Title: Guidance | Filing Definitions and Principles

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These signatures confirm the reviewers agree with the technical content of the document and that this document is approved for implementation across the Melbourne Childrens.

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Document History

Revision	Modified by	Change No.	Description of Change
1.0	CRDO	N/A	New Issue (2022)

Contents

1. PURPOSE

The purpose of this document is to provide introductory guidance to persons involved in maintaining Essential Documents for clinical studies where MCRI is the Sponsor and/or Coordinating Lead Site, and to facilitate the management of essential documents in accordance with Good Clinical Practice and all applicable regulatory requirements.
It may also be used to provide guidance when RCH/MCRI is a site in a clinical study sponsored by an external Sponsor.

Note: A standard operating procedure (SOP) for how to manage essential documents using electronic binders or paper binders is currently being developed by the Clinical Research Development Office (CRDO). In the meantime, please contact CRDO for all advice regarding how to manage essential documents for all human participant research.

2. KEY TERMINOLOGY

2.1. **Essential Documents** are those, which individually and collectively:

- Permit the evaluation of the conduct of a trial and the quality of the data produced.
- Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of Good Clinical Practice and with all regulatory requirements.
- When filed in an appropriate and timely manner, greatly assist in the successful management of a trial by the site investigator

2.2. The **Trial Master File (TMF)** is the collection of essential documents used and maintained by the Sponsor-Investigator/Coordinating Principal Investigator (CPI) (or delegates) and the Central Trial Coordinating Team for management of the trial.

2.2.1. The use of the term TMF in this guideline should be exchanged with **Study Master File** for clinical research that is not a clinical trial. For ease of readability, this guideline will use Trial Master File throughout the document when referring to the essential document repository managed by the Sponsor-Investigator/Coordinating Principal Investigator (CPI).

2.3. The **Site Information File (SIF)** is a subsection of the TMF, which is also maintained by the Sponsor-Investigator/Coordinating Principal Investigator (CPI) (or delegates).

It contains duplicates of site-specific essential documents, which are also held in the corresponding Investigator Site File (ISF) by the site Principal Investigator.

2.4. The **Investigator Site File (ISF)** is a collection of essential documents used and maintained by the Site Principal Investigator/delegate for the management of the trial at the site.

2.5. **Binders** is a collective generic name for repositories of Essential Documents, being the TMF, SIF(s) and/or ISF(s).

3. RESPONSIBILITIES

3.1. For MCRI-sponsored Investigator-Initiated Trials/research, the Sponsor-Investigator/CPI is responsible for maintaining essential documents in the TMF, including the SIF subfolder for each participating site. This responsibility may be delegated to another member of the study team, e.g. Research Coordinator or Lead Trial Coordinator.

3.2. Each Site Principal Investigator is responsible for maintaining the essential documents in the ISF relating to their site. This responsibility may be delegated to another member of the study team, e.g. Study Coordinator or Research Nurse.

3.3. In the case where the Sponsor-Investigator is also the Principal Investigator (PI) at the Melbourne Children's, they are responsible for maintaining both a TMF (to maintain essential documents in accordance with their responsibilities as Sponsor-Investigator/CPI) and an ISF (to maintain essential documents in accordance with their site PI responsibilities).

3.4. When MCRI is the coordinating lead site for multi-centre research with an external sponsor, usually the external sponsor will be responsible for maintaining the TMF, including a SIF subfolder for each participating site.

3.5. There are occasionally exceptions to this principle. For example, when MCRI is working with overseas collaborators and takes on the role of lead site in Australia. In this case, the MCRI Principal Investigator/CPI will need to maintain the sections of the TMF for which they are responsible. e.g. reporting to the TGA (for trials conducted under the Clinical Trial Notification [CTN] Scheme) and monitoring of other Australian sites.

3.6. Supporting departments may also hold documents within their own filing system eg. Pharmacy documents. These documents should be filed at regular intervals to the TMF / ISF as appropriate, and be archived with the TMF/ISF at the end of the study.

4. APPLICABILITY

This guidance covers how the Sponsor-Investigator/delegate and Principal Investigator/delegate at participating sites should manage essential documents for MCRI-sponsored clinical trials.

This guidance may also be used by campus staff in the following situations:

- RCH/MCRI is a site in clinical research/public health study sponsored by an external Sponsor who does not have their own guidance/SOP for managing essential documents
- MCRI-sponsored human participant research that is not a clinical trial.

The guidance applies to both paper and electronic Binders, noting that some aspects of electronic filing will be automated if using Florence eBinders.

5. PROCEDURE

5.1. General Principles

5.1.1. All essential documents should be filed in accordance with the relevant CRDO guidance contents index.

5.1.2. Essential documents may be supplemented or reduced where justified.

5.1.2.1. Use a file note for documents that do not apply to the study and include the justification for why this is the case. In addition, enter "NA" in the comment's column of the relevant section in the SIF Contents Index.

5.1.2.2. Researchers may supplement files with any additional documents that facilitate reconstructing / evaluating trial conduct.

5.1.3. To facilitate search and retrieval of documents, all documents must:

5.1.3.1. Use a consistent file naming convention that identifies the type of essential document and version history, as described in MCTC076 | Guidance: Electronic File Naming Conventions.

5.1.3.2. Identify the type of essential document within the title of the document, e.g. protocol, diary, questionnaire

5.1.3.3. Include a footer that contains the document name, version number and date

5.1.4. Tracked change versions of amended documents must be filed to provide an audit trail of changes.

5.1.5. If using a Computer Drive, documents in draft statusshould be filed in a DRAFT folder within the appropriate section. In all other formats (ie. Florence eBinders, Paper binders, etc.) draft documents will be worked on externally.

5.1.6. Superseded documents must be retained as follows:

5.1.6.1. Superseded **paper documents** must be labelled "superseded" with a strike through, signature and date.

5.1.6.2. Superseded **electronic documents on a computer drive** should be moved from the relevant CURRENT folder to the SUPERSEDED folder.

5.1.6.3. Superseded **documents within Florence eBinders** must be stored in the version history of the superseding document.

5.1.7. Withdrawn documents must not be deleted or destroyed, and retained as follows:

5.1.7.1. The most recent version of the withdrawn **paper documents** must be labelled "Withdrawn" with a strike through, signature and date.

5.1.7.2. All versions of **electronic documents on a computer drive** should be moved into the "SUPERSEDED" folder, in which a new sub-folder may be created called "[Document Name] - WITHDRAWN"

5.1.7.3. Withdrawn **documents within Florence eBinders** must be moved to a new subfolder called "[Document Name] - Withdrawn"

5.1.8. New documents, including version updates, must have evidence of review and approval filed.

5.1.9. Original paper essential documents with wet-ink signatures must be retained in a hard copy. E.g. source documents and documents with participant personal identifiers.

5.1.9.1. Digital versions may also be scanned and filed in a digital binder, provided the original is retained.

5.1.10. Documents should be arranged chronologically with the most recent documents at the front/top of each section. In the case of electronic files, including Florence eBinders, this will occur automatically when following MCTC076 | Guidance: Electronic File Naming Conventions.

5.1.11. Retain relevant correspondence (sent and received) required to reconstruct key trial conduct activities and decisions and file in the corresponding section of the binder.

5.1.12. Binders may exclude some Essential Documents which may be maintained in other departments or locations; for example, investigational product records may

be maintained in pharmacy and signed participant consent forms may be filed in a participant shadow file.

5.1.12.1. For documents stored separately from the Binder, a file note should be kept in the appropriate section detailing the location of the document. A note may also be made in the contents index indicating the location of documents.

5.1.12.2. All essential documents held outside trial binders during the study must be merged into the record at the end of the study and prior to archiving.

5.1.13. Essential documents should be filed as soon as possible and must be filed within two weeks of receipt/generation. All binders must be maintained and kept up to date in readiness for review by representatives of MCRI, the approving HREC, the local Research Governance Office and applicable regulatory bodies (e.g. TGA, MHRA, FDA) and to assist the Sponsor-Investigator/CPI and their team with their oversight responsibilities for participating sites.

5.2. Trial Master File (TMF)

5.2.1. The TMF should be established at the beginning of a study as soon as possible after a final draft protocol is available and/or first contact is made with the trial Sponsor i.e., MCRI for an MCRI IIT, or the collaborative group/commercial company Sponsor when an MCRI employee has taken on the role of CPI.

5.2.2. For multi-centre trials, the Sponsor-Investigator/CPI must also maintain site-specific sub-files within their TMF for essential documents relating to each participating site involved. These files, termed Site Information Files, should be organised according to the MCTC013 | Guidance: Site Information File (SIF) filing guidance.

5.3. Site Information File (SIF)

5.3.1. SIFs should be set up for each participating site as soon as a site has confirmed their participation in a clinical trial and are being added to the lead HREC approval or are proceeding to submit their own ethics application. It is maintained alongside the Trial Master File (TMF) by the Sponsor-Investigator/CPI or the delegated member(s) of their team.

5.3.2. Participating Site Information Files (SIF) only need to contain those essential documents that are specific to the site. Essential Documents that are common to all sites are filed in the TMF only i.e. are not duplicated in the SIFs.

5.3.3. The SIF should include duplicates of site-specific essential documents filed in the ISF to facilitate reconstructing/evaluating trial conduct.

5.3.4. Do not change the section numbering. The ISF / SIF numbering are interrelated for ease of cross-referencing. Where a section is present in one location but not the other, the number has been purposefully omitted.

5.3.5. Any data/documents shared with the Sponsor-Investigator/CPI or uploaded into a database or filing system managed by the Sponsor-Investigator/CPI should only contain data of trial participants that have been pseudonymised.

NOTE: Within Florence eBinders, files flagged as containing PHI (Patient Heath Information) do not need to be pseudonymised, as these are only viewable by those staff with the appropriate permissions.

5.4. Investigator Site File (ISF)

5.4.1. The ISF should be set up for the participating site as soon as a site has confirmed their participation in a clinical trial.

5.4.2. The ISF should include duplicates of documents filed in the TMF which are relevant to the management and conduct of the trial at the site level.

5.4.3. New site-specific documents generated by the Principal Investigator/delegate (either originals or new versions) must have evidence of review and approval filed in the ISF.

5.4.4. Do not change the section numbering. The ISF / SIF numbering are interrelated for ease of cross-referencing. Where a section is present in one location but not the other, the number has been purposefully omitted.

5.4.4.1. Any data/documents shared with the Sponsor-Investigator/CPI or uploaded into a database or filing system managed by the Sponsor-Investigator/CPI should only contain data of trial participants that have been pseudonymised.

NOTE: Within Florence eBinders, files flagged as containing PHI (Patient Heath Information) do not need to be pseudonymised, as these are only viewable by those staff with the appropriate permissions.

6. GLOSSARY

Auditor

An independent person or organisation who performs a systematic and independent examination of research related activities and documents to determine whether trial related activities, documentation, and data management have been conducted according to the protocol, GCP and applicable regulatory requirements.

Clinical Research Development Office (CRDO)

A core group within the Melbourne Children's Trials Centre established to facilitate and increase capacity for clinical and public health research across the Melbourne Children's campus through education and training.

Clinical Trial Notification (CTN)

One of two schemes used by the Therapeutic Goods Administration (TGA) to authorise the supply of unapproved therapeutic goods, including medicines, medical devices and biologicals, to participants participating in clinical trials in Australia.
The CTN scheme is appropriate for trials where the approving ethics committee has enough scientific and technical expertise to review the proposed use of the unapproved therapeutic good(s). The majority of investigator-initiated trials would be in this category.

Coordinating Lead Site

Site selected by a Sponsor to coordinate all aspects of the clinical trial, including providing leadership in directing the clinical aspects of protocol development and implementation at sites, overseeing study governance and ethics submissions on behalf of all participating sites. Added responsibilities for Investigator-initiated research depend on what has been agreed upon with the Sponsor but may include monitoring and maintenance of the Trial Master File.

Coordinating Principal Investigator (CPI)

An individual who takes overall responsibility for a research project and usually submits the project for ethical review. The CPI is responsible for ongoing communication with the reviewing HREC and passing on information from the HREC to the sponsor, the Principal Investigator(s) (PI), and project coordinator at each site conducting the research. The CPI is the PI at their own site and is therefore responsible for passing on information from the HREC to their own site's Research Governance Officer (RGO). An employee of MCRI/RCH/UoM Paediatrics may take on the role of CPI for an externally sponsored trial.

Note: When a trial is sponsored by MCRI, the term 'Sponsor Investigator' rather than CPI is used to describe the lead PI.

Essential Documents

Documents which individually and collectively:

- Permit the evaluation of the conduct of a trial and the quality of the data produced
- Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of Good Clinical Practice and with all regulatory requirements
- When filed in an appropriate and timely manner, greatly assist in the successful management of a trial
- Are usually audited by the sponsors independent audit function and inspected by regulatory authorities as part of the process to confirm the validity of the trial conduct and data collection.

Food and Drug Administration (FDA)

A department of the United States of America's federal government responsible for the control and supervision of food safety, tobacco products, dietary supplements, medications, vaccines, biopharmaceuticals, blood transfusions, medical devices, electromagnetic radiation emitting devices (ERED), cosmetics, animal foods & feed, and veterinary products.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Investigator Site File (ISF)

A standard filing system that contains the essential documents used by the Principal Investigator for the management of the trial at the site. It is also used by Monitors, Auditors, and Inspectors to review and verify whether the Principal Investigator has conducted the trial in accordance with the applicable regulatory requirements and the principles and standards of GCP.

Medicines and Healthcare products Regulatory Agency

An agency of the Department of Health and Social Care in the United Kingdom which is responsible for ensuring that medicines, medical devices and blood components for transfusion are acceptably safe and effective.

Monitor

A person appointed by the Sponsor to undertake the role of monitoring for the trial. Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately.

Pseudonymisation

Replacing information which could be used to identify an individual with a pseudonym / value which does not allow the individual to be directly identified. This is distinct from anonymisation as It is usually possible to identify the subject of pseudonymised data by analysing the underlying or related data.

Site Information File (SIF)

A standard filing system which is a subsection of the TMF. It contains duplicates of site-specific essential documents pertaining to participating sites. Essential Documents that are common to all sites are filed in the TMF only. i.e. are not duplicated in the Site Information File(s). Any data/documents shared with the Sponsor-Investigator/CPI or uploaded into a database or filing system managed by the Sponsor-Investigator/CPI should only contain data of trial participants that has been anonymized.

Sponsor-Investigator

A Sponsor-Investigator is an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a participant. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. For MCRI investigator-initiated trials, the Sponsor-Investigator will usually be based at Melbourne Children's and be the Site Principal Investigator for the MCRI/RCH site.

Sub / Associate Investigator

Any individual member of the clinical study team designated and supervised by the Principal Investigator at a study site to perform study-related procedures and/or to make important study-related decisions (e.g., associates, residents, research fellows, clinical research coordinators). The PI will designate who will be nominated as Associate Investigators for that site.

Therapeutic Goods Administration (TGA)

The Therapeutic Goods Administration (TGA) is Australia's regulatory authority for therapeutic goods.

Trial Master File (TMF)

A standard filing system which contains all essential documents which individually and collectively permits the evaluation of the conduct of a trial and the quality of the data produced. The filing system can be in the form of a single project file or a number of files/filing cabinets, depending on what is deemed most appropriate for a particular clinical trial given its size and complexity. The regulatory documents and approvals within the TMF will be maintained alongside case report forms and source documentations.

7. REFERENCES

Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). 06 December 2018. EMA/INS/GCP/856758/2018.
Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

ICH Topic E6 (R2) Integrated addendum to ICH E6 (R1): Guideline for good clinical practice (ICH E6 R2) with TGA annotations.
Available from: https://www.tga.gov.au/publication/note-guidance-good-clinical-practice

8. RELATED DOCUMENTS

MCTC012 | GUIDANCE | Trial Master File (TMF) filing V1.1
MCTC119 | TEMPLATE | TMF Table of Contents V1.0
MCTC120 | TEMPLATE | TMF paper binder section dividers V1.0
MCTC013 | GUIDANCE | Site Information File (SIF) filing V1.1
MCTC115 | TEMPLATE | SIF Table of Contents V1.0
MCTC116 | TEMPLATE | SIF paper binder section dividers V1.0
MCTC011 | GUIDANCE | Investigator Site File (ISF) filing V1.1
MCTC117 | TEMPLATE | ISF Table of Contents V1.0
MCTC118 | TEMPLATE | ISF paper binder section dividers V1.0
MCTC002 | SOP | Copying and Certifying Essential Documents V2.0
MCTC028 | TEMPLATE | Note to file V3.0