LOUGHBOROUGH UNIVERSITY RESEARCH OFFICE
STANDARD OPERATING PROCEDURE

Loughborough University (LU) Research Office
SOP–1015 LU

Management of Essential Documents and Trial Filing for NHS Research Sponsored by Loughborough University

Effective Date: January 2016

1.0 Introduction

This Standard Operating Procedure (SOP) describes the creation of an audit trail through the retention of essential documents in the Trial Master File (TMF) or Investigator Site file (ISF) for all research sponsored by Loughborough University (LU).

The Essential Documents relating to a research study are those documents which individually and collectively enable both the conduct of the research study and the quality of the data produced to be evaluated. These documents serve to demonstrate compliance with the standards of Good Clinical Practice (GCP) and with all regulatory requirements.

All clinical information must be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the trial subjects remains protected.

A TMF must be prepared prior to study initiation and must be actively maintained and updated until the trial is formally closed. When it becomes available, the final report must be filed in the TMF.

Trial Master File (TMF): This file contains all the essential documents relating to a research study before the trial commences, during trial conduct and after completion of the trial. It is the responsibility of the Chief Investigator to establish a TMF for each research study they initiate. The TMF must be structured in a way that allows the reconstruction of the trial from the documentation. (Further information on site file organisation is available on the NIHR website). The documentation contained within the TMF should be sufficient to adequately reconstruct the trial activities undertaken, along with key decisions made concerning the trial. Consideration should be given to the TMF

being a stand-alone set of documentation that does not require additional explanation as competent authority inspections often take place some years after trial completion when personnel involved may no longer be available.

The documentation listed in Appendix A, Section 8 of ICH GCP and Eudralex Volume 10 should not be used as a definitive checklist for TMF content, but rather a subset of potential documentation that could be regarded as essential for reconstruction of the trial conduct as not all documents essential to reconstruct the trial are included in the above, for example, the sponsor approval document. In addition, it is recommended that an assessment of all activities is undertaken to determine whether they need to be documented to enable reconstruction of the trial conduct from the paperwork alone, for example, training provided by the investigator to site staff.

Where a risk-adapted approach is being followed, however, some documents listed in the guidance may not be in the TMF-for example-IMP temperature storage records. If this is the case the rationale for this must be documented in the trial risk assessment.

Investigator Site File (ISF): This file consists of essential documents relating to the specific investigator site, before the trial commences, during trial conduct and after completion of the trial. It is the responsibility of the Principal Investigator to establish an ISF for each research study they participate in.

A multi-centre study must have a TMF, and also a file for each individual site taking part in the study. It is acceptable to have individual sections rather than files for each site contained within the TMF.

For a single centre study it is acceptable for all documents to be held in one single file which acts as both the TMF and ISF.

A tabulated guide to TMF/ISF documents is contained in Appendix A ((TMF/ISF Index for Non CTIMP studies). The Index may be adapted to reflect specific study requirements.

It is expected that all TMF and ISF are 'inspection ready' at all times. Non-compliance and/or where areas of concern have been identified will be escalated in accordance with the Non compliance SOP 1016 LU.

It is a legal requirement that researchers retain the TMF/ISF and all other study related documentation for a minimum of 5 years following completion of the study. Research where the data are used to support a marketing authorisation have further requirements as per Directive 2003/63/EC. Hence, the documentation should be retained for at least 15 years after completion or discontinuation of the trial, or for at least 2 years after the granting of the last marketing authorisation in the European Community.

2.0 Procedure

2.1 Responsible Personnel

The CI or PI will be responsible for establishing and maintaining the TMF / ISF and may delegate these activities to a research team member. This must be recorded on the Delegation of Authorities & Signature Log. The files must be actively maintained until the trial is formally closed

2.2 Storage of TMF / ISF

All essential documents must be appropriately stored at all times. The TMF/ISF must be stored in a secure location, preferably in a lockable cabinet, but within a secure

locked area with minimal staff access, other than research staff. The Investigator must be able to demonstrate that all reasonable measures have been taken to ensure its security and to protect confidentiality and data integrity. It may not be possible for all documentation to be stored in one file. Where separate file/s are required, a file note must be made in the TMF/ISF which documents the location and title of the additional file/s. Where a separate pharmacy file is created for the purposes of study management, this remains part of the TMF/ISF but can remain in Pharmacy.

2.3 Version Control

All documents must be version controlled, signed and dated where appropriate. All previous versions of documents must be retained, but marked as superseded by striking through the front cover with a single line in red pen and marking as superseded by the later version. A Version Control Tracker should be utilised Appendix B. A file note (signed and dated by the CI/PI) must be placed in the file giving details of any missing or unavailable documents.

2.4 Vendors/Third Party Contractors

Copies of fully executed contracts and any formal technical agreements/plans detailing delegated functions between the Vendor and Sponsor must be maintained within the TMF/ISF. Copies of all documentation generated by either party relating to the agreements and delegated functions must also be present.

2.5 Archiving

Archiving of the TMF/ISF and all associated essential documents must be undertaken as per SOP 1024 LU Process for Study Close Down for NHS Research Sponsored by LU and SOP 1032 LU Archiving of Essential Documents for Research Sponsored by LU.

1. Responsibilities

	Responsibility	Undertaken by	Activity
1.	Chief Investigator/Principal Investigator	Chief Investigator/Principal Investigator	Establishing the TMF/ISF at the beginning of the trial
2.	Chief Investigator/Principal Investigator	Chief Investigator/Principal Investigator	Maintaining the TMF/ISF during the life of the trial.
3.	Chief Investigator/Principal Investigator	Chief Investigator/Principal Investigator	Ensure the safe storage of the TMF/ISF at all times.
4.	Chief Investigator/Principal Investigator	Chief Investigator/Principal Investigator	Ensure the TMF/ISF is archived as per the approved protocol and the SOP 1024 LU Study Close-down and SOP 1032 LU Archiving

This table is used to track the development and approval of the document and any changes made on revised / reviewed versions

DEVELOPMENT AND APPROVAL RECORD FOR THIS DOCUMENT		
Author / Lead Officer:	Jackie Green	**Job Title:** Research Governance Officer
Approved by:	**Ethics Committee**	**Date Approved: 5/2/16**

REVIEW RECORD			
Date	**Issue Number**	**Reviewed By**	**Description Of Changes (If Any)**

DISTRIBUTION RECORD:			
Date	**Name**	**Dept**	**Received**

Appendix A

Trial Master File / Investigator Site File Index
For studies NOT involving Investigational Medicinal Products

SECTION	TITLE	DOCUMENTS
1.	Contact List	Including details of relevant study site staff, responsible REC, R&D contacts, laboratory and pharmacy staff involved in the study
2.	Protocol	Current Protocol signed and dated by PI Superseded Protocol(s) Protocol Deviation Log/File notes *At TMF site level file:* *Signed protocol signature page* *- If applicable, local version and approval of translated version*
3.	Ethics Committee	NRES Application Letter of Favourable Opinion (listing documents approved and approved participating sites) Submission / Notification and REC acknowledgement / opinion of Substantial Amendments Submission / Notification and REC acknowledgement of Minor Amendments GCP Compliance / REC Constitution /Composition / List of members Annual Reports EC Correspondence *At TMF site level file:* *Site Specific Assessment and approval of amendments required*

4.	R & D	R & D application R & D approval Submission / Notification and R&D acknowledgement of Substantial and Non-Substantial Amendments Annual Reports (see section 15) R & D Notification of trial completion R & D Correspondence *<u>At TMF site level file:</u> First R&D approvals and Notification of amendments*
5.	Investigator Site Personnel	Template of Delegation of Authority Log Delegation of Authority Log Original signed and dated current CVs for all study personnel Evidence of GCP training/consent training e.g. certificate Evidence of study specific training *<u>At TMF site level file:</u> Copy of completed delegation of duties / authorised signatures forms, original CV for PI, CVs for other site staff* *Trial Training documentation:- - GCP Training - Protocol-related training / Investigator Meeting documentation*

6.	Study Documentation	Template of all current approved Participant Information Sheets and Informed Consent Forms- approved versions printed on Host Institution headed paper (make sure the version number and date is entered) Superseded Participant Information Sheets and Informed Consent Forms Template of GP letter Any other study related material eg invitation letters, posters questionnaires) Sample Case Report Form *<u>At TMF site level file:</u>* *Sample of Participant Information Sheets and Informed Consent Forms (local version)*
7.	Subject Documentation	Template Screening Log (non identifiable data) Screening Log (non identifiable data) Template Subject enrolment/Identification log Subject enrolment/Identification log (not to be removed from site)
8.	Standard Operating Procedures	Current LU Standard Operating Procedures are available on the Ethics Approvals (Human Participants) Sub-Committee website.
9.	SAE Reporting	SAE reporting Guidelines Please refer to the SOP relating to safety reporting Current SAE form template Serious Adverse Events/ Serious Adverse Reactions/Suspected Unexpected Serious Adverse Reactions (SUSARs). SAE /SUSAR reports and associated acknowledgement correspondence SAE Tracking Log
10.	Informed Consent	Copies of all completed consent forms

11.	Monitoring	Minutes from Initiation/ Pre Study Meeting Monitoring log Monitoring Documentation eg Monitoring visit report and responses Associated correspondence
12.	Clinical Laboratory	Central Laboratories Certificates of accreditation, if applicable Central Laboratories Normal Reference Ranges (including revisions) if applicable Local Laboratories Certificates of accreditation, if applicable Local Laboratories Normal Reference Ranges (including revisions) if applicable Current signed and dated CV s for relevant laboratory staff Lab Manual/sample processing instructions Sample Shipment Receipt/ Tracking Temperature logs for sample storage Sample storage instructions/ Inventory of samples/specimens *<u>At TMF site level file:</u>* *Certificates of accreditation and normal Reference Ranges for local labs of all participating sites*
13.	Study Related Supplies	Shipment/delivery Collection/return Supplies Re-order form templates Others
14.	Financial / Legal	Contracts / Contract Addendums with all investigators and Sub-contractors Confirmation of Sponsorship

		Funding Letter(s) Financial Agreement Insurance and Indemnity Statement for all investigators Clinical Trial Agreement with all investigators Financial Correspondence Records of subject expenses *<u>At TMF Site Level File:</u>* *Copies of all agreements*
15.	Annual /Final report	Annual Reports to REC and R&D Notice to REC and R&D of trial completion
16.	Publications	Copies of all study analysis publications
17.	Correspondence	Correspondence with CI / Sponsor and internal site correspondence, including Newsletters and other study specific correspondence. Meeting Agendas and Minutes General correspondence *<u>At TMF Site Level File:</u>* *Monitoring Confirmation and Follow up correspondence*
18.	Miscellaneous	

Appendix B

VERSION CONTROL TRACKER – keep at front of Trial Master File / Investigator Site File

THE MOST UP-TO-DATE VERSION OF EACH DOCUMENT MUST BE PLACED UPPERMOST IN THE FILE – Retain all earlier versions for audit purposes and mark: 'Superseded by Version (No) on (date)' to avoid accidental use of wrong version.

PROTOCOL

VERSION No.	DATE	DATE APPROVED BY ETHICS	DATE APPROVED BY MHRA	DATE APPROVED BY R&D	DATE IMPLEMENTED	COMMENTS e.g. date new version sent to co-investigator or to participating sites, acknowledgement of receipt, etc

PARTICIPANT INFORMATION SHEET

VERSION No.	DATE	DATE APPROVED BY ETHICS	DATE APPROVED BY MHRA	DATE APPROVED BY R&D	DATE IMPLEMENTED	COMMENTS e.g. date new version sent to co-investigator or to participating sites, acknowledgement of receipt, etc

INFORMED CONSENT FORM

VERSION No.	DATE	DATE APPROVED BY ETHICS	DATE APPROVED BY MHRA	DATE APPROVED BY R&D	DATE IMPLEMENTED	COMMENTS e.g. date new version sent to co-investigator or to participating sites, acknowledgement of receipt, etc

OTHER ……

VERSION No.	DATE	DATE APPROVED BY ETHICS	DATE APPROVED BY MHRA	DATE APPROVED BY R&D	DATE IMPLEMENTED	COMMENTS e.g. date new version sent to co-investigator or to participating sites, acknowledgement of receipt, etc

OTHER ……

VERSION No.	DATE	DATE APPROVED BY ETHICS	DATE APPROVED BY MHRA	DATE APPROVED BY R&D	DATE IMPLEMENTED	COMMENTS e.g. date new version sent to co-investigator or to participating sites, acknowledgement of receipt, etc