SPONSOR OVERSIGHT

Research & Development

Standard Operating Procedure for the Management and Organisational Oversight of West Hertfordshire Hospitals NHS Trust Sponsored Clinical Trials

SOP Number: SOP-11-05	**Effective Date:** October 2021
Version Number: v05	**Review Date:** 2 - 3 years

1.0 BACKGROUND

This document sets out the procedures to be followed by all West Hertfordshire Hospitals Trust (WHHT) staff who are involved in the management and organisational oversight of WHHT sponsored clinical trials.

The Sponsor shall ensure that the relevant trial oversight committees (Trial Management Group (TMG), Trial Steering Committee, Dose Escalation Group, Data Monitoring Committee (DMC) and Independent Data Monitoring Committee (IDMC) 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 protocol, SOPs, Good Clinical Practice (GCP) and with the applicable clinical trial regulations, including the recent medical device guidance resulting from the EU exit (Regulating medical devices in the UK).

2.0 PURPOSE

- To specify which local management and organisational oversight groups should be in place for both single centre and multicentre WHHT sponsored Clinical Trials.
- To outline the roles of the Sponsor, Research & Development Steering Group (RDSG), Clinical Trial Statistician, R&D Department and Chief Investigator (CI) or Designated Individual (DI) 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

Any Trust employee involved with clinical research sponsored by WHHT including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Co-investigators, Consultants, Clinical Trial Pharmacists, Research Managers, Statisticians, Research nurses, Allied Health Professionals, Trial Coordinators, R&D Department, the Research & Development Steering Group (RDSG) & Data Managers.

4.0 RESPONSIBILITIES

4.1 Sponsor

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 R&D Office and existing systems for reporting on trial progress to R&D/RDSG.

4.2 Research & Development Steering Group (RDSG)

The RDSG shall ensure that all WHHT sponsored clinical trials:

- Have an appropriate level of management and organisational oversight, which will be determined before the trial is given RDSG approval
- Have an appropriate membership composition for trials requiring the formation of a DMC/IDMC
- Are monitored to assess the progress of Clinical Trials by reviewing all reports/ recommendations produced by the DMC/IDMC and trial steering committee (see section 5.0 for guidance)

4.3 Clinical Study Statistician

The Clinical Study Statistician will ensure that:

- The first draft of the DMC/IDMC charter is created, which will then be reviewed by all members of the DMC/IDMC and CI/DI before being finalised
- Any amendments to the DMC/IDMC charter are made as required during the study
- The Trial Coordinator/Data Manager are notified of any information on the Serious Adverse Events (SAEs) that may have occurred on the trial up to that point. This should take place at least four weeks before a DMC/IDMC meeting
- The data in the trial database is analysed and commence writing the report to the DMC/IDMC at least two weeks before the meeting
- The DMC/IDMC report is produced and distributed 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/DI to be present at the meeting
- They are available, to attend the DMC/IDMC meeting and guide the committee through the report if required

4.4 R&D Department

The Research and Development Department shall ensure that:

- The oversight requirements are reviewed, as part of the governance checks, and that these requirements are suggested to the RDSG where necessary
- A log of activity of the oversight committee meetings is maintained and the review of the recommendations outlined by the respective oversight committee group by the RDSG is facilitated
- Provision of any feedback from the RDSG to the CI/DI is facilitated following review of the recommendations outlined by the respective oversight committee
- The TMG/Research Team meetings are regularly attended to ensure governance issues are highlighted and complied with correctly. The R&D Department will ensure that any potential serious breaches identified or discussed at these meetings are escalated to the RDSG where necessary (see SOP-10).

4.5 Chief Investigator and/or Delegated Individual

The CI/DI shall ensure that:

- The required oversight committee structure is incorporated into the design of the study protocol at the time of initial submission to R&D for review by the RDSG (Appendix 2)
- All persons involved in the trial including the Study Statistician, Trial Coordinators, Data Managers, Research Nurses, Allied Health Professionals and the R&D Department are made aware that a DMC/IDMC meeting has been organised
- 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
- The Study Statistician is made aware of any other relevant information for the DMC/IDMC report
- The R&D Department's attendance is facilitated during research team meetings/TMG meetings (as required)
- The Organisational Oversight Committee's meetings are facilitated in whatever ways are deemed necessary by RDSG
- Any recommendations that the DMC/IDMC, Trial Steering Committee or Sponsor/RDSG require are abided by

4.6 Pharmacy

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

- All records of the investigational product's delivery, the inventory at the site, the use by each subject, 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
- The investigational product is stored as specified by the sponsor and in accordance with applicable regulatory requirement(s)
- The investigational product is only used in accordance with the approved protocol

5.0 PROCEDURE

5.0.1 The RDSG will decide on the level of oversight required for each study using Appendix 2 as a guideline during the scheduled RDSG meetings. The pre-RDSG comments prepared by the R&D Department for these meetings should also remark on necessary trial oversight.

5.0.2 The RDSG will state the oversight requirements for the study. The RDSG 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 RDSG. The RDSG will ensure that a formal invitation is made to staff who are to form part of the DMC/IDMC for the trial.

5.0.3 The DMC/IDMC should report their recommendations in a letter or report to the CI electronically. The Sponsor representative should be copied into this email who will in turn ensure that the recommendations are reviewed by a member of the RDSG (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.

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

5.0.5 The R&D Department should ensure that records are maintained identifying the activity of study

specific oversight committees. The R&D Department will attend Research Team meetings/scheduled TMG meetings (where required) to assist with the resolution of any governance issues that may occur.

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

6.0 RELATED DOCUMENTS

- SOP-02- SAEs (Sponsored)
- SOP-06- Trial Master File
- SOP-08- Role of CI, pharmacy, nuclear medicine and R&D
- SOP-10- Serious Breaches (Sponsored)
- SOP-33- Risk Assessment Process for CTIMPs

7.0 APPENDICES

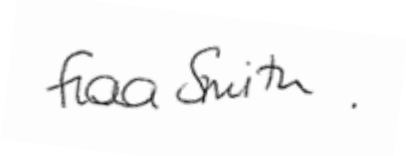
Appendix 1 - Definitions
Appendix 2 - Requirements for the management and oversight of WHHT sponsored CTIMPS

8.0 VERSION HISTORY

Revision Chronology:		
Version Number	**Effective Date**	**Reason for Change**
SOP-11-05	**October 2021**	1. Change from general Standard Operating Procedures (gSOP) to SOP 2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document' 3. Addition of new medical device guidance 4. Other minor changes and clarifications including the clarification that this applies to all Clinical Trials not just CTIMPs
gSOP-11-04	**October 2017**	Minor amendments following review
gSOP-11-03	**07/05/2014**	Minor amendments following review
gSOP-11-02		SOP modified for implementation at ENHT/WHHT
gSOP-11-01 (MVCC)		SOP modified for implementation at MVCC

9.0 AUTHORSHIP & APPROVAL

Author

Signature  **Date** 28/10/2021

R & D Steering Group Approval

Signature  **Date** 28/10/2021

Appendix 1: Definitions

Adverse Event (AE)
An unfavourable outcome that occurs during or after the use of a drug or other intervention, but is not necessarily caused by it.

Chief Investigator (CI)
The investigator with overall responsibility for the research. In a multi-site study, the CI has co-ordinating responsibility for research at all sites. All applications for ethical review should be submitted by the CI. For Trust sponsored trials, the CI had been delegated the pharmacovigilance responsibility for identification, recording and reporting of safety events, including submission of Development Safety Update Reports (DSURs) to the MHRA and REC.

Clinical Trial
A clinical study in which participants are assigned to receive one or more interventions (or no intervention) so that researchers can evaluate the effects of the interventions on biomedical or health-related outcomes. The assignments are determined by the study protocol. Participants may receive diagnostic, therapeutic, or other types of interventions. A Study Type.

Clinical Trial of Investigational Medicinal Product (CTIMP)
A clinical trial that is within the scope of the UK Medicines for Human Use (Clinical Trials) Regulations 2004. An investigation in human subjects, other than a non-interventional trial, intended: a) to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more medicinal products, b) to identify any adverse reactions, or c) to study absorption, distribution, metabolism and excretion, with the object of ascertaining the safety and/or efficacy of those products.

Data Lock Point
This should be the last day of the one year reporting period and the Development Update Safety Report (DSUR) should be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (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 DMC is to review the accruing trial data and to assess whether there are any safety issues that should be brought to participant's attention or any reasons for the trial not to continue. The DMC may comprise of WHHT staff who are independent from the study, but specialists who are independent from WHHT 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 a person of responsibility to carry out their task(s).

Good Clinical Practice (GCP)
Good Clinical Practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects.

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 WHHT that monitor safety and efficacy data while a trial is ongoing. The role of the Independent Data Monitoring Committee (IDMC) 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)
International Conference for Harmonisation, a collaboration between regulators and the

pharmaceutical industry in Europe, the United States and Japan to establish common standards for clinical trials. ICH GCP is a widely recognised standard for Good Clinical Practice in clinical trials.

Investigational Medicinal Products (IMP)
A pharmaceutical form of an active substance or placebo being tested, or to be tested, or used, or to be used, as a reference in a Clinical Trial, and 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)
The investigator responsible for the research site. There should be one PI for each research site. In the case of a single-site study, the chief investigator and the PI will normally be the same person.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)
Any adverse event or adverse reaction that results in:

- death
- is life-threatening*
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- or is a congenital anomaly or birth defect

Comment: Medical judgement should be exercised in deciding whether an adverse event/reaction should be classified as serious in other situations. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.
* Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject 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 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. 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 contains all essential documents held by the sponsor/Chief Investigator which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced.

Trial Steering Committee (TSC)
The role of the Trial Steering Committee (TSC) is to provide the overall supervision of the trial. Ideally, the TSC should include members who are independent of the investigators, their employing organisations, funders and sponsors. The TSC should monitor trial progress and conduct and advise on scientific credibility. The TSC will consider and act, as appropriate, upon the

recommendations of the Data Monitoring Committee (DMC) or equivalent and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

Appendix 2: Requirements for the management and oversight of WHHT sponsored CTIMPS

Single Centre Clinical Trials (50 patients' maximum)

Single centre clinical trials must 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 RDSG.

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 R&D Department.

Single centre trials will be subject to external audit and monitoring by the R&D Department.

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 RDSG. The DMC may be comprised of WHHT 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 R&D Department.

Multicentre 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 RDSG. The DMC may be comprised of WHHT 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 RDSG 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 WHHT to accept sponsorship of larger multicentre 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 RDSG 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 WHHT (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 WHHT 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 RDSG during the setup of the trial. Membership onto the IDMC will be through invitation, initiated by the RDSG. All IDMC members should be independent from WHHT. 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.

multicentre Trials will be subject to external audit and monitoring with monitoring from the R&D Department.

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.