University of Hertfordshire

TRIAL MASTER FILE & INVESTIGATOR SITE FILE

Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the Management of the Trial Master File and Investigator Site File for Clinical Studies Sponsored/co-sponsored by the University of Hertfordshire

SOP Number: gSOP-06-02	**Effective Date:** 16th March 2022
Version Number: 2.0	**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 SOP is mandatory for all UH sponsored or co-sponsored clinical trials which are regulated by the MHRA i.e. clinical trials of investigational medicinal products (CTIMPs), advanced therapy investigational medicinal products (ATIMPs) and clinical trials of medical devices which are not CE-marked, or which are used outside of their CE-marked purpose (clinical investigations). For all other UH sponsored or co-sponsored studies, this SOP should be used as best practice and implemented proportionately in accordance with the risk of the study.

This document provides guidance on how the Trial Master File (TMF) and Investigator Site File (ISF) should be compiled and how these files should be stored to ensure compliance with UH's policies. Where there are potential conflicts between different collaborating organisations' SOPs, project level working instructions should be developed, to determine precedence.

The TMF and ISF contain all essential documents relating to the conduct of a clinical trial which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. Section 8 of ICH/GCP guidance details the essential documents necessary for the conduct of a trial.

Essential documents are those, which individually and collectively:

- Permit the evaluation of the conduct of a trial and the quality of the data produced.
- Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of Good Clinical Practice (GCP) and with all regulatory requirements.
- When filed in an appropriate and timely manner greatly assist in the successful management of a trial by the investigator.
- Are usually audited by the sponsors independent audit function and inspected by regulatory authorities as part of the process to confirm the validity of the trial conduct and data

collection.

2.0 PURPOSE

The Medicines for Human Use (Clinical Trials) Regulation 31A requires that a readily available TMF is kept, which contains the essential documents relating to a specific clinical trial.

- To achieve standard best practice of clinical research documentation for clinical trials sponsored/co- sponsored/co-sponsored by UH.
- To ensure UH meets all regulatory, research governance and UH requirements in the management of TMFs and other related documentation.
- To ensure all clinical trials documentation can be readily available for regulatory and/or other auditing activities.
- To ensure new research staff are appropriately trained in the setup and management of the TMF.

3.0 APPLICABLE TO

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial Managers, Clinical Studies Officers, Data Managers and Research Assistants.

4.0 RESPONSIBILITIES

The TMF should be held and maintained by the Sponsor or delegated individual. Chief Investigators (CI) for multi-centre trials will also establish a suitable ISF is in use at host sites.

The Principal Investigator is responsible for maintaining, storing and arranging archiving of the ISF. This duty may be delegated to another appropriately qualified member of the Research Team and recorded in the Delegation of Study Duties Log.

Following completion of the study, the Principal Investigator (PI) or delegate at each site is responsible for reviewing the ISF to ensure that all the required documents are present and complete. This must be documented through the provision of a completed ISF index to the Sponsor prior to archiving of the ISF.

The Medicines for Human Use (Clinical Trials) Regulations 2004:1031 and subsequent amendments 2006:1928, 2006:2984, 2008:941, 2009:1164 and 2010:1882 outline requirements for Trial Master File and archiving, as follows:

- The Sponsor will keep a TMF for a clinical trial. Where UH is the Sponsor/co-sponsor of the study, this is generally delegated to the CI or delegated individual (DI).
- Where this is the case and UH is also a participating centre in the study, the Site Investigator File (ISF) would be the same as the Trial Master File (TMF).
- Where responsibility for the trial is delegated to a trials unit or external organisation, particularly in the case of co-sponsorship arrangements, the TMF would not be expected to include the ISF.

- The Sponsor will ensure that the TMF is readily available at all reasonable times for inspection by the licensing authority or any person appointed by the Sponsor to audit the arrangements for the trial.

- The CI/DI will ensure access to the TMF and related documents are available upon request of the CTSN to conduct routine Sponsor audits.

- The CI/DI should ensure that the TMF contains the essential documents relating to that clinical trial, which enable both the conduct of the clinical trial and the quality of the data produced to be evaluated. It must also contain evidence of trial conduct in accordance with the applicable requirements.

- The Sponsor should ensure that the essential documents contain information specific to each phase of the trial.

- The Sponsor should ensure that any alteration to a document contained, or which has been contained, in the TMF should be traceable. The Sponsor and the CI should ensure that the documents contained, or which have been contained, in the TMF are retained for at least 5 years after the conclusion of the trial and that during that period are:

  (a) readily available to the licensing authority on request and
  (b) complete and legible.

- The Sponsor and CI should ensure that the medical files of trial participants are retained for at least 5 years after the conclusion of the trial.

- The Sponsor should appoint named individuals within the organisation to be responsible for archiving the documents which are, or have been, contained in the TMF and access to those documents should be restricted to those appointed individuals.

- If there is transfer of ownership of data or documents connected with the clinical trial:

  - the Sponsor should record the transfer; and

  - the new owner should be responsible for data retention and archiving.

- For the purposes of this regulation, an individual is an individual within the sponsor's organisation where:

  - they are employed or engaged by the sponsor;

  - they are acting under arrangements made with the sponsor for the purposes of managing or conducting the clinical trial;

  - where the sponsor is an individual, they are the sponsor; or

  - where the sponsor is a body of persons, they are;

    - a member of the body, or

    - employed or engaged by such a member.

5.0 PROCEDURE

5.1 All clinical trials sponsored/co-sponsored by UH must have a comprehensive and up-to-date TMF. See the Sample Trial Master File Contents Template. The International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) Master File checklist provides guidance. If the trial is multi-centre, ISF should be in use at all host sites.

5.2 The TMF will be verified at the study initiation meeting. This should be used to maintain a current TMF by the Research Team. If units have existing systems for managing the contents of the TMF (e.g. local guidance documents), then the existing system can be used provided it is GCP-compliant.

5.3 Copies of all versions of the protocol should be stored in the TMF and ISF. If older versions of protocols are stored elsewhere, a file note must be added to the TMF. All protocols should be approved by the CI prior to implementation; an authorisation signature and date by the CI should be included in the protocol.

5.4 The TMF and ISF should contain copies of sample Participant Information Sheet (PIS), Consent Forms, GP letters and blank Case Report Forms (CRFs).

5.5 All completed CRFs should be maintained in the TMF and/or Site File or in a secure location within the designated location and a file note must be added in the TMF describing the location and other relevant information (e.g. contact).

5.6 All documentation arising from communication between the study team, the R&D office and the CTSN should be maintained in the appropriate section of the TMF. Prior to study initiation, the CI/DI should ensure a final study approval has been granted. This also applies to all substantial and non-substantial amendments.

5.7 All documentation relating to the study and the ethics committee should be maintained in the TMF and ISF. The CI must ensure all Health Research Authority (HRA) approvals are obtained prior to study start. This also applies to all substantial amendments.

5.8 All communication documentation relating to the study and the Medicines and Healthcare products Regulatory Agency (MHRA) should be maintained in the TMF and ISF, where applicable. The CI must ensure all necessary regulatory approvals are in place prior to study start. For studies involving an Investigational Medicinal Product (IMP), the CI should ensure that an MHRA Clinical Trial Authorisation (CTA) is obtained prior to study start.

5.9 All documentation relating to research governance arrangements should be maintained in the TMF and ISF. Examples of documents include sponsorship letters, Clinical Trials Advisory & Awards Committee (CTAAC), Administration of Radioactive Substances Advisory Committee (ARSAC), Research Agreements and Indemnity Statement.

5.10 For trials involving unlicensed IMPs an Investigator's Brochure (IB) should be maintained in the TMF.
The CI should ensure that updated IBs are in circulation**.** For marketed products, an approved version of the Summary of Product Characteristics (SPC) should be maintained in the TMF and/or ISF. If IBs/ SPCs are not held within the TMF and/or ISF, a File Note should be included in the TMF describing the location**.**

5.11 All documentation relating to pharmacy and the trial should be maintained in the TMF and ISF.
If documents are held in Pharmacy Study File instead of the TMF and ISF, a file note should be added to the TMF and ISF. See file note template.

5.12 All laboratory documentation related to the study should be maintained either within the TMF and ISF or held centrally within the units or designated centres. If held centrally, a file note must be added to the TMF and ISF. Examples of documentations include accreditations, normal reference ranges, investigational product handling, invoices etc.

5.13 The TMF and ISF should contain study site staff records including items such as responsibilities and signature log (delegation log), evidence of GCP training, SOP training, current CVs (recommended to be updated every 2-3 years). If training records are held centrally within units, a file note can be added in the TMF and/or ISF.

5.14 Study specific information, guidance notes and randomisation instructions should be maintained in the appropriate section(s) of the TMF and ISF.

5.15 All information regarding pharmacovigilance should be maintained in the TMF and ISF. Records of Adverse Events (AEs) and Serious Adverse Events (SAEs), including follow-up reports should be maintained in the TMF and ISF. Other items including safety information, sample SAE forms, SAE logs, correspondences, Safety Reports to the MHRA, HRA and annual progress reports should also be held in the TMF and ISF.

5.16 If documents are held elsewhere, a file note should be added to the TMF (see file note template). If, as part of the sponsor agreement, pharmacovigilance was delegated to a co-sponsor that is not UH, then this section does not apply.

5.17 All substantial and non-substantial amendments must be submitted to the CTSNMG for review. All correspondences, including copies of approvals for substantial amendments from the HRA and MHRA should be held in the TMF and ISF.

5.18 All evidence of monitoring activities such as study initiation meetings, progress reports, minutes of research/team meetings, meetings of Data Monitoring Committees and Trial Steering Groups and monitoring logs should be held in the TMF and ISF, where appropriate.

5.19 For trials that have been audited by a monitor/auditor, it is recommended that audit reports are held separately from the TMF. Copies of all audits are maintained by the CTSN.

5.20 The TMF should contain evidence/rationale for the selection of external vendors including a copy of the vendor oversight programme.

5.21 Other miscellaneous documentations such as publications, end-of-trial notifications, archiving etc. should also be maintained in the TMF and ISF as appropriate.

5.22 The TMF should be archived following study conclusion in accordance with UH, Sponsor and regulatory requirements (see gSOP-17).

5.23 Where UH is sponsoring/co-sponsoring a multicentre trial, the UH coordinating trial team should ensure that a site-specific TMF (site level) is set up and maintained during the course of the study. See Sample Trial Master File Contents, Masterfile Checklist and CTSN Investigator Site File Contents Template.

6. RELATED DOCUMENTS

- gSOP-01 SOP on SOPs
- gSOP-02 Adverse Event Reporting (Sponsored/co-sponsored)

- gSOP-04 Informed Consent
- gSOP-05 Adverse Event Reporting (hosted)
- gSOP-07 Research Training
- gSOP-17 Archiving
- gSOP-32 Vendor Assessment
- Sample Trial Master File Contents
- Masterfile Checklist
- CTSN Investigator Site File Contents Template
- File Note Template

7. APPENDICES

- Appendix 1 - Definitions

8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change
2.0		• Change of title to include ISF • Addition of details relating to the creation and management of the ISF • Addition of amendment 2006 1928 relating to Trial Master File & archiving requirements (named individual) • Update to Appendix 2: CTSN Trial Master File Contents Template • Addition to appendices of CTSN Investigator Site File Contents Template

9. AUTHORSHIP & APPROVAL

Author: Megan Smith

Signature  **Date 15/03/2022**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature  **Date 01/03/2022**

10. AGREEMENT

Please detach and retain within <u>your training files</u>

I have read and understood the contents and requirements of this SOP (ref gSOP-06-01) and accept to follow University policies implementing it.

Recipient

Signature: ……Date: ……..

Name & Position: ……

Please retain copy of the signed form for your reference in your training file

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 Authorisation (CTA)

Regulatory approval issued by a competent authority to conduct a clinical trial within an EU Member State.

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).

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)

Investigator 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.

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.

Principal Investigator (PI)
A registered Physician, Dentist, Pharmacist or 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.

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 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.