ANNEXURE 2

PROTOCOL TEMPLATE FOR TRIALS/INTERVENTIONAL STUDIES

1. Title

SPIRIT guidance: Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym.

2.Names protocol contributors

Names of protocol contributors.

3.Summary

The summary should not exceed 500 words. Please minimize the use of abbreviations and do not cite references in the abstract. The abstract must include the following separate sections:

- **Background**: the context and purpose of the study
- **Methods**: how the study will be performed
- **Discussion**: a brief summary and potential implications
- **Trial registration**: If your article reports the results of a health care intervention on human participants, it must be registered in an appropriate registry and the registration number and date of registration should be in stated in this section. If it was not registered prospectively (before enrollment of the first participant), you should include the words 'retrospectively registered'. See our editorial policies for more information on trial registration.

4. Administrative information

Trial registration	SPIRIT guidance: Trial identifier and registry name. If not yet registered, name of intended registry.
Funding	SPIRIT guidance: Sources and types of financial, material, and other support.
Author details	SPIRIT guidance: Affiliations of protocol contributors.

Name and contact information for the trial sponsor	SPIRIT guidance: Name and contact information for the trial sponsor.
Role of sponsor	SPIRIT guidance: 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.

5. Introduction

Background and rationale

SPIRIT guidance: 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of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention.

6.Objectives

SPIRIT guidance: Specific objectives or hypotheses.

7.Methods: Participants, interventions and outcomes

Trial design

SPIRIT guidance: Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory).

Study setting

SPIRIT guidance: 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.

Eligibility criteria

SPIRIT guidance: Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists).

Who will take informed consent?

SPIRIT guidance: Who will obtain informed consent or assent from potential trial

participants or authorised surrogates, and how (see Item 32).

Additional consent provisions for collection and use of participant data and biological specimens

SPIRIT guidance: Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable.

8.Interventions

Explanation for the choice of comparators

SPIRIT guidance: Explanation for choice of comparators.

Intervention description

SPIRIT guidance: Interventions for each group with sufficient detail to allow replication, including how and when they will be administered.

Criteria for discontinuing or modifying allocated interventions

SPIRIT guidance: 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).

Strategies to improve adherence to interventions

SPIRIT guidance: Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests).

Relevant concomitant care permitted or prohibited during the trial

SPIRIT guidance: Relevant concomitant care and interventions that are permitted or prohibited during the trial.

Provisions for post-trial care

SPIRIT guidance: Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation.

Outcomes

SPIRIT guidance: 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.

Participant timeline

SPIRIT guidance: Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly

recommended (see figure at http://www.spirit-statement.org/publications-downloads/).

Sample size

SPIRIT guidance: 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

SPIRIT guidance: Strategies for achieving adequate participant enrolment to reach target sample size.

9.Assignment of interventions: allocation

Sequence generation

SPIRIT guidance: 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.

Concealment mechanism

SPIRIT guidance: 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.

Implementation

SPIRIT guidance: Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions.

10.Assignment of interventions: Blinding

Who will be blinded

SPIRIT guidance: Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how.

Procedure for unblinding if needed

SPIRIT guidance: If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial.

11.Data collection and management

Plans for assessment and collection of outcomes

SPIRIT guidance: 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.

Plans to promote participant retention and complete follow-up

SPIRIT guidance: 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

SPIRIT guidance: 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.

Confidentiality

SPIRIT guidance: 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.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

SPIRIT guidance: 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.

12.Statistical methods

Statistical methods for primary and secondary outcomes

SPIRIT guidance: 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.

Interim analyses

SPIRIT guidance: 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.

Methods for additional analyses (e.g. subgroup analyses)

SPIRIT guidance: Methods for any additional analyses (eg, subgroup and adjusted analyses).

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

SPIRIT guidance: Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation).

Plans to give access to the full protocol, participant level-data and statistical code

SPIRIT guidance: Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code.

13.Oversight and monitoring

Composition of the coordinating centre and trial steering committee

SPIRIT guidance: 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).

Composition of the data monitoring committee, its role and reporting structure

SPIRIT guidance: 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.

Adverse event reporting and harms

SPIRIT guidance: Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct.

Frequency and plans for auditing trial conduct

SPIRIT guidance: Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

SPIRIT guidance: 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).

14.Dissemination plans

SPIRIT guidance: 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.

15.Discussion

This should include a discussion of any practical or operational issues involved in performing the study and any issues not covered in other sections.

16.Declarations

All manuscripts must contain the following subheadings:

- Acknowledgements
- Authors' contributions
- Funding
- Availability of data and material
- Ethics approval and consent to participate
- Consent for publication
- Competing interests
- Authors’ information (optional)
- List of abbreviations

Acknowledgements

Please acknowledge anyone who contributed towards the article who does not meet the criteria for authorship including anyone who provided professional writing services or materials. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements section.

Authors’ contributions

Please use initials to refer to each author's contribution in this section, for example: "AB is the Chief Investigator; she conceived the study, led the proposal and protocol development. CD contributed to study design and to development of the proposal. EF was the lead trial

methodologist. All authors read and approved the final manuscript."

Funding

SPIRIT guidance: Sources and types of financial, material, and other support.

Availability of data and materials

SPIRIT guidance: Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators.

Ethics approval and consent to participate

SPIRIT guidance: Plans for seeking research ethics committee/institutional review board (REC/IRB) approval.

Consent for publication

SPIRIT guidance: Model consent form and other related documentation given to participants and authorised surrogates.

Competing interests

SPIRIT guidance: Financial and other competing interests for principal investigators for the overall trial and each study site.

17.References

Vancouver reference style