University of Hertfordshire

TRIAL MASTER FILE

Clinical Trials Support Network (CTSN)

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

SOP Number: gSOP-06-01	**Effective Date:** 26th April 2018
Version Number: 1.0	**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.

It provides guidance on how the Trial Master File (TMF) 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.

2.0 PURPOSE

- 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 Medicines for Human Use (Clinical Trials) Regulations 2004:1031 (as amended) outlines 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

5.0 PROCEDURE

5.1 All clinical trials sponsored/co-sponsored by UH must have a comprehensive and up-to-date TMF. Appendix 2 provides a sample template for the TMF contents. The International Conference on Harmonisation- Good Clinical Practice (ICH-GCP) Master File checklist is also provided as guidance in Appendix 3.

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. 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 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 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. 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, 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. 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. If IBs/ SPCs are not held within the TMF, 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. If documents are held in Pharmacy Study File instead of the TMF, a file note should be added to the TMF. See Appendix 4 for sample file note.

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

5.13 The TMF 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.

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

5.15 All information regarding pharmacovigilance should be maintained in the TMF. Records of Adverse Events (AEs) and Serious Adverse Events (SAEs), including follow-up reports should be maintained in the TMF. 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.

5.16 If documents are held elsewhere, a file note should be added to the TMF (Appendix 4). 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.

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.

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 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 appendix 2,3 and 4).

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

7. APPENDICES

- Appendix 1 - Definitions
- Appendix 2 - Sample Trial Master File Contents
- Appendix 3 - Masterfile Checklist
- Appendix 4 - File Note Template

8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change

9. AUTHORSHIP & APPROVAL

Author

Signature **Date**

Pro-Vice Chancellor (Research & Enterprise) Approval

Signature **Date**

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

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.

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.

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.

Appendix 2: Sample Trial Master File Contents

Essential documents required for Trial Master File	
1	Trial Summary
2	Version control log
3	Contact details sheet
Trial Specific Documentation	
4	Current approved protocol with signatures
5	Approved Patient Information Sheet (PIS), Informed Consent Form, GP Letter
6	Previous versions of protocol(s), PIS, Informed Consent Form, GP Letter
7	Study specific Standard Operating Procedures
Sponsorship and NHS Permission	
8	Trust Approval Letter
9	Letter of acceptance of sponsorship
10	Peer Review
11	Sponsorship delegation log
12	Project Management Delegation Log
13	Risk Assessment and superseded versions
Site Personnel	
14	Up-to-date, signed and dated CVs and GCP training records
15	Delegation Log

Finance	
16	Grant Application
17	Clinical Trial Agreement / Funding agreement letters
18	Finance correspondence: funder / contracts
19	Indemnity certificates / policy
20	Site Agreements
21	Research Account statements
22	Invoices
23	Finance correspondence with sites
24	Other finance correspondence other than contracts
MHRA and Ethics	
25	EUDRACT number
26	HRA correspondence
27	Adoption onto the NIHR portfolio
28	Ethics application including correspondence
29	Favourable Ethical Approval letter
30	MHRA application including correspondence
31	Clinical Trial Authorisation letter

32	Copy of the Annual Progress Report(s) to Ethics
33	Copy of the end of trial notification form and report sent to Ethics & MHRA
Amendments	
34	Amendments to ethical approval, a separate bundle of documents filed in chronological order for each amendment comprising copies of: 1) all the amended documentation 2) approval – Ethics, MHRA, HRA, R&D (as required)
35	Correspondence regarding the amendment
Pharmacovigilance	
36	Investigator's Brochure (IB) and/or Summary of Product Characteristics (SmPC) and updates
37	Pharmacovigilance SOP inc blank SAE forms
38	SAE reports
39	SUSAR reports
40	DSUR reports
41	Procedure for randomisation, unblinding and code break (if applicable)
42	Details of testing
43	Details of any code breaks
44	Details of any Protocol non-compliance or Serious Breach of protocol
45	Details of any Urgent Safety Measures
46	Notification of sponsors to Investigators of safety information

47	Copies of any adverse event reports made under the normal reporting procedures used by the Trust
Pharmacy	
48	Quality Agreement
49	Instructions for handling IMP (if not included in protocol)
50	Sample of label/ superseded versions of label (if applicable)
51	Shipping records, inc. ordering forms (if applicable)
52	IMP accountability
53	Termination: Documentation of IMP destruction
Data Collection, Analysis and Publication	
54	Data Management Plan
55	Database management
56	Sample case report forms (CRFs) + Copy of other approved data collection instruments (eg questionnaires)
57	Completed CRFs + data collection instruments
58	Data queries
59	Statistical Analysis Plan
60	Interim reports
61	Publication(s)

Monitoring	
62	Monitoring Plan
63	Audit Plan
64	Trial initiation Report
65	Monitoring Reports
66	Audit Reports
67	Close Down Report
68	Correspondence regarding monitoring and/or audit
Meeting	
69	Project team meetings
70	Project team correspondence
71	Trial Steering Committee meeting Terms of Reference
72	Trial Steering Committee meeting minutes
73	Trial Steering Committee correspondence
74	Data Monitoring Committee Charter / Terms of Reference
75	Data Monitoring Committee meeting
76	Data Monitoring Committee correspondence
Laboratory	

77	Lab accreditation certificates
78	Normal values/ ranges
79	Record of retained tissue/ body samples (if any)
80	Material Transfer Agreements
Participant Logs and Consent Forms	
81	Screening/enrolment log (including subject identification list)
82	Signed Consent Forms
Other	
83	Copies of all other correspondence relating to the trial (excluding REC, MHRA and R&D) records of all significant phone conversations relating to trial

Appendix 3: Masterfile Checklist

Ref: Section 8, ICH Guidelines for Good Clinical Practice)

Before the Clinical phase of the Trial Commences

ICH GCP Ref.	Topic	Located in Principal Investigator file (Site File)	Located in Chief Investigator file (Trial Master File)	Located in R&D Office file
8.2.1	Investigator's Brochure	X	X	X (Front Page)
8.2.2	Signed protocol and amendments, if any, and sample Case Report Form (CRF)	X	X	X (Protocol & Amendments)
8.2.3	Information given to trial subject -Informed consent form	X	X	X
	-Any other written documentation (for example GP Letter)	X	X	X
	-Advertisement for subject recruitment	X	X	X
8.2.4	Financial aspects of the trial	X	X	X
8.2.5	Insurance statement (where required)	X	X	X
8.2.6	Signed agreement between involved parties, eg:	X	X	X
	-investigator/ institution and sponsor	X	X	X
	-investigator/ institution and authority(ies) where required	X	X	
8.2.7	Dated, documented approval of Independent Ethics Committee of the following: -protocol and any amendments -CRF (if applicable) - informed consent form(s) -any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) -subject compensation (if any) -any other documents given approval/ favourable opinion	X	X	X
8.2.8	Independent Ethics Committee composition	X	X (where required)	
8.2.9	Regulatory Authority Authorisation (where required)	X (where required)	X (where required)	X (where required)

ICH GCP Ref.	Topic	Located in Principal Investigator file (Site File)	Located in Chief Investigator file (Trial Master File)	Located in R&D Office file

8.2.10	Curriculum vitae and other documents evidencing qualifications of investigator(s) and sub-investigator(s)	X	X	X (CI/ PI only)
8.2.11	Normal values/ranges for medical/laboratory/technical procedures and/or tests included in the protocol.	X	X	
8.2.12	Medical/laboratory/technical procedures/tests - certification or - accreditation or - established quality control and/or external quality assessment or -other validation (where required)	X (where required)	X	
8.2.13	Sample of label(s) attached to investigational medicinal product container(s)		X	
8.2.14	Instructions for handling of investigational medicinal product(s) and trial-related materials (if not in protocol or Investigator Brochure)	X	X	
8.2.15	Shipping records for investigational medicinal product(s) and trial related materials	X	X	
8.2.16	Certificate(s) of analysis of investigational product shipped		X	
8.2.17	Decoding procedures for blinded trials	X	X (third party if applicable)	
8.2.18	Master Randomisation List		X (third party if applicable	
8.2.19	Pre-trial monitoring report		X	X
8.2.20	Trial initiation monitoring report	X	X	X

During the clinical conduct of the trial

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available.

ICH GCP Ref.	Topic	Located in Principal Investigator file (Site File)	Located in Chief Investigator file (Trial Master File)	Located in R&D Office file
8.3.1	Investigator's Brochure updates	X	X	X (Front Page only)
8.3.2	Any revision to: -protocol/amendment(s) and CRF -informed consent form -any other written information provided to subjects (Patient Information Sheets)	X	X	X (Protocol, Informed Consent, Patient Information Sheet))
8.3.3	Dated, documented approval of Independent Ethics Committee of the following: -protocol amendment(s) -revisions of: - informed consent form - any other written information to be provided to the subject (Patient Information Sheets) - any other documents given approval -continuing review of trial (where required)	X	X	X
8.3.4	Regulatory Authority Authorisation where required for -protocol amendment(s) and other documents	X (where required)	X	X
8.3.5	Curriculum vitae for new investigator(s) and sub-investigator(s)	X	X	X (New CI/ PI only)
8.3.6	Updates to normal values/ranges for medical/laboratory/technical procedures and/or tests included in the protocol.	X	X	
8.3.7	Updates of medical/laboratory/technical procedures/tests --certification or - accreditation or - established quality control and/or external quality assessment or -other validation (where required)	X (where required)	X	

ICH GCP Ref.	Topic	Located in Principal Investigator file (Site File)	Located in Chief Investigator file (Trial Master File)	Located in R&D Office file
8.3.8	Documentation of investigational medicinal product(s) and trial-related materials shipment	X	X	
8.3.9	Certificates of analysis for new batches of investigational product		X	
8.3.10	Monitoring visit reports		X	X
8.3.11	Relevant communication other than site visits -letters/ meeting notes/ notes of telephone calls/ printed emails	X	X	
8.3.12	Signed informed consent forms	X		
8.3.13	Source documents	X		
8.3.14	Signed, dated and completed case report forms (CRF)	X (copy)	X (original)	
8.3.15	Documentation of CRF corrections	X (copy)	X (original)	
8.3.16	Notification by originating investigator to sponsor of serious adverse events and related reports	X	X	
8.3.17	Notification by sponsor and/or investigator, where applicable, to Regulatory Authority and Independent Ethics Committee of unexpected serious adverse drug reactions and of other safety information	X (where required)	X	X
8.3.18	Notification by sponsor to investigators of safety information	X	X	
8.3.19	Interim or annual reports to independent ethics committees and Authority	X	X (where required)	X
8.3.20	Subject screening log	X	X (where required)	

8.3.21	Subject identification code list	X		
ICH GCP Ref.	**Topic**	**Located in Principal Investigator file (Site File)**	**Located in Chief Investigator file (Trial Master File**	**Located in R&D Office file**
8.3.22	Subject enrolment log	X		
8.3.23	Investigational medicinal products accountability at site	X	X	
8.3.24	Signature sheet	X	X	
8.3.25	Record of retained body fluids/tissue samples (if any)	X	X	

After completion or termination of trial

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following:

ICH GCP Ref.	**Topic**	**Located in Principal Investigator file (Site File)**	**Located in Chief Investigator file (Trial Master File)**	**Located in R&D Office file**
8.4.1	Investigational medicinal product(s) accountability at site	X	X	
8.4.2	Documentation of investigational medicinal product destruction	X (if destroyed at site)	X	
8.4.3	Completed subject identification code list	X		
8.4.4	Audit certificate (if available)		X	
8.4.5	Final trial close-out monitoring report		X	X
8.4.6	Treatment allocation and decoding documentation		X	

8.4.7	Final report by investigator to Independent Ethics Committee where required	X		
8.4.8	Clinical study report	X (if applicable)	X	

Appendix 4: File Note Template

File Note

Study:	**Principal Investigator:**
Date:	**Time:**

Note:

Print Name .....

Signature .....Date.....

Role ……..