CLINICAL TRIALS SUPPORT OFFICE

ELECTRONIC TRIAL MASTER FILE (eTMF)

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DOCUMENT VERSION HISTORY

Title	Electronic trial master file			
Description	Electronic trial master file (eTMF) guidance, table of contents template and folder structure for investigator-initiated clinical trials.			
Version	**Author**	**Modifications made**	**Date**	**Status**
1.0	-	New document	08 Mar 2017	Superseded
2.0	Sydney Health Partners (SHP) and Clinical Trials Support Office (CTSO)	- Updated guidance, instructions and table of contents - Removed checklist - Combined SHP and CTSO document - ZIP filing template that reflects the table of contents	18 Jun 2021	Approved

Clinical Trials Support Officer, CTSO	Clinical Trials Project Manager, SHP
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1 GUIDELINE

1.1 INTRODUCTION

Trial master files (TMFs) are necessary for the successful management of a clinical trial by investigator/institutions[1] and sponsors[2]. Electronic TMFs (eTMFs) are preferred and should be established at the beginning of your clinical trial, both at the investigator/institution's site and at the sponsor's office. For investigator-initiated clinical trials (IITs) the Principal Investigator usually takes responsibility for ensuring a combined investigator/institution eTMF and sponsor eTMF is complete.

Throughout your clinical trial, participant safety, the quality of data generated and the reliability of trial results must be maintained. The methods used to assure and control the quality of the trial should be proportionate to the risk inherent in the trial and the importance of the information collected. Ensure that all aspects of the trial are operationally feasible and avoid unnecessary complexity, procedures and data collection. Protocols, case report forms and other operational documents should be clear, concise and consistent.

All eTMF documentation and trial records should be sufficient to adequately reconstruct the activities taken in the conduct of the trial, along with the decisions and justifications made concerning the trial. Systems and procedures that assure the quality of every aspect of your trial should be implemented, including procedures to assure the eTMF is complete, legible and accurate.

Clinical trial records may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies). The final close-out of your trial can only be done when the investigator/institution and sponsor files have been reviewed and confirmed that all necessary documents to reconstruct the trial are complete and located within the eTMF.

Please also refer to National Standard Operating Procedures for Clinical Trials, including Teletrials, in Australia for other examples and guidance (see appendix 8 of the resource).

1.2 AVAILABLE SYSTEMS

The University of Sydney		More information…
eNotebook – electronic notebook	🔴🟡🔵	How do I manage my research data?
REDCap – survey and data capture	🔴🟡🔵	What is REDCap?
RDS (via DashR) – networked data storage, large files, HPC access	🔴🟡🔵	What is the Researcher Dashboard (DashR)?
OneDrive/Sharepoint (Enterprise) – cloud storage	+🟡🔵	Imaging Data Service User Guide
Dropbox (Enterprise) – cloud storage	🔴🟡🔵	Sydney Health Partners Data Sharing Accord
Cloudstor – large file transfer, cloud storage	🟡🔵	
Imaging Data Service (IDS) – imaging repository and analytics	🟡🔵	

Data classification key:	
🔴	Highly protected
🟡	Protected
🔵	Public
+	Highly protected data needs additional file encryption

1.3 STRUCTURE AND CONTENTS

(1) Defined by the ICH E6 guideline[3] **essential documents** are "documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced". The investigator/institution should maintain the trial documents as specified in the ICH E6 guideline and as required by the applicable regulatory requirement(s).

Note: This is not an exhaustive list. Depending on the activities being carried out, many trials require additional documents not specifically mentioned, therefore, the sponsor and/or investigator/institution should include any documentation that facilitates reconstruction and evaluation of trial conduct as part of the eTMF.

(2) When starting a clinical trial the sponsor and investigator/institution should identify and maintain a record of the location(s) of all the potential documentation that is considered to form the eTMF, even if several locations, departments, countries, organisations, clinics and systems are involved. There should be a suitable overall index or table of contents to enable tracking of the location(s) of essential documents comprising the eTMF.

(3) If applicable, the **subject identification code list** should be filed in the investigator/institution eTMF only and the **master randomisation list** filed in the sponsor eTMF only. It is possible to combine the delegated part of the sponsor eTMF and investigator/institution eTMF.

Note: Role-based permissions should be established for activities being undertaken, including restricted access to files/documents (e.g. **randomisation codes** and **unblinded adverse event data**).

(4) **Superseded documents** should be retained in the eTMF as they are necessary to reconstruct the trial and demonstrate that all processes and approvals were followed. Superseded documents should be marked as such in the eTMF.

(5) Relevant **correspondence** necessary for the reconstruction of key trial conduct activities should be retained. Ensure that both sent and received correspondence is filed in the eTMF, along with any attachments.

(6) Approval of processes and decisions, and communications regarding matters that arise in the trial conduct and how they were dealt with, should be documented in the eTMF.

(7) Consideration should be given to defining the dates used for document filing, for example, will the trial documents be identified by the date of receipt, date on the document, date of approval or date of expiration. Date of receipt, review, approval and/or implementation should be recorded as applicable.

(8) Timelines for filing of all documents to the eTMF should be defined.

1.4 SECURITY

(1) The eTMF should be managed securely at all times to ensure completeness and to prevent accidental and premature loss, unauthorised alteration or destruction of documents, or corruption of data and documents. Access to the eTMF should be based on a role and permission description. It should contain controls such as user accounts, secure passwords, system for locking/protecting individual documents, regular backup, an audit trial, etc.

(2) The sponsor eTMF and investigator/institution eTMF may contain some information that could unblind personnel who need to **remain blinded** during the trial conduct. This should be appropriately controlled, for example, storage of the documentation in another system or repository and/or by a role and permission description that is defined by the sponsor and/or investigator/institution.

(3) The documents in the investigator eTMF includes some source documents containing **personal data** that enable the data subjects to be directly identified. These records (such as the subject identification

code list, subject-related source documents and signed consent forms) should remain under the sole control of the investigator/institution due to **data privacy requirements**.

(4) In general, information (data/documents) shared with the sponsor should only contain data of trial subjects, which has been **pseudonymised/deidentified**. The documents containing direct identifiers of trial participants (such as the subject medical files, the identification code list and informed consent forms) should be maintained separately by and under control of the investigator/institution.

(5) All staff involved in the conduct of the trial and using the eTMF system should receive appropriate training before being granted access.

(6) **Metadata** are structured data that describe the context, content and structure of a file. They facilitate management, identification, accessibility and retrieval of files. Metadata may include information such as creator, author, date and time so that files can be displayed in chronological order. For documents subject to version control, the use of file names should not replace version details being visible on displays, printouts and within the file header/footer. Any electronic system that holds trial data and metadata required for reconstruction should be filed so that the contained trial data and metadata can be retrieved as usable datasets.

(7) **Risk-based quality checks** (QC) or review processes should be implemented to ensure the eTMF is being maintained up-to-date and that all essential documents are appropriately filed in the eTMF. Areas to consider during QC and review include:

(a) all essential documents generated are available in the eTMF

(b) documents are filed in the appropriate locations and the table of contents/index is correct

(c) documents are being added to the eTMF in a timely manner

(d) documents are only accessible according to the assigned roles and permissions

(e) an audit trail is visible.

1.5 ARCHIVING AND RETENTION

(1) Ensure that essential documents are not destroyed before the end of the required retention period. Archiving should be undertaken after the eTMF has been reviewed and your filed eTMF documentation is complete.

(2) It is important that access to documents and data is maintained for the entire archiving period. This could include maintaining the system (hardware or software) to access the data in its original archived format, the use of a new system to emulate the old software, or migration of the data into a new format to ensure continual access with new software. The transfer of data to new media as technology advances would need to be considered.

(3) Retention periods for the eTMF (including trial data, documents and records) must be followed. It is the responsibility of the investigator/institution to ensure this information is kept for at least the minimum retention period (in some cases permanently). A non-exhaustive list of resources to assist with determining retention times includes:

(a) international standards, guidelines and best practices (e.g. ICH E6 guideline)

(b) local laws and regulations where clinical trial research is conducted (consider regions, jurisdictions, countries, states, territories, provinces, etc)

(c) national laws and regulations

(i) Therapeutic Goods Administration (TGA) and other regulatory bodies

The TGA requires records to be retained by the trial sponsor for at least 15 years following the completion of a clinical trial. However, in Australia, the overriding consideration for trial sponsors with respect to record retention is the issue of product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond the life of a product in the event of a claim against the sponsor as a result of an adverse outcome associated with the use of the product.[3]

(ii) National Health and Medical Research Council (NHMRC) guidelines

(d) state and territory laws and regulations

(i) medical records (including requirements for children), for example in the NSW Health Records and Information Privacy Act 2002:

25(1)(b) in the case of health information collected while the individual was under the age of 18 years—until the individual has attained the age of 25 years.

(e) The University of Sydney policies, procedures and guidelines

(i) Archive research data

(ii) Records, privacy and information

(iii) Data retention periods, for example:

Research data related to…	Must be kept…
Projects of regulatory or community significance. Includes data that is: part of genetic research, including gene therapy; controversial or of high public interest or has influence in the research domain; costly or impossible to reproduce or substitute if the primary data is not available; relates to the use of an innovative technique for the first time; of significant community or heritage value to the state or nation; or required by funding or other agreements to be retained permanently.	Permanently

(f) guidance specific to the type of data obtained, research conducted and entities involved (such as gene therapy, clinical trials, public institutions, etc).

2 REFERENCES

(1) **Investigator/Institution:** An expression meaning “the investigator and/or institution, where required by the applicable regulatory requirements” (ICH E6 1.35)[3].

(2) **Sponsor:** An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial (ICH E6 1.53)[3].

(3) Therapeutic Goods Administration (2018). *Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice ICH E6(R2) – Annotated with TGA comments.* Available from: https://www.tga.gov.au/publication/note-guidance-good-clinical-practice

(4) European Medicines Agency, Science Medicines Health (2018). *Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic).* Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf

3 CONTACT US

(1) Sydney Health Partners

(a) Website: https://sydneyhealthpartners.org.au/
(b) Joan Torony, Clinical Trials Project Manager: joan.torony@sydney.edu.au
(c) Email: sydneyhealthpartners.comms@sydney.edu.au

(2) Research Data Management, The University of Sydney

(a) University intranet: Research data management
(b) Research Data Consultant: digital.research@sydney.edu.au

(3) Clinical Trials Support Office, The University of Sydney

(a) University intranet: Clinical trials at the University of Sydney
(b) Email: clinical-trials.research@sydney.edu.au

4 INSTRUCTIONS

(1) Extract the items in the compressed (zipped) folder containing the eTMF template table of contents and folder structure.

(2) Add and/or update the table of contents and the corresponding folders as appropriate for the conduct of your clinical trial.

(3) Shaded sections of the Table of Contents indicate the minimum required documents (as applicable) before you commence recruiting participants for your trial. For more information, see section 8 of the ICH E6 guideline, “Essential Documents for the Conduct of a Clinical Trial”. This provides a list of the documents that should be kept by an investigator/institution and trial sponsor. For further guidance see section 1.3 above.

(4) Standard operating procedures (or notes to file) should be used to maintain a record of the location(s) of trial records (including source documents), trial-related procedures and/or the risk-based management of the eTMF.

5 APPENDICES

APPENDIX 1: ELECTRONIC TRIAL MASTER FILE FOLDERS

Click the following link (or copy and paste into your browser) to download CTT025A1-eTMF-folders-20210618.zip
https://cdn.sydneyhealthpartners.org.au/wp-content/uploads/2021/08/CTT025A1-eTMF-folders-20210618.zip

APPENDIX 2: ELECTRONIC TRIAL MASTER FILE TEMPLATE

Table of Contents

TRIAL MASTER FILE	SECTION	ICH E6 GCP Reference
1. Site Personnel and Standard Operating Procedures (SOPs)	1.1. Site contact details	
	1.2. Site delegation of responsibility and signature log	8.3.24
	1.3. Investigators' CVs and/or qualifications	8.2.10; 8.3.5
	1.4. Staff CVs and training logs	
	1.5. Site and trial-related SOPs	
2. Investigator's Brochure and Product Information	2.1. Current approved versions	8.2.1; 8.3.1
	2.2. Superseded version	
3. Protocol and Amendments	3.1. Signed current approved versions	8.2.2; 8.3.2
	3.2. Signed superseded versions	
	3.3. Protocol-related correspondence	
4. Case Report Forms (CRFs and eCRFs)	4.1. Current CRF version	8.2.2
	4.2. Superseded versions	
	4.3. CRF completion guidelines	
	4.4. Signed, dated and completed CRFs	8.3.14; 8.3.15
5. Participant Information Sheets and Informed Consent Forms (including all applicable translations)	5.1. Current approved versions	8.2.3; 8.3.2
	5.2. Superseded versions	
	5.3. Signed informed consent forms	8.3.12
6. Advertisements and Recruitment (including all applicable translations)	6.1. Current approved versions	8.2.3; 8.3.2
	6.2. Superseded versions	
7. Participant Tools (including all applicable translations)	7.1. Current approved versions	8.2.3; 8.3.2
	7.2. Superseded versions	
8. Finance	8.1. Finance procedure	
	8.2. Study budget	
	8.3. Financial agreements	8.2.4
9. Insurance Statements and Signed Agreements	9.1. Insurance certificates	8.2.5
	9.2. Indemnity	8.2.6
	9.3. Signed Confidentiality Agreements	8.2.6
	9.4. Signed Clinical Trial Research Agreements (CTRA)	8.2.6
	9.5. Other agreements and contracts	8.2.6

TRIAL MASTER FILE	SECTION	ICH E6 GCP Reference
10. Ethics Including approval of: - Protocol and any amendments - CRF (if applicable) - Informed consent forms - Any other written information to be provided to participants - Advertisement for recruitment (if used) - Subject compensation (if any) - Any other documents given approval/favourable opinion.	10.1. Initial approvals	8.2.7
	10.2. Human Research Ethics Committee (HREC) composition	8.2.8
	10.3. Subsequent approvals	8.3.3
	10.4. HREC-related correspondence	
	10.5. Final report to ethics	8.4.7
11. Regulatory Documents	11.1. Clinical Trial Notification (CTN) or Clinical Trial Approval (CTA) scheme application	
	11.2. TGA acknowledgements	8.2.9; 8.3.4
	11.3. TGA-related correspondence	
12. Research Governance	12.1. Submission documents	
	12.2. Authorisation, approvals, notification letters	8.2.9; 8.3.4
	12.3. Governance-related correspondence	
	12.4. Final report to the Therapeutic Goods Administration (TGA)	8.4.7
13. Medical, Laboratory, Technical Procedures and/or Tests	13.1. Normal values and/or ranges	8.2.11; 8.3.6
	13.2. Certification, National Association of Testing Authorities (NATA) accreditation, quality control and/or external quality assessment	8.2.12; 8.3.7
14. Investigational Products, Medical Devices and Trial-related Materials	14.1. Sample of labels	8.2.13
	14.2. Instructions for handling investigational products and trial-related materials	8.2.14
	14.3. Shipping and receipt records for investigational products and trial-related materials	8.2.15; 8.3.8
	14.4. Certificates of analysis of investigational products shipped	8.2.16; 8.3.9
	14.5. Site accountability logs	8.3.23; 8.4.1
	14.6. Destruction logs/certificates	8.4.2
	14.7. Storage and temperature logs	
15. Randomisation	15.1. Decoding procedures for blinded trials	8.2.17
	15.2. Master randomisation list	8.2.18
	15.3. Treatment allocation and decoding documentation	8.4.6
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	16.2. Pre-trial/trial initiation monitoring report	8.2.19; 8.2.20
	16.3. Monitoring visit reports	8.3.10
	16.4. Final trial close-out monitoring report	8.4.5
	16.5. Monitoring-related correspondence	

TRIAL MASTER FILE	SECTION	ICH E6 GCP Reference
17. Participants	17.1. Source documents	8.3.13
	17.2. Participant screening and enrolment logs	8.3.20; 8.3.22
	17.3. Participant identification code list	8.3.21; 8.4.3
	17.4. Participant contact list	
	17.5. Participant visit schedule	
	17.6. Participant withdrawal/termination	
18. Safety Reports	18.1. Adverse Event (AE) and Serious Adverse Event (SAE) tracking logs	
	18.2. SAE and related reports submitted to sponsor, and corresponding acknowledgements	8.3.16
	18.3. Unexpected Serious Adverse Drug Reactions (USADR) and other safety information submitted to regulatory authorities and HREC, and corresponding acknowledgements	8.3.17
	18.4. Safety information notified by sponsor to investigators	8.3.18
	18.5. Interim or annual reports to ethics and authorities, and corresponding acknowledgements	8.3.19
	18.6. Protocol deviations log	
	18.7. Safety reporting-related correspondence	
19. Biological Samples	19.1. Biological sample storage/destruction log	8.3.25
	19.2. Biological samples shipping records	
	19.3. Shipping materials	
	19.4. Laboratory manuals and certifications	
20. Audit	20.1. Audit certificate/reports	8.4.4
	20.2. Audit-related correspondence	
21. Communications and Study Meetings	21.1. Study meetings	8.3.11
	21.2. Correspondence with sponsor	8.3.11
	21.3. Correspondence with sites	8.3.11
	21.4. Other communications, correspondence and notes	8.3.11
22. Study Reports and Publications	22.1. Clinical study report	8.4.8
	22.2. Publications	