University Hospitals Plymouth NHS Trust

STANDARD OPERATING PROCEDURE

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT FIRST CHECKING IT IS THE LATEST VERSION

The definitive versions of all UHPNT RD&I Dept SOPs appear online, not in printed form, to ensure that up to date versions are used. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the Trust's website: https://www.plymouthhospitals.nhs.uk/researchers

Trial Master File & Investigator Site File

SOP No: P9

Version No: 6.1

Effective Date: Jan 2019

Supersedes: Version 6.0, Sep 2017

Page: **1** of **14**

Last Review Date: Jan 2019 Next review date: Jan 2022

AUTHORISED BY

Name: Chris Rollinson

Job Title: Research Governance Manager

Signature: 

Date: 21st Jan 2019

1 Purpose and Scope

This SOP is to be followed where University Hospitals NHS Trust is the study sponsor or has been delegated the duty of setting up and maintaining a TMF. Study team personnel have responsibility for setting up and maintaining the TMF and must follow this SOP.

The Trial Master File (TMF) is the collection of documentation that allows the conduct of the clinical study, the integrity of the study data and the compliance of the study with Good Clinical Practice (GCP) to be evaluated. The TMF is normally composed of a sponsor TMF, held by the sponsor organisation or delegate, and an Investigator Site File (ISF), held by the investigator. These files together are regarded as comprising the entire TMF for a study and should be established at the beginning of the study.

The documentation generated during the conduct of a study can be quite extensive, therefore effective organisation within the TMF is essential to facilitate inspection and audit but also for those persons involved in conducting the study who will require regular access to the documentation to undertake various tasks.

The documentation contained within the TMF should be sufficient to adequately reconstruct the study activities undertaken, along with key decisions made concerning the study.

Documents should meet the principles of ALCOAC:

- Attributable – traceable to a person, date and visit
- Legible – easy to read and permanent
- Contemporaneous – recorded at the time that it occurred
- Original – the first place that data was recorded
- Accurate – a correct and true representation of the facts. Any changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary.
- Complete – The record should be complete if items are missing or not recorded an explanation should be given.

The documentation listed in section 8 of International Conference on Harmonisation (ICH) GCP and section 3 of the Volume 10 TMF guidance is a useful guide for the minimum documents that are considered essential, but it is not comprehensive, and therefore should not be used as a definitive checklist for TMF content. In addition, not all documents will be of relevance to every study therefore the content of the TMF will differ from study to study. The relevant Sponsor requirements for TMFs should be followed as outlined in the sponsor Standard Operating Procedures (SOPs).

The purpose of this Standard Operating Procedure SOP is to ensure a consistent approach to creating, filing and maintaining essential documents for the TMF including the ISF. This SOP describes the procedure for setting up and maintaining a TMF.

Definitions

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
eTMF	electronic Trial Master File
GCP	Good Clinical Practice
HCA	Health Care Assistant
HRA	Health Research Authority
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
UHPNT	University Hospitals Plymouth NHS Trust
PI	Principal Investigator
RD&I	Research, Development & Innovation
REC	Research Ethics Committee
RO	Research Office
SOP	Standard Operating Procedure
TMF	Trial Master File

2 Who should read this document?

All staff involved in setting up and conducting research e.g. Chief Investigators (CI), Principal Investigators, Research Nurses & Midwives, Health Care Assistants (HCA), RD&I Managers and Clinical Trial Administrative staff

3 Procedure to Follow

3.1 TMF

The Trial Co-ordinator (this maybe, but not limited to, a Research Fellow, Research Nurse or Trial Administrator) is responsible for establishing the TMF at the beginning of the study.

The Trial Co-ordinator is responsible for:

- Organising the TMF in accordance with the standard UHPNT TMF index
- Updating the TMF as the study progresses
- Maintaining adequate document control for all study documents
- Ensuring security of the TMF throughout the life of the study
- Review of the TMF for completeness prior to archiving
- Archiving of the TMF following closure of a study and submission of the final study report.

The Trial Co-originator may delegate tasks relating to set-up, maintenance and archiving of the TMF to other members of the study management team, database managers and study statisticians as appropriate to their role in the study (this should be recorded on the study delegation log). However, the ultimate overall responsibility for these tasks lies with studies Chief Investigator and Sponsor.

3.2 ISF

The responsibility for setting up the ISF rests with the Principal Investigator (PI) or delegate at the study site. If this task is delegated to a member of the study team then this must be formally documented in the site delegation log. The PI at each site is responsible for ensuring security of the ISF throughout the life of the study including following archiving of the file.

Following completion of the study, the PI or delegate 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 TM prior to archiving of the ISF.

3.3 Establishing a TMF

The TMF should be established at the beginning of the study. If UHPNT is the sponsor of the study the beginning is defined as the receipt of confirmation of a successful funding application. If UHPNT is not the sponsor then the beginning is defined as the point of the sponsor's approach to UHPNT to become the lead site.

Currently, UHPNT utilises paper-based TMFs for all studies

The TMF should:

- Be kept in a secure location, for example, a locked filing cabinet within a secure room or department.
- Contain essential documents that are legible, accurate and complete.
- Contain a TMF index at the front of the file to show which documents are stored in the TMF. If an essential document is not considered applicable, this should be documented on the standard TMF index.
    - Where some sections of the TMF are not relevant, the standard UHPNT index should still be used with Not Applicable (N/A) noted against each relevant section of the index. These non-applicable sections should still be retained in the filing system but left empty.
    - Where additional sections need to be added which are not covered within the standard UHPNT TMF Index these should be added in the appropriate place and any numbering of sections adjusted accordingly.
- Reference the location of any documents which are considered applicable but are located out with the TMF. A file note should be added to the relevant TMF section
- If relevant, contain a TMF/ISF SOP log to document any study specific SOPs.

3.4 Maintaining a TMF

The TMF should be updated as the study progresses with documents placed in the TMF in a timely manner, as the regulations require that “the trial master file shall at all times contain the essential documents relating to that clinical trial”.

Maintenance of the TMF includes:

- Ensuring that the most current versions of all documentation are available for all staff assigned to the trial. This includes the requirement for documentation that is relied upon for subsequent activities to be in the TMF before these activities take place.
- Diagonally striking through the front page of all previous versions of study documents and marking them as SUPERSEDED. It is good practice to move these to a superseded section in the TMF to reduce the risk of them inadvertently being referred to.
- Minimising the storage of duplicate documents in multiple sections of the TMF
- Ensuring the TMF is made available for the purposes of monitoring or audit by the sponsor or for regulatory inspection by the competent authority.
- Checking that all outstanding essential documents and file notes have been added to the TMF and the TMF index is completed prior to archiving.
- Ensuring the TMF is securely archived in accordance with Trusts Research Archiving SOP (SC2).

3.5 Establishing the ISF

If the TMF and ISF are filed centrally in the same location, there is no requirement to set up a separate ISF as long as it is clear which documents in the TMF relate to each site. However, in most cases the Sponsor TMF and the studies local ISF/s will be filed in separate locations, so in the majority of cases will be separate filing systems.

The ISF for each participating site should be established at the beginning of the study, prior to any participant recruitment in accordance with the standard UHPNT ISF index and should:

- Be kept in a secure location, for example, a locked cabinet within a locked room.
- Reference the location of the pharmacy file (if established) if this is located separately from the main ISF. The pharmacy file must be archived with the main ISF.
- Contain essential documents that are legible, accurate and complete.
- Contain an ISF index (standard NCTU ISF index) at the front of the file to show which documents are stored in the ISF. If a document is not considered applicable, this section of the Index should be marked as N/A and a reason for this decision should be documented on the index. Non-applicable sections should be left blank in the file.
- Reference the location of any documents which are considered applicable but are not located in the ISF. A file note should be added to the relevant ISF section.
- If relevant, contain a TMF/ISF SOP log to document any study specific SOPs.

3.6 Maintaining an ISF

The ISF should be updated as the study progresses and filing should be done in a timely manner. Maintenance of the ISF includes:

- Ensuring that the most current versions of all documentation are available for all site staff assigned to the study. This includes the requirement for documentation that is relied upon for subsequent activities to be in the ISF before these activities take place
- Ensuring the ISF is made available for the purposes of monitoring or audit by the sponsor and for regulatory inspection.
- Once the study has closed the ISF should be reviewed to ensure that all the required documents are present and complete.
- Provision of the completed ISF index to the Sponsor or NCTU as appropriate, prior to archiving of the ISF.
- Ensuring the ISF is securely archived in accordance with SOP NCTU: TM-016. Archived

ISFs must be retrievable by the PI or delegate in the event of a Sponsor audit or regulatory inspection.

3.7 Filing of correspondence

Throughout the life of a study a large amount of correspondence may be generated through emails, letters, meeting minutes or telephone call reports.

Correspondence can be a key component in reconstructing the study conduct, however only relevant correspondence that is necessary for reconstruction of key activities or decisions or contains other significant information should be retained as part of the TMF and ISF.

Correspondence should be effectively organised using the following guidelines:

- File correspondence by topic area or within the relevant section of the TMF/ISF
- File correspondence in reverse chronological order so the most recent is at the top of the section
- Avoid duplication of documentation e.g. filing the final email in a chain
- Electronically attached documents that are not present elsewhere in the TMF must be included if necessary for reconstruction
- Sections including correspondence must be complete i.e. include letters received as well as those sent out

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a senior RD&I manager***, by the nominated author. These must be ratified by the ***a senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I

internet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

- Inclusion in the Trust weekly e-bulletin Vital Signs
- Direct email to Trust Researchers and or teams

4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

UHPNT SOP - SC2 Archiving

UHPNT Trial Master File Index template

UHPNT Investigator Site File Index template

Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials. 31st March 2017. EMA/15975/2016, Good Clinical Practice Inspectors Working Group (GCP IWG).

Appendix: Essential documentation for the Conduct of an IMP Study (for non CTIMPs ignore drug related documentation) — Appendix 1

BEFORE THE CLINICAL PHASE OF THE STUDY COMMENCES

Investigator's Brochure

To document that relevant and current scientific information about the IMP has been provided to the investigator.

Signed protocol and amendments, if any, and sample case report form

To document investigator and sponsor agreement to the protocol and amendment(s) and case record form.

Information given to trial subjects

- Informed Consent Form – to document the informed consent
- Patient/Parent information sheets and any other written information – to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent
- Advertisement for subject recruitment (if used) – to document that recruitment measures are appropriate and not coercive

Financial aspects of the trial

To document the financial agreement between the investigator/Trust and the study sponsor.

Insurance statement (where required)

To document that compensation to subject(s) for study related injury will be available.

Signed agreement between involved parties

e.g. Investigator/ Trust and sponsor

Dated, documented favourable opinion of Ethics Committee of the following:

- Protocol and any amendments
- Case Record Forms (CRF) (if applicable)
- Informed Consent Forms
- Patient/Parent information sheets and 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

To document that the study has been subject to Independent Ethics Committee review and given approval/favourable opinion. To identify version number and date(s) of the document(s).

Ethics Committee Composition

To document the ethics committee is constituted in agreement with GCP

Regulatory authority authorisation/approval/notification of protocol

To document that appropriate authorisation/approval/notification by the regulatory authority has been obtained prior to initiation of the study in compliance with the applicable regulatory requirements – e.g. CTA certificate

Curriculum vitae and other documents evidencing qualifications of investigator(s) and supporting study staff to whom investigator tasks are delegated The CV should be a two-page resume.
Normal values/ranges for medical/lab/technical procedures and/or tests included in the protocol To document normal values and/or ranges of tests according to the state of the art.
Medical/lab/technical procedures/tests To document competence of facility to perform required tests and support reliability of results Certification or accreditation; established quality control; external quality assessment; other validation.
Instructions for handling of investigational medicinal products and study related materials (if not in protocol or Study File) To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and study related materials.
Distribution records for investigational medicinal products and study related materials (if appropriate) To document distribution dates, batch numbers and method of distribution etc of investigational products and study related materials. To allow tracking of product batch, review of distribution conditions and accountability. If IMP coming from outside the EEA, are the shipping arrangements, Importation Licence and QP sign off documents all in place?
Decoding procedures for blinded studies To document how, in event of an emergency, identity of blinded investigational medicinal product can be revealed without breaking the blind for the remaining subjects' treatment.
Trial initiation monitoring report (externally sponsored studies) To document that study procedures were reviewed with investigator and investigator's research staff.

DURING THE CONDUCT OF THE STUDY

The following should be added to the study file during the trial:

Investigator's brochure updates To document that investigator is informed in a timely manner of relevant information as it becomes available.
Any revision(s) to: ▪ Protocol amendment(s) ▪ CRF ▪ Informed consent form ▪ Any other written information provided to subjects ▪ Patient/parent information sheet ▪ Advertisement for subject recruitment (if used) To document any revisions of these documents during the course of the trial.

Dated, documented favourable opinion of the Ethics Committee of the following:

To document that the amendments and/or revisions have been subject to the Ethics Committees review and were given approval/favourable opinion. To identify the version number and date of the documents.

- Protocol amendment(s)
- Revisions of:
  - Informed consent form
  - Patient/parent Information Sheets
  - Any other written information to be provided to the subject
  - Advertisement for subject recruitment (if used)
  - Any other documents where approval required.

Regulatory authorities approvals where required for:

Protocol amendments and other documents.

To document compliance with applicable regulatory requirements.

Curriculum vitae for new investigator(s) and/or supporting study staff to whom investigator tasks are delegated

Updates to normal values/ranges for medical/laboratory/technical procedures/tests included in the protocol

To document revisions to normal values/ranges during the course of the study.

Updates of medical/lab/technical procedures/tests

To document that tests remain adequate throughout the study period. Certification or accreditation or established quality control and/or external quality assessment or other validation

Documentation of investigational medicinal product and study related materials distribution

Relevant communication

- Letters
- Printed emails
- Meeting reports
- Notes of telephone calls

To document any agreements or significant discussions regarding study administration, protocol violations, study conduct, adverse event reporting.

Signed informed consent forms

To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in the study. Also to document direct access permission.

Source documents

To document the existence of the subject and substantiate integrity of study data collected. To include original documents related to the study, to medical treatment, and history of subject.

Signed dated and completed case report forms If too bulky to store in the SSF they may need to be kept separately. To document that the investigator or authorised member of investigator's staff confirms the observations recorded.
Documentation of CRF corrections To document all changes/ additions or corrections made to CRF after initial data were recorded.
Notification by originating investigator to sponsor of serious adverse events and related reports
Notification by sponsor and /or investigator, where applicable, to regulatory authorities of unexpected serious adverse drug reactions and of other safety information
Notification by sponsor to investigator(s) of safety information Notification by sponsor to investigators of safety information in accordance with 'The detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'.
Interim or annual reports to Ethics Committees and authorities
Subject screening log To document identification of subjects who entered pre-study screening.
Subject enrolment log To document chronological enrolment of subjects by trial number.
Subject identification code list Confidential list of names/hospital numbers of all enrolled subjects and allocated study numbers to allow ease of identification of subjects if required.
Investigational products accountability at site To document that investigational medicinal products have been used according to the protocol
Signature sheet To document signatures and initials of all persons authorised to make entries and/or corrections on the CRFs.
Record of retained body fluids/tissue samples (if any) To document location and identification of retained samples if assays need to be repeated.

AFTER COMPLETION OR TERMINATION OF THE STUDY

All of the documents previously identified should be in the SSF together with the following:

Investigational product(s) accountability at site (if applicable) To document that the investigational medicinal products have been used according to the protocol. To document the final accounting of investigational medicinal products received at the site, dispensed to subjects, returned by the subjects and returned to sponsor
Documentation of investigational product destruction (if applicable) To document destruction of unused investigational products by sponsor or at site
Completed subject identification code list To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time.
Treatment allocation and decoding documentation (if applicable) Returned to sponsor to document any decoding that may have occurred.

Final report by investigator to independent ethics committee where required To document completion of the study
Clinical study report To document results and interpretation of the study.

May or may not have appendices

6 Amendment History

Version Number:	6.1
Date Of Amendment:	Jan 2019
Details Of Amendment:	Updated logo and Trust name
Version Number:	6.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	SOPs G3 & G4 merged, use of new SOP template and SOP reference.
Version Number:	5.0
Date Of Amendment:	Jan 2015
Details Of Amendment:	SOP reviewed, highlighted check of IMP coming from outside the EEA.
Version Number:	4.1 (minor amendment)
Date Of Amendment:	Mar 2012
Details Of Amendment:	Cover page - Change of SOP location address.
Version Number:	4.0
Date Of Amendment:	Jul 2009
Details Of Amendment:	SOP reviewed minor changes to formatting.