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SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials

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Abstract

The protocol of a clinical trial serves as the foundation for study planning, conduct, reporting, and appraisal. However, trial protocols and existing protocol guidelines vary greatly in content and quality. This article describes the systematic development and scope of SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013, a guideline for the minimum content of a clinical trial protocol.

The 33-item SPIRIT checklist applies to protocols for all clinical trials and focuses on content rather than format. The checklist recommends a full description of what is planned; it does not prescribe how to design or conduct a trial. By providing guidance for key content, the SPIRIT recommendations aim to facilitate the drafting of high-quality protocols. Adherence to SPIRIT would also enhance the transparency and completeness of trial protocols for the benefit of investigators, trial participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

The protocol of a clinical trial plays a key role in study planning, conduct, interpretation, oversight, and external review by detailing the plans from ethics approval to dissemination of results. A well-written protocol facilitates an appropriate assessment of scientific, ethical, and safety issues before a trial begins; consistency and rigor of trial conduct; and full appraisal of the conduct and results after trial completion. The importance of protocols has been emphasized by journal editors (1–6), peer reviewers (7–10), researchers (11–15), and public advocates (16).

Despite the central role of protocols, a systematic review revealed that existing guidelines for protocol content vary greatly in their scope and recommendations, seldom describe how the guidelines were developed, and rarely cite broad stakeholder involvement or empirical evidence to support their recommendations (17). These limitations may partly explain why an opportunity exists to improve the quality of protocols. Many protocols for randomized trials do not adequately describe the primary outcomes (inadequate for 25% of trials) (18, 19), treatment allocation methods (inadequate for 54% to 79%) (20, 21), use of blinding (inadequate for 9% to 34%) (21, 22), methods for reporting adverse events (inadequate for 41%) (23), components of sample size calculations (inadequate for 4% to 40%) (21, 24), data analysis plans (inadequate for 20% to 77%) (21, 24–26), publication policies (inadequate for 7%) (27), and roles of sponsors and investigators in study design or data access (inadequate for 89% to 100%) (28, 29). The problems that underlie these protocol deficiencies may in turn lead to avoidable protocol amendments, poor trial conduct, and inadequate reporting in trial publications (15, 30).

In response to these gaps in protocol content and guidance, we launched the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) initiative in 2007. This international project aims to improve the completeness of trial protocols by producing evidence-based recommendations for a minimum set of items to be addressed in protocols. The SPIRIT 2013 Statement includes a 33-item checklist (Table 1) and diagram (Figure). An associated explanatory paper (SPIRIT 2013 Explanation and Elaboration) (31) details the rationale and supporting evidence for each checklist item, along with guidance and model examples from actual protocols.

Development of the SPIRIT 2013 Statement

The SPIRIT 2013 Statement was developed in broad consultation with 115 key stakeholders, including trial investigators ($n = 30$); health care professionals ($n = 31$); methodologists ($n = 34$); statisticians ($n = 16$); trial coordinators ($n = 14$); journal editors ($n = 15$); and representatives from the research ethics community ($n = 17$), industry and nonindustry funders ($n = 7$), and regulatory agencies ($n = 3$), whose roles are not mutually exclusive. As detailed later, the SPIRIT guideline was developed through 2 systematic reviews, a formal Delphi consensus process, 2 face-to-face consensus meetings, and pilot-testing (32).

The SPIRIT checklist evolved through several iterations. The process began with a preliminary checklist of 59 items derived from a systematic review of existing protocol guidelines (17). In 2007, 96 expert panelists from 17 low($n = 1$), middle- ($n = 6$), and high-income ($n = 10$) countries refined this initial checklist over 3 iterative Del-phi consensus survey rounds by e-mail (33). Panelists rated each item on a scale of 1 (not important) to 10 (very important), suggested new items, and provided comments that were circulated in

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subsequent rounds. Items with a median score of 8 or higher in the final round were included, whereas those rated 5 or lower were excluded. Items rated between 5 and 8 were retained for further discussion at the consensus meetings.

After the Delphi survey, 16 members of the SPIRIT Group (named as authors of this paper) met in December 2007 in Ottawa, Ontario, Canada, and 14 members met in September 2009 in Toronto, Ontario, Canada, to review the survey results, discuss controversial items, and refine the draft checklist. After each meeting, the revised checklist was recirculated to the SPIRIT Group for additional feedback.

A second systematic review identified empirical evidence about the relevance of specific protocol items to trial conduct or risk of bias. The results of this review informed the decision to include or exclude items on the SPIRIT checklist. This review also provided the evidence base of studies cited in the SPIRIT 2013 Explanation and Elaboration paper (31). Some items had little or no identified empirical evidence (for example, the title) and are included in the checklist on the basis of a strong pragmatic or ethical rationale.

Finally, we pilot-tested the draft checklist in 2010 and 2011 with University of Toronto graduate students who used the document to develop trial protocols as part of a master's-level course on clinical trial methods. Their feedback on the content, format, and usefulness of the checklist was obtained through an anonymous survey and incorporated into the final SPIRIT checklist.

Definition of a Clinical Trial Protocol

Although every study requires a protocol, the precise definition of a protocol varies among individual investigators, sponsors, and other stakeholders. For the SPIRIT initiative, the protocol is defined as a document that provides sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results.

The protocol is more than a list of items. It should be a cohesive document that provides appropriate context and narrative to fully understand the elements of the trial. For example, the description of a complex intervention may need to include training materials and figures to enable replication by persons with appropriate expertise.

The full protocol must be submitted for approval by an institutional review board (IRB) or research ethics committee (34). It is recommended that trial investigators or sponsors address the SPIRIT checklist items in the protocol before submission. If the details for certain items have not yet been finalized, then this should be stated in the protocol and the items updated as they evolve.

The protocol is a "living" document that is often modified during the trial. A transparent audit trail with dates of important changes in trial design and conduct is an essential part of the scientific record. Trial investigators and sponsors are expected to adhere to the protocol as approved by the IRB and to document amendments made in the most recent protocol version. Important protocol amendments should be reported to IRBs and trial registries as they occur and subsequently be described in trial reports.

Scope of the SPIRIT 2013 Statement

The SPIRIT 2013 Statement applies to the content of a clinical trial protocol, including its appendices. A clinical trial is a prospective study in which 1 or more interventions are assigned to human participants to assess the effects on health-related outcomes. The primary scope of SPIRIT 2013 relates to randomized trials, but the same considerations substantially apply to all types of clinical trials, regardless of study design, intervention, or topic.

The SPIRIT 2013 Statement provides guidance for minimum protocol content. Certain circumstances may warrant additional protocol items. For example, a factorial study design may require specific justification; crossover trials have unique statistical considerations, such as carryover effects; and industry-sponsored trials may have additional regulatory requirements.

The protocol and its appendices are often the sole repository of detailed information relevant to every SPIRIT checklist item. Using existing trial protocols, we have been able to identify model examples of every item (31), which illustrates the feasibility of addressing all checklist items in a single protocol document. For some trials, relevant details may appear in related documents, such as statistical analysis plans, case record forms, operations manuals, or investigator contracts (35, 36). In these instances, the protocol should outline the key principles and refer to the separate documents so that their existence is known.

The SPIRIT 2013 Statement primarily relates to the content of the protocol rather than its format, which is often subject to local regulations, traditions, or standard operating procedures. Nevertheless, adherence to certain formatting conventions, such as a table of contents; section headings; glossary; list of abbreviations; list of references; and a schematic schedule of enrollment, interventions, and assessments, will facilitate protocol review (Figure).

Finally, the intent of SPIRIT 2013 is to promote transparency and a full description of what is planned—not to prescribe how a trial should be designed or conducted. The checklist should not be used to judge trial quality, because the protocol of a poorly designed trial may address all checklist items by fully describing its inadequate design features. Nevertheless, the use of SPIRIT 2013 may improve the validity and success of trials by reminding investigators about important issues to consider during the planning stages.

Relation to Existing Clinical Trial Guidance

With its systematic development process, consultation with international stakeholders, and explanatory paper citing relevant empirical evidence (31), SPIRIT 2013 builds on other international guidance applicable to clinical trial protocols. It adheres to the ethical principles mandated by the 2008 Declaration of Helsinki, particularly the requirement that the protocol address specific ethical considerations, such as competing interests (34).

In addition, SPIRIT 2013 encompasses the protocol items recommended by the International Conference on Harmonisation Good Clinical Practice E6 guidance, written in 1996 for clinical trials whose data are intended for submission to regulatory authorities (37). The SPIRIT Statement builds on the Good Clinical Practice guidance by providing additional recommendations on specific key protocol items (for example, allocation concealment, trial registration, and consent processes). In contrast to SPIRIT, the Good Clinical Practice guidance used informal consensus methods, has unclear contributorship, and lacks citation of supporting empirical evidence (38).

The SPIRIT 2013 Statement also supports trial registration requirements from the World Health Organization (39), the International Committee of Medical Journal Editors (40), legislation pertaining to ClinicalTrials.gov (41), the European Commission (42), and others. For example, item 2b of the SPIRIT checklist recommends that the protocol list the World Health Organization Trial Registration Data Set (Appendix Table, available at www.annals.org), which is the minimum amount of information that the International Committee of Medical Journal Editors mandates for trial registries. Having this data set in its own protocol section is intended not only to serve as a form of trial summary but also to help improve the quality of information in registry entries. Registration-specific data could be easily identified in the protocol section and copied into the registry fields. In addition, protocol amendments applicable to this section could prompt investigators to update their registry data.

The SPIRIT 2013 Statement mirrors applicable items from CONSORT 2010 (Consolidated Standards of Reporting Trials) (43). Consistent wording and structure used for items common to both checklists will facilitate the transition from a SPIRIT-based protocol to a final report based on CONSORT. The SPIRIT Group has also engaged leaders of other initiatives relevant to protocol standards, such as trial registries, the Clinical Data Interchange Standards Consortium Protocol Representation Group, and Pragmatic Randomized Controlled Trials in Health-Care, to align international efforts in promoting transparency and high-quality protocol content.

Potential Effect

An extensive range of stakeholders could benefit from widespread use of the SPIRIT 2013 Statement and its explanatory paper (Table 2). Pilot-testing and informal feedback have shown that it is particularly valuable for trial investigators when they draft their protocols. It can also serve as an informational resource for new investigators, peer reviewers, and IRB members.

There is also potential benefit for trial implementation. The excessive delay from the time of protocol development to ethics approval and the start of participant recruitment remains a major concern for clinical trials (44). Improved completeness of protocols could help increase the efficiency of protocol review by reducing avoidable queries to investigators about incomplete or unclear information. With full documentation of key information and increased awareness of important considerations before the trial begins, the use of SPIRIT may also help to reduce the number and burden of subsequent protocol amendments—many

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of which can be avoided with careful protocol drafting and development (15). Widespread adoption of SPIRIT 2013 as a single standard by IRBs, funding agencies, regulatory agencies, and journals could simplify the work of trial investigators and sponsors, who could fulfill the common application requirements of multiple stakeholders with a single SPIRIT-based protocol. Better protocols would also help trial personnel to implement the study as the protocol authors intended.

Furthermore, adherence to SPIRIT 2013 could help ensure that protocols contain the requisite information for critical appraisal and trial interpretation. High-quality protocols can provide important information about trial methods and conduct that is not available from journals or trial registries (45–47). As a transparent record of the researchers' original intent, comparisons of protocols with final trial reports can help to identify selective reporting of results and undisclosed amendments (48), such as changes to primary outcomes (19, 49). However, clinical trial protocols are not generally accessible to the public (45). The SPIRIT 2013 Statement will have a greater effect when protocols are publicly available to facilitate full evaluation of trial validity and applicability (11, 12, 14, 50).

The SPIRIT 2013 guideline needs the support of key stakeholders to achieve its greatest impact (Table 2), as seen with widely adopted reporting guidelines, such as CONSORT (51). We will post the names of organizations that have endorsed SPIRIT 2013 on the SPIRIT Web site (www.spirit-statement.org) and provide resources to facilitate implementation. Widespread adoption of the SPIRIT recommendations can help improve protocol drafting, content, and implementation; facilitate registration, efficiency, and appraisal of trials; and ultimately enhance transparency for the benefit of patient care.

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	Study Period							
	Enrollment	Allocation	Postallocation					Closeout
Time point*	$-t_1$	0	t_1	t_2	t_3	t_4	etc.	t_x
Enrollment:								
Eligibility screen	X							
Informed consent	X							
[List other procedures]	X							
Allocation		X						
Interventions:								
[Intervention A]								
[Intervention B]			X		X			
[List other study groups]								
Assessments:								
[List baseline variables]	X	X						
[List outcome variables]				X		X	etc.	X
[List other data variables]			X	X	X	X	etc.	X

Recommended content can be displayed using various schematic formats. See SPIRIT 2013 Explanation and Elaboration (31) for examples. This template is copyrighted by the SPIRIT Group and is reproduced with permission. SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

* List specific time points in this row.

Figure.

Example template of recommended content for the schedule of enrollment, interventions, and assessments.

Table 1

SPIRIT 2013 Checklist: Recommended Items to Address in a Clinical Trial Protocol and Related Documents*

Section/Item	Item Number	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry.
	2b	All items from the World Health Organization Trial Registration Data Set (Appendix Table, available at www.annals.org)
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	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
	5d	Composition, roles, and responsibilities of the coordinating center, steering committee, end point adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see item 21a for DMC)
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
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design, including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)
Methods		
Participants, interventions, and outcomes		
Study setting	9	Description of study settings (e.g., community clinic, academic hospital) and list of countries 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 centers and individuals who will perform the interventions (e.g., surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

Section/Item	Item Number	Description
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other 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. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrollment, interventions (including any runins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (Figure).
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
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size
Assignment of interventions (for controlled trials)		
Allocation Sequence generation	16a	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, 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.
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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 (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., 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.
	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
Data management	19	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 found, if not in the protocol.
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol.
	20b	Methods for any additional analyses (e.g., subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol nonadherence (e.g., as-randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)

Section/Item	Item Number	Description
Monitoring		
Data monitoring	21a	Composition of 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.
	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
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor
Ethics and dissemination		
Research ethics approval	24	Plans for seeking REC/IRB approval
Protocol amendments	25	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, RECs/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if 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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial data set, and disclosure of contractual agreements that limit such access for investigators
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
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (e.g., 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
	31c	Plans, if any, for granting public access to the full protocol, participant-level data set, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized 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

DMC = data monitoring committee; IRB = institutional review board; REC = research ethics committee; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

[*] It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation and Elaboration (31) for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group and is reproduced with permission.

Table 2

Potential Benefits and Proposed Stakeholder Actions for Supporting Adherence to SPIRIT 2013

Stakeholder	Proposed Actions	Potential Benefits
Clinical trial groups, investigators, sponsors	Adopt SPIRIT as standard guidance Use as tool for writing protocols	Improved quality, completeness, and consistency of protocol content Enhanced understanding of rationale and issues to consider for key protocol items Increased efficiency of protocol review
Research ethics committees/ institutional review boards, funding agencies, regulatory agencies	Mandate or encourage adherence to SPIRIT for submitted protocols Use as training tool	Improved quality, completeness, and consistency of protocol submissions Increased efficiency of review and reduction in queries about protocol requirements
Educators	Use SPIRIT checklist and explanatory paper as a training tool	Enhanced understanding of the rationale and issues to consider for key protocol items
Patients, trial participants, policymakers	Advocate use of SPIRIT by trial investigators and sponsors	Improved protocol content relevant to transparency, accountability, critical appraisal, and oversight
Trial registries	Encourage SPIRIT-based protocols Register full protocols to accompany results disclosure	Improved quality of registry records Prompt for trialists to update registry record when SPIRIT checklist item 2b (Registration Data Set) is updated Improved quality, completeness, and consistency of protocol content for registries that house full protocols and results
Journal editors and publishers	Endorse SPIRIT as standard guidance for published and unpublished protocols Include reference to SPIRIT in instructions for authors Ask that protocols be submitted with manuscripts, circulate them to peer reviewers, and encourage authors to make them available as Web appendices	Improved quality, completeness, and consistency of protocol content Enhanced peer review of trial manuscripts through improved protocol content, which can be used to assess protocol adherence and selective reporting Improved transparency and interpretation of trials by readers

SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

Appendix Table

World Health Organization Trial Registration Data Set*

Item	Description
1. Primary registry and trial-identifying number	Name of primary registry and the unique identifier assigned by the primary registry
2. Date of registration in primary registry	Date when the trial was officially registered in the primary registry
3. Secondary identifying numbers	Other identifiers, if any Universal Trial Number Identifiers assigned by the sponsor Other trial registration numbers issued by other registries Identifiers issued by funding bodies, collaborative research groups, regulatory authorities, ethics committees/institutional review boards, etc.
4. Sources of monetary or material support	Major sources of monetary or material support for the trial (e.g., funding agency, foundation, company, institution)
5. Primary sponsor	Person, organization, group, or other legal entity that takes responsibility for initiating and managing a study
6. Secondary sponsor(s)	Additional persons, organizations, or other legal persons, if any, who have agreed with the primary sponsor to take on responsibilities of sponsorship
7. Contact for public queries	E-mail address, telephone number, and postal address of the contact who will respond to general queries, including information about current recruitment status
8. Contact for scientific queries	Name and title, e-mail address, telephone number, postal address, and affiliation of the principal investigator and e-mail address, telephone number, postal address, and affiliation of the contact for scientific queries about the trial (if applicable)
9. Public title	Title intended for the lay public in easily understood language
10. Scientific title	Scientific title of the study as it appears in the protocol submitted for funding and ethical review; include trial acronym, if available
11. Countries of recruitment	Countries from which participants will be recruited
12. Health condition(s) or problem(s) studied	Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error)
13. Intervention(s)	For each group of the trial, record a brief intervention name plus an intervention description Intervention name: For drugs, use the generic name; for other types of interventions, provide a brief descriptive name Intervention description: Must be sufficiently detailed for it to be possible to distinguish between the groups of a study; for example, interventions involving drugs may include dosage form, dosage, frequency, and duration
14. Key inclusion and exclusion criteria	Inclusion and exclusion criteria for participant selection, including age and sex
15. Study type	Method of allocation (randomized/nonrandomized) Blinding/masking (identify who is blinded) Assignment (e.g., single group, parallel, crossover, factorial) Purpose Phase (if applicable) For randomized trials: Method of sequence generation and allocation concealment
16. Date of first enrollment	Anticipated or actual date of enrollment of the first participant
17. Target sample size	Total number of participants to enroll
18. Recruitment status	Pending: Participants are not yet being recruited or enrolled at any site Recruiting Suspended: Temporary halt in recruitment and enrollment Complete: Participants are no longer being recruited or enrolled Other

Item	Description
19. Primary outcome(s)	The primary outcome should be the outcome used in sample size calculations or the main outcome used to determine the effects of the intervention For each primary outcome provide: Name of the outcome (do not use abbreviations) Metric or method of measurement used (be as specific as possible) Time point of primary interest
20. Key secondary outcome(s)	As for primary outcomes, for each secondary outcome provide: Name of the outcome (do not use abbreviations) Metric or method of measurement used (be as specific as possible) Time point of interest

*Adapted from www.who.int/ictrp/network/trds/en/index.html.