Standard Operating Procedure

Number:	UoMCTSOP08/2026/V8.0		
Title:	The Creation and Maintenance of Trial Master Files (TMFs) and Essential Documentation		
Version:	8.0	**Effective Date:**	28APR2026
Author:	Lubica Stasinkova & Simon Topham	**Review Date:**	28APR2028
Reviewed by:	Dr Mohammed Zubair	**Approved by:**	Prof Terence O'Neill
Position:	Clinical Trials Manager	**Position:**	CTMG Chair
Signature:		**Signature:**	Approval by email

Version	Date	Summary of Changes
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
8.0	March 2026	Update to the SOP template. SOP references the updated UK Clinical Trials Regs (2025). Updated terminology ("site" has been replaced with "location"). Corrected for ambiguity. Reference to external sponsor has been removed. A number of sections have been added to the TMF/ISF to include Trial Risk Assessments, Audit Reports and Study Monitoring Reports.

Table of Contents

1 Introduction

All clinical trial activities conducted under this SOP are in line with the applicable UK legislation governing clinical trials of investigational medicinal products and/or medical devices. This includes, but is not limited to, the Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments or replacement legislation, such as the Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025, effective from 28 April 2026. All procedures must be carried out in accordance with current guidance issued by the Medicines and Healthcare products Regulatory Agency (MHRA), the Health Research Authority (HRA), relevant Research Ethics Committees (RECs) and updated GCP standards.

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 Scope

This Standard Operating Procedure (SOP) describes the process that must be adhered to for the creation and maintenance of Trial Master Files (TMF) and Investigator Site Files (ISF). It outlines the necessary documentation that is required for inclusion in the TMF/ISF. This SOP is to be followed by the trial teams working on any trial or investigation where the University of Manchester (UoM) Clinical Trials group is the Sponsor. The requirements of this SOP must be met as **a minimum**, and in conjunction with all other applicable University of Manchester and local NHS Trust policies and procedures, and applicable regulatory and governance frameworks.
[*There maybe instances where the TMF may require additional content that is specific for the trial, in which case this should be discussed with the Sponsor*].

3 Responsibilities

3.1 Chief Investigator

3.1.1 The creation and maintenance of the TMF/ISF is the responsibility of the Chief Investigator or Clinical Trial Unit (CTU) following the templates in the appendices of this SOP.

3.1.2 The CI may delegate day-to-day TMF/ISF management to the Clinical Trials Unit (CTU) or other delegated team members; however, overall responsibility and oversight remain with the CI.

3.2 Principal Investigator

3.2.1 The creation of an ISF if one has not been provided.

3.2.2 The maintenance of any ISF is the responsibility of the Principal Investigator or Clinical Trial Unit (CTU). The PI may delegate ISF management tasks to appropriately trained site staff but retains overall responsibility for oversight and compliance.

3.3 Sponsor UoM

3.3.1 The University of Manchester Sponsor Auditors will audit the Trial Master File for compliance to GCP and the SOPs in line with the Sponsor Risk Assessment and the annual Audit Schedule.

3.3.2 The Sponsor provides oversight to ensure that TMF/ISF processes are compliant, proportionate, and aligned with current MHRA and HRA expectations.

4 Related Documents

Reference Number	Document Title
Appendix I	Trial Master File Table of Contents Template
Appendix II	Investigator Site File Table of Contents Template
Appendix III	Trial Master File and Investigator Site File – Table of Contents with descriptions
UoMCTSOP20	Archiving
UoMCTSOP26	Trial Closure

5 Procedures

5.1 Establishing a Trial Master File

5.1.1 The Chief Investigator must 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 must keep location 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:

- Table of contents
- Modification log
- Correspondence
- Protocol and protocol modifications
- Ethics Committee application & approval
- MHRA application and no objection (if under the MHRA jurisdiction)
- HRA approval
- Financial and legal documentation
- Vendor contracts and defined roles (including vendor audits and assessments) (if applicable)
- List of Study Location Staff
- List of Study-related Supplies
- Participant Information Sheets and Consent Forms
- Pharmacovigilance (if applicable)
- Monitoring arrangements
- Clinical Laboratory (if applicable)
- Pharmacy (if applicable)
- Investigator's Brochure/SmPC and Safety Alert Updates
- Trial Risk Assessments
- Audit Reports
- Study Monitor Reports
- Final Report

5.1.2 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).

5.2 Maintenance and Storage of the Trial Master File

5.2.1 The Trial Master File must be contemporaneously maintained from its commencement until the trial is formally archived. While certain

documents, such as the protocol or participant information sheet, may need to be modified during a project, all superseded versions of documents must be retained in the TMF alongside the latest version(s).

5.2.2 The Trial Master File (TMF) will be maintained at the Chief Investigator's (CI) location or the Clinical Trials Unit (CTU). Copies of relevant essential documents will also be held at participating sites in Investigator Site Files, as appropriate.

5.2.3 The TMF must be stored under secure and controlled conditions to ensure the integrity and confidentiality of all trial documentation. This includes:

5.2.3.1 Storing the TMF in a locked, fire-resistant cabinet or a secure, access-controlled room.

5.2.3.2 Maintaining documents in clearly labelled Lever Arch files or an equivalent organised filing system.

5.2.3.3 Ensuring the storage environment protects materials from water damage, pests, excessive humidity, and other environmental risks.

5.2.3.4 Access to trial-related documentation must be limited to authorised study personnel and approved Sponsor representatives, including monitors and auditors. MHRA Inspectors carry a statutory warrant and must be granted **immediate and unrestricted access** to all relevant facilities, data, and personnel upon request.

5.2.3.5 These conditions must be maintained until the TMF is formally archived in accordance with Sponsor and regulatory requirements.

5.3 General Guidance:

5.3.1 All documents must be version controlled. Superseded versions must be annotated with "SUPERSEDED", initialled and dated.

5.3.2 Correspondence and version-controlled documents must be filed in chronological order with the most recent first in each section.

5.3.3 Large sections are permitted to be sub-divided to ease filing.

5.3.4 For studies with multiple locations, the TMF must contain the file location level documents, as specified by the Chief Investigator, in the TMF location-level file. Only copies of original documents are needed in the TMF location-level file, the original documents must be kept at location.

5.3.5 Local versions of documents must be on their Institution letter headed paper and include the UoM logo (for participant facing documentation).

5.4 Electronic Sponsor held File

Where the University is acting as the 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, Clinical Trials Group SharePoint Drive. These documents

will be duplicates of those held in the TMF and any additional discussions and correspondence with the Sponsor, that is essential to support trial reconstruction. The Chief Investigator must ensure that all relevant documents are provided to the Sponsor(s).

5.5 Establishing an Investigator Site File

5.5.1 Chief Investigators conducting multi-centre trials without a CTU must establish an ISF for their own trial location as soon as they have their TMF and will additionally set-up ISFs for all locations participating in the trial.

5.5.2 The Chief Investigator can delegate the ISF creation and maintenance to the Principal Investigator(s).

5.5.3 The ISF will contain the same **sections as the TMF**, as a minimum requirement, although its specific contents might 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).

5.6 Maintenance and Storage of the Investigator Site File

The Investigator Site File will be contemporaneously maintained throughout the trial until it is formally archived. Both the ISF and the source documentation must be stored in a locked cabinet or room in a secure area. Access will only be permitted to authorised study personnel only and Study Monitors.

5.7 Trial Master File Audit prior to Archiving

The Sponsor will audit the TMF for completeness, against the Table of Contents and in accordance with GCP and the SOPs. The Auditor signed Audit report will be provided for filing in the TMF once all audit findings have been appropriately addressed and confirmed

5.8 Archiving of the Trial Master File

The TMF will be archived, once the Sponsor audit has been completed, the Audit Report filed in the TMF and all trial closure activities confirmed, as per UoMCTSOP20 and the University of Manchester Information Governance Office Records Retention Schedule.

5.9 Archiving of the Investigator Site File

Once the Trial Manager has confirmed the completion of the Clinical Trial Close out Checklist Template (see its controlling SOP - UoMCTSOP26), closure of any monitoring actions and filing of all the relevant documentation in the ISF, the Sponsor will give the permission to archive at location. The ISF must be archived for the retention period stated in the Protocol.

5.10 Deviations from the SOP and the escalation process

Any deviation from this SOP discovered through auditing or study monitoring must be reported to the CTMG in first instance. Deviations that are not subsequently resolved or cannot be resolved will be escalated to the RCC.

6 References

1. The Medicines for Human Use (Clinical Trials) Regulations 2004 (UKSI 2004-1031)
2. The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (UKSI 2006-1928)
3. The University of Manchester Information Governance Office Records Retention Schedule.

7 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 location correspondence, including newsletters and other study specific correspondence. Meeting Agendas and Minutes CI Location Monitoring Correspondence *At TMF Location Level File:* *Monitoring Confirmation and Follow up correspondence*
2.	**Protocol / Protocol Modifications** (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 *At TMF Location level file:* *Signed protocol signature page*

		- *If applicable, local version and approval of translated version*
3.	**Research Ethics Committee**	HRA/REC Application Letter of Favourable Opinion (listing documents approved, approved participating locations and the committee composition and constitution) Evidence of addressing any conditions to ethical favourable opinion Submission / Notification and HRA/REC acknowledgement / opinion of Modification Annual Reports Notice to REC of trial completion REC Correspondence *<u>At TMF Location level file:</u>* *Initial approval and approval of modifications 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 modification letters Annual Reports Serious Breaches/Urgent Safety Measure reports Notice to MHRA of trial completion MHRA Correspondence *<u>At TMF Location level file:</u>* *Initial acceptance and acknowledgement letters for modifications*
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 Location level file:</u> Initial R&D approvals and Notification of modifications*
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 (annually updated) Financial Correspondence
7.	**Study Location Staff** (per location as applicable)	Location feasibility forms Local approval letter Contact details for key staff Signature pages from protocol for each location

		PIS/Consent Form/Other participant documentation on local headed paper (Lead location) Location initiation training material and log Location 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 for the CI Honorary Contracts/Letters of Access Location close out documentation Notification and approval of protocol modifications *<u>At TMF Location level file:</u>* *Copy of completed delegation of duties and authorised signatures forms, original CV for PI, CVs for other location staff* *Trial Training documentation: -* *- GCP Training* *- Pharmacovigilance Training* *- Protocol-related training / Investigator Meeting documentation* *If (Investigational New Drug) 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 Location Initiation and activation notification Deviations 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 Location level file:</u>* *Sample of Participant Information Sheets and Informed Consent Forms (local version)*
10.	**Subject Information**	Template Subject ID Form (Confidential Participant ID form) Template Subject recruitment / screening Log Protocol Variance Tracker (for Protocol Deviations / Violations) *<u>At TMF location level file:</u>* *Subject recruitment /screening Log*
11.	**Pharmacovigilance**	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 location level file:</u>* *Certificates of accreditation and normal Reference Ranges for local labs of all participating locations*
15.	**Pharmacy** For Medical Device trials this section should be used for the Manufacturer including: • Development Plan • Requirements Specification	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, re-labelling, storage conditions)

	• Risk Management Plan • Risk Management Report • Instructions for use • Device Label • Investigator's Brochure / SmPC and Safety alert updates • ISO standards • Conformity assessment and UKCA marking	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.	**Trial Risk Assessments**	All Trial Risk Assessments, including the Data Integrity Risk Assessment (DIRA). Evidence of periodic Risk Assessment review and triggered reviews such as after a Substantial Modification.
18.	**Audit Reports**	Draft and Final Audit Reports for audits conducted on the trial
19.	**Study Monitoring Reports**	Draft and Final Study Monitoring Reports for all locations
20.	**End of study report**	REC Funder Publications/Manuscripts
21.	**Clinical study report**	MHRA, final report – outcome of the trial

8 Appendix II Investigator Site File Table of Contents Template

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

Section	Title	Documents
0.	**Table of Contents**	Table of Contents Trial Summary Trial Contact List
1.	**Correspondence**	Correspondence with CI / Sponsor and internal location 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) Modifications** (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**	HRA/REC Location Specific Assessment Application Letter of Favourable Opinion (confirmation of location specific approval, approved documents and the committee composition and constitution) Acknowledgement / REC opinion of Modification GCP Compliance / REC Constitution /Composition / List Annual Reports Notice to REC of trial completion HRA/REC Correspondence
4.	**Competent Authority**	CTA acceptance letter Acknowledgement of modification 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 modifications 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 Location 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 Location) Location initiation training material and log Location 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* Location close out documentation Notification and approval of protocol modifications
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 Participant ID form) Subject recruitment / screening Log Protocol Variance Tracker (for Protocol Deviations / Violations) Completed CRFs Resolved Data Queries / Data Clarification Form
11.	**Pharmacovigilance**	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 SAEs 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 location'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**	Investigational Medicinal Product packaging (label specification and template.) Location Pharmacy manual Instructions for handling trial medication and trial related materials (Randomisation, Re-supply, Return / Destruction, Code breaking, recall, relabelling, storage conditions) Template of Accountability forms / Inventory Forms / Dispensing guides logs / Temperature logs/Local prescription

	Conformity assessment and UKCA marking	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.	**Study Monitor Reports**	Draft and final study Monitoring reports conducted at the location
18.	**Final report**	REC Funder Publications/Manuscripts
19.	**Clinical study report**	MHRA, final report – outcome of the trial

9 Appendix III Trial Master File / Investigator Site File Table of Contents with Description

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

TRIAL MASTER FILE TABLE OF CONTENTS			***INVESTIGATOR SITE FILE TABLE OF CONTENTS***			***DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS***
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
0.	**Table of Contents**	Table of Contents	**0**	**Table of Contents**	Table of Contents	This table of contents can be modified according to study need. A copy of the Table of contents used for the study must be filed in this section. The File Note Log serves the purpose of tracking File Notes that have been generated for the study.

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
1.	**Correspondence**	Correspondence with CI / Sponsor and internal location correspondence, including newsletters and other study specific correspondence. Meeting Agendas and Minutes CI Location Monitoring Correspondence *<u>At TMF Location Level File:</u>* *Monitoring Confirmation and Follow up correspondence*	**1.**	**Correspondence**	Correspondence with CI / Sponsor and internal location correspondence, including newsletters and other study specific correspondence. Meeting Agendas and Minutes Monitoring Confirmation and Follow up correspondence	See General Guidance

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
2.	**Protocol / Protocol Modifications**	Current Protocol (signed and dated by CI) Superseded Protocol(s) (signed and dated by CI) Evidence of peer review Sponsor Risk Assessment *<u>At TMF location level file:</u>* *Signed protocol signature page* *- If applicable, local version and approval of translated version*	**2.**	**Protocol / Protocol Modifications**	Current Protocol (with signature page signed by PI) Superseded Protocols (with signature page signed by PI) If applicable, local version and approval of translated version	See General Guidance

3.	**Research Ethics Committee**	NRES Application Letter of Favourable Opinion (listing documents approved and approved participating locations) Submission / Notification and REC acknowledgement /opinion of modification GCP Compliance / REC Constitution /Composition / List of members Annual Reports Notice to REC of trial completion EC Correspondence *<u>At TMF location level file:</u> First approval and approval of modifications required*		**3.**	**Research Ethics Committee**	NRES Location Specific Assessment Application Letter of Favourable Opinion (confirmation of location specific approval) Acknowledgement / REC opinion of modification GCP Compliance / REC Constitution /Composition / List of members Annual Reports Notice to REC of trial completion EC Correspondence	This section is for all documents pertinent to the Ethics committee, including but not limited to the documents listed. Significant correspondence with the Ethics Committee, including but not limited to, covering letters, acknowledgement letters and REC opinion must be filed in this section. Note REC composition / Constitution may not be a separate document and maybe included in the Letter of Favourable Opinion.

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
4.	**Competent Authority**	Clinical Trial Authorisation (CTA) application CTA acceptance letter Evidence addressing any conditions to acceptance Submission / Acknowledgement of modification letters Annual Reports Serious Breaches/Urgent Safety Measure reports Notice to MHRA of trial completion MHRA Correspondence *<u>At TMF location level file:</u> Initial acceptance and acknowledgement letters for modifications*	**4.**	**Competent Authority**	CTA acceptance letter Acknowledgement of modification letters Serious breaches and Urgent Safety Measure Reports Annual Reports Notice to MHRA of trial completion MHRA Correspondence	This section is for all documents pertinent to Competent Authority (UK – MHRA), including but not limited to the documents listed. Paper copy of documents submitted for CTA and subsequent modifications must be filed in the TMF. Electronic copy of documents can also be saved onto a disk to keep in the TMF. Significant correspondence with the Regulatory Authority, including but not limited to covering letter, notification letter, acceptance letter, must be filed in this section.

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
5.	**HRA**	R & D application HRA application HRA approval Evidence of addressing HRA queries Approved Statement of Activities Approved Schedule of Events NIHR Portfolio adoption application and eligibility Annual Reports HRA Notification of trial completion HRA Correspondence *<u>At TMF location level file:</u> Initial R&D approvals and Notification of modifications*	**5.**	**HRA**	HRA application HRA approval Approved Statement of Activities Approved Schedule of Events HRA Notification / Approval of modifications Annual Reports HRA Notification of trial completion HRA Correspondence	This section is for all documents pertinent to the HRA, including but not limited to the documents listed. Significant correspondence with the HRA must be filed in this section.

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 Approved Pan Man Confirmation of Sponsorship (Sponsor Letter) Funding Letter(s): Application and Award Investigator Agreement		**6.**	**Financial / Legal**	Contracts / Contract Addendums Funding Letter(s): Award Financial Agreement Insurance and Indemnity Statement Investigator Agreement Financial Correspondence Declaration of Helsinki	This section is for all documents pertinent to the financial and legal aspect of the study, including but not limited to the documents listed. Insurance and Indemnity Statement must cover entire the period of the study.

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
		Insurance and Indemnity Statement and certificates Financial Correspondence *Clinical Trial Agreement*				

7.	**Study Location Staff**	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 CV CI Honorary Contracts/Letters of Access Site close out documentation		**7.**	**Study Location Staff**	Completed delegation of duties and authorised signatures form CVs Trial Training Material and documentation: - - GCP Training - Pharmacovigilance Training - Protocol-related training / Investigator Meeting Documentation *If IND study, FDA1572s and Financial Disclosures*	This section is for documents pertinent to location staff education, experience and training. The Delegation of duties and authorised signatures form must be signed by all individuals that perform trial related procedures. CVs are required for personnel that have significant role in the trial. The CV must be personally signed and dated by the individual and updated annually. If IND study, investigators listed on the FDA form 1572 must provide CV and Financial Disclosures. If filed separately, training material must be documented in a file note. Training documentation may be in the form of Training Attendance log or certificate.

TRIAL MASTER FILE TABLE OF CONTENTS			INVESTIGATOR SITE FILE TABLE OF CONTENTS			DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS
SECTION	TITLE	DOCUMENTS	SECTION	TITLE	DOCUMENTS	
		Notification and approval of protocol modifications *<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* *If IND study: FDA1572 forms and Financial Disclosures*				

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8.	**Study Related Supplies**	Sample CRF Data Management / Data Processing document *If applicable:* Sample Diary Cards (Translated templates) Sample Questionnaires (Translated templates) Supplies Re-order form templates	**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	This section is applicable for templates of clinical trial materials provided for data recording, examples of these are: Blank Case Report Form, Questionnaires, and Diary Cards. If the CRF is too bulky to keep with the file, it is acceptable to file this separately and document the location in a File Note. (File note applicable if filed separately from Investigator Site File).

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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 location level file:</u>* *Sample of Participant Information Sheets and Informed Consent Forms (local version)*	**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)	This section is for documents pertinent to subjects' participation in the study. At time of consenting, participant and consenter must sign 3 copies of the consent form: one given to the participant, one to the Investigator Site File, one to the participant's medical notes. Participant must be re-consented if newer version of Participant Information Sheet and Informed Consent Form is available. All versions of ICFs signed by participants must be retained.

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10.	**Subject Information**	Template Subject ID Form (Confidential Participant ID form) Template Subject recruitment / screening Log Protocol Variance Tracker (for Protocol Deviations / Violations) *<u>At TMF location level file:</u>* *Subject recruitment /screening Log*	**10.**	**Subject Information**	Completed subject ID Form (Confidential Participant ID form) Subject recruitment / screening Log Protocol Variance Tracker (for Protocol Deviations / Violations) Completed CRFs Resolved Data Queries / Data Clarification Form	This section is for documents pertinent to subject information. All documents filed in this section must not disclose the subjects' identity. (With the exception of the Subject ID form filed in the Investigator Site File) Subjects' initials and study number may be used. The Protocol Variance Tracker can be set up as one document that can be filed in the TMF if study has a small number of locations or if the study is a multi-centre study, it can be sent up per location and filed in the TMF location level file. If the CRF is too bulky to keep with the file, it is acceptable to file this separately and document the location in a File Note. Resolved data queries can be filed with the participant's completed CRF (File note applicable if filed separately from Investigator Site File).

11.	**Pharmacovigilance**	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)		**11.**	**Pharmacovigilance**	Flow diagram detailing of SAE reporting SAE reporting Guidelines and Pharmacovigilance contact Pharmacovigilance Training handout 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)	This section is for documents and correspondence pertinent to the reporting of all SAE/SUSARs. Documents included but not limited to list. Correspondence includes correspondence from PI to CI / REC / Competent Authority & the other applicable Authorities, e.g. HRA

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12.	**Monitoring**	Monitoring Plan Minutes from Monitoring meetings (pre study) Monitoring log / documentation (e.g. Monitoring visit report)	**12.**	**Monitoring**	Monitoring Plan Minutes from Monitoring meetings (pre study) Monitoring log / documentation (e.g. Monitoring visit report)	This section is for documents pertinent to Monitoring of the trial, including monitoring logs and plans.
13.	**Oversight Committees**	Charters and minutes from meetings: TMG/TSC/DMC CTMG Quarterly Reports	**13.**	**Oversight Committees**	Correspondence between or via the Sponsor/CI from all oversight committees	This section is to contain information relating to all meetings held by the various committees across a trial. For the TMF, all meeting minutes will be held with all downstream correspondence with locations kept in the TMF and ISF.

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 location level file:</u> Certificates of accreditation and normal Reference Ranges for local labs of all participating locations*	**14.**	**Clinical Laboratory**	Certificates of accreditation for central laboratories and 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	Certificates of accreditation for central laboratories and local laboratories must cover the entire period of the study. Normal Reference Ranges for central laboratories and local laboratories must be valid during the period of the study and applicable to the participant group (indication / demographic) covering all tests required by the protocol.
15.	**Pharmacy**	Investigational Medicinal Product packaging (label	**14.**	**Pharmacy**	Investigational Medicinal Product packaging (label	Pharmacy documents if filed separately from the Investigator

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		specification and template.) Pharmacy manual Instructions for handling trial medication and trial related materials (Randomisation, Re-supply, Return / Destruction, Code breaking, recall, relabelling, 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			specification and template.) Location Pharmacy manual Instructions for handling trial medication and trial related materials (Randomisation, Re-supply, Return / Destruction, Code breaking, recall, relabelling, 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*	Site File, i.e. in Pharmacy, must be documented in a file note.

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		The following is applicable when Pharmacy is involved with Investigational Medicinal Product Manufacturing: *- GMP Licence* *- Certificate of Analysis* *- Authorisation of release by Qualified Person*			*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	**16**	**Investigator's Brochure / SmPC and Safety alert updates**	IB / SmPC IMPD Safety alert updates	Current and superseded versions of Investigator's Brochure must be filed in this section. Investigator's Brochure must be updated annually and if update is not required, a file note must document this.
17.	**Trial Risk Assessments**	All Trial Risk Assessments and evidence of periodic review and triggered reviews.	**17.**	**Trial Risk Assessments**	All Trial Risk Assessments and evidence of periodic review and triggered reviews.	
18.	**Audit Reports**	All audit reports from audits conducted on the trial	**18.**	**Audit Reports**	Location specific audit reports	
19.	**Study Monitoring Reports**	Study Monitoring reports from all locations	**19.**	**Study Monitoring Reports**	Location specific Study Monitoring reports	

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20.	**Final report**	REC Funder Publications/ Manuscripts		**20·**	**Final report**	REC Funder Publications/ Manuscripts	Final report will be produced by CI and submitted to REC at the end of the study.
21.	**Clinical study report**			**21·**	**Clinical study report**		Clinical study report will be produced by CI upon analysis of data at the end of the study.