

University of Hertfordshire

MONITORING

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for Monitoring UH Sponsored/co-sponsored/hosted clinical trials

SOP Number: gSOP-12-02	Effective Date: 10/08/22
Version Number: 2.0	Review Date: 3 years (or as required)

1. BACKGROUND

This is a University of Hertfordshire (UH) Standard Operating Procedure (SOP). SOPs are required to assist Researchers in conducting research in accordance with the principles of Good Clinical Practice (GCP) and relevant regulations and guidance.

Quality Assurance (QA) refers to all actions in place to ensure that clinical trials are performed to meet the requirements of GCP. Quality Control (QC) is a system put in place by QA and refers to the set of operational techniques and activities undertaken to verify that the requirements for quality of the trial related activities have been fulfilled. Monitoring has an integral role in the Quality Control (QC) of a clinical trial and is designed to verify the ongoing quality of the trial.

Monitoring is defined as:

‘The act of ‘overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, written procedures, GCP and applicable regulatory requirements.’ ICH GCP, section 1.38.

2. PURPOSE

The purpose of monitoring is to ensure that the safety, welfare and rights of the human subject are maintained and the reported trial data is accurate, complete and verifiable from the source documentation. Implementation of monitoring procedures as a quality control process ensures that where inherent risks associated with the trial intervention(s), vulnerabilities of the protocol design, ongoing trial conduct and risk-benefit profile of the intervention are identified, that effective approaches to mitigate these risks and resolve issues which may impact upon the human subject’s safety and/or integrity of trial data can be effectively implemented and overseen by the Sponsor/co-sponsor.

Monitoring is part of a multi-factoral approach to ensure the quality of research for all UH Sponsored/co-sponsored/hosted clinical trials. This SOP provides guidance on the

monitoring process including the procedure to be followed prior to, during and after a monitoring visit.

3. APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored/hosted by UH, including but not limited to: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Coordinators, Clinical Studies Officers, Data Managers and Research Assistants.

4. RESPONSIBILITIES

4.1 The Sponsor should ensure that;

- Each UH Sponsored/co-sponsored/hosted clinical trial has undergone a risk assessment (CTSN TP-30) and provided approval for the risk adapted monitoring plan.
- There is a standard set of requirements for the management and oversight to both single centre and multi centre clinical trials that ensures appropriate levels of both local management and organisational oversight (see gSOP-11).
- The clinical trial monitor/delegated individual is appropriately qualified and trained in order to have the scientific and/or clinical knowledge to monitor the trial adequately.
- Potential Serious Breaches of GCP and/or the study protocol identified through routine on site and/or central monitoring or through oversight committee meetings are reviewed through UH's Advisory Group for Research Governance of Clinical Studies (AGRGCS) in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s).

4.2 The CI (or delegated individual) should ensure that;

- The trial risk assessment form is completed as part of the application process. This should involve identifying and considering the main hazards inherent in the clinical trial protocol and risks associated with the IMP and/or other intervention(s) being tested.
- The appropriate oversight committee structure is incorporated into the design of the trial protocol at the time of the initial submission to the CTSN for review by the Clinical Trial Support Network Management Group (CTSNMG) (gSOP-11).
- Where a Sponsored/co-sponsored clinical trial has been initiated at a participating site(s) the trial site has the adequate qualifications, resources and facilities, including laboratories, equipment and staff, to safely and properly conduct the trial and that these remain adequate throughout the study period.
- Each participating site on a multi-centre clinical trial undergoes a formal initiation

prior to activation to recruit trial participants and is routinely monitored throughout the lifecycle of the trial utilising monitoring methods identified and described in the trial monitoring plan.

- Potential Serious Breaches of GCP and/or the study protocol identified through routine on site and/or central monitoring or through oversight committee meetings are reviewed through the AGRGCS in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s).

4.3 The NHS Clinical Trials Pharmacist (Clinical Trials of Investigational Medicinal Products (CTIMPs) only) should ensure that;

- The trial specific pharmacy pack is completed and approved by the Trust R&D for all multi-centre trials.
- Potential Serious Breaches of GCP and/or the study protocol identified through routine on site and/or central monitoring or through oversight committee meetings are reviewed through the AGRGCS in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s).

4.4 The CTSN manager and/or delegated trial team individual(s) appointed monitoring responsibilities for the Sponsored/co-sponsored/hosted clinical trial should ensure that;

- Appropriate monitoring plan(s) are developed and approved by the CTSNMG or member of the CTSN according to the assessed risk.
- An initiation visit is conducted for all single centre clinical trials, and for multicentre clinical trials where the trial is being initiated at participating sites, an initiation visit/meeting is completed by the delegated member of the trial coordinating team (see gSOP-18).
- Interim monitoring visits are conducted for single centre clinical trial and at a frequency and intensity specified in the trial monitoring plan. For multi-centre clinical trials the allocated monitor should oversee the specified monitoring processes for the participating site(s) which are performed by the designated member of the trial team.
- A close out monitoring visit is performed for all single centre clinical trials. For multi-centre clinical trials the allocated monitor should oversee the specified monitoring processes for the participating site(s) which are performed by the designated member of the trial team.
- Potential Serious Breaches of GCP and/or the study protocol identified through routine on site and/or central monitoring or through oversight committee meetings are reviewed through the AGRGCS in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s).

5 PROCEDURES

5.1 Extent & Scope of Monitoring

The Sponsor will determine the extent and nature of monitoring required for each sponsored/co-sponsored/hosted clinical trial which should be documented in the trial specific monitoring plan.

The content of the monitoring plan should be based upon the findings of the Sponsor's risk assessment. The Sponsor's risk assessment will identify the core risks inherent in the trial protocol, which impact upon participant safety and rights, and the reliability of the results.

The risk categorisation of the trial will be based upon the marketing status of the IMP (for CTIMPs) and the standard medical care, which in turn will determine the necessary trial procedures for monitoring the safety of the trial participants. In addition, the risk assessment will identify the potential vulnerabilities in the trial design and methodology. A combination of analysis of the inherent risk of the intervention, trial design and methodology in addition to other risk factors (assessment of trial site(s) (where applicable), facilities, experience and training needs of study staff) will determine the focus and intensity of monitoring activity to be performed and the level of management and organisational oversight required for the trial (see also gSOP-11). A Quality Management Monitoring Plan (QMMP) or Monitoring Plan will be written dependent on the assessed risk. In addition, a Safety Management Plan may also be written dependent on the assessed risk.

For all Sponsored/co-sponsored/hosted clinical trials a combination of monitoring methods may be employed which should be trial specific and documented in the monitoring plan and/or trial protocol.

These may include;

- Trial Oversight Structures (Trial Management Group (TMG), Data Monitoring Committee (DMC)/ Independent Data Monitoring Committee (IDMC)) (see gSOP-11)
- On site Monitoring
- Central Monitoring of Trial conduct and data and monitoring activity through the use of meetings/ teleconferences and telephone calls which do not require on site monitoring (see section 5.4).

5.2 Trial Specific Monitoring plan development and Appointment of the Clinical Trial Monitor

The Completion of this document should involve a multidisciplinary approach and involve the Chief Investigator (CI) or delegated individual.

The completed risk assessment and associated monitoring plan(s) (QMMP/ Monitoring Plan/Safety Monitoring Plan) will form the basis of common understanding by all the stakeholders (Sponsor, Investigators, regulators, funders, research governance staff, pharmacy) on the risk of that trial and facilitate a risk proportionate approach to the monitoring of the trial. The extent of safety and data monitoring to be employed for a trial will have implications for the funding and resources required, and as a result it is

recommended that consideration for the extent and scope of monitoring to be employed is made during the initial application and protocol development stage for all Sponsored/co-sponsored/hosted clinical trials. The monitoring plan(s) should be approved by the CTSN/AGRGCS during the set up of the trial.

The trial risk assessment should be revisited periodically over the life cycle of the trial to take into account new information and emergent unanticipated risks that have become apparent after the start of the trial. These may require modification(s) to the extent and nature of monitoring being implemented which require subsequent adaptation to the trial monitoring plans. These changes should be approved by the Sponsor.

The appointment of the trial monitor and designated monitoring responsibilities should be documented in the trial specific monitoring plan. Monitoring activity, however, may be delegated to specific research team members (e.g., trial coordinator, medical monitor, trial manager, data manager). Monitoring responsibilities and applicable personnel should be documented in the monitoring plan.

5.3 Monitoring visit pattern

Single Centre trials

In all cases the Monitor or delegated individual should conduct a study initiation visit (gSOP-18)/ pre-activation meeting and a close out visit (gSOP-21). Interim monitoring visits should be conducted a frequency specified in the study monitoring plan. All single centre trials should be set up to ensure that the appropriate oversight committee structure is established and agreed by the CTSNMG. Oversight committees should meet at a frequency agreed by the CTSNMG as specified in the trial protocol and trial monitoring plan (gSOP11-01).

Multi-centre trials

The procedures for monitoring participating sites will be based on the risk adapted monitoring approach specified in the study specific monitoring plan. Participating sites may be subject to a combination of central and/ or on site monitoring depending on the outcome of the risk assessment. Where multi-centre sites have not been specified to require on site monitoring, a triggered on site visit should be performed under the following circumstances;

- Concern(s) by the CI, TT or TMG raised by a central data review.
- Sites generating a high volume of data queries which are not resolved in a timely manner or with expected quality.
- Sites not entering data or responding to queries within the timelines defined in the Data Management Plan.
- Inappropriate treatment (intervention).
- Concerns are raised regarding review of consent forms.
- High rates of withdrawal.
- Non-conformance issues, serious breaches of protocol or GCP.

Any sites that are causing concern will be reviewed by the Trial Management Group and followed up accordingly.

Site visits may be performed if emergent risks occur during the course of the trial. The

monitoring plan should be amended to reflect the response to these emergent risks.

5.4 Study Initiation Visit

A study initiation visit/meeting should take place before recruitment begins at any recruiting site. Procedures for this are outlined in UH gSOP-18 Study Initiation.

5.5 Interim on site Monitoring Visit(s)

The completion of interim on site monitoring visits is applicable to single centre trials and multi centre trials where on site monitoring has been identified as a requirement following the study risk assessment. For multi-centre trials where on site monitoring is required the responsibility for monitoring may be delegated and should be defined in the monitoring plan. The Sponsor should ensure that the monitor is adequately qualified and trained to perform the monitoring duties pertinent to that trial in such circumstances.

The monitor/designated individual should follow procedures outlined in the monitoring plan and should ensure that the interim monitoring visit report is completed at a frequency defined in the monitoring plan. A monitoring visit log is to be completed at each visit (TP-06).

If routine interim monitoring visits identify any individual events, or a series of events which may be considered a potential serious Breach of GCP/protocol the monitor/designated individual should ensure that the findings are escalated to the CI/PI and Sponsor as soon as possible after they are identified. The escalation process for reporting potential breaches described in gSOP-10 should be followed.

5.6 Central Monitoring and Oversight

The CI/delegated individual should employ a number of different approaches and techniques to monitor the conduct and progress of the trial centrally. This is applicable to both single and multi-centre trials. Procedures to be employed for central monitoring should be defined in the monitoring plan. The methods employed may include but should not be limited to the following;

- Eligibility checks prior to randomisation (where applicable).
- Rates of recruitment, withdrawals and losses to follow up by site.
- Monitoring trial progress from the coordinating centre by the trial team.
- Resolving trial related issues by telephone/email.
- Ongoing training/meetings and teleconferences.
- Documented telephone conversations.
- Checks for missing or invalid data (range and consistency checks).
- Checks that dose adjustments, investigation and management of events are consistent with the protocol.
- Calendar checks.
- Checks for unusual data patterns.
- Assessment of adverse events and toxicity reporting rates.
- Case Report Forms (CRFs) completed by authorised persons.
- Database validation checks.
- External verification (with participant consent) of events (e.g. birth, disease and death registries).
- Web enabled training.

- Ongoing training/meetings and teleconferences.

5.6.1 Trial Oversight Committees

The appropriate level of oversight committee structure should be established during the design of the study protocol and should be proportional to the study design and risk. Procedures for the management of oversight committees and the composition, frequency and structure of committee membership and planned meetings should be detailed in the trial protocol, Committee Terms of Reference and specified in trial specific monitoring plan (UH gSOP-11)

5.7 Study close out monitoring procedures

A close out visit should be performed as soon as practical after the “last patient last visit” or following the premature termination of the trial/ site and after the specified monitoring activity for the trial has been completed.

As part of the close down procedures the monitor/ designated individual should ensure that the monitoring close out checklist is completed and required follow up corrective actions completed by the study CI/ site team and respective pharmacy department as required.

6. RELATED DOCUMENTS

- UH gSOP-02 – Adverse Event Reporting CTIMP (Sponsored/co-sponsored)
- UH gSOP-04 – Informed Consent
- UH gSOP-06 - Trial Master File/Site File
- UH gSOP-07 – Research Staff Training
- UH gSOP-09 - Amendments
- UH gSOP-10 – Serious Breaches
- UH gSOP-11 – Sponsor Oversight
- UH gSOP-13 – Research Applications
- UH gSOP-14 - Writing Research Protocols
- UH gSOP-16 – Development Safety Update Reports
- UH gSOP-17- Archiving
- UH gSOP-18 - Study Initiation
- UH gSOP-21- End of Trial Procedures
- UH gSOP-22 - End of Trial Study Reports
- UH gSOP-28 - Management of Source Data
- CTSN TP-30 Risk Assessment
- CTSN TP-80 Quality Management and Monitoring Plan
- CTSN TP-81 Monitoring Plan
- CTSN TP- 82 Safety Management Plan template
- UH CTSN QMTG Framework
- CTSN GU-07 – Central and On-site Monitoring
- CTSN TP5.1 – Monitoring Source Data Verification Tool
- CTSN TP-06 – Monitoring Visit Log
- CTSN TP-23 – Monitoring Report Template
- CTSN TP-32 – ISF Review Checklist

- CTSN TP-34 Trial Steering Committee ToR
- CTSN TP-38 Data Monitoring and Ethics Committee ToRMRC/DH/MHRA Joint project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Version 10th October 2011
- UK Policy Framework for Health and Social Care research 2017
- The Medicines for Human Use (Clinical Trials) Regulations 2004

7. APPENDICES

- Appendix 1 – Definitions

8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change
2.0	10 Aug 2022	Review of content Expanding scope to all clinical trials not just CTIMPs

9. AUTHORSHIP & APPROVAL

Author

Signature  Date 23/07/2022

**Pro Vice-Chancellor (Research & Enterprise) Approval
Professor J M Senior**

Signature  Date 08/08/2022

10.0 AGREEMENT

Please detach and retain within your training files

I have read and understood the contents and requirements of this SOP (SOP-12-02) 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)

The individual responsible for the conduct of the whole project. For CTIMPs this must be 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.

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 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)

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)

The individual responsible for conduct of the trial at a host site. For CTIMPs this must be 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 TMG 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, CI 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 TMF 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 TSC 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 TSC 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.

Quality Assurance (QA) – refers to all actions in place to ensure that clinical trials are performed to meet the requirements of Good Clinical Practice (GCP).

Quality Control (QC) - a system put in place by QA and refers to the set of operational techniques and activities undertaken to verify that the requirements for quality of the trial related activities have been fulfilled.