Standard Operating Procedure (SOP) for Establishing and Maintaining a Trial Master File (TMF) / Investigator Site File (ISF)

For Completion by SOP Author	
Reference Number	PHU/RDSOP/009
Version	2.1, 28 Sept 2023
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For Completion by Research Dept., SOP Controller	
Name of Responsible Committee	Research Delivery Meeting [ratified 6 Nov 2023]
Issue Date	7th November 2023
Implementation Date	21st November 2023
Review date	21st November 2027
Electronic location	G-Drive – Policies and SOPS – TMF & ISF – Current Version

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If you are reading this SOP in printed form then you are reading an uncontrolled document. You must therefore verify that the version number and date given below are the most recent, by cross-checking with the Trust research website before proceeding with implementation.

Portsmouth Hospitals University NHS Trust is committed to ensuring that, as far as is reasonably practicable, the way we provide services to the public and the way we treat our staff reflects their individual needs and does not discriminate against individuals or groups on any grounds. This SOP has been assessed accordingly

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1. INTRODUCTION

A Trial Master File (TMF) is the collection of documents that, individually and collectively, facilitate the conduct and management of the clinical study and allows the integrity of the study data and Good Clinical Practice (GCP) compliance to be evaluated.

Clinical Trials Regulation (EU) No 536/2014 (referred to as the "Regulation") require that the TMF is maintained to demonstrate compliance with the protocol. It should be readily available and auditable. It can take the form of paper or electronic files and both formats must adhere to the basic requirements set out in this SOP.

The TMF should be held at the coordinating site (usually by the Chief Investigator's office) and for multi-site trials, copies of relevant documents should be kept at each participating site in an Investigator Site File (ISF).

A comprehensive TMF/ISF should:

- Demonstrate compliance with ICH GCP and applicable UK regulations.
- Assist in the effective and successful management of a clinical research study.
- Enable the quality assurance and control of a clinical research study.
- Enable the clinical study to be reproduced and verified by others.
- Facilitate auditing, monitoring and inspection.

An effective research study document management system is required to ensure that all essential documentation is readily locatable, accessible and understandable to others.

2. PURPOSE

The purpose of this document is to provide the standard operating procedure for establishing and maintaining a TMF and/or an ISF.

3. SCOPE

This Standard Operating Procedure applies to:

- All clinical research activity conducted at Portsmouth Hospitals University NHS Trust (PHU).

- All clinical research activity for which PHU is responsible as Sponsor, including studies with external sites.

Who should follow this SOP?

All investigators and staff participating in research, for which PHU is responsible, and those persons outlined in Section 5.

The Trust recognises that some external sponsors, networks, funders and employers may require the use of their own SOPs for the good governance of research. In such cases it is the responsibility of the Portsmouth Hospitals University Trust user (including those individuals contracted to work on behalf of the Trust), to ensure that the external SOP is compatible with the procedure outlined below. If the external SOP contradicts the Trust's procedure then approval must be sought in writing from the Director of Research or a Senior Research Office Manager.

In the event of an infection outbreak, flu pandemic or major incident, the Trust recognises that it may not be possible to adhere to all aspects of this document. In such circumstances, staff should take advice from their manager and all possible action must be taken to maintain ongoing patient and staff safety.

4. ABBREVIATIONS & DEFINITIONS

Abbreviation	Meaning
CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
ICH GCP	International Committee on Harmonisation Good Clinical Practice (GCP)
ISF	Investigator Site File
PHU	Portsmouth Hospitals University NHS Trust
PI	Principal Investigator
SOP	Standard Operating Procedure
TMF	Trial Master File

Term	Definition
Chief Investigator (CI)	A CI is the authorised health care professional, whether or not they are an investigator at any particular site, who takes primary responsibility for the conduct of the clinical research at all sites involved in the study.
Essential Documents	Documents which individually and collectively: • Permit the evaluation of the conduct of clinical research and the quality of the data produced. • Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of GCP and with all regulatory requirements. • When filed appropriately and in a timely manner, greatly assist in the successful management of clinical research by the investigator. • Are usually audited or monitored by the sponsor and inspected by regulatory authorities as part of the process to confirm the validity of the clinical research conduct and data collection. • Section 8 of ICH GCP guidance (referenced) details the essential documents necessary for the conduct of clinical research.
Hosted	Refers to an externally sponsored study for which Portsmouth Hospitals University NHS Trust are acting as a site.
Investigator Site File (ISF)	The ISF forms part of the TMF but is held and managed at participating sites. Each participating site would normally be expected to have and maintain their own ISF. This file may also hold confidential site information and should not be removed from the site until archiving.
PHU Sponsored Studies	Studies which Portsmouth Hospitals University NHS Trust have ultimate responsibility for the initiation, management of and financing for. PHU take primary responsibility for ensuring that the design of the study meets appropriate standards and that arrangements are in place to ensure appropriate conduct and reporting.
Principal Investigator (PI)	The authorised health care professional who takes primary responsibility of the conduct of clinical research at each site.

Research Study Team	The people involved in the conduct of a research project. There may be different research teams for the project at different sites.
Sponsor	A sponsor is, in relation to clinical research, the person/organisation who takes responsibility for the initiation, management and financing (or arranging the financing) of that research.
Trial Master File (TMF)	The TMF is a standard document management system which allows for the effective management, storage and location of essential study documents required for the conduct of clinical research in accordance with the principals of ICH GCP. The filing system may be in the form of a single project file or a number of files/filing cabinets, depending on size and complexity of the study. Increasingly, Sponsors are utilising digital technologies for TMF creation, management and archiving. These are commonly referred to as eTMFs. eTMFs are equally document management systems which must have the same level of controls as traditional, physical TMFs.

5. DUTIES AND RESPONSIBILITIES

Role	Responsibilities
Chief Investigator (PHU-**Sponsored** Studies)	▪ The set-up and ongoing maintenance of the TMF. Note this duty may be delegated to another appropriately qualified member of the Research Team (Research Nurse/Clinical Trials Practitioner/Clinical Trials Assistant) and recorded in the delegation of duties log or supported by Research Office staff. ▪ Checking the TMF against the Trust's TMF filing index (see section 8.0) associated with this document. ▪ Enabling the set up of Investigator Site Files (ISF) at participating sites by ensuring all PIs are provided with PHUs ISF filing structure (see section 8) and core study documentation. This may be delegated to the study Trial Manager or the Research Office. ▪ Make the TMF available for monitoring or audit by the sponsor and/or external inspectors.
Principal Investigators (**Hosted** studies)	▪ The set-up and ongoing maintenance of the Investigator Site File. Note this duty may be delegated to another appropriately qualified member of the Research Team (Research Nurse/Clinical Trials Practitioner/Clinical Trials Assistant) and recorded in the delegation of duties log. ▪ Checking the ISF against the Sponsor's ISF filing index where provided. If not provided establish the ISF using PHU's filing index associated with this document. (See section 8.0). ▪ Make the ISF available for monitoring or audit by the sponsor and/or external inspectors.
Research Study Team & Other Delegated Persons	▪ Are responsible for ensuring any duties delegated by the PI for the maintenance of the TMF/ISF meet the standards of ICH GCP. These should be appropriately documented in the delegation of responsibilities log.
PHU Research Office Staff	▪ Centrally recording the location of all TMFs and ISFs. ▪ For PHU sponsored studies, support the CI and delivery team with TMF/ISF

	creation and management where required and agreed with Research Office Management. ▪ Monitoring TMFs/ISFs where required. For PHU sponsored studies this would be as per the published monitoring plan or when triggered by an event or concern. For hosted studies, this would be when triggered or via facilitation/oversight of self-monitoring conducted by the PI and study team.

6. PROCESS

6.1. Establishing a Trial Master File for PHU Sponsored Clinical Research

The TMF should be established as soon as possible after PHU agreement to Sponsor the study has been confirmed. This will normally be following review at the Research Development Meeting.

The PHU study-level TMF filing index should be used (see section 6.3 and 8.0), ensuring compliance with ICH GCP. The template index can be adapted to fit the study, using a risk based approach. Essential documents for the study can be supplemented or reduced if there is justification based on the importance and relevance of the specific documents to the study (for example, there is no need for IMP related documents for a study not involving IMP).

For single site studies it is acceptable for all essential documents to be held in one file, which will act as both the TMF and the ISF.

The following should be clearly indicated in the filing index or by file note:

- Sections or documents that are not applicable.
- Any part of the study-level TMF that will be held in a separate location, such as Pharmacy (include details of where they are to be found and who the contact there would be).

PHU Sponsored Multi-Site Studies

Chief Investigators of multi-site studies must create an additional file for each participating site, to be held centrally with the study-level TMF. Together, these files comprise of the TMF. This file should hold documentary evidence of all site approvals, pertinent communications and compliance with ICH GCP. The site-level TMF filing index should be used for this process, (see sections 6.3 and 8.0).

In addition, each site should be set up with their own ISF to be held by the PI at the hosting site.

6.2. Establishing an Investigator Site File for Hosted Research

An ISF is prepared by the Principal Investigator as soon as it is known that the study will be progressed. It is common for the external sponsor of the study to provide the ISF to the PI for use.

PHU's ISF filing index is available for use (see Section 8) if one has not been provided by the Sponsor.

All study related documentation should be filed in a timely manner and in intuitive fashion. For example, correspondence should be filed in sequential order, most recent first. Or where there

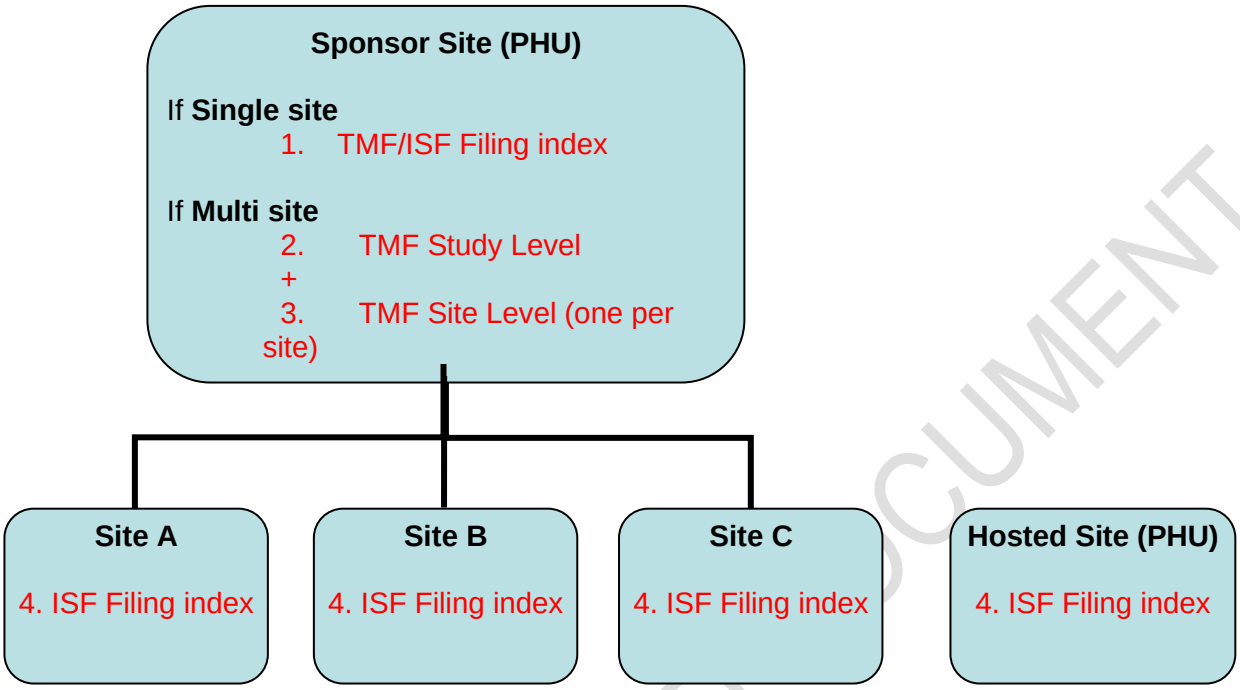
is correspondence relating to a study breach, copies of the related correspondence should be filed with the information pertaining to the breach (rather than the breach report being filed in one ISF location, and the pertinent correspondence in another).

The following should be clearly indicated in the filing index or by file note:

- Sections or documents that are not applicable.
- Any part of the ISF that will be held in a separate location (include details of where they are to be found and who the contact would be).

6.3. TMF/ISF Filing Structure Indices

The four filing structure indices are illustrated below:



1	**TMF / ISF Filing Index**	• For single site studies, sponsored by PHU. • Index for the Trial Master File (TMF). • To be kept by the Chief Investigator/Principal Investigator.
2	**TMF Study Level Filing Index**	• For multi-site studies sponsored by PHU. • Index for the 'study' level documents in the TMF (e.g. regulatory approvals, protocol, patient information sheets and consent forms). • Concerned with information that is at a central/study level. • To be kept by the Chief Investigator.
3	**TMF Site Level Filing Index**	• For multi-site studies sponsored by PHU • Index for the 'site' level documents in the TMF (e.g. signed contracts, localised versions of patient documents, site specific correspondence). • One index is required for each site, • To be kept by the Chief Investigator, as part of the TMF,
4	**Investigator Site File (ISF) Filing Index**	• For external sites hosting a PHU sponsored studies (i.e. a multi site study) or PHU hosted studies (where the sponsor hasn't provided an ISF). • Index for the Investigator Site File (ISF). • To be kept by the Principal Investigator.

6.4. Maintenance and Storage of the TMF/ISF

Content

The investigator must ensure that an appropriate index is used. This should also signpost to any/all other locations study documentation may be held outside of the central TMF/ISF where applicable.

Essential documentation should be filed in a timely manner throughout the study to keep the file up to date. Filing should be in the appropriate section and in date sequential order to provide a clear audit trail.

Essential documents should be complete, legible, accurate, unambiguous, signed and dated as appropriate.

All amended documents must be filed in the TMF/ISF. All superseded versions of approved documents must be retained but scored through, marked “superseded”, initialled and dated. Superseded documents will normally be held within the relevant section of the TMF/ISF to display the audit trail. Some studies may require superseded documents to be filed in the ‘Superseded Documents’ section.

Correspondence necessary for the reconstruction of the study, including key activities and decisions, should be retained. This correspondence should be filed in the sections most relevant to which it relates, not necessarily all filed in one section. General correspondence can be kept in a correspondence section.

The TMF/ISF must be actively maintained. When the study formally closes the TMF/ISF must be complete. For e-TMFs regular back ups should be made.

Storage and access

The Research Study Team will inform the Research Office of the location of all parts that form the TMF/ISF and this should be accurate at all times ensuring it is easily accessible for day-to-day use, monitoring inspections or emergency access.

The TMF/ISF must be stored in a secure location under conditions fit to maintain the documents.

Any temporary change of location should be entered onto the TMF/ISF Tracker (Appendix A) and left in a separate TMF/ISF Tracker File at the agreed location. A permanent change to the location should be notified to the Research Office.

Access to the TMF/ISF should be controlled to ensure any alteration is traceable.

6.5. Electronic TMF/ISF

Electronic TMFs (e-TMF) must enable appropriate security and reliability to be in place, ensuring that no loss, alteration or corruption of data and documents occurs.

e-TMFs are a document management system and will have controls in place to ensure appropriate version control. These would include: user accounts, document locking, audit trails, regular back ups for example.

The e-TMF must be validated to demonstrate functionality is fit for purpose. Where the e-TMF links with other electronic systems further validation will be carried out to ensure the quality and

integrity of data/documents is maintained. Validation will be carried out using a risk-based approach as identified in the risk assessment (performed during study set up).

At PHU, physical TMF/ISFs are still the norm. Where eTMFs/ISFs are held, they are done so either on Trust maintained 'G Drives' or via the EDGE system. Decisions on what PHU sponsored studies may utilised an eTMF/ISF will be made and recorded at the Sponsor Oversight Group, based on the risk factors associated with the study. It is likely that only studies deemed to be low risk would be considered for eTMF/ISF usage, but this is at the discretion of the Sponsored Oversight Group.

6.6. Archiving the TMF/ISF

TMF/ISFs need to be stored in such a way that preserves their integrity and readability, whilst restricting access to appropriate individuals only. The files must be kept safe, but also accessibly in a timely fashion when required by the Sponsor or regulatory authorities.

The TMF/ISF will be archived once the study has been closed and with Sponsor permission.

The ultimate responsibility for the documents to be retained by the investigator sites resides with the site investigator/institution. Details of the storage arrangements should be made available to PHU.

The documents should be retained in a secure storage area with appropriate protection against unauthorised access. The storage area should be weatherproof and have stable environmental conditions to ensure that the records remain in a legible condition. Appropriate protection measures should be in place to protect against fire, flood and the entry of pests and rodents. Basement and attic locations should be avoided as well as areas with water pipes running through them. The storage area should be in a location which will enable prompt retrieval and ensure that essential documents are readily available upon request to the regulatory authorities. It should be regularly monitored to ensure early detection of any problem such as rodent infestation or mould growth.

For archiving of eTMFs a robust monitoring process must be defined to allow for periodic checks to be carried out on the e-TMF to ensure long term readability and the on-going availability of the data. This archive monitoring process should be considered within the monitoring plan (prepared during study set up).

7. TRAINING REQUIREMENTS

All researchers and research department staff should be trained in this procedure. Evidence of training shall be required for all Chief Investigators and individual's delegated specific TMF/ISF responsibilities, during PHU Sponsored studies.

"The Research Dept., will endeavour to notify staff of SOP developments that may be relevant to them. SOPs are available on the Research department website. Updates on SOPs will feature in Research newsletters and communications and disseminate at local research meetings. It is the responsibility of all research active staff to ensure that they read the issued updates that may be relevant to them.

When a new SOP is authorised, or when an existing SOP is revised, self directed training must be carried out by all staff to which the SOP is relevant and this training documented in their training record. A template is provided to support this process. A study specific SOP training plan will be developed for investigators on high risk PHU Sponsored studies.

Staff should take time to read and fully understand the SOP and relevant documents, ensuring that they are able to implement the SOP when required. If clarification is needed then the trainee should approach their line manager and the SOP Controller who will arrange additional training. All staff should complete their training prior to the published implementation date which will normally be between 2-6 weeks after publication.

All staff are responsible for maintaining their own SOP Training Records and copies must be made available to line managers, the SOP Controller or study monitors on request."

8. REFERENCES AND ASSOCIATED DOCUMENTATION

Associated Documents

- TMF / ISF Filing Index
- TMF Study Level Filing Index
- TMF Site Level Filing Index
- Investigator Site File (ISF) Filing Index
- Site File Location form (TMF or ISF)
- TMF/ISF Location Tracker Sheet

Templates available here: SOPs and Templates (porthosp.nhs.uk)

Reference

- The Medicines for Human Use (Clinical Trial) Regulations 2004 and the Medicines for Human Use (Clinical Trial) Amendment Regulations 2006, the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006, the Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008, and the Medicines for Human Use (Miscellaneous Amendments) Regulations 2009. http://www.legislation.gov.uk/uksi/2004/1031/contents

- UK Policy Framework for Health and Social Care Research, V3.3, 07/11/17

- EMA - Guideline on GCP compliance in relation to trial master file 4 (paper and/or electronic) for content, management, 5 archiving, audit and inspection of clinical trials, 31st March 2017

- ICH Guideline for GCP E6 (R2), Step 4, 9th November 2016

- GCP Section 8. Essential documents for the conduct of a clinical trial https://ichgcp.net/8-essential-documents-for-the-conduct-of-a-clinical-trial/

It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in these citations.

9. VERSION HISTORY LOG

Version	Date Implemented	Details of Significant Changes
1.0	31/01/2013	N/A
1.1	07/04/2016	Additional information regarding SOP training added
2.0	09/09/2019	1. Review of whole document. 2. Statement regarding risk based approaches to TMFs added 3. Addition of illustration of TMFs/ISFs indices. 4. Addition of e-TMF section. 5. 'Maintenance and Storage' and 'Archiving the TMFs' updated 6. Removal of compliance section (previous section 9) (monitoring is covered in the SOP for monitoring
2.1	**28 Sept 2023**	**1. Review of whole document, minor changes to reflect current working practice.** **2. Updates to responsibilities of Research Office** **3. Update to correspondence filing guidance** **4. Update to archiving section to make this more comprehensive**

Portsmouth Hospitals University NHS Trust

CONFIRMATION OF SOP TRAINING RECORD

A copy of this record may be kept in your personal training file to confirm your training in a specific SOP. The research department or your line manager may request copies to verify your training. If required by a study Sponsor a record may also need to be kept in the Trial Master Files (TMF) or Investigator Site Files (ISF).

SOP Details: To be completed by the SOP Controller	
Title of SOP	Establishing and Maintaining a Trial Master File (TMF) / Investigator Site File (ISF)
Reference Number	PHU/RDSOP/009
Version	V2.1 28 Sept 2023
Issue Date	
Implementation Date	

Personnel Details	
Name	
Job Title & Research Role	
Date of Training	
Nature of Training	Self Directed
Records of any meetings to clarify details in SOP	

Signatures
I confirm that I have read and consider myself to be sufficiently trained in the above Standard Operating Procedure with regards to my individual roles and responsibilities Signature of Trainee …… Date ……
I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities Signature of Trainer …… Date ……..
Additional Notes & Signatures

Signature of Trainer (where appropriate)

I confirm training in the above SOP was delivered as recorded above and that the trainee may be considered sufficiently trained in their roles and responsibilities

Signature of Trainer …… Date ……..