RDSOP15 Writing a GCP Compliant Protocol for CTIMP’s

Greater Manchester Mental Health NHS Foundation Trust

Improving Lives
# Title of Standard Operating Procedure:

RDSOP15 Writing a GCP Compliant Protocol for CTIMPs

## Document Summary:

The research protocol is a legal document that outlines the study plan. The protocol needs to describe the aims of the study, how these will be adequately answered, and how the design will safeguard the health and safety of the participants. It must contain all the elements required to meet Good Clinical Practice standards and comply with the legislation.

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## Target Audience:

Trust-wide, Research Community, Internal and External Researchers

## Consultation:

R&I Office, research community and R&I Committee members

## Approval Committee:

R&I Committee

## Cross Reference Document(s):

Research Approval Policy  
All Trust R&I SOPs

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## Minimum Monitoring Requirement

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Frequency</th>
<th>Process for monitoring</th>
<th>Evidence</th>
<th>Responsible Individual(s)</th>
<th>Response Committee(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review of SOP content</td>
<td>Annually</td>
<td>Review by Author, redraft, submission to R&amp;I Operational Group</td>
<td>Minutes of R&amp;I Operational Group</td>
<td>Head of R&amp;I Office</td>
<td>Research &amp; Innovation Committee</td>
</tr>
</tbody>
</table>

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Page 1 of 12
Contents

1. Introduction...............................................................................................................................4
2. Purpose ......................................................................................................................................4
3. Roles and Responsibilities .........................................................................................................4
3.1 Duties within the Organisation ..............................................................................................4
4. Protocol Elements ....................................................................................................................5
4.1 Title........................................................................................................................................6
4.2 Cover Page ..............................................................................................................................6
4.3 Table of Contents ..................................................................................................................4
4.4 Background and Rationale .....................................................................................................6
4.5 Trial Objectives .....................................................................................................................7
4.6 Trial Design ............................................................................................................................7
4.7 Participant Selection and Withdrawal ....................................................................................7
4.8 Trial Medications ...................................................................................................................8
4.9 Treatment Procedures by Visit .............................................................................................8
4.10 Assessment of Efficacy .........................................................................................................9
4.11 Assessment of Safety: Recording and Reporting of Adverse Events ....................................9
4.12 Serious Breaches ..................................................................................................................10
4.13 Treatment Stopping Procedures .........................................................................................10
4.14 Data Collection and Management ....................................................................................10
4.15 Statistical Analysis ...............................................................................................................10
4.16 Management of the Trial .....................................................................................................10
4.17 End of the Trial ....................................................................................................................11
4.18 Ethics and Regulatory Approvals .......................................................................................11
4.19 Quality Assurance ..............................................................................................................11
4.20 Dissemination and Publications .........................................................................................12
4.21 Finance and Insurance .........................................................................................................12
4.22 References and Bibliography .............................................................................................12
5. References and Bibliography ..................................................................................................13
Operating Procedure

1. Introduction

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 the research protocol is a legal document that outlines the study plan. The protocol needs to describe the aims of the study, how these will be adequately answered, and how the design will safeguard the health and safety of the participants. It must contain all the elements required to meet Good Clinical Practice standards and comply with the legislation.

2 Purpose

This SOP provides guidance for researchers and applies to all Clinical Trials of Investigational Medicinal Products (CTIMPs) sponsored or co-sponsored by the Trust. A separate SOP (RD SOP16) is available for guidance on those studies not conducted under the Medicines for Human Use (Clinical Trials) Regulations.

A protocol is a document that describes the objective(s), design, methodology, statistical considerations and organisation of a trial and as such this SOP indicates what should be taken into consideration when developing a clinical trial protocol and those which are statutory elements. It will describe the participant’s journey through the research trial and the relevant timelines.

Roles and Responsibilities

3.1 Duties within the organisation

It is the responsibility of the Research & Innovation Office to make Trust R&I SOPs available to all research active staff working on Trust-approved research studies.

It is the responsibility of the study Chief Investigator (CI) or local Principal Investigator (PI) to ensure that up-to-date copies of Trust R&I SOPs are available to research staff.

It is the responsibility of the study Chief Investigator or local Principal Investigator to ensure up-to-date SOPs are filed in the Investigator Site File and are available to research staff, and to inform the Research Support Co-
ordinator of the names of all research staff involved on a study so that copies of SOPs can be distributed appropriately.

It is the responsibility of the study Chief Investigator or Principal Investigator to designate if the SOPs of another organisation are to be followed for a study. For example those of a Clinical Research Network or commercial sponsor. If there is significant conflict between the external SOP and the Trust R&I SOP it is the responsibility of the CI or PI to resolve these with the Research Office prior to starting the study.

It is the personal responsibility of all staff to follow Trust (or the designated alternative organisations) procedural documents.

The Research & Innovation Office is responsible for managing Trust R&I SOPs including their approval, dissemination and archiving. All Trust R&I SOPs must be made available via Q-Pulse and published on the Trust website.

It is the responsibility of the Chief Investigator to supervise the writing of the trial protocol. This may be completed in collaboration with colleagues and will undergo detailed peer review.

The Chief Investigator should complete a full risk assessment for the study using the risk assessment form available from the R&I office as early as possible in the protocol writing process and prior to finalisation of the protocol. This is essentially a process of identifying the potential hazards associated with that trial, and assessing the likelihood of those hazards occurring and resulting in harm. This risk assessment will include the risks to participant safety in relation to the IMP and all other risks related to the design and methods of the trial including risks to participant safety and rights, as well as reliability of results.

It is the responsibility of the sponsor to ensure adequate peer review has been conducted. It would be expected that the Chief Investigator would facilitate this process by providing the names of peer reviewers with suitable expertise. A statistical review may also be required.

4. Protocol Elements

The content of a CTIMP protocol will include, but is not limited to, the following:

4.1 Title

The full title should describe the study design, phase, medicinal product, and nature of the treatment and participant population, so that it is immediately evident what the study is investigating and on whom.

A short title (with/without an ACRONYM) can be used for convenience for the study but this must remain consistent throughout all documentation.
4.2 Cover Page

The cover page should contain:

- Protocol title.
- Trial identifiers (protocol number – this could be the R&I PIN, EudraCT number, ISRCTN [if applicable] and HRA reference).
- Sponsor details (including contact details).
- Chief Investigator details.
- Collaborators/authors details (including statistician).
- Sites and contact details.

Signatory page – The Chief Investigator and the Sponsor’s representative must sign the protocol. It is good practice for all concerned in the trial design to sign and date the protocol to indicate their agreement with that version.

Header & footer – each page of the protocol requires protocol number, IRAS number, date and version number, and page number (e.g. in page 2 of 10 format).

Amended versions of the protocol should also include the version number and date.

4.3 Table of Contents

A full table of contents is required with page numbers.

4.4 Background and Rationale

Summary of the background of trial, participant population and disease to be investigated.

Previous findings from other trials and data from previous studies.

Description and name of Investigational Medicinal Product (IMP).

Summary and evaluation of known and potential risks and benefits to participant population.

Justification for IMP route of administration, dosage, regimen and treatment period(s).

A statement that the trial will be conducted in compliance with the protocol, GCP, the applicable regulatory requirements and the Declaration of Helsinki.
4.5 Trial Objectives

The aim of the trial (hypothesis).
The objectives of the trial.

4.6 Trial Design

The protocol requires a full description of the design of the trial, to include:

The primary (and secondary) endpoints to be measured.
The type of trial - arms, minimising bias (blinding, randomisation), placebo-controlled, parallel design.
Sample size selection (calculation of power).
Level of significance.
Randomisation (how is it to be done, stratification, by whom, method of participant randomisation, recording randomisation, un-blinding procedures [who can break the randomisation codes and under what circumstances], any interim un-blinding for analysis).
Treatment and duration, including follow-up periods.
Identification of any data to be recorded directly on the Case Report Forms and therefore to be considered to be source data.
What are the possible side effects with the IMP and how will/should these be treated.
What are the expected adverse reactions with these types of IMPs or within this disease condition? (To prevent unnecessary reporting of SUSARs).
Description of plan for the provision of any additional care of participants once their participation has ended, where it differs from what is normally expected according to the participants’ medical condition.
A flowchart/schematic diagram of the trial (if appropriate) to clarify trial procedures and activities involved at each stage.
Provision of a qualitative aspect to the trial, (certain clinical trials may include qualitative measures such as questionnaires on quality of life or beliefs).

4.7 Participant Selection and Withdrawal

Inclusion criteria.
Exclusion criteria.

Participant numbers (qualified statisticians must be involved in protocol design and provide an appropriate power calculation to meet the needs of the trial).
Where and how the participants will be recruited (sites). What screening and enrolment process will be used? The format and content of the Patient/Carer Information Sheets and Consent forms should comply with requirements set out in ICH-GCP Topic E6 R1 and must follow the Patient/Carer Information Sheets and Consent form templates available from the R&I Office.
Justification for including participants who are incapable of giving informed consent or other special populations such as children (where appropriate).
Participant withdrawal – by research team or participant and consequences including;
When and how to withdraw participants from the trial/treatment (e.g. Pregnancy),
Any extra tests required despite the participant being withdrawn to ensure their safety,
The type and timing of the data to be collected for withdrawn participants and what happens to the data already collected – must it be discarded or used to point of withdrawal,
Whether and how participants are to be replaced,
The follow-up for participants withdrawn from trial treatment including basic safety data,
A screening log is recommended as a means of monitoring accrual and withdrawal.
Participant withdrawal – a statement emphasising that participant safety is paramount and is a priority over adherence to the protocol (e.g. the investigator must withdraw the participant if s/he feels that participation presents the potential for harm).

4.8 Trial Medications

All trial medications must be processed through the clinical trials team within the pharmacies allied to GMMH. The pharmacy team will advise on receipt of drug, placebo, comparators, appropriate certification of the trial drugs/placebos, labelling, storage and dispensing to ensure that the procedures comply with the Medicines for Human Use (Clinical trials) regulations. The following information is required:

IMP manufacturer and Marketing Authorisation holder.
IMP dosage, packaging and labelling.
Prescribing details.
Treatment – product, doses, dosing schedule, route of administration, treatment periods, washout and follow-up periods.
Management of dose adjustment, overdose or temporary omission of drug.
Medications permitted (including rescue medication) and not permitted before and/or during the trial.

Compliance procedures (how will compliance/non-compliance be monitored, under what circumstances will a participant’s data be excluded from the study as a whole due to non-compliance, how will non-compliance be measured and assessed by the research team).
Drug/placebo/comparator accountability procedures (e.g. returns -are drug packs to be returned to the research team, how [e.g. addressed envelopes, on final out- patient visit]).
Disposal of trial drugs (returned drugs and unused drugs at end of trial).
4.9 Treatment procedures by visit

A table or listing of visits or interactions throughout the lifetime of the trial with all the procedures/tests required for the trial at the appropriate times. Treatment procedures should be identified as study assessments and/or safety assessments.

If a participant needs to be seen 3 weeks after an intervention, appropriate guidelines on the leeway allowed before impacting on trial results should be included e.g. 21 days (± 3 days), so that appropriate breaches of protocol can be identified.

4.10 Assessment of Efficacy

Specify efficacy parameters.

Methods and timing for assessing, recording and analysing of efficacy parameters (At what point will efficacy be assessed, e.g. interim analysis after a certain number of participants).

Who will do assessment?

4.11 Assessment of Safety: Recording and Reporting of Adverse Events

Specify safety parameters by reference to the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC).

Procedures for eliciting reports of adverse events and inter-current illnesses from participants (when and how).

Definition of Adverse Events, including exceptions to the standard criteria (e.g. Serious Adverse Events that do not require expedited reporting, Adverse Events that do not require reporting). Refer to RDSOP8A: Pharmacovigilance for Trust-Sponsored MHRA-regulated Clinical Trials.

The type and duration of the follow-up of participants after adverse events.

Who is responsible for assessing the seriousness, causality and expectedness of adverse events (individual researchers, the PI, the CI, a designated group, delegation if that individual is absent).

How will adverse events be recorded and reported locally.

Procedures for recording and reporting (e.g. study specific SAE form) of serious adverse events/reactions (SAEs/SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) to the appropriate organisations.

How will adverse events be disseminated to the wider research team (locally and other sites).

Withdrawal and follow-up criteria if a participant or the partner of a participant should become pregnant during the trial.

Responsibility for preparing and sending Annual Safety Reports to the MHRA.
4.12 Serious Breaches

The Medicines and Healthcare products Regulatory Agency (MHRA) define a “serious breach” as a breach which is likely to effect to a significant degree: (a) the safety or physical or mental integrity of the participants of the trial (this should be relevant to trial participants in the UK); or (b) the scientific value of the trial. Procedures for recording and reporting serious breaches of the protocol and Good Clinical Practice.

4.13 Treatment Stopping Procedures

When and under what circumstances will treatment be stopped? What needs to happen when treatment is stopped for safety reasons (e.g. gradual dose reduction, alternative medications)? What happens if a participant wants to withdraw from the trial?

4.14 Data Collection and Management

Data collection methods, data management, data protection and security. Refer to RDSOP17: Research Data Management and Security.

4.15 Statistical Analysis

Details of when and what statistical analysis will be performed on the results.

Interim analysis.

Criteria for termination of the trial. Procedure for accounting for missing, unused and spurious data. Selection of participants to be included in analysis (e.g. all randomised participants, all dosed participants, all eligible participants, evaluable participants).

4.16 Management of the Trial

There are three trial management groups which may be involved in the set up and management of a clinical trial, depending on the trial size, design and number of sites. The Research & Innovation Office can advise and provide more detail on the roles of these groups. If they are included in the study set up, details should be included in the protocol with reference to any accompanying documents.
Trial Steering Committee

The TSC must have a majority independent representation, including the Chair, meet regularly and send reports to the sponsor. The Chief Investigator can suggest names of independent members to the sponsor.

Data Monitoring (and ethics) Committee

The DMEC should meet regularly. Ideally the Chief Investigator would set this up and send reports to the sponsor.

Trial management team

The trial management team must meet regularly to ensure all practical details of the trial are progressing well and working well and everyone within the trial understands them. Minutes of the meetings and actions should be kept for reference.

4.17 End of Trial

State when the end of the trial will be reached (e.g. after last treatment visit of last recruit, 2 months after last recruit, after final follow-up visit [which must be before the end of the trial]).

Provision for any tissue samples retained following the end of the trial.

Archiving arrangements.

4.18 Ethics and Regulatory Approvals

A statement that the investigator/ organisation will permit trial related monitoring, audits, HRA review and regulatory inspection, providing direct access to source data/documents. Any ethical considerations relating to the trial.

4.19 Quality Assurance

What Quality Assurance measures are in place for the trial besides the TSC and/or DMEC, the planned and systematic actions to ensure that the trial is performed and data are generated, documented (recorded) and reported in compliance with GCP and the regulatory requirements.

Quality Control.

Describe any operational techniques and activities undertaken within the Quality Assurance system used to verify that the requirements for quality of the trial-related activities have been fulfilled. This may include periodic operational checks to verify that data are generated, collected, handled, analysed, and reported according to protocol, SOPs and GCP; ensuring a
strict definition of eligibility is followed when recruiting participants into a trial; ensuring adherence to medication where this is not directly supervised. Who will verify the reported data? Which clinicians within the team are responsible for signing off Case Report Forms (lead investigator or designee). Include any study specific data entry procedures or methods (including timescales). Risk management and any ongoing risk: benefit analysis conducted. What are the monitoring arrangements, by whom, and how often.

4.20 Dissemination and Publications

Who is responsible for writing publications and publication policy (especially for multi-centre trials) and how will the results from the trial be disseminated.

4.21 Finance and Insurance

Details of funding source (allocation and support to other sites can be included in sponsor agreements required by GMMH for other sites). Insurance details (especially if co-sponsored, or University employed authors).

4.22 References and Bibliography

List details of any references supporting the Protocol.
5. References and Bibliography

HRA Protocol Development:
https://www.hra.nhs.uk/planning-and-improving-research/research-planning/protocol/

ICH Good Clinical Practice Guidelines:

Declaration of Helsinki:
https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

The Medicines for Human Use (Clinical Trials) Regulations 2004 (Plus subsequent amendments):