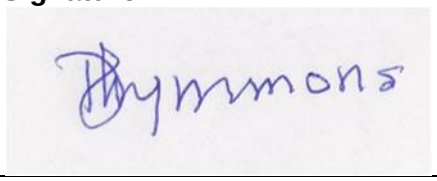
The University of Manchester

Standard Operating Procedure

Number:	UM/UoM TMF/SOP08/6.0		
Title:	**The Creation and Maintenance of Trial Master Files and Essential Documentation**		
Version:	6.0 (March 2018)	**Effective Date:**	March 2018
Author:	Mrs Catherine Barrow / Victoria Sheard	**Review Date:**	March 2020
Reviewed by: Dr Mohammed Zubair		**Approved By:** Prof Deborah Symmons	
Position: Research Governance, Ethics and Integrity Manager		**Position:** Chair of Clinical Trials Management Group	
Signature: 		**Signature:** 	

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**

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.

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 Community. The Directive sets out how clinical trials investigating the safety or efficacy of a medicinal product for use in humans must be conducted, and includes clinical trials involving healthy volunteers as well as small scale or pilot studies. The Directive also requires clinical trials to be conducted in compliance with the principles of Good Clinical Practice (GCP), with detailed standards subsequently published as the European Directive 2005/28/EC (usually referred to as "the GCP Directive").

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 are intended to protect the rights, safety and well-being of research participants in Clinical Trials of Investigational Medicinal Products (CTIMPs) and to harmonise, and make transparent, regulatory processes relating to clinical trials of medicines for human use.

In order to be compliant with the law, organisations conducting CTIMPs must have clearly documented Standard Operating Procedures (SOPs) covering all aspects of conducting Clinical Trials.

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 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 refers to clinical trials of an investigational medicinal product (CTIMPs) or a clinical investigation of a medical device – 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 policies and procedures and the policies and procedures of the relevant NHS Trust.

3.0 Roles and Responsibilities

All clinical trials sponsored or co-sponsored by the University of Manchester will be monitored for GCP compliance. 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 TMF being held by the Sponsor. If the 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 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). All documentation must be version controlled.

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.

4.3 Sponsor File

Where the University is acting as Sponsor or co-sponsor, the University will maintain a file containing copies of essential approval documents. This will be kept at the Research Governance, Ethics and Integrity Office at the University of Manchester. These documents may be duplicates of those held in the TMF. The Chief Investigator must ensure that relevant documents are sent to the Sponsor(s). The co-sponsor will also wish to maintain a sponsor file,

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.

5.0 Related Templates

Appendix I Trial Master File Table of Contents Template
Appendix II Investigator Site File Table of Contents Template
Appendix III Trial Master File/Investigator Site File Table of Contents with Description

Appendix I Trial Master File Table of Contents Template

Full Project Title:	
EudraCT Number	
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**	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 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 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 Approved Pan Man 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 CV CI Honorary Contracts/Letters of Access Site close out documentation Notification and approval of protocol amendments *At TMF site level file:*

		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**	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**	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.	**Final report**	REC Funder Publications/Manuscripts
18.	**Clinical study report**	

Appendix II Investigator Site File Table of Contents Template

Full Project Title:	
EudraCT Number:	
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 / Protocol Amendments**	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
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 from protocol for each site 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**	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)
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**	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**	

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:	
Site Investigator (if applicable)	
Funding body	
Sponsor(s):	
Site (If applicable)	

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 study with multiple sites, the TMF must file site level documents, as specified by Chief Investigator, in TMF site-level file. Only copies of these documents are needed in the TMF site-level file, the original must be kept at site.
* Local versions must be on Institution letter headed paper.

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.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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*	**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	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 Amendments**	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 site level file:</u>* *Signed protocol signature page* *- If applicable, local version and approval of translated version*	**2.**	**Protocol / Protocol Amendments**	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

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
3.	**Research Ethics Committee**	NRES Application Letter of Favourable Opinion (listing documents approved and approved participating sites) Submission / Notification and REC acknowledgement /opinion of Amendment GCP Compliance / REC Constitution /Composition / List of members Annual Reports Notice to REC of trial completion EC Correspondence *<u>At TMF site level file:</u> First approval and approval of amendments required*	**3.**	**Research Ethics Committee**	NRES Site Specific Assessment Application Letter of Favourable Opinion (confirmation of site specific approval) Acknowledgement / REC opinion of Amendment 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.

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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 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*	**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	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 amendments 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.

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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 site level file:</u> Initial R&D approvals and Notification of amendments*	**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	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.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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 Insurance and Indemnity Statement and certificates Financial Correspondence	**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.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
7.	**Study Site 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 Notification and approval of protocol amendments *<u>At TMF site level file:</u>* *Copy of completed delegation*	**7.**	**Study Site 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 site 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.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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)*	**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.

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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*	**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	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 sites or if the study is a multi-centre study, it can be sent up per site and filed in the TMF site 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 patient's completed CRF (File note applicable if filed separately from Investigator Site File).

TRIAL MASTER FILE TABLE OF CONTENTS			*INVESTIGATOR SITE FILE TABLE OF CONTENTS*			*DESCRIPTION OF DOCUMENTS AND FILING INSTRUCTIONS*
SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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 templateand 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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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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 sites kept in the TMF and ISF.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
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*	**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 patient group (indication / demographic) covering all tests required by the protocol.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
15.	**Pharmacy**	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 -	**14.**	**Pharmacy**	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/dispa	Pharmacy documents if filed separately from the Investigator Site File, i.e. in Pharmacy, must be documented in a file note.

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SECTION	**TITLE**	**DOCUMENTS**	**SECTION**	**TITLE**	**DOCUMENTS**	
		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*			tch/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	**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.	**Final report**	REC Funder Publications/ Manuscripts	**17·**	**Final report**	REC Funder Publications/ Manuscripts	Final report will be produced by CI and submitted to REC at the end of the study.

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SECTION	**TITLE**	**DOCUMENTS**		**SECTION**	**TITLE**	**DOCUMENTS**	
18.	**Clinical study report**			**18.**	**Clinical study report**		Clinical study report will be produced by CI upon analysis of data at the end of the study.