SOP number	**51.016**	Version	**7.0**
Title	**Preparation and Maintenance of a Trial Master File**		

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SOP category	NHS GG&C Sponsor R&I

Staff category

Staff Category	R	A	C	I
Research & Development Systems Manager		X		
Research Governance	X			
Sponsor Research Co-ordinator	X			
Innovation Sponsor Co-ordinator	X			
Senior Research Administrators	X			
R&I Sponsor Pharmacy	X			
Project Managers	X			
University of Glasgow Head of Research Regulation and Compliance			X	
Data Management	X			
Statistics	X			
Chief Investigator				X
Laboratories (Involved in Primary and Secondary End Points)				X

1. Scope

This procedure applies to Clinical Trial Investigational Medicinal Products (CTIMPs) and Clinical Investigations of Medical Devices (CIMDs) sponsored by NHS Greater Glasgow Health Board (NHSGGC), or co-sponsored with University of Glasgow (UoG). It covers the preparation, maintenance, quality control, and archiving of the Trial Master File (TMF) by all Sponsor/Co-Sponsor functions and associated teams or third parties involved in the oversight and conduct of these trials.

2. Purpose

The purpose of this SOP is to define the requirements for establishing and maintaining a TMF that contains the essential documentation necessary to demonstrate compliance with The Medicines for Human Use (Clinical Trials) Regulations 2012 (SI 2004/1031), as amended by the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 (SI 2025/538), This enable effective oversight of trial conduct by the Sponsor/Co-Sponsor and ensures that the conduct of the trial and the quality of the data can be adequately evaluated and reconstructed

3. Procedures

3.1. TMF Overview

The TMF contains all trial essential documentation which should be sufficient to adequately reconstruct the trial activities undertaken, along with key decisions made concerning the trial. The complete TMF includes the Sponsor/Co-Sponsor TMF, Investigator Site File (ISF) as well as participant medical records.

An electronic Trial Master File (eTMF) is a validated electronic system used to create, maintain and manage the TMF, ensuring that essential trial documents are securely stored, version-controlled and readily available for regulatory inspection.

NHSGGC utilises a paper-based TMF and does not routinely use a validated eTMF. Whilst study-related documents may be stored electronically for operational purposes, such documents are not considered part of the official TMF unless they are held within a validated electronic system approved for the storage and management of TMF records.

TMF documents must not be maintained solely in an electronic format unless they are stored within a validated electronic system that complies with applicable regulatory and organisational requirements. Where the use of a validated electronic system is approved for specific TMF records, the relevant section of the paper TMF will clearly identify the location of the records and provide instructions for access. The location of electronically held TMF records will also be documented on Form 51.016J.

R&I NHSGGC Sponsor/Co-Sponsor team includes a number of sub departments/teams and representatives from these teams form the overall Sponsor/Co-Sponsor team assigned for individual CTIMP/CIMD oversight. All teams will follow this SOP and prepare their designated section of the complete TMF index (Form 51.016A) independently, after being notified that a Sponsored CTIMP/CIMD funding application has been successful.

For international trials where NHSGGC are acting as Lead Co-ordinating Centre for the UK, the Sponsor Research Co-ordinator (SRC) will liaise with Sponsor after a successful application to determine what files (if any) will be retained by NHSGCC and how long for. Arrangements for these files will be detailed in the contract with the Sponsor and disseminated to all relevant teams and/or third parties.

3.2. TMF Preparation and Maintenance

3.2.1. Sponsor/Co-Sponsor Trial Master File (TMF)

The Sponsor/Co-Sponsor TMF index is divided in sections and covers the following teams and third parties:

A. R&I Sponsor Systems/Innovation (Sections 1-9)
B. Pharmacy (Section 10)
C. Pharmacovigilance (Section 11)
D. Monitoring (Section 12)
E. Governance (Section 13)-
F. Project Management (Section 14)
G. Data Management (Section 15)
H. Statistics (Section 16)
I. Vendors (i.e. Laboratories) (Section 17)

All required documents, as per the complete TMF index (Form 51.016A), will be printed and filed to comprise a paper TMF and stored centrally within the R&I department where each department has a locked cabinet. These documents will be added to each team's file once available (or at a minimum every 6 months) and a copy of each document will be saved in the trial e-folder held on the R&I common drive/project specific SharePoint.

Where TMF documents are stored electronically (as per section 3.2), the location of such documents must be clearly documented within the paper TMF. These must be recorded and maintained on the TMF Cover Sheet (Form 51.016J) with details as follows:

- Record the system(s) in which the electronic documents are held (e.g. shared drives, restricted access folders, document management systems)
- Provide a clear pathway to enable retrieval of documents (e.g. file path, system name, folder structure

The pathway must be sufficiently detailed to allow authorised individuals for to access the documents without any prior knowledge of the system the purposes of audits/inspections. Where applicable, pathways should be tested to ensure access can be gained.

Sections of the TMF will be maintained by the appropriate individuals of the relevant team for the whole lifetime of the trial until archived according to SOP 51.024. All study documents must be filed in sequential order with the most recent on top. It is essential to maintain the file with up-to -date information, anything not printed and filed within the paper TMF section (except those stored electronically as described above) will be considered missing information.

Sponsor/Co-Sponsor email correspondence detailing decision making will be filed in the appropriate sections of the TMF, and a copy will be stored electronically in the trial e-folder. All other relevant Sponsor/Co-Sponsor email correspondence will also be stored in the trial e-folder held on the R&I common drive/project specific SharePoint and on the corresponding department/institution's server.

If other individuals wish to add/ amend/ remove a document from the TMF, they must make the responsible individual(s) aware.

A. R&I Sponsor Systems/Innovation (Sections 1-9)

The Senior Research Administrator (SRA) will be responsible for creating the R&I Systems/Innovation TMF file (Sections 1-9) after being notified that a Sponsored CTIMP/CIMD funding application has been successful and maintaining the file for the duration of a trial. The SRC/Innovation Sponsor Co-ordinator (ISC) will be responsible for QA checks at a minimum every 6 months and prior to archiving. The R&I Systems/Innovation File will contain the cover sheet (Form 51.016J) indicating the storage locations, format and point of contact for all wider Sponsor/Co-Sponsor team files as well as third party vendor files.

B. Pharmacy (Sections 10)

The IMP section of the TMF will be stored in a secure room within a locked cabinet. The designated trial Sponsor Pharmacist and/or pharmacy technician will be responsible for creating the IMP section of the TMF (Section 10) with support from the Pharmacy facilitator. The QC checks will be undertaken by the same team members allocated to the trial, ensuring filing is up to date with all essential documents present.

C. Pharmacovigilance (Section 11)

The pharmacovigilance section of the TMF will be stored in a secure room within a locked cabinet. The senior pharmacovigilance administrator and pharmacovigilance and safety manager will be responsible for the creation and upkeep of the TMF for each study. The PV office administrators are responsible for maintaining the sections relating to SAE reports and related correspondence; these sections are kept electronically within an appropriate document repository. QC checks will be carried out either the senior pharmacovigilance administrator or the pharmacovigilance and safety manager to ensure all relevant essential documentation is in place.

D. Monitoring (Section 12)

The monitoring section of the TMF will be stored in a secure room within a locked cabinet. The designated trial/CIMD CTM to the trial and will be responsible for creating the Monitoring (Section12) of the TMF. The monitor will be responsible for the QC checks, ensuring filing is up to date with all essential documents present. A member of the monitoring/governance team can support in the administration of the TMF. Non-compliances and Protocol deviations managed by monitors are stored in this section of the TMF and managed by the designated monitor. However, summaries, updates and closure of escalated non-compliances (SOP51.008) which are reported to GHSPRAG will be filed after each GHSPRAG by the Governance Facilitator in section 12.4

E. Governance (Section 13)

The Governance section of the TMF will be stored in a secure room within a locked cabinet. The Research Governance Manager/Research Governance Facilitator will be responsible for creating the Governance Section (Section13) of the TMF. The Governance team will be responsible for the QC checks, ensuring filing is up to date with all essential documents present. A member of the governance team can support in the administration of the TMF.

F. Project Management (Section 14)

Project Managers (PMs) or their designees working across Glasgow Oncology Clinical Trials Unit (GO CTU) coordinating CTIMPs and CIMDs will maintain components of the TMF as per this SOP and GO CTU SOPs.

All other PMs including those in the Project Management Unit (PMU), the University of Glasgow (UoG), Robertson Centre for Biostatistics (RCB), the Innovation team as well as external PMs coordinating CTIMPs and CIMDs will maintain the relevant components of the TMF following this SOP.

G. Data Management (Section 15)

Data Management centres including RCB and other third-party data processors will be responsible for preparing, maintaining and archiving their corresponding section of the TMF in accordance with this SOP. This will be detailed in any contracts/collaboration agreements/Co-Sponsorship agreements as appropriate.

H. Statistics (Section 16)

Statistics providers including RCB and other third-party data processors will be responsible for preparing, maintaining and archiving their corresponding section of the TMF in accordance with this SOP. This will be detailed in any contracts/collaboration agreements/Co-Sponsorship agreements as appropriate.

I. Vendors (e.g. Laboratories) (Section 17)

If the CTIMP/CIMD involves the use of a vendor (e.g. laboratories for sample processing and analysis), the vendor will maintain and store documents that they are responsible for and will make them available for audit/inspection as required. Storage and maintenance of trial documents will be clearly documented in the appropriate contracts/collaboration agreements/Co-Sponsorship agreements as appropriate. This will be prepared by the SRC liaising with the Vendor.

The Sponsor/Co-Sponsor will provide vendors and any partners external to the R&I Department with a TMF plan, as recommended by the MHRA that cover the following points:

- Who holds the official TMF (or which parts each party holds when this is divided)
- The process of filing documentation in the TMF
- Documents that both parties must retain
- The structure of indexing of the TMF
- When eTMF is used - details of the system and validation
- Access arrangements in place for both parties for oversight and trial management
- Expected QC intervals to maintain the TMF Section
- How TMF would be available if either party was inspected
- Arrangements for when the trial is completed - Archiving

The vendor/external partner TMF plan will be included in the contractual arrangement between the Sponsor/Co-Sponsors and the vendor involved in the trial and will be captured on Form 51.016L. Section 16 will be required for all Vendors used within the trial, regardless of whether or not they have undergone a vendor assessment in accordance to SOP 51.015.

The TMF Index should be discussed at the outset of the trial, mainly to identify if any sections require to be added due to the nature of the trial.

Guidance on completing the TMF sections is available in Guideline 51.016B.

3.3. Delegated Sections of the Sponsor/Co-Sponsor TMF

Sections 15 (Data Management), 16 (Statistics) and Section 17 (Vendors) are sections that generally require responsibility to be delegated out with the R&I Department. (e.g. University of Glasgow (Robertson Centre for Biostatistics) or other external vendors). This will be decided on a study-by-study basis and details will be included in any signed contracts/collaboration/Co-Sponsorship agreements between the parties. Some vendors may work with a validated eTMF system, and this will be fully documented within such agreement and the vendor/external partner TMF plan. Sponsor/Co-Sponsor must ensure that they have access to these delegated sections of the TMF to ensure oversight.

3.4. TMF Labelling

All TMF folders will be labelled using the template document Form 51.016N.

3.5. Investigator Site File (ISF)

The ISF file is prepared by the PMs using Form 51.016C and sent to each participating location as per SOP 56.001. Participating locations will be responsible for preparing, maintaining and archiving their corresponding part of the TMF (in the form of the ISF) independently of one another according to their local processes and/or as per Sponsor/Co-sponsor instructions or agreed terms within the mCNA and this SOP.

The source data plan (Form 56.002M) will cover information on the local flag system for medical records of the participants in the trial. This will also be discussed prior to/at the Location Initiation Visit in order to ensure that the participants' medical records will be retained for the duration of archiving period of the trial as well as according to the local policies.

3.6. File Notes

On occasion it may be required to add a file note to the TMF to explain a particular course of action taken during the trial or clarify the information present for future observers. Form 51.016M may be used to document this information. Other organisations involved in the running of the trial may have their own format for file notes which may be used, for activity relating to that which NHSGGC R&I are responsible for, Form 51.016M should be used and signed by R&I staff. A file note cannot be used in place of Non-Compliances or SOP waivers and are simply there to document and explain events that have taken place for ease of understanding the TMF documentation at a later date.

3.7. Quality Control (QC)

All sections of the TMF will be subject to QC review at least once in the lifetime of the of a trial: during set-up, conduct, close-out/reporting and before archiving. However, the QC activity does not need to comprise a complete check of all content of the TMF in a single instance, the contents of the TMF should be QC'd on an ongoing basis as the documents are filed or at minimum, every 6 months. This can be limited to an individual section that is being updated and only apply to the documentation being filed in that moment. For example, if the monitoring section is updated with paperwork relevant to a single visit for a single site, just this paperwork will be QC's at the time of filing without the need to QC any existing sections.

The QC review will involve the reviewer (the corresponding representative of each Sponsor/Co-Sponsor team) ascertaining that the TMF contents match the TMF index requirements and that the locations of documents is correct according to the index and any other directions provided. The review will be captured by each team in the corresponding cover page in Form 51.016K and any inconsistencies/ errors/ omissions will be actioned to correct the issue. The line listing of the QC check should detail the limits of what has been QC checked at the time, as mentioned previously it does not need to comprise a QC check of the entire TMF or even an entire section.

Once addressed, the person performing QC will add their name and the date in the "Signature/Date" part of the corresponding QC section. Actions must then be taken, where possible, to remove any issues identified within the TMF. Individual TMF Files may also be subject to QC review and audit by a designated member of the Research Governance team. When a review by the Governance Team has been completed, this will be documented by an audit, and an audit report will be provided to the individual responsible and they will correct any inconsistencies/ errors/ omissions in a timely fashion. Details of checks to be made during the QC of the TMF are available in Guideline 51.016A.

3.8. Archiving of TMF

The TMF will be archived according to SOP 51.024.

3.9. Updates to TMF Index

The version of the TMF index current at the time of trial initiation should be used to establish the TMF structure. In most cases, this version will remain in use for the duration of the trial and there is no requirement to retrospectively update the TMF to align with subsequent versions of the index.

From time to time, updates to the TMF index may be issued to address identified issues, errors, or improvements to the filing structure. Adoption of an updated index for an ongoing trial is optional and should only be considered where there is a clear benefit to the management of the TMF.

The TMF structure is designed so that individual sections can be updated independently without affecting other sections. Therefore, where appropriate, a specific section of the TMF may be transitioned to a newer version of the index whilst the remainder of the TMF continues to use the version implemented at trial initiation.

Where a decision is made to adopt a revised index for any TMF section, this must be documented in a file note. The file note should record the section(s) affected, the version change implemented, the date of implementation and the rationale for the update to maintain an appropriate audit trail.

4. Referenced documents

- Form 51.016A - Complete R&I TMF Index
- Form 51.016C - Principal Investigator Site File: Essential clinical trial documentation for academic (non-commercial) trials
- From 51.016J - TMF Cover Sheet
- Form 51.016K - TMF index pages
- Form 51.016L - Vendor TMF Plan Template
- Form 51.016M - TMF/ISF File Note
- Form 51.016N – TMF Spine Label Template
- GUI 51.016A - Quality Control of Trial Master File
- GUI 51.016B - Sponsor TMF Index Guidelines
- SOP 51.015 – Assessment of Vendors
- SOP 51.024 - Archiving Essential Documents from Clinical Research – Process for a Sponsored Clinical Trial of an Investigational Medicinal Product (CTIMP)
- SOP 56.001 - Location Set Up – Green for Go Process
- Form 56.002M - Source Data Plan

5. Related documents

- https://tmfrefmodel.com/ (CDISC – Trial Master File Reference Model)

6. Document history

Version	Date	Description	Retrospective Implementation
1.0	06/11/2013	Release of first version	No
2.0	14/07/2016	Updated to template v1.4 and to reflect inspection outcomes.	No
3.0	17/12/2018	Staff category, Author and Approver updated	No
4.0	04/10/2021	Author updated. Reference to two of the associated forms updated (CI site file – form 51.016B now CI file and Sponsor file now TMF index – 51.016A). Admin updates (job titles and R&I office name change included). Section 6 updated to reflect current SOP numbering. Version updated.	No
5.0	24/07/2023	Author updated. Significant text change to clarify the procedures covered. Creation of Forms K & L along with Removal of Forms B, D, E, F, G, H & I. Creation of Guideline 51.016A.	No
6.0	08/05/2025	Restructured info for clarity, updated CRUK CTU to GO CTU and further information on Vendors and file notes.	No
7.0	16/07/2026	Description of an eTMF and clarification of when this can be used. Addition of Sections B-E which were missing their description of who is responsible for creating their sections. Clarifications added to QC checks required. Added section on updates to TMF Index.	No