

Standard Operating Procedure (SOP) for Protocol Development

For Completion by SOP Author	
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Portsmouth Hospitals NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

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1. INTRODUCTION

The protocol is the blueprint of a research project. Generally speaking, the protocol should describe the study objectives, the design, the participants, the treatment schedule, medications and dosages, statistical plan, study outcomes and study organisation. The participant's journey through the study should be clearly described and the safety implications, recording and reporting should also be specified. It is important to remember that your protocol will be reviewed by an NHS Research Ethics Committee (if applicable) which consists not only of health professionals but also lay members of the public so make sure that appropriate language is used throughout the document. Since the study sponsor bears overall responsibility for the design of the study (and therefore it is responsible for any indemnity issues) the protocol must be designed in agreement with the sponsor.

In the case of a protocol for Clinical Trials for Investigational Medicinal Products (CTIMPs) the Medicines for Human Use (Clinical Trials) regulations (2004) [statutory Instrument 2004/1031] and subsequent amendment in 2006 (statutory instrument 2006/1928) require that clinical trials are conducted according to the protocol. Under these regulations therefore **the research protocol is a legal document** that outlines the study plan. In order to confirm whether your study is a CTIMP, please refer to MHRA guidance:

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/317952/Algothrim.pdf

2. PURPOSE

All studies sponsored by PHT must adhere to the information provided in this SOP as per Good Clinical Practice and the Research Governance Framework.

3. SCOPE

- This SOP applies to research staff involved in writing protocols for research sponsored by Portsmouth Hospitals NHS Trust.
- The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Director of Research.
- In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety

4. ABBREVIATIONS & DEFINITIONS

Insert the meaning of any commonly used abbreviations (e.g. SOP = Standard Operating Procedure) and definitions.

CTIMP: Clinical Trial of an Investigational Medicinal Product

CTU: Clinical Trials Unit

CI: Chief Investigator

DMC: Data Management Committee

IMP: investigational Medicinal Product
PHT: Portsmouth Hospitals NHS Trust
PPI: Patient & Public Involvement
RDS: Research Design Service
REC: Research Ethics Committee
SAP: Statistical Analysis Plan
SOP: Standard Operating Procedure
TSC: trial Steering Committee
TMG: Trial Management Group

5. DUTIES AND RESPONSIBILITIES

The Investigator and investigation team are responsible for:

- Familiarising themselves with the study protocol
- Ensuring all study procedures are conducted as per protocol
- Documenting protocol deviations
- Notifying the sponsor of protocol amendments
- Assessing the impact of protocol amendments
- Ensuring that all members of the study team are aware of protocol amendments

6. PROCESS

6.1. PROTOCOL DEVELOPMENT TEAM

The protocol should be developed in collaboration with key contributors to the research project. These can include (but are not limited to):

- CI
- Key investigators
- Clinical Trials Pharmacist (If an IMP is involved)
- Statistician
- Pathology Department or laboratory contact (if involving tissue samples)
- Members of any proposed TSC/DMC/TMG
- Members of the funding award body
- Commercial supporters (if applicable)
- PPI members
- Sponsor Methodologist (or RDS staff)
- Research Nurse

The above is essential for high risk studies such as CTIMPs and randomized controlled trials where a multidisciplinary approach is often required in order to safeguard patient safety.

For low risk and observational studies however, the protocol development team might consist of a lead researcher and a consultant who will liaise with the sponsor's methodologist (or RDS staff). They might ask for the opinion of a statistician in order to define the statistical aspects of the research.

6.2. DESIGNING AND DEVELOPING THE PROTOCOL

6.2.1 Study outline and feasibility

The initial idea should be defined as a research question and study details provided using the Study Outline and Feasibility form which is designed to provide the Research & Innovation Office (R&I office) with key information about the study plan and potential feasibility issues.

The objective of this process is to help the R&I office understand the purpose of the study and to provide points for discussion on the first meeting. The outline of the study will also be employed by the R&I office to make a decision as to the feasibility of the project.

6.2.2 Protocol development

Using the relevant protocol templates available from the R&I office, the protocol development process will involve several meetings between the study team and the R&I office which will be an opportunity to discuss the details of the project and provide feedback. The number of meetings required and the length of the protocol development process is often dependent on the complexity of the project, the number of staff and departments involved and the risk of the project. Once the protocol is considered finalised and all relevant departments have confirmed their agreement to be involved, the study will be considered to enter the setup stage.

6.2.3 Study design

It is important to remember that the scientific integrity of the trial and the credibility of the data from the trial depend substantially on the study design. A fundamental decision in the design of a study is whether to conduct an observational study or to apply an intervention and examine its effects in a clinical trial.

Amongst observational studies, common designs are:

- Cohort studies (prospective or retrospective)
- Cross-sectional studies
- Case-control studies

There are various types of design for clinical trials; however the randomised, controlled blinded trial is widely considered to provide the gold standard of evidence. For more details into randomisation and blinding please refer to PHT/RDSOP/014 "SOP for Randomisation and Blinding".

6.2.3 Study Methods

The methods section usually receives close scrutiny from the Research Ethics Committee and other reviewers as it will serve as the "operations manual" for carrying out the study. Some aspects of the method section that need careful consideration and must be described in detail are:

- Study participants: consider your study population and inclusion/exclusion criteria
- Sample size: this is best determined with the help of a statistician
- Informed consent: For details on informed consent please refer to PHT/RDSOP/005 "SOP for Recruiting and Consenting patients into clinical research".
- Statistical plan: this is a pre-specified statistical methodology documented for a study, either directly in the protocol or in a separate document such as the Statistical Analysis Plan (SAP).

6.2.4 Finalising the protocol

After all study procedures have been agreed by all stakeholders, the protocol is finalised by following these steps:

- Confirm the correct template has been used and completed appropriately.
- The protocol must be version controlled

- The final version of the protocol must be approved by the protocol development team including as a minimum the CI, the statistician and the pharmacist (if applicable).
- The final version of the protocol sent for regulatory approval must be signed and dated by the CI. It is then kept in the TMF.

6.3. PROTOCOL AMENDMENTS

No matter how carefully the study is designed and the procedures pre-tested, problems often appear once the study has begun and the need for an amendment becomes apparent. Once the decision has been taken to amend the protocol (or patient related documents), the R&I office must be contacted immediately as they, as study sponsor, must make a decision as to whether the intended changes constitute a minor or a substantial amendment.

In general, the following steps should be followed with regards to amendments:

- Any change to the protocol will constitute an amendment either substantial or minor. The sponsor will confirm whether the change is substantial or not.
- For substantial amendments, you will need to inform the REC and MHRA (If CTIMP)
- In the case of urgent safety measures the protocol can be amended without delay. Refer to PHT/RDSOP/006 'SOP for Reporting Urgent Safety Measures in Clinical Research'.
- Changes must be reviewed and approved by the appropriate personnel such as CI, pharmacist, statistician, etc.

7. TRAINING REQUIREMENTS

- The Research Dept will endeavour to notify individuals of SOP developments that may be relevant to them. Updates on SOPs will feature in research newsletters and communications. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.
- When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process.
- Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.
- All staff are responsible for maintaining their own SOP training Records and copies must be made available to line managers, the SOP Controller or study monitors and sponsors on request.
- A study specific SOP training plan will be developed for investigators on high risk PHT Sponsored studies.

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Cambridge Clinical Trials Unit SOP CCTU/SOP043 "Writing a clinical research protocol"

Hulley et al. 2007. Designing clinical research. Third Edition. Wolters Kluwer Health.

9. VERSION HISTORY LOG

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of Significant Changes
V1.0	23 May 2016	New document

10. APPENDICES

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	Protocol Development
Reference Number	Insert SOP Reference Number. PHT/RDSOP/015
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Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed/Delivered by etc
Records of any meetings to clarify details in SOP	

Signatures
<p>I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities</p> <p>Signature of Trainee Date</p>
<p>I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities</p> <p>Signature of Trainer Date</p>

Additional Notes & Signatures

Signature of Trainer (where appropriate)

I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities

Signature of Trainer Date

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