# INITIATION

## Research & Development

## Standard Operating Procedure for the Initiation of West Hertfordshire Hospitals NHS Trust Sponsored Clinical Trials

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| **SOP Number:** SOP-18-06 | **Effective Date:** October 2021 |
| **Version Number:** v06 | **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 recruitment and initiation of investigator sites for research projects sponsored by WHHT.

It provides guidance on the steps involved in the selection of sites, the assessment and initiation of a site, and who is responsible for obtaining the local approvals necessary for a study to commence, to ensure compliance with the Trust's policies.

### 2.0 PURPOSE

The purpose of this SOP is to describe the responsibilities and procedures prior to, during and following the trial initiation visit(s).

Initiation of WHHT Sponsored Clinical Trials and participating sites (for multicentre trials) ensures that all the required trial documentation are in place and that the trial procedures are reviewed with the Chief Investigator (CI)/Principal Investigator (PI) and the wider study team in accordance with the trial protocol, trust SOPs, Good Clinical Practice (GCP) and the applicable regulatory requirements, including the recent medical device guidance resulting from the EU exit (Regulating medical devices in the UK).

Trial/site initiation is integral to the Quality Control (QC) to ensure the quality of every aspect of the clinical trial including the participating sites involved in Trust sponsored Clinical Trials for Investigational Medicinal Products (CTIMPs) and medical devices.

In the Clinical Trials Regulations it is a GCP requirement that,

- The Investigator and Sponsor shall consider all the relevant guidance with respect to commencing and conducting a clinical trial
- Before the trial is initiated, foreseeable risks and inconveniences have been weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits outweigh the risks
- A trial shall be initiated only if the Research Ethics Committee (REC) and the Licensing Authority (MHRA) comes to the conclusion that the anticipated therapeutic benefit and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored
- The initiation of the trial within the Trust and participating sites (where applicable) ensures;

- All regulatory and research governance approvals are in place prior to commencement of the trial and providing the regulatory green light to commence recruitment
- Documented evidence is in place that the site is aware of the Sponsor's procedures outlined within the trial protocol and Sponsor's SOPs and their responsibilities in order to ensure the quality of every aspect of the conduct of the study
- Each participating site is aware of their responsibilities
- All other essential documents are in place prior to the study commencing in accordance with the approved protocol and Sponsor SOPs
- An effective working rapport is established with the study trial team/site and its staff prior to recruitment of trial participants
- That all study staff involved in the trial have documented GCP training which is current and up to date within the past 2-3 years (see SOP-07)
- The delegation of duties for the study has been discussed and is adequately completed and authorised by the CI/PI for all applicable site staff before any trial related activity has occurred
- The Clinical Trial Pharmacist(s) is provided with the notification to proceed with ordering the Investigational Medicinal Product (IMP) and must ensure that the procedures for receipt, dispensing, accountability, and other related documents, as specified in the applicable pharmacy SOP, are present (see SOP-08)

An initiation visit/meeting should take place for all participating sites prior to Sponsor authorisation being issued for the site to commence recruitment.

The study/site initiation may take one or more of the following forms and should be recommended by and documented within the study specific monitoring plan;

- Single centre Clinical Trials: A study team pre-activation initiation visit conducted by the CI/delegated individual (DI) prior to issue of the final R&D confirmation letter
- Multi-centre Clinical Trials: An on site initiation visit to the participating site conducted by an adequately trained study team member from the Sponsor organisation. Where required the CI/DI may also attend the site initiation to provide additional support during the visit. All key study team members from the participating site should attend the initiation
- Conference call; via video conference platform services or telephone conferencing
- Telephone call with site in circumstances where the options listed above are not feasible with the study site.

## 3.0 APPLICABLE TO

Any relevant Trust employee involved with Clinical Trial research sponsored by WHHT including, but not limited to, Unit Heads, Chief Investigators (CI), Principal Investigators (PI), Consultants, Co-investigators, Research Fellows, Clinical Trial Pharmacists, Research Managers, Statisticians, Research Nurses, Allied Health Professionals , Trial Coordinators, the RDSG & Data Managers.

## 4.0 RESPONSIBILITIES

### 4.1 The Sponsor

The Sponsor should ensure;

- The quality control of all Trust sponsored Clinical Trials. A site initiation visit should be completed to ensure the quality of the setup of the trial and compliance with the currently approved protocol/amendments(s), GCP, Trust policies, SOPs and the applicable UK clinical trial regulations, including the recent medical device guidance resulting from the EU exit (Regulating medical devices in the UK).
- The CI/DI is appropriately qualified and trained in order to have the scientific and/or clinical knowledge to initiate the trial adequately

**4.2 The Chief Investigator/Delegated Individual**

The CI/DI should ensure that;

- The trial does not commence without the completion of an initiation visit (for all single and multicentre Clinical Trials)
- The site PI is present during the initiation visit/conference/telephone call for all participating sites in multicentre Clinical Trials
- Where a participating site has been initiated, oversight of this process has been demonstrated by completion of the initiation visit checklist, prior to the issue of the regulatory green light for the site to commence recruitment

**4.3 Pharmacy**

The Clinical Trials Pharmacist/DI should ensure that;

- The required set up procedures are completed as described in the applicable pharmacy SOPs
- For multicentre trials a Pharmacy Pack has been completed and included as part of the site initiation guidance pack
- Where required they are available to attend initiation conferences/telephone initiations where specific input/training is required for the site pharmacy staff (as recommended by the study monitoring plan)

**5.0 PROCEDURES**

**5.1 Before the Initiation Visit**

Prior to the initiation visit/meeting the CI/DI should ensure;

**For Single centre trials**
The collection and verification of all approvals and essential documentation according to the initiation visit checklist. For single centre Clinical Trials the CI/DI should ensure that all the applicable essential documentation is maintained within the main study Trial Master File (TMF) (see SOP-06) and the Sponsor R&D file.

**For Multicentre Trials**

- The site feasibility questionnaire has been completed and received from the participating site.
- Participating sites should be in receipt of the relevant study specific documentation in the form of the study initiation guidance pack for completion of the Investigator Site File (ISF).
- The following documents are requested from the site and present in the TMF (site level) as a minimum:
  - Completed site feasibility questionnaire
  - Site R&D confirmation (including subsequent R&D amendments)
  - Fully signed clinical trial site agreement
  - Signed PI protocol authorisation signature page

- Local institution headed information to be provided to research participants (e.g. informed consent forms, Participant Information Sheets (PIS), questionnaires)
- Completed delegation of responsibilities log
- Completed site source document location identification sheet (PI signature)
- PI CV (copy)
- PI GCP training certificate (copy)
- Completed copy of the source document location identification sheet
- Copy of trial site laboratory accreditations/reference ranges
- Copies of signed consent forms

- The CI/PI and the other relevant trial/site staff have had up to date training in the relevant areas. In addition to GCP training completion the CI/DI should ensure that the trial team have completed the required mandatory training as per Trust SOPs and policies. (see SOP-07)

- Where a conference/telephone call is planned to function as the initiation process that all the relevant participating site staff receive the study specific initiation training presentation slides and sign the initiation training log.

- Ensure that the CI/PI and relevant trial staff including the trial pharmacy staff are made aware of the initiation visit, format, objective and expectations and are able to attend. It is mandatory that the CI and PI are present during the visit. A site initiation invitation email/letter should be issued to the site.

## 5.2 During the Initiation visit

### For Single Centre or Multicentre Trials

- Provide the initiation presentation training as required to include training in the Sponsor SOPs and protocol specific requirements. For multicentre studies where a conference/telephone call is the specified method for initiation, the opportunity for the site team to answer questions regarding the initiation handouts and other trial specific information should be given. Any issue highlighted at initiation which are not resolved at that time point should be followed up after the visit and specified on the initiation visit checklist.

- Ensure that the CI/PI and relevant trial staff sign the initiation visit/meeting attendance log.

- Verify that the CI has signed the delegation of responsibilities log. Where possible the CI/DI should verify that the CI has authorised the delegation of duties for the relevant trial staff including the pharmacy study staff (see SOP-08 for list of these responsibilities). This should be an ongoing process throughout the course of the study.

- Ensure that the CI/PI has defined what will be considered as source data for the trial and that this has been adequately authorised and verified during the visit. (see SOP-28)

- Ensure that the CI/PI is aware of their obligation to provide direct access to source documents for each trial participant and how this will be achieved.

- Ensure that the CI/PI and relevant trial/site staff are aware of the Sponsor's requirements for recording and reporting adverse events and potential serious breaches of GCP/trial protocol or implementation of Urgent Safety Measures (see SOP-10).

- Verify that the correct version(s) of the safety profiles for the IMP(s) are available and retained within the TMF (Investigator's Brochure (IB) and/or Summary of Product Characteristics (SPC) (see SOP-06).

- Review and verify all the IMP(s) procedures including, but not limited to receipt, storage, dispensing, accountability, return and destruction.

- Review and verify the storage conditions and methods for monitoring storage of the IMP(s) even if the IMP has not arrived on site. In addition and where applicable verify the storage conditions and custody of sample management for trial specific samples. Where the IMP(s) have not arrived on site the DI should ensure that a separate visit to pharmacy is scheduled upon receipt of the IMP. For multicentre CTIMPs the delegated study team member conducting the initiation visit should ensure that the site has received the pharmacy pack and provide the opportunity for the site to ask questions relevant to the management of the IMP(s) before the site is activated.

- Verify that the CI/PI has all of the appropriately trained staff, facilities and equipment to perform the trial according to the trial protocol and all the protocol specific requirements (including the management and oversight of any trial related samples).

- Ensure that the C/PI is aware of the extent and method of the monitoring to be performed for the study as detailed in the study specific monitoring plan.

- Ensure that participating sites are aware of their responsibility to inform the CI/DI if they are notified of any upcoming (regulatory or internal) inspections or audits.

- Ensure that the CI is aware of all their contractual obligations and reporting obligations to external parties (where required).

- Ensure that the CI/PI is aware of their responsibility to ensure adequate cover during absences and of their obligation to have ongoing oversight of the trial.

As part of the initiation process for multicentre Clinical Trials where a conference/telephone call initiation is conducted the study team should ensure that the initiation visit checklist is completed prior to activation of the site. This may be done in real time during the meeting or following the meeting. An initiation visit checklist should be completed for all the participating sites and retained within the TMF (site level) within the coordinating office. The completed site initiation visit checklist should be forwarded to the R&D Department electronically for verification prior to final sign off.

## 5.3 Following the Initiation Visit

### For Single centre Clinical Trials

- Authorisation of the initiation visit checklist
- Resolution of critical issues prior to the issue of the final confirmation letter
- Once outstanding issues resolved issue the R&D confirmation letter to the study team
- Information sent by the CI to pharmacy and any other relevant support departments including as a minimum the R&D confirmation letter, regulatory approval letters, protocol, protocol authorisation signature page, signed agreements (copies)
- Upload approved protocol onto the hospital intranet document repository
- Ensure the trial is active on the Trust R&D database with applicable essential documentation uploaded as required

### For Multicentre Clinical Trials

- Authorisation of the initiation visit checklist (CI/DI)
- Resolution of critical issues prior to issue of site ‘green light Sponsor authorisation to commence recruitment email’
- Ensure site specific essential documents and completed attendance logs/training records are filed in the site level TMF at coordinating centre

- Pharmacy to send 'green light Sponsor authorisation to commence recruitment' as an email/letter to the site coordinating team and site trial pharmacy staff

## 6.0 RELATED DOCUMENTS

- SOP-06 TMF
- SOP-07 Research Staff Training
- SOP-08 Role of the CI, Pharmacy, Nuclear Medicine and R&D
- SOP-10 Serious Breaches (Sponsored)
- SOP-28 Source Data
- ICH GCP
- UK policy framework for health and social care research
- Clinical Trial Regulations

## 7.0 APPENDICES

Appendix 1 - Definitions

## 8.0 VERSION HISTORY

| Revision Chronology: | | |
|---|---|---|
| **Version Number** | **Effective Date** | **Reason for Change** |
| **SOP-18-06** | **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. Addition of new medical device guidance<br>4. Other minor changes and clarifications including the clarification that this applies to all Clinical Trials not just CTIMPs |
| **gSOP-18-05** | **October 2017** | Minor amendments following review |
| **gSOP-18-04** | **01/10/2015** | Minor amendments following dissolution of consortium |
| **gSOP-18-03** | **22/05/2014** | Minor amendments following review |
| **gSOP-18-02** | | |
| **gSOP-18-01** | | |

## 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.

**Case Report Form (CRF)**
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

**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.

**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.

**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.

**Investigator Site File (ISF)**

The Investigator Site File contains all essential documents held by the Principal Investigator(s) conducting a trial which individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced.

**Mandatory**
Training which must be completed by all employees and any other staff involved in clinical trials and is therefore compulsory.

**Monitoring**
The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted and recorded in accordance with the protocol, Standard Operating Guidelines (SOP's), Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

**Monitoring Plan**
The agreed process for monitoring a CTIMP sponsored by WHHT as specified in the study monitoring plan determined by the risk based monitoring strategy

**Participant Information Sheet (PIS)**
A document explaining all relevant study information to assist the potential subject in understanding the expectations and requirements of participation in a clinical trial.

**Pharmacovigilance**
The science relating to the detection, assessment, understanding and prevention of the adverse effects of medicines.

**Pharmacy Pack**
The Pharmacy Pack must cover the following:

- Contact details of Sponsor
- Trial synopsis, with reference to which version of the protocol pack has been prepared with.
- Study medication:
    - Formulation
    - Storage
    - Labelling/Labels
    - Reconstitution / Dilution or (Aseptic) preparation
    - Stability
    - Administration
    - Ordering & receipt of first and subsequent supplies
- Randomisation
- Prescribing
- Dispensing
- Accountability forms
- Patient returns
- Destruction
- Hazards
- Forms/Templates

**Pharmacy Trial File**
A collection of files that contain all the pharmacy relevant documents pertaining to a specific clinical trial.

**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.

**Quality Control (QC)**
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

**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.

**Site Feasibility Form**
The form sent to each site to collect the site contact details e.g. the CI/PI, Trials Pharmacist, Research Nurse or Trial Co-ordinator and allow assessment of site and their facilities versus requirements for a given trial

**Site File**
Site Files are held by the PI at sites and contain copies of the essential documents, local approvals, signed consent forms and completed data forms.

**Site Initiation Guidance Pack**
This pack is sent both electronically and a hard copy placed in the Investigator Site File (ISF) which contains the following logs tailored to each trial to allow Sponsor and site oversight of trial conduct;

- Site Registration Form
- Coordinating Centre Contact Sheet
- WHHT TMF Contents
- CI/PI Protocol Authorisation Signature Sheet
- WHHT site specific delegation log
- Subject Screening Log
- Subject enrolment, withdrawal and study completion log
- Study/Site eSAE log study & specific template & guidance email
- Subject master identification code list
- Substantial/ Non substantial amendment log
- Trial monitoring visit log
- UK clinical trial regulations site self-completion compliance checklist & guidance (to include summary monitoring plan requirements and responsibilities for participating sites)

- Study SAE report form, guidance documents & applicable contacts and PV guidance training presentation slides for WHHT sponsored CTIMPs
- WHHT potential GCP breach report forms/ Urgent Safety Report Forms and applicable guidance & contacts)
- Pharmacy pack for multi-centre trials (to include study specific guidance)
- Initiation presentation slide handouts for staff training (to include protocol specific and Sponsor SOP requirements)
- Study/site initiation attendance log
- Staff protocol training completion log/ initiation handout review checklist (participating sites)
- Source document location identification checklist

**Source Document Location Identification Checklist**
A quality control document which is reviewed and validated by the CI/PI to ensure consistent management of the location of source data for protocol specific assessment results and diagnostic and or translational research conducted as part of the trial. The document is designed to improve the quality of the management and oversight procedures of source data by the Sponsor.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**
An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction.

**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 Initiation Presentation/Handouts**
This is the presentation that will be presented to the CI/PI and their Research Team at the site and will cover the following topics as a minimum. Topics covered should be completed in the initiation visit checklist.

- Responsibilities of investigator/site
- Delegation of responsibilities
- Sponsor's forms and logs for trial conduct
- Sponsor SOPs
- Informed consent and recruitment
- Trial IMP- storage, ordering supplies, preparation, labelling, dispensing, return/disposal of IMP(s)
- Imaging or other specialist requirements/procedures
- Screening procedures
- Randomisation procedure
- Management of protocol/ treatment deviations
- Monitoring procedures
- Data management (CRF completion and expected follow up timeframes)
- Biological sample handling (if applicable)

- Pharmacovigilance & Urgent Safety Measures (USM)
- Amendments
- End of Trial and Archiving
- Ongoing staff training
- UK Regulations and CTIMP legislations
- Sponsor contact details

**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 Site**
The location(s) where trial-related activities are actually conducted as per the REC and MHRA submissions.

**Unexpected Adverse Reaction**
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's brochure for an unauthorised investigational product or summary of product characteristics (SmPC) for an authorised product).

**Unexpected Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)**
An adverse event that meets the definition of serious and is not listed in the protocol, IB, SmPC or the most recent informed consent document for the study (list of unexpected SAE will be trial specific).