STANDARD OPERATING PROCEDURE

S43 – Establishing and Maintaining Trial Master Files and Investigator Site Files for RD&E Sponsored studies

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Controlled document

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DISCLAIMER

This generic R&D Standard Operating Procedure (SOP) must be followed unless a study specific SOP exists.

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Full History			
Version	**Date**	**Author**	**Reason**
1.0	22.12.2011	Assistant R&D Manager	
1.1	03.01.2014	Lead Research Nurse	Corrected grammar errors throughout and updated format.
1.2	18.01.2017	Clinical Research Officer	Overall review and update, including link to new Intranet
2.0	13.02.2018	Clinical Research Officer	Update content to include CTUs and reference to GCP E6 R2) Addendum. Transferred into new template.
3	31.07.2021	Quality Assurance Coordinator	Overall review and update. Addition of electronic TMFs/ISFs.

Associated Trust Policies/ Procedural documents:	S03 Archiving S01 Preparation of Standard Operating Procedures in Research and Development WI43
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Contents

1 INTRODUCTION

The Trial Master File (TMF) plays a key role in the successful management of a trial. The essential documents and data records stored in the TMF enable operational staff as well as monitors, auditors and inspectors to evaluate compliance with the protocol, the research study's safe conduct and the quality of the data obtained.

The TMF is usually composed of a Sponsor TMF which is held by the Sponsor organisation and an Investigator Site File (ISF) which is held by the Investigator/Institution where the research is taking place. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 Regulation 31a requires that a readily available Trial Master File (TMF) be kept, which contains the essential documents relating to a clinical trial, whilst demonstrating compliance with the principles of Good Clinical Practice (GCP).

International Conference on Harmonisation (ICH) - GCP guidelines define the study documents to be filed as "those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced ". The filing of study documents in an orderly and timely manner also greatly assists the smooth running of the trial and any future audit or inspection.

Essential Documents are those which:

- Enable both the conduct of the research study and the quality of the data to be evaluated;
- Show whether the research study is, or has been, conducted in accordance with GCP standards and all other applicable regulatory requirements;
- Contain information specific to each phase of the research study: before, during and after.
- Examples include: Protocol, Investigator Brochure, Regulatory Approvals, Signed Informed Consent Forms.

This SOP refers to the current minimum standard of documentation required in the TMF, as outlined in the ICH GCP sections 8.2, 8.3 and 8.4. Use of this SOP will result in a standardised method for collating and maintaining relevant documentation. The updated Guideline for Good Clinical Practice E6(R2), which came into effect in June 2017, states that the list of essential documents may be supplemented or reduced where justified, based on importance and relevance of specific documents as determined by a risk assessment at the start of the trial.

Importantly, although it is a legal requirement to maintain a TMF only for Clinical Trials of Investigational Medicinal Products (CTIMPs), the principles should still apply for the filing of study related documentation for ALL research projects within the NHS, which have to meet the UK Policy Framework for Health and Social Care Research and any other clinical research which may have an impact on the safety and wellbeing of human participants.

2. PURPOSE

The purpose of this Standard Operating Procedure (SOP) is to outline the standard procedures to be followed when creating a TMF and ISF in clinical research sponsored by the Royal Devon & Exeter NHS Foundation Trust, hereafter called the Trust. All clinical trials sponsored by the Trust will be monitored for GCP compliance and adherence to this SOP.

3. SCOPE

This SOP is applicable to Chief Investigators, Principal Investigators and any personnel delegated with responsibility for the TMF and ISF, as well as by the relevant parties in R&D who are involved in its make-up e.g. the R&D Delivery Team and R&D Professional Services.

4. DEFINITIONS

ASR	Annual Safety Report
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
GOG	R&D Governance Oversight Group
HRA	Health Research Authority
IB	Investigator Brochure
ISF	Investigator Site File
PIS	Participant Information Sheet
R&D	Research & Development
SAE	Serious Adverse Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
Sponsor	An individual, company, institution or organisation which takes responsibility for the initiation, management and financing of a clinical trial. Sponsorship activities may be delegated to the Investigator, CTU and/ or other organisations as appropriate
TMF	Trial Master File

5. DUTIES AND RESPONSIBILITIES OF STAFF

The **Chief Investigator (CI)** is responsible for establishing and maintaining a TMF/ISF. The CI may delegate this to a Clinical Trials Unit (CTU) or a member of the CI's research team. Any delegation will be clearly documented.

The **R&D Professional Services Team** is responsible for providing a template TMF/ISF Index and ensuring this is accessible.

Clinical Research Delivery Team personnel can be delegated by the CI to be responsible for maintaining the TMF/ISF.

The **Sponsor Team** is responsible for overall oversight/compliance. Clinical Trials Sponsored by the Trust will be subject to risk-based monitoring from a member of R&D. The CI will be formally notified of this in advance in order to give the team time to prepare for the visit.

6. PROCEDURES

6.1 Establishing a Trial Master File (TMF)

6.1.1 The CI (or suitably delegated personnel) will ensure that a TMF is established as soon as possible after an outline protocol becomes available. For multi-centre research studies, the CI will keep site-specific sections within their TMF for the approvals relating to each of the other centres taking part.

6.1.2 TMFs should be created using the templates as provided by R&D. These are available on the RDE Research website. The TMF File Index applies to both paper and electronic formats and details the recommended format and sections for a TMF.

Alternative templates must be discussed and agreed with the Sponsor prior to use.

6.1.3 The CI (or delegate) will identify and maintain a record of the location(s) of all the potential documentation that is considered to form the TMF. The TMF could be entirely paper, entirely electronic or a hybrid of both. There should be a suitable overall index or table of contents to enable the location of essential documents in the TMF to be traced.

6.1.4 Where multiple files exist, the contents and volumes must be clearly indicated on the spine of the file (e.g. Lab results) or named correctly for electronic TMF.

6.2 Maintenance and Storage of the TMF

6.2.1 The TMF will be actively maintained from its establishment until the study is formally closed. While certain documents, such as the protocol or participant information sheet, may need to be amended during a project, all superseded versions of documents must be retained in the TMF alongside the new amended version(s). *See WI43 for more details. Document version control is covered in S01.

6.2.2 The TMF will be held at the CI's site, and copies of relevant documents will be kept at participating sites (see ISF section 6.4). The TMF will be stored in a locked cabinet or room in a secure area with appropriate environmental controls and adequate protection from physical damage, or secure server in the case of an eTMF. Access will be by authorised study personnel, Sponsor's representative, authorised monitors and regulatory authorities only.

6.2.3 In addition, Electronic TMFs should enable appropriate security and reliability, ensuring that no loss, alteration or corruption of data and documents occur. The primary eTMF is a system for managing documents that should contain the following controls:

- User accounts
- Secure passwords for users
- Regular back-up
- System to lock or protect individual documents of the entire eTMF e.g. at time of archiving, to prevent changes to documents
- Periodic test retrieval to confirm ongoing availability and integrity of data
- Audit trail
- Role-based permissions such as restricted access to files or documentation e.g. randomisation codes; unblended adverse event data

There should be a standardised labelling convention for electronic documents so that files can be stored easily in chronological order e.g. standard date format, file name, version. For documents subject to version control, the use of files names should not replace version details being visible on displays and printouts.

Copies of documentation in the eTMF that irreversibly replace originals should be certified copied of the original. QC checks should include the following:

- Quality of image should allow readability as per the original
- Congruency of information contained between the original and certified copy
- Accuracy of file name

6.2.4 The TMF must be easily accessible by the CI. This is to ensure access of information on the conduct of the trial is always available as well as to enable regular filing.

6.2.5 The TMF or content must not go off site, and electronic records should not be moved from the primary server unless specified and approved by the Sponsor.

6.3 Tracking of Essential Documents

In some cases it may be necessary to hold essential documents, such as the Investigator Brochure/SmPC, Participant Information Sheets (PIS) and Consent Forms (ICF) in additional files in locations separate to the TMF (eg on a ward) or on approved electronic systems e.g. EDGE.

Where this occurs, it is the responsibility of the CI or delegated individual to track where these documents are held and ensure that when amendments are implemented, the previous version of the amended documentation is removed and replaced by the updated version. This will ensure that research team members are using the correct documents to recruit and review participants. File notes must be made and filed accordingly to indicate where the documents can be found. The updated Guideline for GCP E6(R2), makes reference to this in Section 8. Any essential documentation which is not contained within the TMF should be referred to on the Source Document Tracking Log (Section 10 in the TMF Template) and/or, if applicable, by a File Note indicating exact location. Examples of source documents include blood test results, biochemistry results, investigation reports, wet ink signed Consent Forms, X-rays and ECG results.

6.4 Establishing an Investigator Site File (ISF)

6.4.1 CIs conducting multi-centre research studies will also establish an Investigator Site File (ISF) for other sites involved with the research project. PIs at each of the participating sites will compile and maintain their own ISF using the R&D template provided by the CI. The ISF will contain the same sections as the TMF as a minimum requirement, although its specific contents may differ. The R&D ISF Index template details the recommended format and sections for an ISF. The Index includes a Table of Contents which is a supporting document or filing plan that describes in greater detail the documents which will be filed in each section of the ISF. If alternative templates are to be used, these must be discussed and agreed with the Sponsor prior to use.

6.4.2 Documentation in the ISF will include some source documents containing personal data that enable research participants to be directly identified e.g. screening documentation, participant identification code list, signed consent forms. These should remain under the sole control of the PI / participating site due to data privacy requirements.

6.4.3 CIs conducting single centre studies are not required to establish a separate ISF at their own centre, as the site specific documents (normally retained in an ISF) may be held collectively in the TMF.

6.5 Maintenance and Storage of the ISF

The ISF will be actively maintained from its establishment until the trial is formally closed. Both the ISF and the available source documentation will be stored in a locked cabinet, or room in a secure area, or secure server in the case of eISFs. Access will be by authorised study personnel, sponsor representative, authorised monitor and regulatory authority only.

6.6 R&D (Sponsor) File

Separate to the TMF, a file containing copies of essential approval documents will be held and maintained by the Trust's R&D Office, as part of the governance process for Trust Confirmation of Capacity & Capability. Where the Trust is Sponsor, R&D

may hold additional documents to those needed for the local approval process in order to ensure compliance with the Sponsor's requirements under the UK Policy framework.

6.7 Archiving of the TMF and R&D (Sponsor) File

The TMF, R&D Sponsor File and all trial essential documentation will be archived once the trial has been closed and the final study report produced. Archiving will be performed as detailed in R&D/Archiving of Essential Documents/S03 and in the accompanying Work Instruction WI03.

6.8 Archiving of the ISF

It will be documented during study set up who has responsibility for archiving the ISF.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the RDE Research website shortly after having been released.

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

7.3 *If applicable, a training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the contents of this SOP.*

8. MONITORING COMPLIANCE AND EFFECTIVESS OF THIS SOP

8.1 In order to monitor compliance with this SOP, the auditable standards will be monitored as follows:

No	Minimum Requirements	Evidenced by
1.	R&D TMF/ISF Index template has been used.	TMF/ISF checks.
2.	It should be documented who the CI/PI has delegated to maintain the TMF/ISF.	Delegation Log checks
3.	The CI (or delegate) will identify and maintain a record of the location(s) of all the potential documentation that is considered to form the TMF.	TMF/ISF
4.	The TMF/ISF, will be actively maintained from its establishment until the study is formally closed	TMF/ISF checks.

8.2 Outcomes from audit will be presented to the R&D Governance Oversight Group (GOG) which will monitor any resulting action plans until all issues have been addressed to satisfaction.

8.3 Issues identified via the audit process which require escalation will be referred to GOG.

9. ARCHIVING ARRANGEMENTS

9.1 The original of this document will remain with the R&D Quality Assurance Coordinator. An electronic copy will be maintained on the R&D section of the Q-Pulse document management system and a pdf copy on the RDE Research website.

9.2 Archive copies must be maintained for any documents which have been superseded. Archive copies in electronic format should be retained indefinitely.

10. REFERENCES

SO1 Preparation of Standard Operating Procedures in Research and Development
SO3 Archiving

Guideline for Good Clinical Practice E6(R2)
ICH GCP sections 8.2, 8.3 and 8.4
The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 Regulation 31a
UK Policy Framework for Health and Social Care Research
Guideline on the content, management and archiving of the clinical trial master file (paper and/ or electronic) 2018 European Medicines Agency