



Protocol Development
209-00

1. Purpose

The purpose of this SOP is to guide authors on the content requirements when developing clinical trial protocols.

2. Responsibilities

Principal Investigator / Sponsor: The Principal Investigator / Sponsor is responsible for writing and developing a protocol that adheres to scientific standards and methodology.

3. Procedures

- 3.1 A study protocol is “a document that describes the objectives, design, methodology, statistical considerations, and organization of a trial.” ICH GCP 1.44.
- 3.2 Each study protocol should be written based on current scientific and methodological expertise and in accordance with the current principles of the ICH/GCP guidelines.
- 3.3 Protocol development involves the following steps:
 - 3.3.1 Systematic review of literature
 - 3.3.2 Establishment of a team of investigators (both local and external)
 - 3.3.3 Assignment of areas of responsibility
 - 3.3.4 Drafting and circulation of protocol for:
 - 3.3.4.1 Internal review
 - 3.3.4.2 External review
 - 3.3.5 Protocol finalization
 - 3.3.6 Piloting, if applicable, and corresponding updates
 - 3.3.7 Evaluation for feasibility
 - 3.3.8 Circulate protocols
- 3.4 Study protocols may be developed for randomized controlled trials (RCTs) and non-randomized controlled trials (non-RCTs).
- 3.5 Protocol content may vary depending on the objectives and methodology of the study (e.g. RCT vs. non-RCT).
- 3.6 Refer to Appendix 5.1 for a protocol template with annotations.

4. References

- 4.1 Friedman LM, Furberg CD and DeMets DL. Fundamentals of Clinical Trials Third Edition. Need to get proper reference info...

5. Appendix

- 5.1 Protocol Template

FULL PROTOCOL TITLE

(If not apparent from the protocol title, consider adding a subtitle that summarizes the trial)

Study Chair / Principal Investigator / Sponsor

(List Study Chair's name, degree, position and affiliation)

Supported by:

(List funding agencies, include application or grant numbers when available)

Study Intervention Provided by:

(Name of pharmaceutical company, if any, providing support)

Sponsor of IND / Trial Registry Number:

(If applicable, IND holder, including IND number, Trial registry number)

(Any modification to the protocol should be annotated on the coversheet or in an appendix. The annotation should note the exact words that are changed, the location in the protocol, the date the modification was approved by the Executive Committee, and the date it became effective.)

Version

Date

TABLE OF CONTENTS

Study Summary

Rationale for Trial

- Problem
- Study Question/Objectives
- Systematic Reviews of Literature and Scientific Rationale for the Intervention
- How Will the Results be Used
- Risks to the Safety of Participants Involved in the Trial

Trial Design

- Trial Design
- Trial Interventions (Criteria for Discontinuation)
- Selection and Enrolment of Participants
- Allocation of Participants to Treatment Groups
- Schedule of Evaluations

Statistical Considerations

- General Design Issues
- Primary and Secondary Outcome Measures
- Sample Size and Accrual
- Number of Clinical Sites Participating in the Trial
- Type and Frequency of Planned Subgroup Analyses

Data Collection, Site Monitoring, and Adverse Event Reporting

- Data Collection
- Site Monitoring
- Adverse Event Reporting

Trial Management

- Day-to-day management of the trial
- Principal Investigator & Co-Investigators
- Trial Committees

Publication of Research Findings

Appendices

STUDY SUMMARY

The following page should provide a brief outline of the study.

Study Title

Specify the full title of the study.

Objectives

Specify the primary and secondary objectives.

Design and Outcomes

Provide a very brief description of the study design (e.g. multicentre, randomized, double-blinded, Phase II), including the outcome variables for the primary and secondary objectives.

Interventions and Duration

Briefly describe the interventions to be compared. Indicate the total length of time each subject will be on study (intervention period + additional follow-up off intervention, as applicable).

A brief statement about the schedule and type of evaluations to be performed during the study may also be included.

Sample Size and Population

Briefly describe the number and type (patient population) of subjects to be studied.

If the randomization will be stratified, list the stratification factors. If there will be separate objectives and outcome variables for the strata, list these in the appropriate sections.

RATIONALE FOR THE TRIAL

Problem

Spell out the need, relevance and priority for the study.

Study Question / Objectives

Primary Question / Objective

State the hypothesis in quantifiable terms. For statistical purposes, it may be worthwhile to state both the null and the alternative hypotheses. This primary objective must match the one used in the Statistical Design section.

Secondary Question / Objectives

Secondary objectives may or may not be hypothesis driven, may include secondary outcomes, and may include more general non-experimental objectives.

Systematic Reviews of Literature and Scientific Rationale for the Intervention

Provide the scientific and medical data that justifies the study, its design, and the intervention groups. If applicable, include any pilot data.

Summarize known and potential risks of the interventions. Name and describe the intervention regimens, and justify why these particular interventions have been chosen. Describe and justify the route of administration, dosage regimen, intervention period, etc...

How Will the Results Be Used?

Describe the utility of the study results.

Risks to the Safety of Participants Involved in the Trial

Discuss the known risks to study participants based on current literature.

TRIAL DESIGN

Trial Design

Briefly describe the study design and indicate, in general terms, how the design will fulfill the intent of the study. Use diagrams to explain design complexities.

Trial Interventions

Indicate each study intervention, including how it is administered and the schedule, as well as potential side effects. Indicate where the subject will be treated (e.g. intensive care unit). State guidelines for use of appropriate supportive care medications or treatments (e.g. weaning protocols). Describe the criteria to be used for discontinuation of the trial intervention.

Note mechanisms (if any) for blinding study interventions.

Allocation of Participants to Treatment Groups

Describe procedures for allocating trial participants to treatment intervention (e.g. randomization). Include any procedures used to protect against sources of bias.

Selection and Enrolment of Participants

Inclusion Criteria

- *The disease or disorder under study, and how it is to be documented, i.e. diagnostic methods, criteria for classification, etc...*
- *Clinical indicators of current status*
- *Prior therapy, if any. Consider listing specific prior treatments. Consider listing the allowable duration prior therapy for the specific population to be studied (e.g. treatment-naïve, treatment-experienced, or prior-treatment-failed subject).*
- *Demographic characteristics (e.g. gender, age) as applicable*

Exclusion Criteria

- *List specific clinical contraindications. Specify grades of signs/symptoms.*
- *Clinical/laboratory indicators of current status. List specific tests to be performed and the narrowest acceptable range of laboratory values for exclusion, consistent with safety.*
- *Use of (excluded drugs, devices) within XX days prior to study entry.*
- *For drug studies: Allergy/sensitivity to study drugs or their formulations.*
- *Specify any clinical (e.g. life expectancy, co-existing disease), demographic (e.g. age) or other characteristic that precludes appropriate diagnosis, treatment or follow-up in the trial.*
- *Inability or unwillingness of subject or legal guardian/representative to give written informed consent.*

Schedule of Evaluations

The Schedule of Evaluations should include all study evaluations. The schedule should be followed with definitions for the evaluations, provide timelines, and include special considerations or instructions for evaluations.

<i>Evaluation</i>	<i>Enrolment</i>	<i>D1</i>	<i>D2</i>	<i>D3</i>	<i>D4</i>	<i>Follow-up</i>
<i>Informed Consent</i>	X					
<i>Randomization</i>	X					
<i>Clinical Assessments</i>		X	X	X	X	X
<i>Labs</i>		X		X		X
<i>Study Intervention</i>		X	X	X	X	

STATISTICAL CONSIDERATIONS

General Design Issues

Describe general design issues including:

- *Primary and secondary hypotheses and how they relate to choice of primary and secondary outcome measures;*
- *The validity and reliability of the primary and secondary outcome measure;*
- *Whether the documentation of an outcome will be reviewed and adjudicated by a committee, how quickly the committee will perform the adjudication, and whether the committee will be blinded to the subject's intervention group assignment;*
- *Choice of study design*
- *Details of why certain design features were chosen*
- *What factors will be used to stratify the randomization, if applicable*

Primary and Secondary Outcome Measures

List the statistical methods to be used to analyze the primary and secondary outcomes. Specify confounding variables for which it is anticipated adjustment will be made. Specify whether an intention-to-treat analysis will be performed, and explain how missing data, outliers, noncompliance and losses to follow-up will be handled in the analyses.

Sample Size and Accrual

Describe the statistical and clinical bases for the sample size calculation. State the assumptions made regarding accrual rate, event rate, noncompliance rate, loss to follow-up rate, etc...

Describe the plan for compensating for failures in these assumptions. Also describe what the power will be for assessing secondary outcomes.

If the randomization will be stratified, indicate whether there is a sample size goal for each stratum.

Number of Clinical Sites Participating in the Trial

Discuss the number of participating sites based on the planned recruitment rate.

Attach a list of participating sites in the appendix.

Type of Frequency of Planned Subgroup Analyses

Outline plans for any subgroup analyses.

DATA COLLECTION, SITE MONITORING, AND ADVERSE EVENT REPORTING

Data Collection

Site Monitoring

Briefly describe methods for assuring protocol compliance, ethical standards, regulatory compliance and data quality at the clinical sites, including review of records, consent forms, etc

Adverse Event Reporting

Indicate how adverse events are to be recorded and reported, and within what timeframe. Detailed definitions of adverse events, a table for grading their severity, and details of how clinical sites are to report them, may appear in a separate Implementation manual, which may be referred to here.

Include:

- *A list of expected adverse events for each study intervention*
- *Criteria for subject management and modification of the study intervention regimen*
- *Procedures for modification (forms, additional labs, and change regimen)*
- *List alphabetically by adverse event*

TRIAL MANAGEMENT

Day to Day Management of the Trial

Describe CERU and the services provided, including electronic data capture, if applicable.

Attach a list of contacts in the appendix.

Principal Investigator & Co-Investigators
Roles of PI and co-Investigators.

Trial Committees

Outline the different trial committees (e.g. executive committee, DMC), their purpose, membership and any guidelines or procedures.

PUBLICATION OF RESEARCH FINDINGS

Describe the how results will be published and any rules associated with publication

REFERENCES

List references here.

APPENDICES

A: CLINICAL SITES PARTICIPATING IN THE STUDY

List the name and address of each participating clinical site investigator, including telephone and fax numbers and email address.

B: METHODS CENTRE CONTACTS

List individuals who play a key roles in the development and execution of the study, especially those who may need to be contacted by the sites during the course of the study. Include address, telephone, fax, email address of each individual listed.

C. ETC...