# Monitoring

## Research & Development

## Standard Operating Procedure for Monitoring of Sponsored Clinical Trials

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| **SOP Number :** SOP-12-04 | **Effective Date:** October 2021 |
| **Version Number:** v04 | **Review Date:** 2-3 years |

### 1.0 BACKGROUND

This document sets out the roles, responsibilities and procedures to be followed by West Herts Hospitals Trust (WHHT) staff are involved in the monitoring of research studies.

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

### 2.0 PURPOSE

Monitoring is an integral process in the Quality Control (QC) of sponsored Clinical Trials, including of an Investigational Medicinal Product (CTIMPs), and is the act of overseeing the progress of the clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, applicable SOPs & policies, Good Clinical Practice (GCP), and the applicable regulatory requirement(s). The purpose of monitoring is to ensure that the safety, welfare and rights of the human subject is 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 Investigational Medicinal Product (IMP), or device, vulnerabilities of the protocol design, ongoing trial conduct and risk-benefit profile of the IMP 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.

Monitoring is part of a multifactorial approach to ensuring the quality of research for all sponsored Clinical Trials.

### 2.1 Extent & Scope of Monitoring

The Sponsor will determine the extent and nature of monitoring required for each sponsored 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 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 also identify the potential vulnerabilities in the trial design and methodology. A combination of analysis of the inherent risk of the IMP or device, 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 SOP-11)

As part of the risk adaptive approach assessment to determine the required extent, focus, method and intensity level of monitoring to be performed for an individual trial, the trial risk based strategy summary sheet should be completed as part of the trial monitoring plan.

For all sponsored 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 SOP 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)

## 2.2 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 (DI).

The completed risk assessment and associated monitoring plan will form the basis of common understanding by all the stakeholders (Sponsor, investigators, regulators, funders, R&D 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 CTIMPs. The monitoring plan should be approved by the Research & Development Steering Group (RDSG) and submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) alongside the Clinical Trials Authorisation (CTA) application during the setup of the trial. The final monitoring plan should receive approval by the RDSG.

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 plan. These changes should be approved by the Sponsor and provided to the MHRA for information only.

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.

## 3.0 APPLICABLE TO

Any Trust employee involved with clinical research including, but not limited to, Chief Investigators (CI), Principal Investigators (PI), Co-Investigators, Consultants, Clinical Trial Pharmacists, Research Managers, Research Nurses, Allied Health Professionals, Trial Coordinators and Data Managers.

## 4.0 RESPONSIBILITIES

### 4.1 The Sponsor

The Sponsor should ensure that:

- Each Trust sponsored Clinical Trial has undergone a risk assessment 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 multicentre Clinical Trials that ensures appropriate levels of both local management and organisational oversight (see SOP 11)
- The Clinical Trial Monitor/DI 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 the Trust's RDSG in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s) (see SOP-10).

### 4.2 The Chief Investigator

The CI/DI 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 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 R&D Department for review by the RDSG (see SOP-11).
- Where a 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 multicentre 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 RDSG 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 Pharmacy

The Clinical Trials Pharmacist should ensure that:

- The trial specific pharmacy pack is completed and approved by the RDSG for all multicentre 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 Trust's RDSG in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s) (see SOP-10).

**4.5 The R&D Department**

The Associate Director of R&D and/or delegated trial team individual(s) appointed monitoring responsibilities for the sponsored Clinical Trial should ensure that:

- A trial specific monitoring plan is developed and approved by the RDSG.

- An initiation visit is conducted for all single centre Clinical Trials, and 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 SOP-18).

- Interim monitoring visits are conducted for single centre Clinical Trials and at a frequency and intensity specified in the trial monitoring plan. For multicentre 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 multicentre 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 RDSG in order to determine the appropriate approach to take with respect to corrective action(s), expedited reporting and implementation of preventative measure(s) (see SOP-10).

**5.0 PROCEDURES**

**5.1 Monitoring visit pattern**

5.1.1 **Single centre trials**

In all cases the Monitor/DI should conduct a study initiation visit/pre-activation meeting and a close out visit. Interim monitoring visits should be conducted at 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 RDSG. Oversight committees should meet at a frequency agreed by the RDSG as specified in the trial protocol and trial monitoring plan (see SOP 11).

5.1.2 **Multicentre 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 multicentre sites have not been specified to require on site monitoring, a triggered on site visit should be performed under the following circumstances;

- Quality concerns at site following central monitoring checks
- Clinical Trial Regulations Compliance Self Completion Checklist
- Identification of a potential risk to the trial.
- Investigation into a potential serious breach of the trial protocol/GCP.
- Other reasons as recommended by the trial site or Sponsor (e.g. site selection for regulatory inspection, provision of trial specific training to the site staff personnel, random selection)

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.

## 5.2 Study Initiation Visit

A study initiation visit/meeting should take place before recruitment begins at any recruiting site. (see SOP-18).

## 5.3 Interim on-site Monitoring Visit

The completion of interim on-site monitoring visits is applicable to single centre trials and multicentre trials where on site monitoring has been identified as a requirement following the study risk assessment. For multicentre 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/DI 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.

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/DI 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 SOP-10 should be followed.

## 5.4 Central Monitoring and Oversight

The CI/Dl 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

5.4.1 **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 and specified in trial specific monitoring plan (see SOP 11).

**5.5 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/DII 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.

## 6.0 RELATED DOCUMENTS

- SOP-02 - SAEs (Sponsored)
- SOP-04 - Informed Consent
- SOP-06 - TMF
- SOP-07 - Research Staff Training
- SOP-08 - Role of CI, Pharmacy, Nuclear Medicine and R&D
- SOP-09 - Amendments
- SOP-10 - Serious Breaches (Sponsored)
- SOP-11 - Sponsor Oversight
- SOP-13 - Research Applications
- SOP-14 - Writing Research Protocols
- SOP-16 - DSURS
- SOP-17- Archiving
- SOP-18 - Trial Initiation
- SOP-21 - Trial Closure
- SOP-22 - End of Trial Study Reports
- SOP-28 - Source Data
- ICH GCP Research Governance Framework Second edition April 2005
- The Medicines for Human Use (Clinical Trials) Regulations 2004
- MRC/DH/MHRA Joint project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. Version 10th October 2011

## 7.0 APPENDICES

Appendix 1 - Definitions

## 8.0 VERSION HISTORY

| Revision Chronology: | | |
|---|---|---|
| **Version Number** | **Effective Date** | **Reason for Change** |
| **SOP-12-04** | **October 2021** | 1. Change from general Standard Operating Procedures (gSOP) to SOP<br>2. Removal of the '10.0 Agreement' from the template - all agreement signatures will be collated on a new 'SOP Signature Sheet Document'<br>3. Other minor changes and clarifications following review, including the clarification this is for all Clinical Trials not just CTIMPs |
| **gSOP-12-03** | **October 2017** | Minor amendments following review |
| **gSOP-12-02** | **07/05/2014** | Minor amendments following review |

## 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 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.

**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.

**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

**The Medicines & Healthcare products Regulatory Agency (MHRA)**
The MHRA is the competent authority for the UK in relation to the Directive 2001/20/EC and the Clinical Trials Regulations, and for Medical Devices, the competent authority in relation to the Medical Devices Regulations 2002.

**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.