MRC Clinical Trials Unit

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TRIAL MASTER FILE MANAGEMENT POLICY

VERSION 1.0

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For the Revision History please see the Version History Summary in SOPbox.

POLICY TITLE

TABLE OF CONTENTS

The following symbols may be used in this Policy:

Indicates a link to a related document

Indicates instructions to document trial-specific processes elsewhere

Throughout this document the MRC Clinical Trials Unit at UCL, will either be referred to as 'MRC CTU at UCL' or 'the unit'. In instances where neither read well in the sentence, 'the CTU' may be used.

1 BACKGROUND AND RATIONALE

A TMF is a collection of essential documents that facilitates the conduct and management of the clinical trial and allows the integrity of the trial data and the compliance of the trial with GCP to be evaluated.[2] The TMF is used by sponsors and investigators for the management of the trial and by auditors, monitors and inspectors to assess whether the sponsor and the investigator(s) have complied with the Regulation, the principles and guidelines of GCP and with other applicable regulatory requirements.

According to recital 52 of the Clinical Trials Regulation (536/2014)[1] "*in order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file (TMF), containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States), should be kept by the sponsor and by the investigator*". Articles 57 and 58 of the Regulation make this mandatory.

According to Article 57 of the Regulation, the essential documents are "*those pertaining to the trial which allow verification of the conduct of the trial and the quality of the data generated*"; therefore documents resultant from following the systems and procedures that assure the quality of every aspect of the trial are considered essential documents. Furthermore, Article 57 states "*the clinical trial master file shall at all times contain the essential documents relating to that clinical trial*." The requirement "*at all times*" means that the TMF should be updated, and completed in a timely manner.

Article 58 of the Regulation also requires that "*any alteration of the content of the trial master file shall be traceable*". The TMF should provide for document identification, version history, search, and retrieval, also, as stated in Articles 57 (and 58) "*it shall be readily available, and directly accessible upon request, to the (competent authorities of the) Member States*".

Article 47 of the Regulation also requires sponsors and investigators to take appropriate account of ICH GCP E6 (R2)[3] and to conduct the trial in accordance with GCP principles, two of which are:

- *"all clinical trial information should 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"*
- *"systems with procedures that assure the quality of every aspect of the trial should be implemented"*

1 EU Clinical Trial Regulation (536/2014)
2 Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials (Mar 2017)
3 ICP GCP guidelines Addendum E6(R2)

2 PURPOSE

The purpose of this Policy is:

- To provide guidance for setting up and maintaining a TMF in compliance with the principles of GCP, EU Clinical Trials Regulation (536/2014) the UK Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, and other relevant local regulations.
- To define the roles involved in setting up and maintaining a TMF and their respective responsibilities.
- To provide guidance on the content and format of the TMF.

3 RESPONSIBILITY AND ROLES

The following table lists the roles relevant to this Policy and a brief description of their responsibilities.

This Policy will be circulated to be Read and Understood to all appropriate roles identified in the training matrix.

ROLE	RESPONSIBILITIES
Sponsor	• Overall responsibility for the TMF, but may delegate some or all of this responsibility to MRC CTU as per agreed contracts.
Project Lead	• Approval of the TMF plan. (See MRC_CTU_TT_0500_eTMF plan)
Trial Management Team (TMT) and Trial Management Group (TMG)	• Collecting, validating and providing to relevant parties the essential documents during the life of the study in a timely fashion. • Writing any trial-specific TMF Working Practices/Plans and development of related tracking tools. • Maintaining and keeping the TMF up to date throughout the duration of the trial.

4 PROCEDURES

4.1 TRIAL MASTER FILE PLAN

As early as possible in the trial, a Trial Master File (TMF) Plan should be put in place to outline the management and maintenance principles for the TMF for the study. It should clearly outline who has responsibility for ensuring the TMF is of high-quality and remains fit for purpose.

The plan should be reviewed and updated as necessary by the TMT whenever changes are made to the study (for example addition or removal of an arm/IMP, changes in responsbility for the TMF) or associated policies and/or SOPs are updated.

See the eTMF Plan Template (MRC_CTU_TT_0500)

See the Paper TMF Plan Template (MRC_CTU_TT_0501)

4.2 TRIAL MASTER FILE STRUCTURE

The TMF is usually comprised of a sponsor TMF and Investigator Site Files which reside at sites (see section 4.5). Within the unit, there are two main systems for maintaining the sponsor TMF, paper or eTMF. For trials that have started in the unit since 2021, it is expected that eTMF will be used. There may be some documents held outside of the paper/eTMF, therefore all TMFs would be considered hybrid TMFs. A trial specific TMF structure will be prepared and agreed prior to recruitment of patients into a trial and will be broadly based on the TMF Reference Model. The structure of the TMF will be documented in the TMF plan.

Paper based trials that started prior to the release of this policy will continue to use their current filing structure and should ideally use the paper trial master file plan template referred to in section 4.1 above.

See the eTMF Filing Structure Tool - Document Mapping (MRC_CTU_TT_0507)

4.3 TRIAL MASTER FILE STORAGE AND SECURITY

The TMF should be secure at all times so as to protect the contents from unauthorised activity, which may result in loss, alteration or corruption of data and/or documents. Access to documents in the TMF should be controlled where necessary based on role, e.g. to keep trial team members blinded. Applicable roles and responsibilities should be detailed in the TMF Plan for the study.

Paper TMFs will be allocated adequate and suitable space to store the hard copy documents. To ensure that the TMF is secure, the allocated storage facility will either be a lockable cabinet or a lockable room with restricted access.

eTMFs will be stored using the PhlexGlobal eTMF system. This system is compliant with Good Clinical Practice requirements relating to TMF management and is also 21 CFR Part 11 compliant.

For both eTMF and paper TMF, any documentation that needs to be stored electronically on the network, should be done so in a secure folder(s) with restricted access and will be backed up

according to the appropriate ICTM IS procedures. TMF documents that are stored electronically on the network, should be stored in folders that match the TMF filing structure. A zip file containing the eTMF filing structure is available for copying to the appropriate area on the S drive.

See the eTMF Filing Structure Tool – Folder Structure (MRC_CTU_TT_508)

In order to be granted permission to access the secure folders for trials, personnel's details should be added to the STOPOver database prior to access being granted.

4.3.1 Trial Master File Data/Documents Stored in Associated Systems

There are some data/documents which form part of the Sponsor TMF which are stored in other unit systems. These include:

- Patient data for eDC studies, which will be retained in the study database
- Trial Team delegation logs which may be stored electronically in STOPOVER
- Unit SOPs which are stored in SOPbox
- Internal staff training records which are stored in TAPP and in training folders

The location of all parts of the TMF should be documented in the TMF Plan.

4.4 TRIAL MASTER FILE CONTENT

TMFs should be established as early as possible in the trial lifecycle. Therefore, it is important to ensure that during the protocol design stage of a trial, the Programme/Project Lead keeps all the relevant documents for inclusion in the TMF. These documents include:

- Documentation relating to protocol design decisions
- Documentation relating to IMP provision arrangements
- Documentation relating to vendor selection
- Evidence of review by MRC CTU SSG

The TMF will be created by the TMT and all relevant documents will be moved into and maintained within the newly created TMF.

Documents from trials that do not gain approval will be filed and archived as appropriate.

4.4.1 Essential Documents

Essential documents are those documents that individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced. Responsibility for these documents will be documented in the trial agreements and in the TMF plan. These documents demonstrate the compliance of the investigator and sponsor with the principles of GCP and all relevant regulatory requirements. The documentation contained within the TMF should therefore be sufficient to adequately reconstruct the trial activities undertaken, along with key decisions made concerning the trial. Consideration must be given to the TMF being a stand-alone set of documentation that does not require any additional explanation. Essential documents should be complete, legible, accurate, unambiguous, signed and dated as appropriate.

The documentation generated during the conduct of a trial can be quite extensive, and effective organisation within the TMF is essential to facilitate inspection, audit and trial management.

4.4.2 Filing and Version Control

The TMF must be kept up to date, with documents filed in the appropriate section of the TMF in a timely manner and documents within the TMF should be version controlled where appropriate. Filing systems should be agreed and documented in the TMF Plan.

4.4.3 Superseded Documents

If key documents are superseded, previous versions should be kept as part of the TMF so that any alterations to the records are traceable and an audit trail is maintained. Where a process requires that key drafts of documents be retained, e.g. to demonstrate input from specific trial team members, these should be kept in the TMF with the version of the document they relate to.

4.4.4 Correspondence

Correspondence that is necessary for reconstruction of key trial conduct activities and decisions, and those which contain other significant information should be filed. Examples of correspondence that should be filed include discussions with ethics committees, data monitoring committees and regulatory authorities, or communications regarding issues that arise in the trial conduct and the decisions made, such as confirmation that the IMP can continue to be used after a temperature excursion.

Correspondence should be filed in the appropriate, relevant section of the TMF rather than all in one section. It should be filed in reverse chronological order (paper TMF) and duplication of documentation in chain emails should be avoided. A full audit trail should be filed, for example both letters received and sent out, rather than just those received.

See the Correspondence Guidance Sheet (MRC_CTU_WI_080)

4.4.5 Contemporariness of the Trial Master File

As Article 57 states that the "*TMF shall at all times contain the essential documents relating to that clinical trial*"; it is important to keep the TMF up to date, with documents placed in the TMF in a timely manner. This greatly assists the successful management of a trial by the investigator and sponsor (or party to whom the sponsor has delegated its duties). In trials that have more complex TMF arrangements with multiple parties involved, the timelines for submission and filing of documents to the TMF should be defined in the TMF Plan.

4.4.6 File Notes

File Notes may be used when an event, decision or situation requires explanation and there are no other study documents designed or suitable to capture this information, or where documents might be kept by other parties. They should be used sparingly and not replace other source documents or essential documents. Other points for consideration:

- File Notes should:
    - Be Accurate, Legible, Contemporaneous, Original, Attributable, Complete, Consistent, Enduring, & Available when needed (the ALCOACCEA criteria).
    - Be attributable as confirmed by means of a signature. They should be dated contemporaneously and never backdated.

  - Be documented by the individual responsible for the work or situation described. For example, a monitor might assist the investigator site staff to formulate a File Note concerning an issue at the site, but should not take responsibility for the documentation. The note should be attributable to the staff member most responsible. Depending on the topic of the note, it might be appropriate for the Principal Investigator to document the note or at least acknowledge responsibility by signing.
  - Describe (or make reference to) the corrective and preventive actions (CAPA) plans that were put in place to correct the problem and prevent recurrence. Accompanying documentation of any related communication and corrective and preventive action should also be retained and filed appropriately.
  - Be factual and used to help clarify a complex situation or sequence of events.
- File Notes should not:
  - Be used to replace the need to document and escalate any protocol deviations.
  - Be used to describe working practices - if something happens once and will not take place again, this can be documented in a File Note. If it is a process which will be repeated, it should be documented in a working practice document.

The Trial Master file should contain an associated File Note log to facilitate locating of File Notes held within the TMF.

See the File Note Template (MRC_CTU_TT_0184)

See the File Note Log Template (MRC_CTU_TT_0182)

4.5 INVESTIGATOR SITE FILE CONTENT AND FORMAT

Each site is required to have an Investigator Site File (ISF); this will be stored at the site and maintained by the site staff. A trial specific ISF structure must be provided to sites, and/or agreed by the Trial Manager, that lists all the essential documents that should be in place prior to recruitment of patients into the trial. The site/investigator should have control over the essential documents and records generated by the site before, during and after the trial.

A self-assessment form may be provided as part of central monitoring activities for sites to complete and return prior to opening the site, to confirm that all the necessary essential documents are filed. Alternatively, the site file may be assessed for completeness by a monitor at a visit prior to site opening. Templates are available in SOPbox that can be modified as appropriate.

See the Template Trial ISF Assessment Form (MRC_CTU_TT_0113)

Sites may also be asked to complete a full ISF review on further occasions during the trial. The frequency of this may depend on the duration of the trial, the number of amendments, or repeated failure to return confirmation of receipt documents. Trial teams may create specific guidance on the expectations for ISF self-assessment for the site staff and include this in training materials. In addition to monitoring the content of the ISF centrally, trial teams may choose to carry out site file

reviews as part of on-site monitoring visits. Procedures and frequency of any site file review should be detailed in the trial Quality Management and Monitoring Plan.

See the Monitoring SOP (MRC_CTU_SOP_060)

See the Local Investigator Site File Assessment Form (MRC_CTU_TT_0282)

See the Trial ISF Self-Assessment Template (MRC_CTU_TT_0113)

4.5.1 MAINTAINING THE INVESTIGATOR SITE FILE

Throughout the trial, if any additional key documents are provided such as an updated protocol or documents relating to a substantial amendment, the trial team will provide sites with a confirmation of receipt document that they should complete to confirm all necessary documents have been received and filed.

4.6 QUALITY ASSURANCE

The TMF and its structure will be reviewed and updated on a regular basis by the trial team until archiving to ensure all the essential documents are legible and the TMF complete. This includes checking that documents have been approved and signed-off where required. This should be documented in the TMF Plan.

Periodically the TMF (or part of it) may be audited or inspected. As a result of this audit a list of corrective actions will be recommended to the trial team for improvement or additions required to the TMF. These actions should be addressed in line with timelines laid out by the Lead Auditor for the review.

See the Management of MRC CTU Internal Audit SOP (MRC_CTU_SOP_015)

4.7 CONTRACT RESEARCH ORGANISATIONS AND OTHER SUB-CONTRACTORS

The EMA guidance document on GCP compliance in relation to the TMF contains guidance on management of the TMF where multiple contractors are involved. The sponsor may choose to outsource duties and functions of the sponsor to a CRO. In conducting contracted duties and functions, the CRO will be generating documentation that will need to reside in the TMF. Where there is co-sponsorship of a trial, there should be arrangements put in place for the TMF based upon the responsibilities that each co-sponsor holds. The contract or other document or procedure agreed between all parties such as the TMF plan, should outline the arrangements for the TMF in some detail:

- which party holds the TMF (or which parts of the TMF each party holds when this is divided)
- the process for filing documentation in the TMF

- the access arrangements for the involved parties
- the structure and indexing of the TMF
- where an e-TMF is being used, the details of the system
- lists of applicable procedures to be followed and training requirements
- documents that both parties should retain
- agreed formats for electronic data (e.g. databases, images, laboratory data)
- arrangements for managing correspondence
- how the TMF would be made available if either party were to be inspected
- arrangements for when the trial is completed (the CRO may archive the TMF [or parts there of] on behalf of the sponsor)
- arrangements for oversight of the quality control/quality assurance of the TMF by the sponsor and how this would be documented (e.g. audit reports, QC reports)
- retention times
- procedures in case of an involved party closing down its business due to any reason

4.8 FINALISING/CLOSING OUT THE TRIAL MASTER FILE

A final close-out of a trial should be done when the investigator and sponsor have reviewed investigator/institution ISFs and TMF as appropriate, and confirmed that all necessary documents are filed.

4.9 ARCHIVING AND RETENTION OF THE TRIAL MASTER FILE

The TMF should be archived appropriately to provide access to the documents after the clinical trial has ended and for the entire archive period. Archiving should only take place once the procedures in 4.8 have been completed.

The retention period for the TMF will depend on the nature of the study and the requirements of relevant regulations and Sponsor, however usual UK/EU retention requirement is for 25 years for the Sponsor TMF. This should be detailed in the TMF Plan and communicated to investigators.

 See the Database Archiving SOP (MRC_CTU_SOP_075)

 See the Long-term Storage Procedures for Paper Documents SOP (MRC_CTU_SOP_023)

5 RELATED DOCUMENTS

For further information on this topic, see also:

MRC_CTU_SOP_109 – Paper Trial Master File Management SOP
MRC_CTU_SOP_108 – Electronic Trial Master File Management SOP
MRC_CTU_TT_0501 – Paper TMF Plan Template
MRC_CTU_TT_0500 – eTMF Plan Template
MRC_CTU_TT_0502– Certified Copy Form
MRC_CTU_WI_080 – Correspondence Guidance Sheet
MRC_CTU_TT_508 – eTMF Filing Structure Tool – Folder Structure.zip
MRC_CTU_TT_507 – eTMF Filing Structure Tool – Document Mapping.xls

6 REFERENCES

1. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use. http://data.europa.eu/eli/reg/2014/536/oj
2. Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials (31 Mar 2017) EMA/15975/2016
3. Intergrated addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). Step 4 version; 9 Nov 2016.