University of Hertfordshire UH

University of Hertfordshire

SPONSOR OVERSIGHT

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the
Management and Organisational Oversight of University of Hertfordshire
Sponsored/Co-sponsored Clinical Trials

SOP Number: gSOP-11-01	**Effective Date:** 26th April 2018
Version Number: v1.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire standard operating procedure. This document describes the procedures for the management and organisational oversight of University of Hertfordshire (UH) sponsored/co-sponsored clinical trials. University of Hertfordshire (UH) acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

The sponsor shall ensure that the relevant trial oversight committees (Trial Management Group, Trial Steering Committee, Dose Escalation Group, Data Monitoring Committee and Independent Data Monitoring Committee where applicable) are employed to ensure that the rights, safety and well-being of the trial participants are protected and to ensure that the trial is conducted, recorded and reported in accordance with the currently approved protocol and any amendments, SOPs, Good Clinical Practice and with the applicable clinical trial regulations.

This SOP is specifically for Clinical Trials of Investigational Medicinal Products, however in the absence of a documented procedure can be used as guidance for any other clinical study.

2.0 PURPOSE

- To specify which local management and organisational oversight groups should be in place for both single centre and multicentre UH Sponsored/co-sponsored clinical trials
- To outline the roles of the sponsor/co-sponsor, Clinical Trials Support Network (CTSN), Clinical Trial Statistician, NHS R&D Department and Chief Investigator (or Designated Individual) in the management and organisational oversight for single centre and multicentre clinical trials.
- To outline the procedures for implementation and management of the respective oversight committee structures established for single and multicentre trials (appendix 2)

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including: Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Clinical Trial Pharmacists, Research Managers, Statisticians, Research nurses, Allied Health Professionals, Trial Coordinators, CTSN, NHS R&D Department & Data Managers.

4.0 RESPONSIBILITIES

4.1 The **Sponsor** shall ensure that there is a standard set of requirements for the management and oversight of both single centre and multicentre clinical trials that ensures appropriate levels of both local management and organisational oversight. This will complement the continual programme of clinical trials monitoring and audit conducted by the sponsor and existing systems for reporting on trial progress to the CTSN/CTSNMG. A project-specific Sponsor oversight arrangement for co-sponsored studies that incorporate the requirements of co-sponsoring organisations may be developed.

4.2 The **Clinical Trial Support Network Management Group (CTSNMG)** shall ensure that all UH sponsored/co-sponsored clinical trials:

a) Have an appropriate level of management and organisational oversight, which will be determined before the trial commences
b) Have an appropriate membership composition for trials requiring the formation of a Data Monitoring Committee(DMC)/Independent Data Monitoring Committee (IDMC) (see appendix 2)
c) Are monitored to assess the progress of CTIMP trials by reviewing all reports/ recommendations produced by the DMC/IDMC and trial steering committee (see section 6.0 for guidance)

4.3 The **Clinical Study Statistician** will ensure that the following responsibilities are carried out:

a) Create the first draft of the DMC/IDMC terms of reference, which will then be reviewed by all members of the DMC/IDMC and CI (or DI) before being finalised
b) Make any amendments to the DMC/IDMC terms of reference as required during the study
c) Liaise with the trial coordinator/data manager to ensure they are notified of any information on the Serious Adverse Events that may have occurred on the trial up to that point. This should take place at least four weeks before a DMC/IDMC meeting
d) Ensure that the data in the trial database is analysed and commence writing the report to the DMC/IDMC at least two weeks before the meeting
e) Produce the DMC/IDMC report and distribute it to members of the DMC/IDMC at least 1 week before the meeting. This is to ensure that there is a sufficient interim period for the members to review the report and consider whether they require a study statistician and/or CI (or DI) to be present at the meeting
f) Ensure they are available, to attend the DMC/IDMC meeting and guide the committee through the report if required

4.4 For UH sponsored/co-sponsored clinical studies the **CTSN** shall ensure that all the following responsibilities are carried out:

a) Review the oversight requirements as part of the governance checks and suggest requirements to the CTNSMG where necessary
b) Maintain records of activity of the oversight committee meetings and facilitate the review of

the recommendations outlined by the respective oversight committee group by the CTNSMG.

c) Facilitate provision of any feedback from the CTSNMG to the CI and/or designee following review of the recommendations outlined by the respective oversight committee where required.
d) Attend Trial Management Group /research team meetings as appropriate to ensure governance issues are highlighted and complied with correctly. The CTSN will ensure that any potential serious breaches identified or discussed at these meetings are escalated to the Advisory Group Research Governance for Clinical Studies where necessary.

4.5 The **Chief Investigator and/or Delegated Individual** shall ensure the following responsibilities are carried out:

a) That the required oversight committee structure is incorporated into the design of the study protocol at the time of initial submission to the CTSN for review by the CTSNMG (Appendix 2)
b) That all persons involved in the trial including the Study Statistician, Trial Coordinators/Data Manager, Research Nurses, Allied Health Professionals and the CTSN are made aware that a DMC/IDMC meeting has been organised
c) Review the status of the study database is reviewed at least 4 weeks before a scheduled DMC/IDMC meeting, and ensure that any required **data locks** have been completed at least 2 weeks prior to the DMC/IDMC meeting
d) That the Study Statistician is made aware of any other relevant information for the DMC/IDMC report
e) Facilitate the CTSN attendance during research team meetings/Trial Management Group meetings (as required)
f) Assist in facilitating the Organisational Oversight Committee's meetings in whatever ways are deemed necessary by CTSNMG
g) Abide by any recommendations that the DMC/IDMC, Trial Steering Committee or sponsor/CTSNMG require

4.6 Where responsibility for investigational product(s) accountability at the trial site has been delegated to the NHS Pharmacy Department, the **Clinical Trials Pharmacist** shall ensure the following responsibilities are carried out:

a) All records of the investigational product's delivery, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product is maintained. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product and trial subjects
b) That the investigational product is stored as specified in the protocol and in accordance with applicable regulatory requirement(s)
c) That the investigational product is only used in accordance with the approved protocol

5.0 PROCEDURE

5.1 The CTSNMG will decide on the level of oversight required for each study using Appendix 2 as a guideline during the scheduled CTSNMG meetings.

5.2 The CTSNMG will state the oversight requirements for the study. The CTSNMG will define a timeframe within which the first DMC/IDMC meeting should have occurred and will identify that the recommendations outlined by the oversight committee must be reviewed by the CTSNMG.

5.3 The DMC/IDMC should report their recommendations in a letter or report to the CI electronically. The chair of the CTSNMG should be copied into this email who will in turn ensure that the recommendations are reviewed by a member of the CTSNMG (usually the original reviewer of the study) If there is any information in the recommendations that is thought not to be shared with the CI, then the recommendations should only be sent to the Study Statistician. In this case, the Study Statistician should also be advised what to report to the CI. These recommendations should be filed in the appropriate electronic folder along with the DMC/IDMC report by the Study Statistician.

5.4 The CI should ensure that recommendations raised by the DMC/IDMC are responded to and address the issues raised in the recommendations.

5.5 The CTSN should ensure that records are maintained identifying the activity of study specific oversight committees. A member of the CTSN will attend research team meetings/scheduled TMG meetings (where required) to assist with the resolution of any governance issues that may occur.

5.6 A written acknowledgement will be issued following the review of the recommendations outlined by the DMC/IDMC to the CI by the CTSNMG and will detail any additional recommendations made by the CTSNMG to the CI. This written response should be maintained within the TMF by the CI and/or DI.

6.0 RELATED DOCUMENTS

- gSOP-02 Adverse Event Reporting (Sponsored/co-sponsored)
- gSOP-06 TMF/Site File
- gSOP-10 Serious Breaches (Sponsored)
- gSOP-33 Risk Assessment
- CTSNMG Terms of Reference
- AGRGCS Terms of Reference
- UH Research Policy Framework – Escalation Plan

7.0 APPENDICES

- Appendix 1 - Definitions
- Appendix 2 - Requirements for the management and oversight of UH sponsored/co-sponsored clinical studies

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**

9.0 AUTHORSHIP & APPROVAL

Author

Signature **Date**

Pro Vice Chancellor (Research & Enterprise) Approval

Signature **Date**

10.0 AGREEMENT

Please detach and retain in your training files

I have read and understood the contents and requirements of this SOP (gSOP-11-01) and accept to follow UH policies implementing it.

Recipient

Signature: ……Date: ……..

Name & Position: ……..

Appendix 1: Definitions

Adverse Event (AE)
Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Chief Investigator (CI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

Clinical Trial
A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

Clinical Trial of Investigational Medicinal Product (CTIMP)

A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

Data Lock Point
This should be the last day of the one year reporting period and the DSUR should be submitted to the MHRA and the REC no later than 60 days after the data lock date.

Data Monitoring Committee (DMC): A group of experts (including Clinical experts, Statisticians and if appropriate Ethicists and Patient Advocates) not associated with the trial that monitor safety and efficacy data while a trial is ongoing. The role of the Data Monitoring Committee 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 may comprise of UH staff who are independent from the study, but specialists who are independent from UH can also be included. As a minimum, an Independent Chair, Statistician and Clinician to the study should be present during DMC meetings.

Delegated Individual (DI)
An individual delegated by the PI to carry out their task(s).

Good Clinical Practice (GCP)
As defined in the Regulations.

Independent Data Monitoring Committee (IDMC)
A group of experts (including Clinical Experts, Statisticians and if appropriate Ethicists and Patient Advocates) not associated with the trial and all independent of UH that monitor safety and efficacy data while a trial is ongoing. The role of the Independent Data Monitoring Committee 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.

International Conference on Harmonisation (ICH)
The ICH produced a series of guidelines in 1996, E6 being the guideline on Good Clinical Practice, otherwise known as (ICH-GCP).

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

(a) used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
(b) used for an indication not included in the summary of product characteristics under the authorisation for that product, or
(c) used to gain further information about the form of that product as authorised under the authorisation

Principal Investigator (PI)
A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any untoward medical occurrence or effect that at any dose results in:
- Death
- Is life-threatening*
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

* "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

The Regulations
Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

Trial Management Group (TMG): The Trial Management Group for each trial is set up to oversee the clinical and practical aspects of the day to day management of the trial. The TMG normally includes individuals such as the Chief Investigator, Trial Physician(s), Statistician, Trial Coordinator, Research Nurse, and Data Manager(s). The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

Trial Master File
The Trial Master File (TMF) will be held at the principal site by the sponsor, Chief Investigator or at the co-ordinating Centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A Trial Master File should be set up at the beginning of a trial and maintained up-to-date throughout the trial until trial conclusion.

For trials currently running, it is recommended that Section 8 of the ICH-GCP Guideline is followed as guidance in order to meet statutory requirements. However, some of the documents listed may not be available or applicable in many non-commercial trials. The appropriate documentation will vary according to the trial and sponsor requirements.

Trial Steering Committee (TSC): The role of the Trial Steering Committee is to provide overall supervision and monitoring of the trial towards its interim and overall objectives and to oversee adherence to the protocol and patient safety. The Trial Steering Committee should accept the approved trial protocol and agree on subsequent amendments to the study protocol before they are submitted to the sponsor. In addition the TSC should provide advice to the investigators on all

aspects to the trial. A Trial Steering Committee should have members who are independent of the investigators (i.e. independent to the study). Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the Trial Steering Committee, taking into account reports/advice of the (I)DMC.

Appendix 2: Requirements for the management and oversight of UH sponsored/co-sponsored clinical trials

Single Centre Clinical Trials (50 patients' maximum)

Single centre clinical trials should be managed by a local Trial Management Group (TMG). The Trial Management Group must include individuals who are responsible for the day to day management of the trial for example the CI, Trial Coordinator, Statistician, Research Nurse and Data Manager. This would usually be part of the research team meeting, where all staff involved in the trial contributes to discussion around trial progress, in particular reviewing adverse events. The frequency of TMG meetings is not mandated but is likely to be greater initially (2-3 times per year) ensuring that a minimum of 1 meeting is held annually. The frequency may reduce once the trial is in follow up (once a year or as required).

The frequency of meetings should be stated in the trial protocol or monitoring plan which will be approved by the CTSNMG.

The CI/DI should ensure that minutes from all TMG meetings are maintained and where necessary issues which require escalation should be highlighted to the Sponsor. A copy of the minutes, approved by the CI or DI should be retained within the Trial Master File. Email approval of any documentation, including the minutes is considered sufficient. The Clinical Trial Coordinators/Data Managers should monitor the action points and ensure members understand and undertake actions agreed at this meeting. Where necessary issues identified which require escalation to the Sponsor should be communicated to the CTSN.

Single centre trials will be subject to external audit and monitoring by the CTSN.

Single Centre Clinical Trials (In excess of 50 patients)

For Single Centre Trials with a recruitment target in excess of 50 patients a TMG must be set up as detailed above. In addition a Data Monitoring Committee should be established, the membership of which will be formally agreed by the CTSNMG. The DMC may be comprised of UH staff and as a minimum should comprise a Chair, Trial Statistician and a further Clinician. Alternatively DMC members maybe from other institutions. The CI will be invited to suggest suitable candidates for the DMC, and it may be appropriate for a DMC to take responsibility for a number of clinical trials in similar areas of investigation.

The role of the DMC should be to safeguard the interests of the trial participants, monitor the main outcome measures, including safety and efficacy, and monitor the overall conduct of the trial. The DMC should meet at least annually. For high risk studies additional meetings of the DMC should be convened at the discretion of the sponsor and/or the DMC.

Single Centre Trials will be subject to external audit and monitoring by the CTSN.

Multi Centre Trials (Maximum 3 centres)

For such studies a Trial management group must be established and should include representation from all of the participating centres. The frequency of TMG meetings should occur at least every 3 months and may occur more frequently for high risk studies.

A Data Monitoring Committee must also be established. The membership of which will be formally agreed by the CTSNMG. The DMC may be comprised of UH staff and as a minimum should comprise a Chair, Trial Statistician and a further Clinician. Alternatively DMC members maybe from other institutions.

The CI will be invited to suggest suitable candidates for the DMC,
and it may be appropriate for a DMC to take responsibility for a number of clinical trials in similar areas of investigation. The DMC meeting should convene at least annually but can be convened more frequently at the discretion of the sponsor and/or DMC.

Evidence of systems for monitoring the conduct of trial activity at participating sites is required prior to CTSNMG approval and should include both systems for central monitoring of participating sites and arrangements for onsite monitoring as may be required

Each group should have a defined constitution with terms of reference and a formal schedule of meeting dates. In order to ensure DMC meetings carry out their full purpose for the clinical trials, a charter should be produced by the clinical trial statistician to provide a clear structure for these meetings.

Trials Exceeding 3 Centres

In order for UH to accept sponsorship of larger multi centre trials, the research team would be required to formally establish:

Evidence of systems for monitoring the conduct of trial activity at participating sites is required prior to CTSNMG approval and should include both systems for remote monitoring and arrangements for on-site source data verification.

1. A Trial Management Group (TMG)
2. A Trial Steering Committee (TSC)
3. An Independent Data Monitoring Committee (IDMC)

1. The Trial management group should include members from UH (as detailed in section 1.1) involved in trial design and conduct as well as representation from some/all of the coordinating centres.

2. The Chair of the Trial Steering Committee should be independent of the study team. Other members may include UH Clinicians or Scientists who are also independent of the Study Investigators.

3. Membership to the IDMC for such trials should be initiated and formally agreed by the CTSNMG during the set up of the trial. All IDMC members should be independent from UH. The frequency with which both the IDMC and TSC meetings convene must be at least annually but can be convened more frequently at the discretion of the sponsor and/or IDMC/TSC.

Multi Centre Trials will be subject to external audit and monitoring with monitoring from the CTSN.

Each group should have a defined constitution with terms of reference and a formal schedule of meeting dates. In order to ensure IDMC meetings carry out their full purpose for the clinical trials, a charter should be produced by the clinical trial statistician to provide a clear structure for these meetings.

Both the IDMC and the TSC should be established in accordance with MRC Guidelines.