Standard Operating Procedure

Title: **Quality Assurance of Trial Master Files (TMFs) for MCRI Sponsored Investigator-Initiated Clinical Trials**

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Document History

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CONTENTS

ABBREVIATIONS

CAPA	Corrective and Preventative Actions
CPI	Coordinating Principal Investigator
DMP	Data Management Plan
DVP	Data Validation Plan
GCP	Good Clinical Practice
ICH-GCP	International Council of Harmonisation Good Clinical Practice
IIT	Investigator-Initiated Trial
IMD	Investigational Medical Device
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MCRI	Murdoch Children's Research Institute
MCTC	Melbourne Children's Trials Centre
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SIF	Site Information File
TMF	Trial Master File

1. PURPOSE

To describe the activities required to prepare, initiate, conduct, and report on Trial Master File (TMF) reviews for quality assurance (QA) and quality control (QC) purposes. The objective of TMF review is to:

- Ensure compliance in the management and conduct of MCRI-sponsored investigator-initiated clinical trials (IITs)
- Assess the adequacy of the procedures and systems supporting the conduct of MCRI sponsored IITs
- Assess the quality and integrity of the data generated during MCRI sponsored IITs.

1.1. Quality Improvement

Quality assurance and quality control is integral to any clinical trial to ensure GCP compliance and to ensure that the TMF is in a ready state for any audit program and/or inspection by regulatory bodies.

2. BACKGROUND

Quality Assurance (QA) refers to planned and systematic actions that are established to ensure that a trial is performed, and the data generated, documented (recorded) and reported in compliance with the principles of Good Clinical Practice (GCP) and the applicable regulatory requirements (ICH-GCP Section 1.46)1. Key QA activities include internal audits [MCTC199 SOP | Internal Auditing], developing Standard Operating Procedures (SOPs) and training staff that facilitates the conduct of clinical trials according to standards and regulations.

Quality Control (QC) refers to the set of operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial related activities have been fulfilled (ICH-GCP Section 1.47)1. It is a proactive process that identifies and corrects non-compliance/errors. Key QC activities include data verification, cross-checking source documents and reviewing completeness of essential documents repository, e.g., the TMF.

QA and QC activities involve auditing and monitoring, respectively, against the trial protocol and sponsor's Standard Operating Procedures (SOPs). The sponsor is responsible for implementing and maintaining robust SOPs to ensure that trials are conducted, and data is generated, documented, recorded, and reported in compliance with the protocol and GCP regulatory requirements. QA/QC is to be applied to each stage of the trial including management of essential documents in the TMF.

3. SCOPE

This SOP describes the QC process to review the quality of essential documents management in the TMF for MCRI-sponsored investigator-initiated trials.

This SOP provides the procedures for TMF QC reviews commissioned by:

- Sponsor-Investigator/Central Trial Coordinating Teams: i.e. to ensure the TMF is in a ready state for audit and/or inspection
- MCRI Sponsorship Committee: i.e. ad hoc risk-based reviews to ensure compliance with institutional SOPs and regulatory requirements. Note: these reviews will be completed by the campus Internal Audit Program [MCTC199 SOP | Internal Auditing].
- MCRI and/or RCH REG: as part of the Melbourne Children's Internal Audit Program [MCTC199 SOP | Internal Auditing].

This SOP does not provide the procedure for monitoring of either:

- TMFs for externally sponsored clinical trials
- Investigator Site Files (ISFs) for externally sponsored trials
- ISFs for sites participating in MCRI-sponsored trials. Refer to MCTC046 SOP Monitoring Visit Activities for Clinical Trials of Investigational Products

4. RESPONSIBILITY

This SOP applies to all staff involved in monitoring the quality of essential documents filed in MCRI-sponsored IIT TMFs.

In the event of a self-directed QC review of the TMF, the Sponsor-Investigator is responsible for:

- Selecting a Monitor to conduct a QC review of their TMF in accordance with this procedure
- Ensuring the Monitor has direct access to the TMF and any other essential documents that are at the time of the monitoring visit, sitting outside the main binder, e.g. Clinical Trial Pharmacy
- Defining the scope of the QC TMF review.

In the event of a QC review of the TMF commissioned by the campus Internal Audit program, the Sponsor-Investigator must:

- Permit monitoring by the Internal Auditor
- Ensure the Internal Auditor has direct access to the TMF and any other essential documents that are at the time of the monitoring visit, sitting outside the main binder, e.g. Clinical Trial Pharmacy.

5. PROCESS

The following sections provide a description of the processes to be followed.

5.1. Identification of IITs for TMF QC Review

All MCRI sponsored IITs will require QC review of the Trial Master File (TMF) and corresponding Site Information Files (SIFs) on an annual basis, in accordance with this SOP as part of the self-directed/peer system review. The Sponsor-Investigator is responsible for identifying a suitable team member to complete self-directed TMF QC reviews.

In the event of QC reviews commissioned by the Campus Internal Audit Program, the audit program will identify a suitable TMF QC reviewer and document the nominated QC peer reviewer within the TMF QC Planning Form [MCTC064] and communicate the plan to the Central Trial Coordinating Team.

5.2. Process of TMF QC Review

This Each TMF will be reviewed for the following:

- Review of trial documentation providing study oversight, e.g.
  - Sponsorship Approval and ongoing review documentation
  - Trial Oversight Charters/Terms of References and meeting minutes
  - Medical Review Plans, where applicable
  - Data Management Plan (DMP) / Data Validation Plan (DVP), where applicable
  - Safety Monitoring/Pharmacovigilance plans, where applicable
- Completeness of regulatory and ethical documentation
- Completeness of safety/pharmacovigilance reporting documentation, where applicable
- Completeness of pharmacy-related documentation, where applicable
- Completeness of research sub-studies related documentation, where applicable
- Completeness of Central Trial Coordinating Team Roles & Responsibilities, and documentation of evidence of Training and Delegation
- Filing/record keeping of relevant correspondence and/or significant emails
- Use of consistent naming conventions
- Use of consistent versioning and tracking
- Review of any duplications of documents/mis-filed documents
- Currency of all documentation filed
- Overall TMF completeness and accuracy

5.3. Frequency of TMF QC Reviews

Self-directed TMF QC reviews should be scheduled annually.

In addition to annual QC reviews, reviews of certain TMF sections may be conducted on an ad-hoc basis as commissioned by the internal audit program or RCH REG team, should systematic findings be identified from previous reviews or via other methods i.e. via reporting/identification of a suspected serious breach by the Sponsor or via internal or external audit or inspection findings.

5.4. Scope of the TMF QC Reviews

All Central Trial Coordinating Teams should schedule for annual self-directed QC reviews of the TMF throughout trial conduct. This may include full TMF QC review of all folders and documents applicable to the trial (i.e. 100% review) or a risk-based approach, whereby a sub-set of TMF folders and key study documents are reviewed. The justification for a risk-based approach must be detailed in the trial risk assessment/management plan. See MCTC035 Guidance & Template Risk Assessment and Risk Management Tool for Clinical Trials

During the clinical trial life cycle, that the Sponsor-Investigator must schedule at least one self-directed QC review of the TMF where the entire TMF is reviewed (i.e. all applicable folders and documents will be reviewed).

- For each IIT undergoing TMF QC review, QC review of applicable folders will be conducted as identified within the TMF QC Planning Form [MCTC064], including any additional trial-specific documentation requiring review.
- Folders not applicable or subject to review will be indicated as "Not Applicable" for review on the TMF QC Planning Form [MCTC064] and the TMF QC Binder Review Checklist [MCTC067]. Refer to section 4.5 below for further details.
- All TMFs must undergo a 100% QC review for completeness, currency, and accuracy prior to archiving.
- Approximately 20% of corresponding SIF folders will be peer reviewed per annual review. For single-centre IITs where the TMF and SIF is combined, a single QC review will occur. Depending on the outcome of previous QC reviews, increasing the percentage of SIF QC reviews at the next scheduled review may be required. For multi-centre trials, ensure selection of a different set of SIFs at subsequent annual TMF QC reviews.

- SIF Folders not applicable or subject to review will be indicated as "Not Applicable" for review on the SIF QC Binder Review Checklist [MCTC066]. Refer to section 4.5 below for further details.
- All Central Trial Coordinating Team members may be required to participate in the QC review processes and implement corrective and preventative actions (CAPA) arising from the QC review, as required.

5.5. Method of Performing QC Reviews

The TMF Review process is expected to occur over a 6-week period: 3 weeks for the nominated peer-reviewer to conduct the QC and a further 3 weeks for the Central Trial Coordinating Team to address any findings identified during the TMF QC.

The following steps will be undertaken when performing TMF QC reviews:

- The TMF QC Planning Form [MCT064] is initially completed by the Central Trial Coordinating Teams (Part 1 and Part 2) and returned to the Internal Audit Program Lead upon completion.
- The TMF QC Binder Review Checklist [MCTC067] and the SIF QC Binder Review Checklist [MCTC066], Parts 1 and 2, are also initially completed by the Central Trial Coordinating Teams and returned to the Internal Audit Program Lead upon completion.
- The Internal Audit Program Lead will nominate a suitable peer reviewer who will follow the requirements of the TMF QC Planning Form [MCTC064].
- For MCRI sponsored IITs utilising Florence eBinders to maintain their TMFs, Internal Audit Program Lead in collaboration with the MCRI Florence Organisational Administrator, will ensure that the nominated TMF QC peer reviewer has previous experienced in the use of Florence eBinders, and will assign the allocated peer reviewer the temporary role of "TMF QC Reviewer" within Florence eBinders for the duration of the TMF QC period only. The Florence "TMF QC Reviewer" role has been established with limited user permissions, ensuring that the integrity and quality of the existing TMF is not compromised and that participant privacy and confidentiality is not breached.

- The TMF QC Planning Form will clearly outline the following:
  - Nominated peer reviewer
  - Name of clinical trial selected for review
  - Contact name/s for the Central Trial Coordinating Team
  - Reason for the review
  - TMF/SIF Format e.g. Paper TMF, Florence eBinders, Network Drive etc

- Completion timelines/dates of the QC review
- Current versions of the Protocol and corresponding consent documentation
- If applicable, various sections of the TMF that are not applicable/subject to review
- SIFs selected for review
- If applicable, various sections of the SIFs that are not applicable/subject to review

- The TMF QC Binder Review Checklist [MCTC067] and SIF QC Binder Review Checklist [MCTC066] (if applicable), will be used by the peer reviewer when performing the TMF QC review, to document the review outcome and any additional findings of the review. The peer reviewer will complete the review checklists and must clearly:
  - Indicate whether a document is present/on file within the corresponding binder
  - Check for missing documentation
  - Check for use of consistent naming conventions
  - Check for use of consistent versioning and tracking
  - Check for any duplications of documents/mis-filed documents
  - Check for completeness of 'Version Tracking Logs'
  - Check the currency of all documentation filed
  - Check for overall TMF consistency and logic
  - Indicate whether any follow-up/CAPAs are required
- The review process must be completed within the specified timelines/dates as outlined within the TMF QC Planning Form [MCTC064]. For internal auditors using this SOP, timelines may be amended to accommodate time critical clinical trial management/project requirements of both the peer-reviewer and Central Trial Coordinating Teams.

- Upon completion of the QC review, peer-reviewers must return completed and signed TMF QC Binder Review Checklists [MCTC067] and SIF QC Binder Review Checklists [MCTC066] (if applicable) to both the Central Trial Coordinating Teams and the Internal Audit Program Lead.

- Any inconsistencies or issues identified by the TMF QC Reviewer must be addressed by the Central Trial Coordinating Team within 3 weeks of the TMF QC review undertaken by the peer-reviewer. Refer to Section 4.6 for further details.

- All activities regarding the TMF QC review will be overseen by the Melbourne Children's Internal Audit Program to ensure completion to plan and adherence to this SOP.

- Copies of all completed TMF QC Review documentation, i.e. the TMF QC Planning Form, TMF QC Binder Review Checklists and SIF QC Binder Review Checklists must be filed in the TMF - Study Quality Assurance, Monitoring, Audits & Inspections\Monitoring Visit Reports.

5.6. Follow Up Actions as a Result of TMF QC Review

Upon completion of the TMF QC review, members of the Central Trial Coordinating Team who are responsible for essential document management, will make themselves available for a brief meeting to examine and discuss the outcomes and/or findings of the QC review. In addition, the following actions will be undertaken upon completion of the review:

- Where identified as required, a corrective and preventative action plan (CAPA) will be completed by the Central Trial Coordinating Team (or delegate) in collaboration with the peer reviewer.

- Proposed CAPAs must be forwarded to the MCRI Sponsorship Committee (mctc@mcri.edu.au) and Research Ethics and Governance (rch.ethics@rch.org.au) for acknowledgement.

- A responsible person(s) from the Central Trial Coordinating Team will action the CAPA within the specified timeframe.

- Upon completion of any required CAPAs, CAPAs will be reviewed by the Sponsorship Committee (or delegate) in collaboration with a representative of the Central Trial Coordinating Team to assess requirements for process improvement or additional training needs.

- Ensure all CAPAs are recorded on your Central CAPA Log or Central Protocol Deviation Log and maintained within your TMF.

6. GLOSSARY

Central Trial Coordinating Centre

A group of MCRI researchers organised to coordinate the planning, development, operations and conduct of an MCRI-sponsored IIT, multi-centre, clinical trial.

Clinical Research Development Office (CRDO)

CRDO provides education and training to facilitate and increase capacity for clinical and public health research across the Melbourne Children's campus. This includes the development and implementation of Standard Operating Procedures and templates to enable researchers to conduct high quality research.

Clinical Trial

The World Health Organization (WHO) definition for a clinical trial is: 'any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes'.

Corrective and Preventive Action Plan

A Corrective and Preventive Action (CAPA) plan is a quality system plan and incorporates:

1. Identifying the issue, including scope and impact
2. Identifying the root cause of the issue – how/why it occurred
3. Identifying actions to prevent recurrence of the issue (corrective action) or, identify actions to prevent an issue from occurring (preventive action)
4. Documenting that the corrective actions/preventive actions were completed
5. Documenting that the corrective/preventive action has resolved the problem

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator, Sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements. Filing essential documents at the Sponsor site and participating trial sites also assists with the successful management of the trial.

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 participants are protected.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. There are four types of Investigator roles used to describe Investigators with different levels of responsibility for the conduct of clinical trials. These are described below.

Associate Investigator

Any individual member of the clinical trial team designated and supervised by the Principal investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). May also be referred to as sub-investigator.

Coordinating Principal Investigator (CPI)

If a study is conducted at more than one study site, the Principal Investigator taking the additional responsibility for coordination of the study across all sites in a region is known as the Coordinating Principal Investigator (CPI). This role applies to externally sponsored studies where the Sponsor may be a collaborative research group, commercial Sponsor or an institution. The Principal Investigator at each site will retain responsibility for the conduct of the study at their site.

Principal Investigator

The PI is the person responsible, individually or as a leader of the clinical trial team at a site, for the conduct of a clinical trial at that site. As such, the PI supports a culture of responsible clinical trial conduct in their health service organisation in their field of practice and, is responsible for adequately supervising his or her clinical trial team.

The PI must conduct the clinical trial in accordance with the approved clinical trial protocol and ensure adequate clinical cover is provided for the trial and ensure compliance with the trial protocol.

Sponsor-Investigator

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 (eg, 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.

Investigator-Initiated Trials (IITs)

A clinical trial which is initiated and organised by an Investigator i.e. an individual rather than a collaborative group, company, or organisation. In these cases, the Investigator will take on the role of the trial sponsor and will then be responsible for the extensive GCP and regulatory requirements associated with both the management and conduct of the trial.

Investigator Site File (ISF)

Filing repository controlled by the site Principal Investigator. It is held at the trial site and contains all the essential documents necessary for the site trial team to conduct the trial as well as the essential documents that individually and collectively permit evaluation of the conduct of the trial at the site and the quality of the data produced.

Melbourne Children's
The campus encompassing all staff from The Royal Children's Hospital, Murdoch Children's Research Institute and Department of Paediatrics University of Melbourne who initiate or carry out research under one or more of these institutional affiliations.

Melbourne Children's Trials Centre (MCTC)
Melbourne Children's Trials Centre (MCTC) is a collaboration between the Royal Children's Hospital, The Murdoch Children's Research Institute, The Royal Children's Hospital Foundation and The University of Melbourne. This Centre brings together expertise in research, clinical practice, and education and incorporates anyone who initiates or carries out research under one or more of these institutional affiliations.

Murdoch Children's Research Institute (MCRI)
An Australian paediatric medical research institute located in Melbourne, Victoria, affiliated with the Royal Children's Hospital and the University of Melbourne. The institute has six research themes: cellular biology, clinical sciences, genetics, infection and immunity, population health, and data science.

MCRI Sponsorship Committee
The Sponsorship Committee is responsible for reviewing and determining applications for MCRI to act as sponsor for Investigator-Initiated Trials conducted on the Melbourne Children's campus. As an additional responsibility, the Sponsorship Committee reviews data access and sharing requests in respect of data in a collection and decides on requests where the study in question no longer has an active Custodian. The Sponsorship Committee includes senior representatives from MCRI's Statistics, Data Management, and IT Divisions. The Sponsorship Committee meets monthly.

Research
"Includes at least investigation undertaken to gain knowledge and understanding or to train researchers" (National Statement on Ethical Conduct in Human Research 2007 [Updated May 2015]). For the purpose of this guidance, research includes any research that requires submission to and approval from an HREC and/or research governance office. This may include (but is not limited to) observational research, clinical trials, quality assurance projects and laboratory research.

Research Ethics and Governance Office (REG)
REG supports the HREC and institutional research governance processes at MCRI.

Royal Children's Hospital (RCH)
The Royal Children's Hospital is major specialist paediatric hospital in Victoria, the Royal Children's Hospital provides a full range of clinical services, tertiary care, as well as health

promotion and prevention programs for children and young people. Its campus partners are the Murdoch Children's Research Institute and The University of Melbourne Department of Paediatrics, which are based on site at the hospital.

Source Data

Source data is the original recording of an item of data. "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial." (Section 1.51, Notes for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Annotated with TGA Comments).

Source Document

Source documents are documents which contain source data. When data is entered directly into your electronic Case Report Forms (data collection forms) or database, the Case Report Form/database becomes your source document for that information.

Sponsor

An individual, organisation or group taking on responsibility for securing the arrangements to initiate, manage and finance a study. For investigator-initiated trials, MCRI or RCH will act as the Sponsor but delegate many sponsor responsibilities to the Coordinating Principal Investigator. In this case the CPI has the role of both Sponsor and Investigator and hence the MCTC has adopted the term **Sponsor-Investigator** to reflect the dual role of the CPI in investigator-initiated trials.

Standard Operating Procedure (SOP)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

Study Team

Refers to the extended group of people involved in a research study. This includes the investigator team and any additional members of staff who are involved in the set-up or conduct of the study e.g. research nurse, research assistants.

Trial Master File (TMF)

Filing repository controlled by the Sponsor/Sponsor-Investigator. It is the collection of essential documents that allows the Sponsor responsibilities for the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with Good Clinical Practice (GCP) to be evaluated.

Trial Management Group (TMG)

The TMG is a group of key people at the coordinating or principal site who oversee the day-to-day conduct and progress of a clinical trial, including safety oversight activities and/or acting on

advice from other individual(s) or group(s) providing safety oversight. For many investigator-initiated trials, the TMG performs the role of a TSC (see below) and/or the DSMB.

7. REFERENCES

1. ICH-GCP Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

8. RELATED DOCUMENTS

MCTC006 SOP | Management of Essential Documents

MCTC011 Guidance | Investigator Site File (ISF) Filing Guidance

MCTC012 Guidance | Trial Master File (TMF) Filing Guidance

MCTC013 Guidance | Site Information File (SIF) Filing Guidance

MCTC035 Guidance & Template Risk Assessment and Risk Management Tool for Clinical Trials

MCTC046 SOP | Monitoring Visit Activities for Clinical Trials of Investigational Products

MCTC061 SOP | Continuous Improvement: A Corrective and Preventative Action (CAPA) Plan

MCTC064 Form | TMF QC Review Planning Form

MCTC066 Form | SIF QC Binder Review Checklist

MCTC067 Form | TMF QC TMF Quality Assurance Review Checklist

MCTC115 Template | SIF Table of Contents

MCTC117 Template | ISF Table of Contents

MCTC119 Template | TMF Table of Contents

MCTC199 SOP | Internal Audit SOP

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