The University of Manchester

Standard Operating Procedure

Number:	UoMCTSOP08/2024/V7.0		
Title:	The Creation and Maintenance of Trial Master Files (TMFs) and Essential Documentation		
Version:	7.0 (May 2023)	**Effective Date:**	23 Feb 2024
Author:	Lubica Stasinkova	**Review Date:**	26 Feb 2026
Reviewed by: Dr Mohammed Zubair		**Approved By:** Terence O'Neill	
Position: Research Governance, Ethics and Integrity Manager		**Position:** Deputy Chair of Clinical Trials Management Group	
Signature: 		**Signature:** Signed via email	

Version	Date	Reason for change
2.0	**January 2013**	Update of weblinks and office details
3.0	**May 2014**	Addition of version control statement for SOP
4.0	**October 2015**	Update of weblinks and office details
5.0	**August 2016**	Updates, including weblinks and office details
6.0	**March 2018**	Update to current processes
7.0	**February 2024**	Updates of weblinks, minor changes to text and inclusion of Medical device requirements

When using this document please ensure that the version you are using is the most up to date either by checking on the Research Governance, Ethics and Integrity Team website (http://www.staffnet.manchester.ac.uk/services/rbess/governance/) for any new versions or contacting the author to confirm the current version. The document is part of Sponsor QMS system, designed to manage best practice throughout clinical research and study management.

1.0 Background

The European Clinical Trials Directive 2001/20/EC ("the Directive") was introduced to establish a standardised framework for good practice in the management of Clinical Trials throughout the European Union.

The Directive was transposed into UK law as the Medicines for Human Use (Clinical Trial) Regulations 2004, statutory instrument SI 2004/1031, which came into force on 1 May 2004. This statutory instrument and all its subsequent amendments (including SI 2006/1928, which transposed into UK law the GCP Directive), will be referred to as "the Regulations" in the rest of the document.

The regulations state that clinical trials will be conducted according to the principles of GCP as defined in SI 2004/1031 and 2006/1928. Regulation 31A (Trial master file and archiving) requires that a readily available Trial Master File (TMF) is kept, which contains the essential documents relating to that clinical trial. Whilst demonstrating compliance with the principles of GCP, the filing of essential documents in an orderly, timely manner also assists the smooth running of the trial and any future audit or inspection. With the large volume of documentation required for each trial, a satisfactory filing system is necessary.

2.0 Purpose

This Standard Operating Procedure (SOP) describes the process, that must be adhered to for the creation and maintenance of trial master files (TMF) and gives a description of the necessary documentation that is relevant and required for inclusion in the TMF. This SOP is to be followed for clinical trials of an investigational medicinal product (CTIMPs/ATIMPs) or a clinical investigation of a medical devices – where the University of Manchester (UoM) is the Sponsor. The requirements of this SOP should be applied as **a minimum** to such trials and in conjunction with all applicable University of Manchester and relevant NHS Trust policies and procedures. **There maybe instances where the TMF may require additional content that is specific for a trial in which case this should be discussed with the Sponsor.**

3.0 Roles and Responsibilities

All clinical trials sponsored or co-sponsored by the University of Manchester will be monitored for GCP compliance and adherence to this SOP, under the UoM Audit Programme. The UoM, when acting as Sponsor, will delegate the requirement to maintain a TMF to the Chief Investigator (CI) or Clinical Trial Unit (CTU).

3.1 Clinical trials sponsored by the Partner Organisations

It is the responsibility of the Chief Investigator to establish a TMF for each clinical trial they initiate, by utilising the TMF template associated with this SOP (see appendix I). Chief Investigators conducting multi-centre trials will also establish an Investigator Site File (ISF) for each site, utilising the Investigator Site File (ISF) template associated with this SOP (see appendix II). For Chief Investigators 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, where the TMF is held at site.

3.2 Clinical trials with an external Sponsor

Where there is an external Sponsor, the local Principal Investigator may be provided with an ISF for their site, with the requirement to maintain a TMF being the responsibility by the external Sponsor. If the external Sponsor does not provide an ISF, it is the responsibility of Principal Investigators to establish one for their site.

4.0 Procedures

4.1 Establishing a Trial Master File

The Chief Investigator will ensure that a TMF is established as soon as possible after an outline protocol is available and/or first contact is made with the trial Sponsor(s). For multi-centre trials, the Chief Investigator will keep site specific sections within their TMF for the approvals relating to each of the other centres taking part. Where this duty is delegated to a CTU, local SOPs should be followed.

The **TMF** should contain the following sections as a minimum requirement (record keeping):

- Table of contents
- Amendment log
- Correspondence
- Protocol and protocol amendments
- Ethics Committee application & approval
- MHRA approval
- HRA approval
- Financial and legal documentation
- Vendor contracts and defined roles (including vendor audits and assessments)
- List of Study Site Staff
- List of Study-related Supplies
- Participant Information Sheets and Consent Forms

- Pharmacovigilance
- Monitoring arrangements
- Clinical Laboratory
- Pharmacy
- Investigator's Brochure/SmPC and Safety Alert Updates
- Final Report

The **Trial Master File Table of Contents template** (see appendix I) details the recommended format and content for a TMF and is included as an example of good practice. The **TMF/ISF Table of contents with description** 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 (see appendix III).

4.2 Maintenance and Storage of the Trial Master File

The file will be actively maintained from its commencement 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).

The TMF will usually be held at the Chief Investigator'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 authorised by study personnel only.

General Guidance:
* All documents must be version controlled. Superseded versions can be marked by a line through the front cover, noting "SUPERSEDED", initialled and dated.
* Correspondence and version-controlled documents must be filed in chronological order with the most recent on top.
* Some sections can be sub-divided to ease filing.
* For studies with multiple sites, the TMF must contain the file site level documents, as specified by Chief Investigator, in the TMF site-level file. Only copies of these documents are needed in the TMF site-level file, the originals must be kept at site.
* Local versions must be on Institution letter headed paper and includes UoM logo (for patient facing documentation).

4.3 Sponsor File

Where the University is acting as Sponsor or co-sponsor, the University will maintain an electronic file containing copies of essential approval documents. This will be kept on the Research Governance, Ethics and Integrity Office Shared Drive. These documents may be duplicates of those held in the TMF and any additional discussions and correspondence, that is

essential to support trial reconstruction. The Chief Investigator must ensure that relevant documents are sent to the Sponsor(s).

4.4 Establishing an Investigator Site File

Chief Investigators conducting multi-centre trials may establish an ISF for their own centre participating in the trial as soon as they have set up their TMF, and may additionally wish to set-up ISFs for all sites participating in the trial.

Where the Chief Investigator does not set up the host centres' ISF, Principal Investigators at each of the other participating sites will establish and maintain their own ISF.

The ISF will contain the same **sections as the TMF**, as a minimum requirement, although its specific contents will probably differ. The **Investigator Site File Table of Contents template** (appendix II) details the recommended format and content for an ISF and is included as an example of good practice. The **TMF/ISF Table of Contents with Description** is a supporting document or filing plan which describes in greater detail the documents which will be filed in each section of the ISF (see appendix III).

4.5 Maintenance and Storage of the Investigator Site File

The file will be actively maintained from its commencement until the trial is formally closed. Both the ISF and the available source documentation must be defined and stored in a locked cabinet or room in a secure area. Access will be by authorised study personnel only.

4.6 End of the Trial Master File review prior to Archiving

The Sponsor will review the TMF for completeness, against the Table of Contents and in accordance with GCP. The 'End of the TMF Audit report' will be provided for filing in the TMF.

4.7 Archiving of the Trial Master File

The TMF will be archived, once the Sponsor review has been completed, the 'End of the TMF Audit report' filed in the TMF and all trial closure activities finalized, as per SOP20 and the University of Manchester retention policies, in collaboration with the designated Archivist.

4.8 Archiving of the Investigator Site File

Once the Trial Manager has confirmed the completion of the remote close out checklist, resolution of the monitoring actions and filing of the relevant documentation in the ISF, the Sponsor will give the permission to archive at site. The ISF should be archived for the retention period agreed, from the end of the trial, as defined in the protocol.

4.9 Deviation from adherence with SOP and escalation process

Any deviation from the standards and requirements related to TMF maintenance as required by GCP and Sponsor will be reported to the CTMG in first instance. Escalation to the RCC will follow for deviations and audit findings that cannot be resolved.

5.0 Related Templates

Appendix I Trial Master File Table of Contents Template
Appendix II Investigator Site File Table of Contents Template

Appendix I Trial Master File Table of Contents Template

Full Project Title:	
EudraCT Number (if applicable)	
ISRCTN/Other Public Registry Number:	
Chief Investigator:	
Funding body	
Sponsor(s):	

Section	Title	Documents
0.	**Table of Contents**	Table of Contents Trial Summary Trial Contact List
1.	**Correspondence**	Correspondence with CI / Sponsor and internal site correspondence, including newsletters and other study specific correspondence. Meeting Agendas and Minutes CI site Monitoring Correspondence *<u>At TMF Site Level File:</u>* *Monitoring Confirmation and Follow up correspondence*
2.	**Protocol / Protocol Amendments** (to be altered for Medical device trials, as required, depending on the use of documentation in place, the supportive text to be deleted before use)	Current Protocol (signed and dated by CI) Current Clinical Investigation Plan CIP (with Signature page signed by PI) Superseded Protocol(s)/ CIP(s) (signed and dated by CI) Evidence of peer review Sponsor Risk Assessment *<u>At TMF site level file:</u>* *Signed protocol signature page* *- If applicable, local version and approval of translated version*
3.	**Research Ethics Committee**	REC Application Letter of Favourable Opinion (listing documents approved, approved participating sites and the committee composition and constitution)

		Evidence of addressing any conditions to ethical favourable opinion Submission / Notification and REC acknowledgement / opinion of Amendment Annual Reports Notice to REC of trial completion REC Correspondence *<u>At TMF site level file:</u>* *Initial approval and approval of amendments required*
4.	**Competent Authority** (SAE reporting documentation in section 11)	Clinical Trial Authorisation (CTA) application CTA acceptance letter Evidence addressing any conditions to acceptance Submission / Acknowledgement of amendment letters Annual Reports Serious Breaches/Urgent Safety Measure reports Notice to MHRA of trial completion MHRA Correspondence *<u>At TMF site level file:</u>* *Initial acceptance and acknowledgement letters for amendments*
5.	**HRA**	HRA application HRA approval Evidence of addressing HRA queries Approved Statement of Activities Approved Schedule of Events NIHR Portfolio adoption application and eligibility (not required if submission via CWOW (Combined Way of Working) Annual Reports

		HRA Notification of trial completion HRA Correspondence *<u>At TMF site level file:</u> Initial R&D approvals and Notification of amendments*
6.	**Financial / Legal**	Contracts / Contract Addendums with all investigators and Sub-contractors (e.g. Sponsor/Pharmacy/Laboratory/Manufacturer) including any CDAs/Permissions/Licences/template model agreements Vendor Contracts including a Delegation of Duties (Audits and assessments to be filed here) Financial Agreement Annual Reports to Funder Confirmation of RSM engagement, PURE record and R-Code Confirmation of Sponsorship (Sponsor Letter) Funding Letter(s): Application and Award Investigator Agreement Insurance and Indemnity Statement and certificates Financial Correspondence
7.	**Study Site Staff** (per site as applicable)	Site feasibility forms Local approval letter Contact details for key staff Signature pages from protocol for each site PIS/Consent Form/Other participant documentation on local headed paper (Lead site) Site initiation training material and log Site Activation letter Screening/enrolment logs Template of Delegation of duties log and authorised signatures forms Trial specific SOPs (including training) Sponsor SOPs/CTU SOPS – as applicable, a list of SOPs that are being followed is sufficient

		CV CI Honorary Contracts/Letters of Access Site close out documentation Notification and approval of protocol amendments *<u>At TMF site level file:</u>* *Copy of completed delegation of duties and authorised signatures forms, original CV for PI, CVs for other site staff* *Trial Training documentation:-* *- GCP Training* *- Pharmacovigilance Training* *- Protocol-related training / Investigator Meeting documentation* *If IND study: FDA1572 forms and Financial Disclosures*
8.	**Study Related Supplies**	Approved CRF Instructions for CRF Completion Data Management Plan Database development/validation/specification/ testing/ approval Data entry instructions Code Break instructions Randomisation and registration instructions Statistical Analysis Plan Site Initiation and activation notification Major deviation document Study Risk Management Plan *If applicable:* Sample Diary Cards (Translated templates) Sample Questionnaires (Translated templates)
9.	**Participant Information and Consent**	Template of all Participant Information Sheets and Informed Consent Forms

		If applicable: Template of translated Participant Information Sheets and Informed Consent Forms Template and translated templates of GP letter and other Advertisement materials, e.g. Referral packs *<u>At TMF site level file:</u>* *Sample of Participant Information Sheets and Informed Consent Forms (local version)*
10.	**Subject Information**	Template Subject ID Form (Confidential Patient ID form) Template Subject recruitment / screening Log Protocol Variance Tracker (for Protocol Deviations / Violations) *<u>At TMF site level file:</u>* *Subject recruitment /screening Log*
11.	**Pharmacovigilance** (additional section for Medical Devices Vigilance should be added as applicable to the project requirement, please see UoM SOP28 for more details)	Flow diagram detailing of SAE reporting SAE reporting Guidelines and Pharmacovigilance contact Current SAE form template and superseded SAE form templates Competed SAE forms SAE / SUSAR reports and associated correspondence Pregnancy forms: notification and outcome Overdose form Serious Breaches Notifications Annual Safety reports Unbinding guidelines (including testing of the code break)
12.	**Monitoring**	Monitoring Plan Minutes from Monitoring meetings (pre study) Monitoring log / documentation (e.g. Monitoring visit report)
13.	**Oversight Committees**	Charters and minutes from meetings: TMG/TSC/DMC CTMG Quarterly Reports and Monthly reports
14.	**Clinical Laboratory**	Central Laboratories Certificates of accreditation and key contact details Central Laboratories Normal Reference Ranges (including revisions)

		Sample Labels Lab Manual including sample labels, sample tracking, retainment, shipment and analysis documentation Calibration of Equipment Laboratory and GCP training *<u>At TMF site level file:</u>* *Certificates of accreditation and normal Reference Ranges for local labs of all participating sites*
15.	**Pharmacy** For Medical Device trials this section should be use for Manufacturing including: Development Plan Requirements Specification Risk Management Plan Risk Management Report Instructions to Use Device Label Investigator's Brochure / SmPC and Safety alert updates ISO standards Conformity assessment and UKCA marking	Investigational Medicinal Product packaging (label specification and template.) Pharmacy manual Instructions for handling trial medication and trial related materials (Randomisation, Re-supply, Return / Destruction, Code breaking, recall, relabeling, storage conditions) Template of Accountability forms / Inventory Forms / Dispensing guides logs / Temperature logs/Local prescription Batch Accountability - Supply/Shipping/dispatch/delivery/receipt IMP Risk Assessment *The following is applicable when Pharmacy is involved with Investigational Medicinal Product Manufacturing:* *- GMP Licence* *- Certificate of Analysis* *- Authorisation of release by Qualified Person*
16.	**Investigator's Brochure /**SmPC**and Safety alert updates**	IB / SmPC IMPD Safety alert updates
17.	**End of study report**	REC Funder Publications/Manuscripts
18.	**Clinical study report**	MHRA, final report – outcome of the trial

Appendix II Investigator Site File Table of Contents Template

Full Project Title:	
EudraCT Number (if applicable):	
ISRCTN/Other Public Registry Number::	
Chief Investigator:	
Site Investigator:	
Funding body:	
Sponsor(s):	
Site:	

Section	Title	Documents
0.	**Table of Contents**	Table of Contents Trial Summary Trial Contact List
1.	**Correspondence**	Correspondence with CI / Sponsor and internal site correspondence, including newsletters and other study specific correspondence. Meeting Agendas and Minutes Monitoring Confirmation and Follow up correspondence
2.	**Protocol (or CIP) / Protocol (or CIP) Amendments** (to be altered for Medical device trials, as required, depending on the use of documentation in place, the supportive text to be deleted before use)	Current Protocol (with Signature page signed by PI) Current CIP (with Signature page signed by PI) Superseded Protocols/CIPs (with Signature page signed by PI) If applicable, local version and approval of translated version
3.	**Research Ethics Committee**	REC Site Specific Assessment Application

		Letter of Favourable Opinion (confirmation of site specific approval, approved documents and the committee composition and constitution) Acknowledgement / REC opinion of Amendment GCP Compliance / REC Constitution /Composition / List Annual Reports Notice to REC of trial completion REC Correspondence
4.	**Competent Authority**	CTA acceptance letter Acknowledgement of amendment letters Serious breaches and Urgent Safety Measure Reports Annual Reports Notice to MHRA of trial completion MHRA Correspondence
5.	**HRA**	HRA application HRA approval Approved Statement of Activities Approved Schedule of Events HRA Notification / Approval of amendments Annual Reports HRA Notification of trial completion HRA Correspondence
6.	**Financial / Legal**	Contracts / Contract Addendums Funding Letter(s): Award Financial Agreement Insurance and Indemnity Statement Investigator Agreement Financial Correspondence

7.	**Study Site Staff**	Completed delegation of duties and authorised signatures form Signature pages for protocol CVs PIS/Consent Form/Other participant documentation on local headed paper (Lead site) Site initiation training material and log Site Activation letter Screening/enrolment logs Trial specific SOPs (including training) Trial Training Material and documentation:- - GCP Training - Pharmacovigilance Training - Protocol-related training / Investigator Meeting documentation *If IND study, FDA1572s and Financial Disclosures* Site close out documentation Notification and approval of protocol amendments
8.	**Study Related Supplies**	Sample CRF Data Management/ Data processing document *If applicable:* Diary Cards (Local versions) Questionnaires (Local versions) Completed order forms / shipping records
9.	**Participant Information and Consent**	Sample of local versions of all Participant Information Sheets and Informed Consent Forms, GP letter Signed Participant Information Sheets and Informed Consent Forms *If applicable:* GP letter and other Advertisement materials, e.g. Referral packs (Local Versions)
10.	**Subject Information**	Completed subject ID Form (Confidential Patient ID form) Subject recruitment / screening Log

		Protocol Variance Tracker (for Protocol Deviations / Violations) Completed CRFs Resolved Data Queries / Data Clarification Form
11.	**Pharmacovigilance** (additional section for Medical Devices Vigilance should be added as applicable to the project requirement, please see UoM SOP28 for more details)	Flow diagram detailing of SAE reporting if available SAE reporting Guidelines and Pharmacovigilance contact Pharmacovigilance Training handout For Medical devices – detail of MORE system for reporting SAE's to the MHRA Current SAE form template and superseded SAE form templates Competed SAE forms SAE / SUSAR reports and associated correspondence Pregnancy forms: notification and outcome Overdose form Serious Breaches Notifications Annual Safety reports Unbinding guidelines (including testing of the code break)
12.	**Monitoring**	Monitoring Plan Minutes from Monitoring meetings (pre study) Monitoring log / documentation (e.g. Monitoring visit report)
13.	**Oversight Committees**	Correspondence between or via the Sponsor/CI from all oversight committees
14.	**Clinical Laboratory**	Certificates of accreditation for central laboratories and site's local laboratories Normal Reference Ranges (including revisions) for central laboratories and local laboratories Labels

		Lab Manual including sample labels, sample tracking, retainment, shipment and analysis documentation Calibration of Equipment records Laboratory and GCP training
15.	**Pharmacy** **(for Medical Device trials this section should be use for Manufacturing including:** **Development Plan** **Requirements Specification** **Risk Management Plan** **Risk Management Report** **Instructions to Use** **Device Label** **Investigator's Brochure / SmPC and Safety alert updates** **ISO standards** **Conformity assessment and UKCA marking**	Investigational Medicinal Product packaging (label specification and template.) Site Pharmacy manual Instructions for handling trial medication and trial related materials (Randomisation, Re-supply, Return / Destruction, Code breaking, recall, relabeling, storage conditions) Template of Accountability forms / Inventory Forms / Dispensing guides logs / Temperature logs/Local prescription Batch Accountability - Supply/Shipping/dispatch/delivery/receipt *The following is applicable when Pharmacy is involved with Investigational Medicinal Product Manufacturing:* *- GMP Licence* *- Certificate of Analysis* *- Authorisation of release by Qualified Person*
16.	**Investigator's Brochure / SmPC and Safety alert updates**	IB / SmPC IMPD Safety alert updates
17.	**Final report**	REC Funder Publications/Manuscripts
18.	**Clinical study report**	MHRA, final report – outcome of the trial