Standard operating procedure title:
**Protocol Development and Amendment Procedure**

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Created by ICRIN (QM subgroup). Version XX. Date:........... Page 1 of 13
Table of contents

Glossary of terms, acronyms and abbreviations will be provided in a separate document for all SOPs
INTRODUCTION

Within the INSTITUTION, trials, studies and other research activities are identified and conducted in different ways and therefore the following tasks may be performed at different stages. Indeed, some may not be relevant to all trials or studies. If this is the case then a justification should be filed in the Trial Master File (TMF).

The SOPs in principle, apply to all research activities, whether they are trials with an Investigational Medicinal Product (IMP), randomized trials looking at optimal treatment regimens in the licenced indications, comparison of surgical or other non-drug treatment interventions or observational studies. Trial-specific working practices will provide supplemental information on the specific procedures applying to each trial.

In the case of observational studies and some randomized trials where no investigational product is being studied, the EU Directive requirements, in the main, are not applicable, however, the principles of GCP are adhered to in all INSTITUTION research activities.

A research protocol is a document that outlines the study plan for a clinical trial. The plan must be carefully designed to protect the health and safety of participants as well as answer specific research questions. A protocol describes who the participants are in a study, the schedule of events such as visits, procedures, tests medications and dosages as well as the duration of the study. While enrolled in a clinical study, the subjects will have regular visits, during which, the research staff will monitor their health and determine the safety and efficacy of their treatment.

It is recommended that the protocol template in Appendix 1 is used for clinical trials involving investigational medicinal products (IMP) and Appendix 2 contains a template for non-IMP protocols, for all other types of trials the non-applicable sections can be disregarded.

1. Purpose

A Protocol is a document that describes the objectives, design, methodology, statistical considerations, and organisation of a clinical trial. Adherence to the clinical trial protocol is confirmed in an agreement between the INSTITUTION and the investigator regarding the conduct of the clinical trial.

The purpose of this SOP is:

- To describe the development of the Trial Protocol and subsequent Amendment(s) (if applicable)

- To provide guidance with respect to local and international regulatory requirements such as the European Union (EU) Clinical Trials Directive the US Code of Federal Regulations, and and other national laws and regulations.
The International Conference on Harmonisation Good Clinical Practice (ICH GCP) details that the contents of a protocol involving an IMP should include the following topics:

1.1 General Information
   a. Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s)
   b. Name and address of the Sponsor and monitor (if other than the sponsor)
   c. Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the sponsor.
   d. Name, title, address and telephone number(s) of the sponsors medical expert for the trial
   e. Name and title of the investigator(s) who is/are responsible for conducting the trial, the addresses(es) and telephone number(s) of the trial site(s)
   f. Name, title, address and telephone number(s) of the qualified physician who is responsible for all trial-site related medical decisions
   g. Name(s) and address(es) of the clinical laboratories and other medical and/or technical department(s) and/or institution(s) involved in the trial

1.2 Background information
   a. Name and description of the investigational product(s)
   b. A summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial
   c. A summary of the known and potential risks and benefits, if any, to human subjects
   d. A description of and justification for the route of administration, dosage, dosage regimen and treatment period(s).
   e. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
   f. A description of the population to be studied.
   g. References to literature and data that are relevant to the trial, and that provide background to the trial

1.3 Trial Objectives and Purpose
   A detailed description of the objectives and purpose of the trial

1.4 Trial Design
   The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:
a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

b. A description of the type/design of the trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages

c. A description of the measures taken to minimise/avoid bias including randomisation and blinding

d. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging and labelling of the investigational product(s).

e. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any

f. A description of the stopping rules or discontinuation criteria for individual subjects, parts of the trial and the entire trial

g. Accountability procedures for the investigational product(s) including placebo(s) and comparator(s), if any

h. Maintenance of the trial treatment randomisation codes and procedures for breaking codes

i. The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of the data), and to be considered the source data

1.5 Selection and Withdrawal of Subjects

a. Subject inclusion criteria

b. Subject exclusion criteria

c. Subject withdrawal criteria (i.e. terminating IMP treatment/trial treatment and procedures specifying:
   (i) When and how to withdraw subjects from the trial/investigational product treatment
   (ii) The type and timing of data to be collected for withdrawn subjects
   (iii) Whether and how subjects are to be replaced
   (iv) The follow up for subjects withdrawn from the investigational product treatment/trial treatment

1.6 Treatment of Subjects

a. The treatment(s) to be administered, including name(s) of all the product(s) and dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including follow up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial

b. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial

c. Procedures for monitoring subject compliance
1.7 Assessment of Efficacy

a. Specification of the efficacy parameters
b. The methods and timing for assessing, recording and analysing efficacy parameters

1.8 Assessment of Safety

a. Specification of the safety parameters
b. The methods and timing for assessing, recording and analysing safety parameters
c. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses
d. The type and duration of follow up of subjects after adverse events

1.9 Statistics

a. A description of the statistical methods to be employed, including timing of any planned interim analyses(es)
b. The number of subjects planned to be enrolled. In multi-centre trials, the number of enrolled subjects projected per site should be specified. Rationale for choice of sample size including reflections on (or calculations of) the power of the trial and clinical justification.
c. The level of significance to be used.
d. Criteria for terminating the trial
e. Procedures for accounting for missing, unused and spurious data
f. Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or the final report, as appropriate)
g. The selection of subjects to be included in the analyses (e.g. all randomised subjects, all dosed subjects, all eligible subjects, evaluate-able subjects)

1.10 Direct Access to Source Data/Documents

The Sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection(s) by providing direct access to source data/documents.
1.11 Quality Control and Quality Assurance

A description of procedures to maintain quality control and quality assurance

1.12 Ethics

A description of ethical considerations relating to the trial

1.13 Data Handling and Record keeping

A description of the data management procedures

1.14 Financing and Insurance

Finance and insurance, if not addressed in a separate agreement

1.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

2. Responsibility

This SOP applies to all permanent and contracted INSTITUTION personnel and all non-INSTITUTION personnel involved in the development of Trial Protocols and Amendments for an INSTITUTION sponsored, Co-Sponsored or Joint Sponsored trials or when delegated this responsibility by a collaborator/sponsor.

Protocols prepared by the INSTITUTION will be based on a previously submitted concept sheet, or grant application and developed by the designated Principal Investigator, Trial Physician and Trial Manager in collaboration with the other operational, functional and scientific members of staff and collaborators from outside the INSTITUTION. The protocol should be reviewed and approved by the INSTITUTION Protocol Review Committee, the Trial Steering Committee (TSC) and Trial Management Team (TMT) prior to being submitted to the appropriate Competent Authority (CA) or Research Ethics Committee (REC).

If an Independent Data Monitoring Committee (IDMC) has been convened, this committee may also be given an opportunity to comment on the protocol.

In addition, if a decision is made by those developing the trial to submit the protocol to a peer review journal or to publish the protocol, comments received by those reviewers should be considered.
2.1. Trial Management Team (TMT)

The Trial Management Team (TMT) is led by the Principal Investigator (PI) who is responsible for leading all activities associated with trial management. Because management of a trial requires specialised expertise from multiple functions, the TMT is comprised of representatives from many departments. The responsibilities and membership of the TMT is described in the signature log, which the appropriate delegation of responsibilities clearly indicated.

The TMT is a group established by the Principal Investigator to manage the trial. Membership will include the Principal Investigator, Trial Statistician and Trial Manager. It may also include a Pharmacist, Research Nurse, Data Management, other investigators and members of collaborating groups who are involved in the decision making and provide trial-specific additional expertise e.g. a pharmaceutical company representative. The division of responsibilities will be prepared for each TMT and will be filed in the Trial Master File (TMF) in the INSTITUTION signature log with delegation of responsibility.

The Trial Management Team (TMT) is the operational team that undertakes the day to day management of the trial. The TMT is lead by the Principal Investigator (PI) and the Trial Manager (TM) and consists of the following members who should be represented at all meetings as required:

- Principal Investigator
- Trial Manager
- Trial Physician - if applicable
- Regulatory Affairs Manager
- Database Programmer
- Data Manager
- Biostatistician
- Trial Assistant
- Quality Manager

The TMT is responsible for providing input to the protocol/amendments related to their area of expertise and ensuring that any changes to the trial activities or other trial documents following an amendment are correctly addressed.

3. Procedures

3.1. Protocol Approval

Protocol development is coordinated by the Trial Manager (TM) with important contributions from the Principal Investigator, Trial Physician, Statistician and other relevant members of the TMT. Other necessary experts may also input to the protocol, depending on the nature of the trial.
The Trial Protocol is a document that describes the background, objective(s), rationale, design, methodology, statistical considerations, and organization of a trial and must contain all elements required by current regulatory requirements, as indicated in section 1. The format and content of the protocol are defined in the current version of the [Institution] Trial Protocol Template.

The Trial Protocol for a trial of an Investigational Medicinal Product (IMP) must also be consistent with all available sources of information including but not limited to the Investigator Brochure (IB), Core Data Sheet, Summary of Product Characteristics (SmPC) and newly received or identified safety information.

The TM will take all relevant input into account when finalising the document and prior to submitting it for approval and signature to the PI, the Trial Statistician, and trial Collaborators (industry or non-commercial). The TM will ensure that the protocol and any related amendments are registered on the relevant external clinical trial or protocol registration systems to allow for future publication of trial results (e.g. ISRCTN, Clinicaltrial.gov) as well as fulfilling regulatory requirements (e.g. EUDRACT).

Following approval of the document and before implementation, the protocol and protocol amendments (if any) must be signed and dated by the PI and other signatories as relevant to the specific trial. The Principal Investigator (PI) at each trial centre will also confirm that he/she will follow the latest trial protocol and each subsequent amendment.

4. Protocol amendments

4.1 Preparation, Approval and Submission

A protocol amendment describes any revision to a final protocol, after a favourable ethical opinion or approval by a regulatory body has been given. They can be made to the protocol or other essential documentation or other aspects of the study arrangements. A protocol amendment may affect all participating sites or may be specific to certain countries or sites.

Changes to the protocol before it has been submitted to the first CA and/or REC are managed by protocol versioning and do not constitute a protocol amendment.

Protocol changes and amendments must be addressed to and approved by the TMT. The Trial Manager coordinates the revision/amendment procedures.

Amendments may be either substantial, non-substantial (minor) or urgent:

Substantial amendments require to be sent to the REC, that gave a favourable opinion, or CA, or both using a notice of substantial amendment. (EUDRACT Notice of substantial amendment template (http://eudract.emea.europa.eu/document.html#forms) A substantial amendment cannot be implemented until a favourable opinion is received. A substantial amendment is one which significantly affects:

a. The safety or physical or mental integrity of the subjects of the trial; or
b. The scientific value of the trial; or

c. The conduct or management of the trial; or

d. The quality or safety of any investigational medicinal product used in the trial

Examples of substantial amendments include:

A. Protocol
   (i) Purpose or Design of the Trial
   (ii) Inclusion/Exclusion criteria
   (iii) Safety monitoring
   (iv) Recruitment procedure
   (v) Measures of efficacy
   (vi) Addition/deletion of tests
   (vii) Sampling procedures
   (viii) Number of subjects recruited
   (ix) Age range of subjects recruited
   (x) Duration of exposure to IMP
   (xi) Dose changes of IMP
   (xii) Change of comparator

B. Study Documentation
   (i) Informed Consent (IC)
   (ii) Participant Information Leaflet (PIL)
   (iii) Letters of invitation
   (iv) Information for relatives or carers
   (v) Questionnaires
   (vi) IMP Dossier

C. Trial Arrangements
   (i) Change of principal investigator or addition of new PIs (i.e. Lead investigator in each site)
   (ii) Change of coordinating investigator
   (iii) Change of trial site or addition of new sites
   (iv) Change of Sponsor or legal representative
   (v) Change in definition of end of trial
   (vi) Change of IMP supplier
Non-Substantial amendment

Non-substantial (minor) amendments are changes to the detail of the study which do not have a significant impact either on the subjects enrolled in the trial or the conduct, management or scientific value of the trial. These minor amendments may be reflected in the next update to the IB or included in the next substantial amendment, or in the annual safety report. Documentation for minor amendments needs to be maintained and be able to be presented for audit purposes.

Examples of non-substantial amendments include:

(i) Minor clarifications to the protocol  
(ii) Correction of typographical errors in the protocol  
(iii) Changes to the Trial Team (TT) except for changes to the Coordinating of proincipal investigator)  
(iv) Changes in funding arrangements  
(v) Changes in the Trial Case Report Form (CRF)  
(vi) Changes in logistics of trial drug supply and storage

Urgent Amendments

Urgent amendments should be made, if there is an emergency safety issue. In order to protect trial subjects from immediate safety risk it may be decided to take specific safety measures. These measures may be taken without any prior CA and favourable REC opinion. However, the CA and REC must be immediately informed of the new safety risk, the measures taken and the plans for further actions.

Amendments need to be created with the support of the relevant TMT members, collaborator/sponsor representatives (as appropriate) and other relevant individuals. Amendments are reviewed and approved using the same process as the creation of the original protocol. The format and content of a protocol amendment is defined in the INSTITUTION current version of the Trial Protocol Amendment Template. The TM, as directed by the PI will coordinate all appropriate input when finalising the document and prior to submitting it for approval and signatures. Amended protocol signatories should hold the same role or responsibilities as the signatories on the previously approved protocol.

Urgent amendments should be made, if there is an emergency safety issue. In order to protect trial subjects from immediate safety risk it may be decided to take specific safety measures. These measures may be taken without any prior CA and favourable REC opinion. However, the CA and REC must be immediately informed of the new safety risk, the measures taken and the plans for further actions.
4.2 Protocol Amendment Change Control

The TM reviews with the TMT the impact of the amendment on all other trial related documents (e.g. Patient Information Sheet (PIS) and Informed Consent Form (ICF), CRF, Monitoring Plan, Data Validation Plan, Statistical Analysis Plan etc) and ensures that the necessary changes are implemented. Similarly, any changes impacting on the safety monitoring/reporting process as well as service provider/collaborator/site activities must also be reviewed and changes implemented, if appropriate. An amendment and any related documentation change must be sent to and approved by the RAs and/or RECs before implementation, unless regulations allow otherwise (e.g. minor or urgent amendments).

4.3 List of Protocol Amendments

The Trial Manager will ensure the maintenance of an up-to-date list of all Protocol Amendments issued since final protocol and will ensure that the list is filed in the Trial Master File and investigator site file.

4.4 New Working Protocol

The new approved version of the protocol incorporating ALL the amendments will result in a new working protocol and the date of implementation will be stated in a letter sent out with the new protocol to all sites and other relevant collaborators.

The TM will check that the "working protocol" is reviewed and quality controlled prior to distribution to the trial team members and sites.

The TM/Data Manager (DM) will check that the site(s) use the most recent version of the protocol. Sites will be reminded by the TM/DM to destroy extra copies of outdated protocols and to keep one copy in the site file together with all amendment documentation.

5 Related Working Instructions/Templates

- Trial Protocol Template for IMP study (Template XXXX)
- Trial Protocol Template for non-IMP study (Template XXXX)
- Trial Protocol Amendment Template (Templatexxxx)
- Patient Information Sheet Template (Template XXXX)
- Signature List and Delegation of Responsibilities (TemplateXX)
- Notice of substantial amendment template (Template XX)

6 References

ICH Harmonised Tripartite Guidline for Good Clinical Practice (19996)
http://www.ich.org/LOB/media/MEDIA482.pdf
EU COMMISSION DIRECTIVE 2005/28/EC