trial design and methods, including items from the World Health Organization Trial Registration Data Set                                                                                    | Page 2 (Structured Abstract) and WHO Trial Registration Data Set provided as a supplement. |
| Protocol version                       | 2  | Version date and identifier                                                                                                                                                                                       | Page 14 (Version 2.0, 2026-05-26)                                                          |
| Roles and responsibilities             | 3a | Names, affiliations, and roles of protocol contributors                                                                                                                                                           | Page 1 (Author list and affiliations)                                                      |
|                                        | 3b | Name and contact information for the trial sponsor                                                                                                                                                                | Page 15 (Sponsor section)                                                                  |
|                                        | 3c | Role of trial sponsor and funders in design, conduct, analysis, and reporting of trial; including any authority over these activities                                                                             | Page 14–15 (Funding: No role in study design or reporting)                                 |
|                                        | 3d | Composition, roles, and responsibilities of the coordinating site, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable | Page 15 (Described under 'DMC')                                                            |
| <b>Open science</b>                    |    |                                                                                                                                                                                                                   |                                                                                            |
| Trial registration                     | 4  | Name of trial registry, identifying number (with URL), and date of registration. If not yet registered, name of intended registry                                                                                 | Page 3 (Trial registration: German Clinical Trials Register (DRKS), DRKS00034188)          |
| Protocol and statistical analysis plan | 5  | Where the trial protocol and statistical analysis plan can be accessed                                                                                                                                            | Page 14 (Described under 'Availability of data and materials')                             |
| Data sharing                           | 6  | Where and how the individual de-identified participant data (including data dictionary), statistical code, and any other materials will be accessible                                                             | Page 14 (Described under 'Availability of data and materials')                             |
| Funding and conflicts of interest      | 7a | Sources of funding and other support (e.g., supply of drugs)                                                                                                                                                      | Page 14–15 (Funding source: Joint Federal Committee of the Federal Republic of Germany)    |
|                                        | 7b | Financial and other conflicts of interest for principal investigators and steering committee members                                                                                                              | Page 14 (No competing interests declared)                                                  |
| Dissemination policy                   | 8  | Plans to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., reporting in trial registry, plain language summary, publication)                      | Page 14 (Described under 'Dissemination policy')                                           |
| <b>Introduction</b>                    |    |                                                                                                                                                                                                                   |                                                                                            |

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| Background and rationale                                     | 9a  | Scientific background and rationale, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention                                                                                                           | Page 3 (Background and rationale)                                                                                |
|                                                              | 9b  | Explanation for choice of comparator                                                                                                                                                                                                                                | Page 3–4 (Described under ‘Introduction’)                                                                        |
| Objectives                                                   | 10  | Specific objectives related to benefits and harms                                                                                                                                                                                                                   | Page 4 (Described under ‘Introduction’)                                                                          |
| <b>Methods: Patient and public involvement, trial design</b> |     |                                                                                                                                                                                                                                                                     |                                                                                                                  |
| Patient and public involvement                               | 11  | Details of, or plans for, patient or public involvement in the design, conduct, and reporting of the trial                                                                                                                                                          | Page 4–5, 15 (Described under ‘Methods’ and under ‘Declarations/Patient and public involvement’)                 |
| Trial design                                                 | 12  | Description of trial design including type of trial (e.g., parallel group, crossover), allocation ratio, and framework (e.g., superiority, equivalence, non-inferiority, exploratory)                                                                               | Page 4–5 (Described under ‘Methods’, hybrid design: implementation research approach + patient-level RCT)        |
| <b>Methods: Participants, interventions, and outcomes</b>    |     |                                                                                                                                                                                                                                                                     |                                                                                                                  |
| Trial setting                                                | 13  | Settings (e.g., community, hospital) and locations (e.g., countries, sites) where the trial will be conducted                                                                                                                                                       | Page 4–5 (Conducted across seven districts in the German East Westphalia-Lippe (Ostwestfalen-Lippe, OWL) region) |
| Eligibility criteria                                         | 14a | Eligibility criteria for participants                                                                                                                                                                                                                               | Page 6–7 (Inclusion and exclusion criteria, see Table 1)                                                         |
|                                                              | 14b | If applicable, eligibility criteria for sites and for individuals who will deliver the interventions (e.g., surgeons, physiotherapists)                                                                                                                             | Page 6–7 (No special site eligibility)                                                                           |
| Intervention and comparator                                  | 15a | Intervention and comparator with sufficient details to allow replication including how, when, and by whom they will be administered. If relevant, where additional materials describing the intervention and comparator (e.g., intervention manual) can be accessed | Page 7 (Described under ‘Care and case management intervention’)                                                 |
|                                                              | 15b | Criteria for discontinuing or modifying allocated intervention/comparator for a trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)                                                                | Pages 8 and 15 (Described under ‘Data Collection Strategy’ and ‘Data Monitoring Committee [DMC]’)                |
|                                                              | 15c | Strategies to improve adherence to intervention/comparator protocols, if applicable, and any procedures for monitoring adherence (e.g., drug tablet return, sessions attended)                                                                                      | Page 8 (Ongoing contact between case managers, study nurses, and participants; no special adherence tools)       |

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|                                             | 15d | Concomitant care that is permitted or prohibited during the trial                                                                                                                                                                                                                                                           | Not specified in detail; refer to the exclusion criteria (see Section 14a)                                                                                                 |
| Outcomes                                    | 16  | Primary and secondary outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome                                                    | Pages 4, 7, 8, and 9 (Endpoints defined; see also Fig. 3, in accordance with SPIRIT 2025)                                                                                  |
| Harms                                       | 17  | How harms are defined and will be assessed (e.g., systematically, non-systematically)                                                                                                                                                                                                                                       | Pages 8-9 and 15 (Described under 'Data Collection Strategy' and 'Data Monitoring Committee [DMC]')                                                                        |
| Participant timeline                        | 18  | Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)                                                                                                                                           | Page 9 (Described in narrative + Fig. 3 following SPIRIT 2025 recommendations)                                                                                             |
| Sample size                                 | 19  | How sample size was determined, including all assumptions supporting the sample size calculation                                                                                                                                                                                                                            | Size 10 (Sample size and assumptions listed)                                                                                                                               |
| Recruitment                                 | 20  | Strategies for achieving adequate participant enrollment to reach target sample size                                                                                                                                                                                                                                        | Page 7 (Recruitment strategies listed)                                                                                                                                     |
| <b>Methods: Assignment of interventions</b> |     |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                            |
| Randomization:                              |     |                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                            |
| Sequence generation                         | 21a | Who will generate the random allocation sequence and the method used                                                                                                                                                                                                                                                        | Page 5 (Described under 'Methods'; Randomization: automated within the secuTrial® eCRF system using computer-generated block randomization)                                |
|                                             | 21b | Type of randomization (simple or restricted) and details of any factors for stratification. To reduce predictability of a random sequence, other details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions | Page 5 (Allocation ratio: 1:1; computer-generated block randomization stratified to balance potential site-specific differences in care delivery or resource availability) |
| Allocation concealment mechanism            | 22  | Mechanism used to implement the random allocation sequence (e.g., central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions are assigned                                                                                              | Page 5 (Randomization is implemented centrally via the eCRF, ensuring allocation concealment until assignments are released)                                               |
| Implementation                              | 23  | Whether the personnel who will enroll and those who will assign participants to the interventions will have access to the random allocation sequence                                                                                                                                                                        | Page 5 (Randomization is performed automatically within the secuTrial® system,                                                                                             |

|                                                           |     |                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        |
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|                                                           |     |                                                                                                                                                                                                                                                                                                                                                                                        | which generates and stores the allocation sequence centrally. The allocation sequence itself is not accessible to recruiting staff or investigators. Following randomization, the group assignment is visible only to the care and case managers and the study nurse, who are responsible for coordinating the subsequent study procedures and intervention delivery.) |
| Blinding                                                  | 24a | Who will be blinded after assignment to interventions (e.g., participants, care providers, outcome assessors, data analysts)                                                                                                                                                                                                                                                           | Page 5 (Open-label: no blinding used)                                                                                                                                                                                                                                                                                                                                  |
|                                                           | 24b | If blinded, how blinding will be achieved and description of the similarity of interventions                                                                                                                                                                                                                                                                                           | Not applicable (open-label)                                                                                                                                                                                                                                                                                                                                            |
|                                                           | 24c | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial                                                                                                                                                                                                                                   | Not applicable (open-label)                                                                                                                                                                                                                                                                                                                                            |
| <b>Methods: Data collection, management, and analysis</b> |     |                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                        |
| Data collection methods                                   | 25a | Plans for assessment and collection of trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of trial instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be accessed, if not in the protocol | Pages 8 and 14 (Described under 'Data collection strategy' and 'Availability of data and materials')                                                                                                                                                                                                                                                                   |
|                                                           | 25b | 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 8 and 10 (Described under 'Data collection strategy' and 'Statistical analysis')                                                                                                                                                                                                                                                                                 |
| Data management                                           | 26  | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be accessed, if not in the protocol                                                                                                                 | Pages 5, 8 and 11 (Data entry, quality control and management via eCRF)                                                                                                                                                                                                                                                                                                |
| Statistical methods                                       | 27a | Statistical methods used to compare groups for primary and secondary outcomes, including harms                                                                                                                                                                                                                                                                                         | Page 10 (Statistical analysis of endpoints described)                                                                                                                                                                                                                                                                                                                  |
|                                                           | 27b | Definition of who will be included in each analysis (e.g., all randomized participants), and in which group                                                                                                                                                                                                                                                                            | Page 10 (Statistical analysis of endpoints described)                                                                                                                                                                                                                                                                                                                  |
|                                                           | 27c | How missing data will be handled in the analysis                                                                                                                                                                                                                                                                                                                                       | Page 10 (Handling of missing data described)                                                                                                                                                                                                                                                                                                                           |

|                               |     |                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                 |
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|                               | 27d | Methods for any additional analyses (e.g., subgroup and sensitivity analyses)                                                                                                                                                                                                                                                                  | Page 10 (Described in Section 'Statistical analysis')                                                                           |
| <b>Methods: Monitoring</b>    |     |                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                 |
| Data monitoring committee     | 28a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and funder; conflicts of interest 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 | Page 15 (DMC described)                                                                                                         |
|                               | 28b | Explanation 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                                                                                                                                                                        | Pages 5 and 15 (Interim report after 12 months)                                                                                 |
| Trial monitoring              | 29  | Frequency and procedures for monitoring trial conduct. If there is no monitoring, give explanation                                                                                                                                                                                                                                             | Page 15 (Monitoring described)                                                                                                  |
| <b>Ethics</b>                 |     |                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                 |
| Research ethics approval      | 30  | Plans for seeking research ethics committee/institutional review board approval                                                                                                                                                                                                                                                                | Pages 11 and 14 (Ethics Committee of the Medical Association of Ostwestfalen-Lippe; Reference Number: 2024-057-f-S)             |
| Protocol amendments           | 31  | Plans for communicating important protocol modifications to relevant parties                                                                                                                                                                                                                                                                   | Page 11 and 14 (Protocol amendments to be submitted to DRKS and under 'DECLARATION/Ethics approval and consent to participate') |
| Consent or assent             | 32a | Who will obtain informed consent or assent from potential trial participants or authorized proxies, and how                                                                                                                                                                                                                                    | Page 11 (Informed consent by case managers)                                                                                     |
|                               | 32b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable                                                                                                                                                                                                          | Not applicable (Study does not involve biological specimens, experimental drugs, or invasive procedures)                        |
| Confidentiality               | 33  | 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 11 (Described under 'Ethical considerations')                                                                              |
| Ancillary and post-trial care | 34  | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation                                                                                                                                                                                                                  | Page 15 (Described under 'Data Monitoring Committee [DMC]')                                                                     |

\*We strongly recommend reading this checklist in conjunction with the SPIRIT 2025 Explanation and Elaboration and the SPIRIT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant SPIRIT extensions. See [www.consort-spirit.org](http://www.consort-spirit.org)

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