Department	Research & Development
Title of SOP	Trial Oversight SOP for HUTH-sponsored CTIMPs
SOP reference no:	R&D SOP 11
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Current version number and date:	Version 3, 17.01.2022
Next review date:	17.01.2025
Target audience:	Research, Pharmacy and R&D staff
Distribution:	HUTH R&D internet Click on GCP SOPs for HUTH-sponsored CTIMPs *\\hri_data3\clinicalgov\Research\GCP SOPs & forms\SOPs & WIs\1.0 R&D GCP SOPs\R&D GCP SOP 11 Trial oversight\Current version*

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This page should detail the version history for this SOP and the main changes corresponding to the versions.

Version Log		
Version number and date	**Author**	**Details of significant changes**
Version 1, 06.11.12	J Pacynko & J Illingworth	Original SOP approved by R&D Committee on 01.11.12
Version 2, 04.04.16	K Date	Weblinks updated. Hyperlinks removed. New wording in red type.
Version 3, 17.01.2022	G Constable	Updated to new format. Weblinks updated ● **3 Types of trial oversight, Sponsor,** *amended wording to bring in-line with GCP Monitoring SOP.*

Please note for definitions of acronyms refer to Appendix 2 of Management of SOPs. Refer to Appendix 3 of Management of SOPs for the standards to which clinical trials that investigate the safety and/or efficacy of a medicinal product are conducted.

All the HUTH R&D GCP SOPs are available at:
https://www.hey.nhs.uk/research/researchers/gcp-sops-for-hey-sponsored-ctimps/

1 Background and purpose

- The Medicines and Healthcare products Regulatory Agency (MHRA) are the government organization that regulates and inspects clinical trials involving the use of medicines. The MHRA require that there is oversight of all aspects of the set up and conduct of clinical trials. Adequate oversight needs to be established by the Sponsor, Chief Investigator and funding organizations.

- The purpose of this SOP is to describe the different ways in which to oversee the progress of HUTH-sponsored clinical trials and to ensure their conduct to GCP and the UK clinical trial regulations. The type of oversight will depend on the size and duration of the clinical trial.

2 Who should use this SOP

- This SOP should be used by:
  - All research staff involved with HUTH-sponsored CTIMPs – Chief/Principal Investigator, other study medics, research nurses, project managers, clinical trial co-ordinators, data managers, administrators etc.
  - Clinical trials pharmacy staff – technicians and pharmacists.
  - All HUTH R&D staff.
  - Research staff involved with HUTH-sponsored non-CTIMPs may find this SOP a useful guide, although the SOP will need to be adapted for the non-CTIMP study.
  - Research staff involved with clinical trials sponsored by an external organisation where the sponsor has no SOP for trial oversight. HUTH R&D SOPs are defaulted to in this case.

3 Types of trial oversight

Sponsor oversight

- HUTH-sponsored CTIMPs are monitored by the R&D clinical trials monitor, or a suitably trained delegate, according to the GCP monitoring SOP (R&D GCP SOP 15). Monitoring visits occur prior to the start of the trial, once 3-5 patients have been recruited and at predefined points throughout the trial (additional monitoring can be implemented if deemed to be required) and after the study has finished.

Study investigator meetings

- For a single centre study it may be sufficient to have regular meetings with the staff involved with the study to discuss any patient safety issues, recruitment or any study management issues. It is important that points discussed and actions agreed are documented after meetings and that a copy is filed in the Trial Master File. It is recommended that study meetings are held every 2 – 4 weeks. The actions from a study meeting should be reviewed at the next meeting.

Trial Management Group (TMG)

- For multi-centre or long-running single centre studies, it is recommended that a Trial Management/ Group (TMG) is formed to oversee the study. The TMG/ is responsible for the day-to-day management of the trial and will oversee all aspects of the conduct of the trial. Membership of the TMG should include: Chief/Principal Investigator, Co-investigators, Sponsor Representative, Trial Manager/Coordinator, Statistician, Research Nurses, Clinical Trial Administrators, lay member(s) (optional) etc. Regular TMG meetings should be held e.g. monthly or every 2 - 3 months. Minutes of TMG meetings should be produced and a copy kept in the TMF. Minutes of previous meetings should be reviewed at the next TMG meeting. An example for the Terms of Reference for a TMG is in Appendix 1.

Trial Steering Committee (TSC)

- For large multi-centre studies, it is recommended that a Trial Steering Committee (TSC) is appointed. For trials funded by a grant body e.g. the NIHR Health Technology Assessment (HTA) programme, it is often a requirement to establish a TSC. The TSC is a committee whose role is to oversee and supervise the progress of the trial and ensure that it is being conducted in accordance with ICH GCP and the UK Clinical Trial Regulations. The TSC should agree any protocol amendments and provide advice to the investigators on all aspects of the trial. A TSC may have members who are independent to the investigators, in particular an independent chairperson. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the TSC.

The HTA's guidelines for the responsibilities, constitution, composition and role of the chairperson for a Trial Steering Committee are set out in Appendix 2.

- In summary, the TSC is an independent body which includes a majority of members who are not involved in running the trial. The TSC ultimately considers options and makes any major decisions about the trial recommended by the DMC and Ethics Committee.

- Responsibilities:

  - To take major decisions such as a need to change the protocol for any reason.
  - To monitor and supervise the progress of the trial in relation to its interim and overall objectives.
  - To review relevant information from other sources.
  - To consider recommendations from the DMC and Ethics Committee.
  - To inform and advise the TMG on all aspects of the trial.

Data Monitoring Committee (DMC)

- For large multi-centre studies, it is recommended that a Data Monitoring Committee (DMC) is appointed. For trials funded by a grant body e.g. the HTA, it is often a requirement to establish a DMC. The DMC is a committee whose role is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The DMC should be independent of both the investigators and the funder/sponsor and should be the only body that has access to unblinded data. It normally makes recommendations to the Trial Steering Committee or Trial Management Group. The HTA's guidelines for the role and constitution of a Data Monitoring Committee are set out in Appendix 3.

- The DMC is an independent body whose members are not involved in the trial; it usually has at least 3 members (including one or more clinicians and one or more statisticians with experience in trials). The members should be the only people to see the results separated by treatment group during the trial. They are independent and look at the trial from the point of view of trial participants, future patients and society in general. It is their responsibility to prevent patients being exposed to any excess risks by recommending the trial stops early if the safety or efficacy results are sufficiently convincing. The trial statistician is usually invited to attend each DMC meeting to present the most current unblinded data from the trial.

- **Responsibilities:**
  - To determine how frequently interim analysis of trial data should be undertaken.
  - To consider the unblinded interim data from the trial and relevant information from other sources.
  - To report (following each DMC meeting) to the TSC and to recommend whether the trial should continue, the protocol be modified or the trial be stopped.
  - To consider any requests for unblinding and release of interim trial data and to recommend to the TSC on the importance of this.

Sponsor Oversight Group

- The role of this SOG will be to provide expertise to ensure the documented oversight of these studies, monitor the conduct and progress of these trials, ensure that the protocol is adhered to, take appropriate action to safeguard participants and ensure the quality of the trial data. Furthermore, the SOG will act as decision making body and escalation route for the Trust (as

Sponsor) whilst documenting, assessing and reviewing the ongoing risk assessment of all HUTH Sponsored CTIMPs.

- Membership of the SOG should reflect the disciplines and clinical specialties necessary to interpret the data from the clinical study and to fully evaluate subject safety. It should include representatives from the following groups/directorates:
    - SOG Chair (Director of R&D not involved in HUTH Sponsored CTIMPs)
    - Deputy Chair
    - Sponsor representative (R&D Manager, QA Manager or Clinical Trial Monitor)
    - UoH and HHTU representative(s)
    - Chief Investigators (UoH Academic Lead and NHS Lead)
    - Clinical Trials Pharmacy representative(s)
    - Clinical Trial Co-ordinator / Trial Manager
    - A statistician (if applicable)
    - Research Nurse (if applicable)
    - Lay member(s)
    - Other support services co-opted as required.
    - IT Support and representation co-opted as required.
- When an issue is to be raised within the SOG regarding a specific issue, WI 54 SOG; Escalation Form,

4 Implementation

- Implementation of this SOP will conform to the process outlined in R&D SOP 01 Management of SOPs.

Appendix 1

Trial Management Group
Terms of Reference
<Enter date>

1. BACKGROUND

The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the chief investigator, statistician, trial manager, research nurse, data manager, sponsor representative. The role of the group is to monitor the conduct and progress of the trial, ensure that the protocol is adhered to, take appropriate action to safeguard participants and ensure the quality of the trial data.

2. TERMS OF REFERENCE

- To monitor patient safety in order to protect the rights, safety and well-being of trial patients.
- To assess the safety and efficacy of the interventions during the trial.
- To monitor and ensure the quality of the trial data.
- To monitor the conduct of the clinical trial, in particular the timely progress of the trial and adherence to the protocol.
- To review at regular intervals relevant information from other sources (e.g. related trials).
- To provide clinical and professional advice relating to the trial design, where relevant.
- To advise on and approve substantial amendments to the trial design during the course of the trial, where relevant.
- To provide a robust audit trail of decisions to increase doses in HUTH-sponsored dose escalation studies (as per MHRA Inspection recommendations).
- To ensure that the results of the trial are adequately disseminated and that due consideration is given to the implementation of the results into clinical practice.
- To agree to any relevant statistical analysis plans (e.g. DMC plans, interim analysis plans).
- To consider interim safety and efficacy data (if deemed appropriate) from interim analyses and relevant information from other sources. Any recommendations relating to patient safety may be subject to expedited reporting to the MHRA and Ethics Committee.
- To review safety data to look for any emerging trends, including increases in severity or frequency of expected Serious Adverse Reactions/Events such that they would require expedited reporting to the MHRA and Ethics Committee.
- To aid the implementation of the Trust's MHRA GCP Inspection Action Plan (where applicable)
- To provide a general interim review of the trial's progress (tailored to the needs of the trial and information supplied – i.e. toxicity data, SAEs, recruitment figures, protocol deviations, monitoring reports, external data).
- Specifically the TMG will be responsible for:
    - Pharmacovigilance compliance and safety reporting/trend analysis oversight.
    - Monitoring of screening, recruitment, consent, treatment and follow-up procedures, safety, data quality and compliance with UK Clinical Trials Regulations and GCP.
    - Escalating any issues for concern to the Sponsor, specifically where the issue could compromise patient safety or the integrity of the trial or quality of the trial data.
    - Identifying and addressing concerns about the safety or efficacy of one or more of the treatment arms.

- Informing the Sponsor of the trial where the results show;
  - a benefit of one treatment arm over another that is so large, and precise, that it is likely to convince a broad range of clinicians to change practice, or
  - it is evident that if the trial continued it would fail to show a clear benefit for any treatment arm, or
  - where accrual is so low that it is unlikely that a sufficient number of patients would be recruited to provide meaningful results.

- To produce minutes of each TMG meeting with points discussed and actions decided, to review the minutes of TMG meetings at the next TMG meeting and to file a copy of the minutes in the Trial Master File.

3. MEMBERSHIP

Membership should include representatives from the following groups/directorates:

- TMG Chair (Independent Chair or deputy)
- Chief/Principal Investigator
- A statistician (if applicable)
- Clinical trial coordinator / Trial manager
- Research nurse
- Data manager (if appropriate)
- Clinical trial administrator (if appropriate)
- Lay member(s) (optional)
- Sponsor representative (R&D Manager, QA Manager or Clinical Trial Monitor)
- Research Business Manager (if appropriate)
- Radiation Physics representative(s) (if appropriate)

4. QUORUM

Four members on the TMG including the Chair or Deputy Chair, a representative from R&D and the Chief/Principal Investigator.

5. FREQUENCY OF MEETINGS

It is proposed that the TMG meets every 2 months with the provision for extraordinary meetings to be called at short notice as required.

6. REPORTING ARRANGEMENTS

Reports to R&D Committee (minutes to be sent).

7. EFFECTIVENESS

The effectiveness of the terms of reference will be assessed annually by the TMG.

8. ACTION

- Circulate this ToR to all relevant personnel requesting any feedback be sent to the R&D Manager.

9. RECOMMENDATION

The TMG are asked to endorse the outlined TMG Terms of Reference.

Appendix 2

HTA's Guidelines
Trial Steering Committee (TSC)

https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

After funding has been approved by the HTA, investigators are required to nominate to the HTA an independent chair and members for a TSC. Investigators should contact nominees to ascertain their availability and willingness to be appointed. The NIHR HTA Programme Director, will formally appoint the Chair and Members by letter.

The role of the TSC
The role of the TSC is to provide overall supervision for a trial on behalf of the Trial Sponsor and Trial Funder and to ensure that the trial is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. It should be noted that the day-to-day management of the trial is the responsibility of the Chief Investigator, and as such the Chief Investigator may wish to set up a separate Trial Management Group (TMG) to assist with this function.

The main features of the TSC are as follows:
- To provide advice, through its Chair, to the Chief Investigator(s), the Trial Sponsor, the Trial Funder, the Host Institution and the Contractor on all appropriate aspects of the trial.
- To concentrate on progress of the trial, adherence to the protocol, patient safety and the consideration of new information of relevance to the research question.
- The rights, safety and well-being of the trial participants are the most important considerations and should prevail over the interests of science and society.
- To ensure appropriate ethical and other approvals are obtained in line with the project plan.
- To agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments.
- To provide advice to the investigators on all aspects of the trial.

Standard Constitution TSC
The following list identifies the minimum constitution requirements, a set of outline terms of reference, and the primary reporting line for TSCs:
- All primary research projects are required to establish a TSC.
- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members.
- All TSCs are to have an independent chair.
- All TSCs are to have a minimum of 75% majority of independent members.
- Only appointed members will be entitled to vote and the chair will have a casting vote.
- The minimum quoracy for a meeting to conduct business is 67% of appointed members.
- The chair and members to sign and maintain a log of potential conflicts and/or interests.
- Attendance at TSC meetings by non-members is at the discretion of the chair.
- The primary TSC reporting line is via the chair to the NIHR HTA Programme Director.

Composition of the TSC
- An independent chair (UK based and/or holding a substantive UK based appointment).
- Independent clinicians with relevant expertise.
- Independent statisticians/epidemiologists/diagnosticians with relevant expertise.
- At least one individual who is able to contribute a patient and/or wider public perspective.
- Ideally, the TSC should invite observers, including a representative of the sponsor and a representative from the research network to meetings.
- An indication of any proposed overseas members should have been given at the full application stage and feedback on such proposals supplied following the Commissioning Board's consideration of the application.

- Although there may be periods when more frequent meetings are necessary, the TSC should meet at least annually.
- Meetings should be scheduled to follow shortly after DMC meetings so that reports from that group can be considered.
- Minutes of meetings should be sent to all members, the Sponsor, the Funder and the TSC, and filed in the Trial Master File.
- The responsibility for calling and organising TSC meetings lies with the Chief Investigator, in association with the Chair.
- There may be occasions when the Trial Sponsor or the Trial Funder will wish to organise and administer these meetings for particular trials.
- In the NIHR HTA programme's case this is unlikely, but it reserves the right to attend any meeting and the right to convene a meeting of the TSC in exceptional circumstances.

The Role of the Chair of TSC

The Chair of the TSC is directly answerable to the NIHR HTA programme, as funder. The Chair's responsibilities include:

- Arranging an inaugural meeting to finalise the protocol and to set up a schedule of meetings to align with the project plan.
- Establishing clear reporting lines – to the Funder, Sponsor, etc.
- Being familiar with relevant guidance documents and with the role of the DMC.
- Providing an independent, experienced opinion if conflicts arise between the needs of the research team, the funder, the sponsor, the participating organisations and/or any other agencies.
- Leading the TSC to provide regular, impartial oversight of the trial, especially to identify and pre-empt problems.
- Ensuring that changes to the protocol are debated and endorsed by the TSC; letters of endorsement should be made available to the project team when requesting approval from the funder and sponsor for matters such as changes to protocol.
- Being available to provide independent advice as required, not just when TSC meetings are scheduled.
- Commenting on any extension requests and, where appropriate, providing a letter of recommendation to accompany such a request.
- Commenting in detail (when appropriate) regarding the continuation or termination of the project.

Independence

The definition of independent is as follows:

- Not part of the same institution as any of the applicants or members of the project team.
- Not part of the same institution that is acting as a recruitment or investigative centre.
- Not related to any of the applicants or members of the project team.
- For the chair only – not an applicant on a rival proposal.

Appendix 3

HTA's Guidelines
Data Monitoring Committee (DMC)

https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

The role of the DMC

The DMCs main role is as follows:

- It is the only body involved in a trial that has access to the unblinded comparative data.
- The role of its members is to monitor these data and make recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue.
- The safety, rights and well-being of the trial participants are paramount.
- The DMC considers whether an interim analysis is necessary, considers the data from any analysis and advises the TSC regarding the release of data and/or information.
- The DMC may be asked by the TSC, Trial Sponsor or Trial Funder to consider data emerging from other related studies.
- If funding is required above the level originally requested, the DMC may be asked by the Chief Investigator, TSC, Trial Sponsor or Trial Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not unblind the trial.
- Membership of the DMC should be completely independent, small (3- 4 members) and comprise experts in the field, e.g. a clinician with experience in the relevant area and expert trial statistician.
- Responsibility for calling and organising DMC meetings lies with the Chief Investigator, in association with the Chair of the DMC. The project team should provide the DMC with a comprehensive report, the content of which should be agreed in advance by the Chair of the DMC.
- The DMC should meet at least annually, or more often as appropriate, and meetings should be timed so that reports can be fed into the TSC.
- Minutes of meetings should be sent to all members, the Sponsor, the Funder, the TSC and filed in the Trial Master File. It should be noted that the minutes may have 'in camera' items redacted from some copies.

Standard Constitution DMC

The following list identifies the minimum constitution requirements, a set of outline terms of reference and the primary reporting line for the DMC:

- Most primary research projects are required to establish a DMC.
- The NIHR HTA Programme Director will vet the nominees and appoint the chair and members.
- All DMC members are to be independent (with at least one member being UK based and/or holding a substantive UK based appointment).
- Only appointed members will be entitled to vote and the chair will have a casting vote.
- The minimum quoracy for a meeting to conduct business is 67% of appointed members.
- The chair and members to sign and maintain a log of potential conflicts and/or interests.
- Attendance at DMC meetings by non-members is at the discretion of the chair.
- The primary DMC reporting line is via the chair to the TSC.

Independence

The definition of independent is as follows:

- Not the Chief Investigator or a member of the TSC.
- Not part of the same institution as any of the applicants or members of the project team.
- Not part of the same institution that is acting as a recruitment or investigative centre.
- Not related to any of the applicants or members of the project team
- For the chair only - not an applicant on a rival proposal.