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Research Ethics Board Standard Operating Procedures

The Use of SPIRIT Guidelines In Clinical Trial Protocol Development

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APPROVED BY	Vice President, Research		

The WCH REO webpage version of this document is considered the most current.

Please ensure that you have reviewed all linked documents and other reference material within this SOP

1.0 POLICY STATEMENT:

The Purpose of this Standard Operating Procedure (SOP) is to provide Principal Investigators with guidance for developing clinical trial protocols based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement. SPIRIT provides recommendations for a minimum set of scientific, ethical, and administrative elements that should be addressed in a clinical trial protocol.

The objective of this SOP is to ensure that clinical trials are conducted at WCH in a manner that meets ethical standards while implementing robust scientific elements based on a high-quality protocol. Through evidence-based recommendations, the SPIRIT guidance facilitates the discussion and addressing of important issues when creating a clinical trial protocol. This is achieved by following the guidelines to ensure that all aspects of a complete research protocol (including administrative information, introduction, methods, data collection and management, research ethics, and dissemination) are addressed and articulated.

2.0 DEFINITION(S):

See Glossary of Terms.

3.0 RESPONSIBILITY:

The responsibility of this SOP applies to the Principal Investigator tasked with creating the clinical trial protocol. In circumstances where the Principal Investigator is not an author of the protocol (e.g., industry sponsor-initiated trials), the investigator should encourage all research team members involved in authoring the protocol to adhere to the SPIRIT guidelines. It is also the responsibility of the research staff (e.g., co-investigators, research staff and trainees) to ensure that the clinical trial protocol is correctly executed. It is strongly recommended that the Principal Investigator follow the SPIRIT guidelines using the SPIRIT checklist (refer to Appendix A) and explanatory paper (Chan A-W et al, BMJ 2013) in order to improve protocol completeness and reduce the possibility of any delays in the initial research ethics board review and approval process.

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4.0 PROCEDURES:

When creating a clinical trial protocol, principal investigators and protocol authors are encouraged to consult the full SPIRIT Statement and explanatory paper, which can be downloaded from this link: http://www.spirit-statement.org/publications-downloads/.

4.1 Administrative Details

For a description of the administrative details that should be included in a clinical trial protocol, please refer to the most current version of the SPIRIT checklist at www.spirit-statement.org.

4.2 Clinical Trial Introduction

The introduction should be a summary of how the clinical trial will be conducted. Included must be a well-written background and rationale examining the harms and benefits of carrying out the study protocol. The introduction should also clearly describe the research question and articulate the justification for undertaking of the trial in the discussion of the hypothesis and objectives of the intervention/trial.

4.3 Methods

4.3.1 Trial Participants and Implementing Interventions

- Clear description outlining the process of involvement with the participants, intervention implementation, and expected outcomes.
- For study location, indication of: where data will be collected or list of study sites if a multi-site clinical trial is being conducted
- For involvement with participants, indication of: eligibility criteria, description of targeted population and rationale, estimated sample size number, recruitment process to reach target sample size
- For intervention implementation, indication of: individual(s) administering intervention, criteria to continue or eliminate a participant during intervention, procedures in monitoring adherence to said intervention, and any deviation of intervention protocol by participants
- For outcomes, explanation of all outcomes (primary, secondary, etc.) and relevant significance to clinical trial, benefits or harms discovered during trial, etc.

4.3.2 Assigning interventions in Controlled Trials

- Assigning allocation sequence: indicate the method and outline any restrictions or blocking that might serve to reduce the possibility of a random sequence

- Creating an allocation sequence: describing a clear process of how the allocation sequence was implemented and measures taken to ensure that the allocation sequence will be hidden from research staff
- Implementing allocation sequence: describing who will create the allocation sequence, who will enroll the participants and assign them to the trial interventions
- For blinding studies, indication of: the acceptable conditions to “breaking-the-blind”, the process in revealing the intervention associated with a specific participant during the trial, and the individuals from the research staff who will be blinded

4.3.3 Data Collection and Analysis

- For data collection, indication of: plans for data collection and assessment of baseline and trial data, a complete description of study instruments to be used with their reliability and validity status, any plans involved in data analysis for participants who experiences deviations from the outlined trial intervention
- The explanation of data entry, data coding procedures for data quality and how the data will be securely stored
- For data analysis, indication of: methods for statistical and other data analysis of primary and secondary outcomes with a protocol of analyzing protocol to handle incomplete data

4.3.4 Monitoring

- Create a plan outlining who and how the data collected during the study will be monitored, by providing a detailed description on the structure of a Data Monitoring Committee, or explain why one is not needed
- Indicating a plan to manage and report adverse events (AEs), serious adverse events (SAEs), or serious unexpected serious adverse reactions (SUSARs) during the course of the trial to the study sponsor and REB
- Plans for trial monitoring/auditing and specific details on who will be conducting the monitoring/auditing (ie. independent clinical monitor) and frequency of the monitoring/auditing process

4.4 Research Ethics

- Indication of a plan to: obtain Research Ethics Board (REB) approval(s), and submit clinical trial amendments and study personnel change applications

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- Ensuring that consenting participants have not been influenced or forced to participate in a clinical trial against their free-will, and that a copy of the consent form will be given to the participant and authorized proxies
- Ensuring that privacy and confidentiality policies are followed and listing conflicts of interests
- Indication of a plan of care or compensation to participants who have suffered any AEs during the trial and reimbursement plan for expenses directly related to participating in the trial (ie. parking, child care, loss of employment income)
- Listing who will have access to the final dataset and any procedures in place to limit access to unauthorized personnel
- Including a plan outlining methods for the collection, lab evaluation, and storage of biological specimens

4.5 Dissemination

- Creating of a plan for the sponsor and investigator to share any trial information with the public through publications, conferences, or other venues

4.6 Consent Forms and Other Documentation Given To Participants

- Ensuring that there is REB approval for all participant-facing documentation including: informed consent forms, surveys, questionnaires, interview scripts, focus group guides, etc.
- Ensuring that only the most recent version and dated approved REB forms and documents are used during the study

5.0 REFERENCES:

1. Chan, A.-W., Tetzlaff, J. M., Altman, D. G., Laupacis, A., Gotzsche, P. C., Kreza-Jeric, K., . . . Moher, D. (2013, January 8). SPIRIT 2013 Statement: Defining Standard Protocol Items for Clinical Trials. *Annals of Internal Medicine*, 200-207.
2. Chan, A.-W., Tetzlaff, J. M., Gotzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., . . . Moher, D. (2013, January 9). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *British Medical Journal*, 346.
3. SPIRIT. (2013). *Publications & downloads*. Retrieved from The SPIRIT Statement: http://www.spirit-statement.org/publications-downloads/
4. SPIRIT. (2013). *SPIRIT 2013 Checklist.* Retrieved from The SPIRIT Statement: http://www.spirit-statement.org/publications-downloads/
5. SPIRIT. (2013). *The SPIRIT Statement*. Retrieved from SPIRIT Statement website: http://www.spirit-statement.org/spirit-statement/

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

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No.	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
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
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 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)
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 (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

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
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)
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 (eg, 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 (eg, drug tablet return, laboratory tests)
	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 (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	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)

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 enrolment to reach target sample size

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
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, 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

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
	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 (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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
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
	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 research ethics committee/institutional review board (REC/IRB) approval
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)

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised 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 dataset, 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, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*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.