STANDARD OPERATING PROCEDURE

S43 – Establishing and Maintaining a Trial Master File and Investigator Site File)

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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.

Once printed this is an uncontrolled document

Full History			
Version	**Date**	**Author**	**Reason**
1.0	15 December 2011	Assistant R&D Manager	New Policy
1.1	03 January 2014	Lead Research Nurse	Corrected grammar errors throughout and updated format.
1.2	18 January 2017	Clinical Research Officer	Overall review and update, including link to new Intranet
2.0	13 February 2018	Clinical Research Officer	Update content to include CTUs and reference to GCP E6 R2) Addendum. Transferred into new template.

Associated Trust Policies/ Procedural documents:	S04 Auditing processes in R&D S03 R&D SOP Archiving
Key Words:	TMF ISF SOP
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Contents

1 INTRODUCTION

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.

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 only a legal requirement to maintain a TMF 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 well-being 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 in clinical research Sponsored or co-sponsored by the Royal Devon & Exeter NHS Foundation Trust, hereafter called the Trust. All clinical trials sponsored and co-sponsored by the Trust will be monitored for GCP compliance and adherence to this SOP.

3. SCOPE

This SOP should be read by, at a minimum, the Investigator, Study Coordinator and Administrator with responsibility for the TMF, as well as by the relevant parties in R&D who are involved in its make-up eg Clinical Research Officers, Network and Non-Network R&D Facilitators.

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
HRA	Health Research Authority
IB	Investigator Brochure
ISF	Investigator Site File
PI	Principal Investigator
PIS	Participant Information Sheet
R&D	Research & Development (Department)
SAE	Serious Adverse Events

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File

5. DUTIES AND RESPONSIBILITIES OF STAFF

5.1 Clinical Trials/Research Sponsored by the RD&E

It is the responsibility of the Chief Investigator (CI) to establish and maintain a TMF for each Clinical Trial/Research project that they initiate. Upon receiving Trust Confirmation of Capacity and Capability, the CI will be offered the option for the Research and Development (R&D) department to set up the TMF on their behalf. Otherwise, this task can be delegated to a Clinical Trials Unit (CTU) or a member of the CI's research team. All TMFs must be created: it is strongly recommended that the TMF template(s) agreed by R&D are used. These are available on the Trust Intranet under Research & Development as well as on the dedicated R&D website www.rderesearch.co.uk under Safety & Governance. Alternative templates must be discussed with the Sponsor prior to use. A designated person may take responsibility for the maintenance of the TMF; however this must be clearly documented on the Delegation Log.

CIs conducting multi-centre trials/research will also establish an Investigator Site File (ISF). To do this, as with TMFs, it is strongly recommended that the R&D template(s) for ISFs are used. These are available on the Trust Intranet under Research & Development as well as on the dedicated R&D website http://www.rderesearch.co.uk/ under Safety & Governance. If alternative templates are to be used, these must be discussed with the sponsor prior to use. For CIs conducting single-centre trials, it is acceptable for all documents to be held in one single file which will act as both the TMF and ISF.

CIs for multi-centre trials/research will ensure that a suitable ISF is in use at host sites and should consider providing ISFs to the Principal Investigator (PI) at each of the other site locations. R&D can assist the CI in creating additional ISFs and providing them to other sites, should this be required.

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.

5.2 Clinical Trials/Research with an external Sponsor

Where there is an external Sponsor, the PI may be provided with an ISF for their site with the TMF being held by the Sponsor. If the Sponsor does not provide an ISF, the PI must establish one for themselves and may use the ISF template as mentioned above.

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 trials/research, 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 The TMF can consist of a series of files, or a single file. Where multiple files exist, the contents must be clearly indicated on the spine of the file (e.g. Lab results) and documentation held in other files clearly signposted on the internal contents.

6.1.3 Essential Documents are those which:

- Enable both the conduct of the clinical trial and the quality of the data to be evaluated;

- Show whether the trial is, or has been, conducted in accordance with applicable requirements;
- Contain information specific to each phase of the trial: before, during and after.

6.1.4 Essential documents must be filed in separate sections covering the following topics:

- Protocol and Patient Information
- Investigator's Brochure (IB)/Investigational Medicinal Product Dossier (IMPD)
- Summary of Product Characteristics (SmPC)
- Safety Alert Updates (CTIMPs only)
- Ethics, HRA and any other Regulatory Submissions
- Regulatory Agreements/Approvals
- Financial and Legal Documentation
- Correspondence
- Location Tracker for Essential Documentation and Source Documents
- Serious Adverse Events (SAEs)
- Annual Safety Reports (ASRs) / Progress Reports
- Staff and Training
- Patient Documents
- Data Collection
- Site Staff
- Pharmacy
- Clinical Laboratory (if applicable)
- Study-related Supplies
- Monitoring
- Final Report

The TMF File Index details the recommended format and sections for a TMF. The Table of Contents is a supporting document which acts as a filing plan and describes in greater detail the documents which will be filed in each section of the TMF.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.

6.2 Maintenance and Storage of the TMF

6.2.1 The file will be actively maintained from its establishment until the trial 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).

6.2.2 The TMF will be held at the CI's site, and copies of relevant documents will be kept at participating sites. The TMF will be stored in a locked cabinet, or room in a secure area. Access will be by authorised study personnel, sponsor's representative, authorised monitors and regulatory authorities only.

6.2.3 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.

6.2.4 The TMF or content must not go off site, 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).

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.

6.4 R&D (Sponsor) File

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; this is to ensure compliance with the Sponsor's requirements under the UK Policy framework. These documents may be duplicates of those held in the TMF.

6.5 Establishing an Investigator Site File (ISF)

6.5.1 CIs conducting multi-centre trials are not required to establish an ISF at their own centre, as the site specific documents (normally retained in an ISF) may be held collectively in the TMF. The CI will be required to provide a template ISF for all sites participating in the trial. This can be done with the assistance of R&D if required.

6.5.2 PIs at each of the other participating sites will compile and maintain their own ISF using the template provided by the CI/R&D.

The ISF will contain the same sections as the TMF as a minimum requirement, although its specific contents will probably differ. The ISF File Index template details the recommended format and sections for an ISF.

The ISF Table of Contents is a supporting document or filing plan which describes in greater detail the documents which will be filed in each section of the ISF.

6.6 Maintenance and Storage of the ISF

The file 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. Access will be by authorised study personnel, sponsor representative, authorised monitor and regulatory authority only.

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 is the responsibility of the Local Site PI and Host Organisation to ensure that the their ISF and all trial/study essential documentation are archived according to local SOP or policy once the trial has been closed and the final study report produced.

7. DISSEMINATION AND TRAINING

7.1 This SOP and associated templates and forms will be uploaded to the Trust intranet and external 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.

8. MONITORING COMPLIANCE AND EFFECTIVESS OF THIS SOP

8.1 This SOP will be audited in line with S04 Auditing processes in R&D.

8.2 Outcomes from audit will be presented to the R&D Quality Assurance Group 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 the R&D Divisional Governance Group.

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 Trust Intranet.

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

10. REFERENCES

Guideline for Good Clinical Practice E6(R2)

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 Regulation 31a

UK Policy Framework for Health and Social Care Research