Guidance for DAIDS Electronic Trial Master Files (eTMF)

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2 Purpose and Scope

A Trial Master File (TMF) is the collection of essential documents used by sponsors, clinical research organizations, and investigators for the management of a clinical trial. A TMF contains documents that individually and collectively permit the evaluation of the conduct of a clinical trial and the quality of the data produced.

Decentralized Sponsor TMF

In May 2021, the Division of Acquired Immunodeficiency Syndrome (DAIDS) decided to utilize a decentralized approach for new TMFs. TMF documents will be stored in multiple DAIDS-approved electronic systems maintained by Electronic System Owners.

This guidance document outlines the supporting documentation, processes, and timelines for DAIDS electronic Trial Master Files (eTMFs). This guidance does not provide information on inspection processes which are covered under other applicable DAIDS SOPs and Policies.

3 eTMF Documentation

DAIDS documentation that governs the TMF process includes the below documents which are discussed further in this section:

- **DAIDS TMF Index** – Defines the documents required to be in the TMF and the Authoritative Source (AS) responsible for provision of the documents
- **DAIDS TMF Plan** – Defines the processes and procedures to ensure a high-quality and complete TMF
- **DAIDS Electronic Systems Mapping Document** – Defines the electronic system approved by DAIDS to maintain TMF documents
- **DAIDS TMF Naming and Filing Guidelines** – Defines the metadata requirements, naming conventions, and filing classifications for TMF documents
- **Standard Operating Procedures** – Defines specific processes involved in generating and maintaining eTMF documentation
- **eTMF System Resources Documents** – Provide instructions and processes for using an eTMF System
    - DAIDS RSC VV eTMF System: DAIDS Veeva Vault (VV) TMF System User Guide, System Quick Reference Card and Read and Understood Workflows in the VV System.
    - Other DAIDS-Approved Electronic Systems: User Guide and other applicable documents, as defined by DAIDS. It is recommended that other Electronic System Owners provide TMF resource documents as appropriate.

3.1 DAIDS TMF Index

The DAIDS TMF Index identifies the documents required for DAIDS eTMFs and provides a list of the applicable DAIDS Primary Contacts (PCs) and AS for all documents filed in the TMF.

The AS is a person or group of people in an organization who have ownership of a document and can be called upon to speak about its contents during a regulatory inspection. The AS may be a person or group in DAIDS or outside DAIDS (e.g., grantee or contractor/vendor). An AS outside DAIDS collaborates with the DAIDS PC to determine the specific types and number of documents to submit to the eTMF within a given zone.

The DAIDS PC is a DAIDS employee or group who can answer questions regarding documents they are responsible for in the TMF when interviewed by a regulatory inspector. The DAIDS PC collaborates with the appropriate AS to determine the content in a given zone(s) of the eTMF. A DAIDS PC may also be an AS. The DAIDS PC is responsible for a technical review of documents they are responsible for, per the protocol-specific DAIDS TMF Index, ensuring sponsor oversight of documents in the TMF.

The DAIDS TMF Team is a team within the DAIDS Office for Policy in Clinical Research Operations (OPCRO) Office of the Director (OD) responsible for ensuring Sponsor oversight of DAIDS TMFs, establishing protocol-specific TMF management documents, and collaborating with DAIDS staff and vendors to ensure DAIDS TMF compliance.

An Electronic System Owner is a person or organization responsible for the development, procurement, integration, modification, operation, and maintenance, and/or final disposition of an electronic system.

The DAIDS TMF Index template is compliant with International Council for Harmonisation (ICH) E6 requirements.

Protocol-specific TMF Indices will be regularly reviewed and maintained by the DAIDS TMF Team and DAIDS Regulatory Support Center (RSC) per DAIDS Work Instruction DAIDS-OPC-A15-WI-0004. DAIDS RSC generates a DAIDS TMF Index for each study and sends it to all DAIDS PCs and AS for review. The final protocol-specific TMF Index is sent to the DAIDS TMF Team for final review, approval, and signature.

DAIDS PCs and AS follow the DAIDS TMF Index to provide documents to the TMF. Details on how to identify and provide the documents, and to whom to provide these documents, are discussed further in Section 7.

3.2 DAIDS TMF Plan

The protocol-specific DAIDS TMF Plan outlines the required processes and procedures to ensure a high-quality TMF. The plan outlines how records for each clinical trial are managed and stored during and after the clinical trial, including protocol-specific processes and documentation for archiving, transfer, and destruction of records. The document references the DAIDS TMF Index and details roles and responsibilities for the TMF as well.

3.3 DAIDS Electronic Systems Mapping Document

For each study, DAIDS develops an Electronic Systems Mapping document that defines the electronic systems used during the course of a study and which electronic systems are approved by DAIDS, to maintain TMF documents. All Electronic System Owners need to meet specific DAIDS-defined requirements, DAIDS Work Instruction DAIDS-OPC-A15-WI-0003, in order to be allowed to maintain TMF documents in their system. Those Electronic System Owners who do not meet these requirements will migrate their documents into the DAIDS RSC VV System.

3.4 DAIDS TMF Naming and Filing Guidelines

To ensure consistent naming and that documents can be easily found in electronic systems, AS and DAIDS PCs will use the DAIDS TMF Naming and Filing Guidelines or other established Electronic System Owner naming convention when submitting documents to Electronic Systems. All Electronic System Owners will ensure they have a standard naming and filing guideline established to ensure appropriate document names, filing, and metadata items are completed during internal quality reviews.

3.5 Standard Operating Procedures (SOPs)

All Electronic System Owners must have SOPs in place regarding TMF-related processes.

4 Roles and Responsibilities

Role	Responsibilities
DAIDS PC	• In collaboration with the AS, identifies documentation for the eTMF • Completes the DAIDS PC Technical Review of documents in electronic systems per DAIDS Work Instruction DAIDS-OPC-A15-WI-0002 • Works with the AS and/or Electronic System Owner(s) to resolve issues with documentation • May or may not be an AS/Record Owner
Authoritative Source	• Identifies and uploads documentation for the eTMF • Certifies documentation that requires certification per Section 5 Certification of Documents • Works with the DAIDS PCs and/or Electronic System Owner to resolve issues with documentation
Electronic System Owner	• Acknowledges receipt, tracks, uploads, reviews, and processes documentation to the respective electronic system • Works with the DAIDS PCs and AS to resolve any issues with documentation in their electronic system • Generates metrics reports for tracking progress and health of the eTMF • Maintains SOPs for applicable electronic system
DAIDS TMF Team	• Completes ongoing reviews of documents in all electronic systems that make up the sponsor eTMF and review applicable metrics reports to ensure the overall health of the eTMF as part of Sponsor oversight per DAIDS Work Instruction DAIDS-OPC-A15-WI-0006

5 Certification of Documents

Originals may be generated in paper or electronic format. Certified copies are necessary when original records are copied, and the originals are destroyed or irreversibly replaced the original record.

Per International Council for Harmonisation (ICH), Guideline for Good Clinical Practice, E6:

- **1.63. Certified Copy: A copy (irrespective of the type of media used) of the original record that has been verified (e.g., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Any transfer or conversion (e.g., digitization or printing), which does not fulfill the criteria for a certified copy, is not suitable to replace an original file.**
- **8. Essential Documents for the Conduct of a Clinical Trial: When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.**

Documents submitted to the DAIDS eTMF are not expected to replace the original documents and therefore are not required to be certified copies. If the documents filed in the DAIDS eTMF will be used in place of the original document and/or the original document will be destroyed, the AS must certify the relevant copies within the eTMF and notify the Sponsor of their intent to destroy the originals. Destruction of original documents cannot occur without prior Sponsor approval.

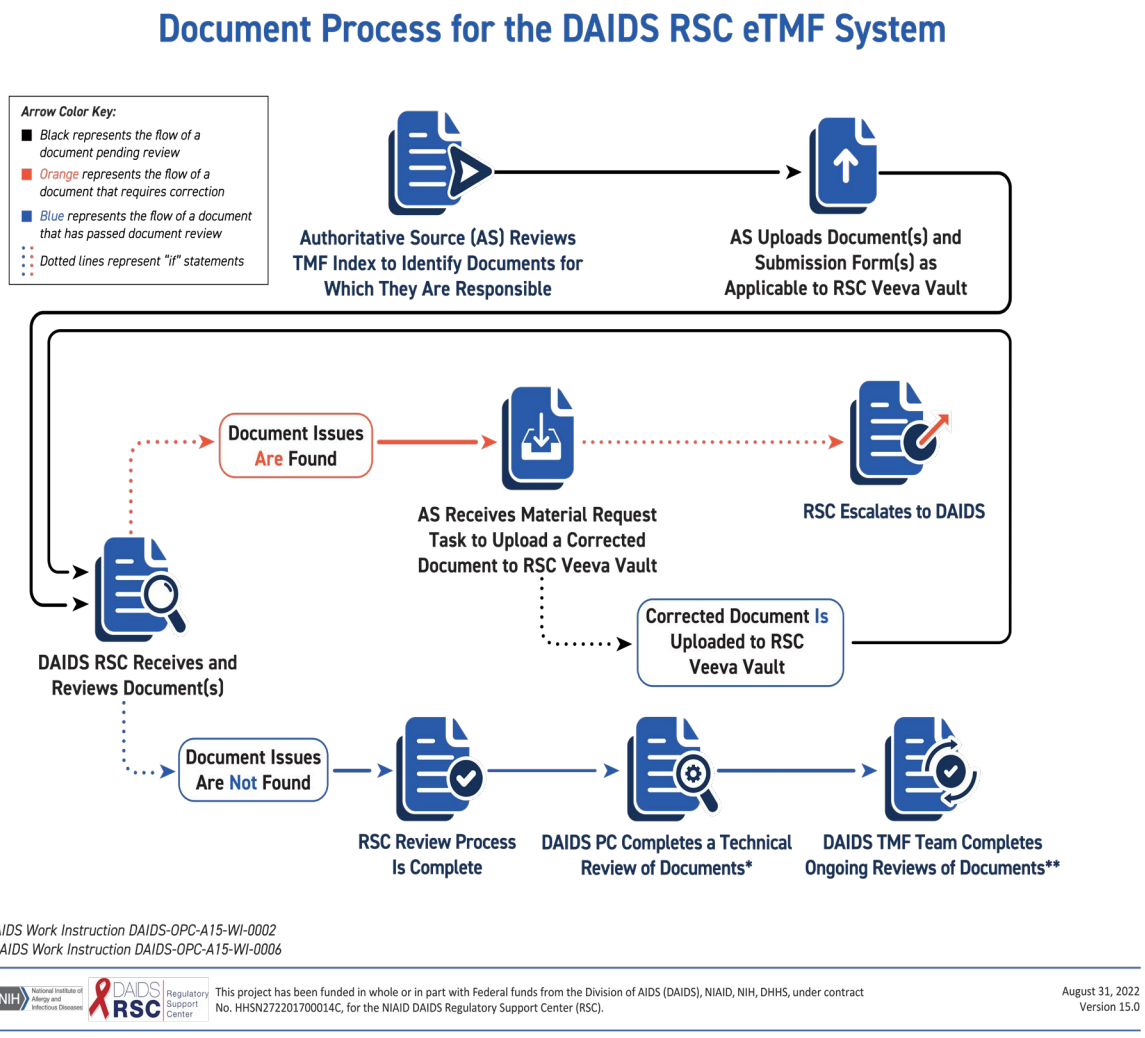
In the instance certification is required:

- Within an electronic system (e.g., DAIDS RSC VV system): certification is completed as part of a validated workflow. This certification confirms that the electronic file uploaded into the electronic system is an exact copy of the original document. This certification process within the electronic system is included in the document-specific audit trail.
- Outside an electronic system: certification will be per applicable Electronic System Owner SOPs. If certification is not completed within the electronic system, documentation is needed per applicable procedures.

NOTE: All documents must continue to be certified for the following protocols: IMPAACT 2014, 2017, 2019, 2032, HPTN 083, 084, 083-01, 084-01, MTN-034, -042, -43, A5300B/I2003/PHOENIx, and A5359. If a document applies to multiple TMFs and will be filed for any of these protocols, the document must be certified.

6 Overview of Workflow

The below image illustrates the process for adding an applicable document to the DAIDS RSC VV eTMF system and obtaining required approvals to ensure the TMF is ready for inspection. Each step is discussed further in Section 7 below.



** All other Electronic System Owners must have their own workflow and processes according to their SOPs.*

7 Processing Documentation within an Electronic System

All Electronic System Owners must have their own workflow and processes for the maintenance of TMF records documented in SOPs. The DAIDS RSC is responsible for processing documentation within the DAIDS RSC VV eTMF System and not for the maintenance of TMF records in other electronic systems.

7.1 Documentation Identification and Submission of Documents to the eTMF

7.1.1 All DAIDS PCs and AS identify the documents they are responsible for as part of their review of the draft protocol-specific DAIDS TMF Index.

7.1.2 TMF documentation is submitted by the AS or designee, throughout the clinical trial, as defined in the protocol-specific DAIDS TMF Index, to the applicable DAIDS-approved electronic system. *Note*: Documents are targeted to be submitted to all electronic systems **within 10 business days** of the date a document is finalized to ensure the TMF is contemporaneous. Any retrospective document submissions should be submitted per DAIDS timelines.

- For the RSC VV eTMF System, each document should be a separate file.

  Note: Correspondence documentation may be submitted as batched files.

7.1.3 For documents to be submitted to the DAIDS RSC VV eTMF System, each AS or designee prepares the eTMF Submission Form, when applicable,(Appendix 1.1, provided as an Excel document) comprised of the DAIDS TMF Index Zone, DAIDS Document Name, and Number of Expected Documents (or alternate DAIDS-approved information).Other Electronic System Owners must have, and follow, an established process for defining what information is provided by the AS when submitting documents (e.g. submission documentation).

7.1.4 The AS or designee utilizes the naming conventions per the DAIDS TMF Naming and Filing Guidelines or established Electronic System Owner naming conventions.

7.1.4.1 If the AS or designee is uploading documentation directly to an electronic system, they must upload the requested document(s), and complete the appropriate submission documentation when applicable (e.g., eTMF Submission Form for the RSC VV eTMF System).

7.1.4.2 If the AS or designee is submitting via email, they send the document(s), and the appropriate, completed submission documentation to the applicable Electronic System Owner and copy the DAIDS TMF Team. For the DAIDS RSC VV eTMF System, the AS should email the document(s) and eTMF Submission Form (when applicable) to the DAIDS RSC TMF (DAIDS_TMF@tech-res.com) and copy the DAIDS TMF Team (NIAIDDAIDSTMF@mail.nih.gov).

7.2 Receipt, Upload, and Processing of TMF Documents

7.2.1 The Electronic System Owner acknowledges and tracks the receipt of the documents, and ensures documents are uploaded/filed to the correct Zone and artifact of the electronic system.

7.2.2 After a document is in the electronic system, the Electronic System Owner conducts a basic review of the document (e.g., pages in order, legibility, etc.) and adds relevant metadata to the electronic system. Internal quality reviews of this information are conducted based on the Electronic System Owner SOPs.

7.2.3 While processing the documents, the Electronic System Owner follows-up with the AS or designee directly per their procedures, to resolve any issues. As needed, the AS or designee re-submits documentation to the System Owner. For the DAIDS RSC VV eTMF System, the AS should resolve open issues within 10 business days. Any issues that are not resolved within 30 business days are escalated to the DAIDS TMF Team.

7.3 DAIDS PC Technical Review

7.3.1 The DAIDS PC will complete a technical review of documents in applicable electronic systems as part of Sponsor oversight per DAIDS Work Instruction DAIDS-OPC-A15-WI-0002.

7.4 DAIDS TMF Team Review of the eTMF

7.4.1 On a timeline approved by DAIDS, the Electronic System Owner sends summary/metric reports for eTMF completeness to the DAIDS TMF Team.

7.4.2 The DAIDS TMF Team completes ongoing reviews of documents in all electronic systems that make up the sponsor eTMF and reviews applicable metrics reports to ensure the overall health of the eTMF as part of Sponsor oversight per DAIDS Work Instruction DAIDS-OPC-A15-WI-0006.

8 Glossary

Term	Abbreviation
AS	Authoritative Source
DAIDS	Division of Acquired Immunodeficiency Syndrome
eTMF	Electronic Trial Master File
ICH	International Council for Harmonisation
NIAID	National Institute of Allergy and Infectious Diseases
OPCRO	Office for Policy in Clinical Research Operations
PC	Primary Contact
POC	Point of Contract
RSC	Regulatory Support Center
SOP	Standard Operating Procedure
TMF	Trial Master File
VV	Veeva Vault eTMF System

9 Sponsor Approvals

Name	Title	Signature and Date
Melissa Kin, M.S., M.B.A.	Associate Director, OPCRO, DAIDS, NIAID	Melissa L. Kin -S Digitally signed by Melissa L. Kin -S Date: 2022.09.14 09:09:44 -04'00'

10 Version History

Version Number	Summary of Changes	Version Date
1.0	Guidance for DAIDS eTMF creation	August 20, 2021
2.0	Updated to reflect changes to the TMF process including contemporaneous filing timeline**,** roles and responsibilities, eTMF document process workflow, and submission form	December 15, 2021
3.0	Updated to reflect changes to the TMF process including contemporaneous filing timeline**,** roles and responsibilities, certification of documents, eTMF document process workflow, and submission form	April 14, 2022
4.0	Updated to reflect changes to the eTMF document process workflow and document processing	June 28, 2022
5.0	Updated to reflect changes to the eTMF document process workflow and language around the use of a submission form during document submissions	September 13, 2022

11 Appendix

11.1 eTMF Submission Form

DAIDS RSC eTMF Submission Form								
Authoritative Source Name:								
Authoritative Source Email:								
Submission Date:								
Protocol #:								
DAIDS TMF Index Zone	**Section Name** (You must select Zone first to populate this field)	**Artifact Name** (You must select Section first to populate this field)	**Number of Expected Documents**	**Version**	**Date of Document**	**Site**	**Document Filename**	**Additional Information/Comments**