STANDARD OPERATING PROCEDURE 4

Trial/Research Study Protocol

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Revision Chronology:	Effective date:	Reason for change:
Version 4.0	15 March 2024	Biennial review: Format changes. Consideration of using cloud-based systems. Change from MIS to REALMS for NIHR studies. Refresh of the approval process.
Version 3.0	21 December 2021	Biennial review: Update to new format. Minor amends to text.
Version 2.2	16 August 2019	Biennial review: Minor amends to text, web links updated. Change to new format.
Version 2.1	17 January 2017	Biennial review: Minor amends to text, web links updated. Change to new format.
Version 2.0	31 July 2014	Format change. Addition of protocol writing template to include SPIRIT guidance.
Version 1.2	18 May 2010	Update web links.
Version 1.1	31 January 2008	Format change. Addition of text (protocol definition). Update web-links.
Version 1.0	March 2006	

STANDARD OPERATING PROCEDURE 4

Trial/Research Study Protocol

1. Purpose and Scope

The purpose of this Standard Operating Procedure (SOP) is to outline the elements that should be included in a clinical trial or research study protocol and the process for protocol development and sign-off. It is applicable to anyone involved in the protocol development process.

2. Definitions

Protocol	A document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial
Protocol Amendment	A written description of a change(s) to, or formal clarification of a protocol

3. Background

A well-written protocol facilitates an appropriate assessment of scientific, ethical, and safety issues before a study begins; consistency and rigor of study conduct; and full appraisal of the conduct and results after study completion. The use of protocols should not be limited to clinical trials, and it is best practice for a protocol to be produced for all research studies, in particular those that involve the NHS or social care. All clinical trials or research studies within the NHS should have a full protocol regardless of whether they are funded or not.

An international group of stakeholders launched the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Initiative with the primary aim of improving protocol content. The main output is the SPIRIT 2013 Statement, providing guidance for key content and minimum recommended protocol items. Details and the content checklist are available online.
The SPIRIT recommendations facilitate the drafting of high-quality protocols. Adherence to SPIRIT also enhances the transparency and completeness of protocols for the benefit of investigators, participants, patients, sponsors, funders, research ethics committees or institutional review boards, peer reviewers, journals, trial registries, policymakers, regulators, and other key stakeholders.

The SPIRIT statement has many extensions to address the specific needs of studies. For example, in 2018 guidance on protocol content relating to patient reported outcomes (PROs) was published.

Other guidance on the development of protocols is available e.g., the COMET Initiative (Core Outcome Measures in Effectiveness Trials) which brings together researchers interested in the development and application of agreed standardised sets of outcomes, known as a 'core outcome set' (COS). These sets represent a standardised minimum data which should be collected and reported in all clinical trials, audits of practice or other forms of research for a specific condition.

Also, the equator network (Enhancing the QUAlity and Transparency Of health Research) contains guidelines for the reporting of all main study types.

Funding bodies may require different formats and review processes for protocols. Researchers should ensure they are aware of the funding body's requirements.

4. Procedure

4.1 Responsibilities

Chief Investigator (CI) (or delegate)	• Produce the protocol and gain the applicable approvals prior to use. This is usually in collaboration with other personnel e.g., Co-applicants, Senior Project Managers, Research Fellows, Statisticians, Health Economists, Quality Assurance Team, Trial Managers/Coordinators etc. • Responsible for the submission, approval and implementation of amendments • Responsible for documentation and assessment of any deviations from the protocol
Sponsor	• Review and approval of protocol prior to submission to authorities for approvals

4.2 When?

It is good practice to produce the first draft during the study design phase. However, some funding bodies do require an abbreviated protocol (or detailed project description) to be submitted as part of the application process, so researchers must be aware of their funding bodies requirements. A current version of the protocol should be in place throughout the life of the study.

4.3 How?

Protocol writing templates have been developed which take the SPIRIT Statement into account, including SPIRIT PRO.

The following template protocol writing documents are available on the WCTU website and should be used to ensure that all necessary items are included:

- T15: Protocol Writing Template Document non-CTIMP
- T16: Protocol Writing Template Document CTIMP
- HRA Qualitative Protocol Guidance and Template: HRA Protocol Guidance

The HRA website also provides further guidance on the requirements for protocols for Clinical Trials of Investigational Medicinal Products (CTIMPs).

The main sections of a protocol should be:

- Contact names and numbers
- Table of contents
- Trial summary
- List of abbreviations/glossary
- Background information
- Trial objectives and purpose
- Trial design and treatments
- Selection and withdrawal of participants
- Methods and assessments (efficacy & safety)
- Adverse event management/Pharmacovigilance
- Data management
- Statistical analysis
- Health economic evaluation

- Ethics
- Finance and insurance
- Trial organisation and oversight
- Monitoring and quality assurance/quality control procedures
- Patient and public involvement
- Dissemination and publication plans
- Data sharing statement
- References
- Appendices

4.3.1 Procedure for the generation, review and approval of a research protocol

Protocols should be drafted (using a standard template) by an individual with an appropriate level of knowledge and experience. The draft document should be circulated for review by other personnel who have relevant knowledge or experience sufficient to comment on the content of the document (this may include, but is not limited to; statisticians, health economists, QA staff, co-applicants, funding body, steering committee etc.). Departmental consideration should be given to using a cloud-based system to facilitate simultaneous document review in a single location. Permissions to access/edit the file should be set appropriately.

Text within the statistics section of a protocol should be reviewed and checked by another suitably trained statistician and the checks documented, this can be done using the Statistics Review Form (T64) available on the WCTU SOP templates webpage.

For WCTU managed studies, documentation of double checks of elements of the statistics section of the protocol (and any subsequent amendments if changes to the section are required) will be evidenced with a clear audit trail (e.g. using Q-Pulse and adding a note to the Properties section or using a review/approval form).

Appropriate version control measures should be implemented to ensure distinction between each version (e.g., 1st draft = v0.1, second draft = v0.2, first approved version = v1.0, subsequent drafts = v1.1, v1.2 etc. until the final version is saved asv2.0). If a cloud-based system is used, consideration should be given to this process using automated version control. For more information see SOP 45 'Document Management'.

When, after appropriate review, the document is ready to be finalised, there should be a formal sign-off by the CI and those involved in its production and the new document changed to become version 1.0 before being submitted for ethical (and regulatory if applicable) approvals.

Sign-off should be in place prior to submission to authorities for approval with an agreed process for each study. An audit trail of the process should be retained using an appropriate system and retained within the Trial/Study Master File (T/SMF). This may include using the Q-Pulse electronic quality management system, a paper or electronic review/approval form (T09), or email confirmation from appropriate staff using a professional (non-personal) email account.

Where an **amendment to the protocol** is required, the process described above should be followed for its generation, review and approval. It is good practice to prepare a summary of the changes, so that those undertaking the review can easily identify what changes have been made (this may be a

table indicating page numbers or sections where amends have been made and details of the previous and new text). Consider adding an appendix to the protocol to provide a summary of the changes made for each version.

The Trial/Study Management Group (T/SMG) should discuss all amendments and identify if any other study documents or the Risk Assessment/Monitoring Plan will be impacted by the amendment and ensure they are revised as appropriate (e.g. Participant Information Sheets, Consent Forms). The study statistician should also check that any amendment does not impact on the statistical section, and approve any changes as required. This process should be documented.

See also SOP 6 'Amendments to Approved Study Documents' for further details.

N.B. If the project is funded by the National Institute for Health and Care Research (NIHR), the relevant Programme Manager may also need to review the initial protocol and be made aware of any substantial amendments before documents are submitted to the Research Ethics Committee (REC). Documents must be uploaded to the appropriate NIHR management system for review. For example, uploaded to the REsearch Awards Lifecycle Management System (REALMS) for HTA Programme Manager review.

For externally sponsored studies and/or non-NIHR funded studies, appropriate review and approval processes should be agreed on a case-by-case basis ensuring that the relevant sponsor's SOPs and requirements are followed.

4.3.2 Terminology

A research study may be referred to as a 'trial' or 'study' as appropriate, but one or other term should be used consistently throughout the protocol. Similarly, use of either 'subject' or 'participant' is acceptable, but one or the other should always be used throughout (it may be useful to involve Patient and Public Involvement (PPI) representatives to determine the most appropriate term).

The protocol is 'final' when it is ready to be submitted to the appropriate REC, Medicines and Healthcare products Regulatory Agency (MHRA) (if applicable) and the funding body/Trial Steering Committee (TSC)/Data Monitoring Committee (DMC).

The protocol should be version controlled (version number and dated) to ensure the current approved version is in use. The new version number must be added to the cover page and footer, with superseded versions listed on the version control section (also usually on the cover page).

List of abbreviations

CI	Chief Investigator
COMET	Core Outcome Measures in Effectiveness Trials
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMC	Data Monitoring Committee
EQUATOR	Enhancing the QUAlity and Transparency Of health Research
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health and Care Research
PPI	Patient and Public Involvement
PRO	Participant Reported Outcomes
REALMS	REsearch Awards Lifecycle Management System
QA	Quality Assurance
R&IS	Research & Impact Services
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TM	Trial Manager
T/SMF	Trial/Study Master File
T/SMG	Trial/Study Management Group
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

Template Documents

T09	Key Document Review/Approval Form
T15	Protocol Writing Template Document non-CTIMP
T16	Protocol Writing Template Document CTIMP

Qualitative Protocol Guidance and Template – link to HRA website