University of Hertfordshire UH

University of Hertfordshire

STUDY INITIATION

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the Initiation of University of Hertfordshire Sponsored/co-sponsored Clinical Trials

SOP Number: gSOP-18-01	**Effective Date:** 26th April 2018
Version Number: v1.0	**Review Date:** 3 years (or as required)

1.0 BACKGROUND

This is a University of Hertfordshire standard operating procedure. University of Hertfordshire (UH) acknowledges West Hertfordshire Hospitals NHS Trust (WHHT) Research & Development (R&D) which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

This document sets out the procedures to be followed by all University of Hertfordshire (UH) staff who are involved in the recruitment and initiation of investigator sites for research projects sponsored/co-sponsored by UH. Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

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 UH's policies and SOPs.

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

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 UH Sponsored/co-sponsored CTIMPs 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, UH SOPs, Good Clinical Practice (GCP) and the applicable regulatory requirements.

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 UH sponsored/co-sponsored Clinical Trials for Investigational Medicinal Products (CTIMPs).
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 UH 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 gSOP-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 NHS Clinical Trial Pharmacist(s) is provided with the notification to proceed with ordering the Investigational Medicinal Product (IMP) and that the procedures for receipt, dispensing, accountability, and other related documents, as specified in the applicable pharmacy SOP, are present

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 CTIMPs: A study team pre-activation initiation visit conducted by the CI/delegated individual (DI) prior to issue of the final green light to commence
- Multi-centre CTIMPs: An onsite 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
- Telephone call with site in circumstances where the options listed above are not feasible with the study site

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored 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, Research Assistants and Students.

4.0 RESPONSIBILITIES

4.1 The Sponsor

The Sponsor should ensure:

- The quality control of all UH sponsored/co-sponsored CTIMPs. 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, UH policies, SOPs and the applicable UK clinical trial regulations.
- 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 CTIMPS).

- The site PI is present during the initiation visit/conference/telephone call for all participating sites in multicentre CTIMPs.

- 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 NHS 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 CTIMPs the CI/DI should ensure that all the applicable essential documentation is maintained within the main study Trial Master File (TMF) and the Sponsor 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 UH SOPs and policies.

- 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 NHS 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 NHS pharmacy study staff. 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.

- 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 gSOP-02 and gSOP-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 gSOP-06).

- Review and verify that 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, 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 are in receipt of 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 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 CTIMPs 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 CTSN/R&D Department electronically for verification prior to final sign off.

5.3 Following the Initiation Visit

For Single centre CTIMPs

- 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 Sponsor/R&D confirmation letter to the study team
- Information sent by the CI to NHS pharmacy and any other relevant support departments including as a minimum the Sponsor/R&D confirmation letter, regulatory approval letters, protocol, protocol authorisation signature page, signed agreements (copies)
- Upload approved protocol onto the appropriate shared area/hospital intranet document repository.
- Ensure the trial is active on the Trust R&D/UH Sponsor database with applicable essential documentation uploaded as required

For Multicentre CTIMPs

- 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

6.0 RELATED DOCUMENTS

- gSOP-02 Adverse Event Reporting (Sponsored/Co-Sponsored)
- gSOP-04 Informed Consent
- gSOP-06 Trial Master File
- gSOP-07 Research Staff Training
- gSOP-09 Amendments
- gSOP-10 Serious Breaches (Sponsored)
- gSOP-11 Sponsor Oversight
- gSOP-13 Research Applications
- gSOP-14 Writing Research Protocols
- gSOP-15 CRF Design
- gSOP-16 DSURs
- gSOP-17 Archiving

- gSOP-21 Trial Closure
- gSOP-22 End of Trial Reports
- gSOP-28 Management of Source Data
- gSOP-40 Data Management Overview
- ICH GCP
- UK Policy Framework for Health and Social Care Research
- Clinical Trial Regulations 2004

7.0 APPENDICES

- Appendix 1 - Definitions

8.0 VERSION HISTORY

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

9.0 AUTHORSHIP & APPROVAL

Author

Signature **Date**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature **Date**

10.0 AGREEMENT

Please detach and retain in your training files

I have read and understood the contents and requirements of this SOP (gSOP-18-01) and accept to follow UH policies implementing it.

Recipient

Signature: ……..……..……..….Date: ……...……..

Name & Position: ……..…….

Appendix 1: Definitions

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

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)
A registered Physician, Dentist, Pharmacist or 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).

Delegated Individual (DI)
An individual delegated by a person of responsibility to carry out their task(s).

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

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 -

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

Investigator Site File (ISF)
The file(s) held at each site taking part in the trial which hold the essential trial document set necessary for local approval and trial conduct at site.

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

Monitoring

A Quality Control (QC) activity which involves a system of ongoing real time checks to detect discrepancies and faults in order to correct them, and prevent the failure from recurring so that the specified output is produced consistently, in this context compliance with the UK Regulations, Sponsor SOPs, approved protocol and GCP.

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

Participant Information Sheet (PIS)
A document that explains all relevant study information to assist the trial participant in understanding the expectations and requirements of participation in a clinical trial.

Pharmacovigilance
The regulations outline procedures for the recording and reporting of safety events (Adverse Events or Suspected Unexpected Serious Adverse Reactions) arising from clinical trials.

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)
A registered Physician, Dentist, Pharmacist or Nurse who has responsibility for the conduct of the trial at a host site

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 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.

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
- TMF Contents
- CI/PI Protocol Authorisation Signature Sheet
- Site specific delegation log
- Participant Screening Log
- Participant 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 UH sponsored/co-sponsored CTIMPs
- UH 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)
All suspected adverse reactions related to an Investigational Medicinal Product (IMP) that is both unexpected and serious.

The Medicines & Healthcare products Regulatory Agency (MHRA)
UK competent authority responsible for regulation of clinical trials.

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 (TMF) will be held at the principal site by the Sponsor, Chief Investigator or at the co-ordinating centre. The TMF should contain all essential documents defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. A 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 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 (IB) for an unapproved 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).