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 TMF Documentation

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

- **DAIDSTMF Index** – A protocol specific document that identifies the expected documents for a given DAIDS-Sponsored study and provides a list of Authoritative Sources, DAIDS PCs, and applicable electronic systems that compromise the Sponsor TMF.
- **DAIDS TMF Plan** – A protocol specific document that defines the processes and procedures to ensure a high-quality and complete TMF.
- **DAIDS Electronic Systems Mapping Document** – A document that provides a list of electronic systems used during the course of a study to maintain TMF documents. The ESM document is protocol specific and confirms the validation status of each system, provides a list of document types stored within each system, confirms if a system has inspector access, and identifies each System's Owner. **Note**: This document applies to only to those systems used to house TMF related documents generated during the course of a study.
- **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 expected documents for a given DAIDS- Sponsored study and provides a list of Authoritative Sources, DAIDS Primary Contacts (PCs), and applicable electronic systems that compromise the Sponsor TMF. All DAIDS TMF Indices are protocol specific.

The AS is a person or group of people within DAIDS or outside of DAIDS (e.g., vendor- grantee and/or contractor) who have ownership of a document and are responsible for filing the document(s) in the Sponsor TMF. The AS is responsible for the content of the document and may be called upon to speak about its contents during a regulatory inspection.

The DAIDS PC is a DAIDS employee or group that ensures documents generated during the course of the study have been filed in the Sponsor TMF. A DAIDS PC may also be an AS.

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 assessing the health 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.

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-00004. 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 protocol specific 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 protocol specific TMF Index and details roles and responsibilities for the TMF as well. Electronic system owners may have a plan for how they manage TMF documents in their electronic system (eTMF). However, this plan must align with the DAIDS TMF plan for a study.

3.3 DAIDS Electronic Systems Mapping Document

For each study, DAIDS develops an Electronic Systems Mapping (ESM) document that provides a list of electronic systems used during the course of a study to maintain TMF documents. The ESM document is protocol specific and confirms the validation status of each system, provides a list of document types stored within each system, confirms if a system has inspector access, and identifies each System's Owner. All Electronic System Owners need to meet specific DAIDS-defined requirements, DAIDS Work Instruction DAIDS-OPC-A15-WI-00003, 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. **Note**: This document applies to only those systems used to house TMF related documents generated during the course of a study. **If a system is not listed on the ESM for a study, it cannot be used to house TMF documents.**

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 conventions when submitting documents to Electronic Systems. All Electronic System Owners will ensure they have a standard naming and filing guidelines established to ensure appropriate document names, filing, and metadata items are

completed during internal quality reviews. The Naming and Filing Guidelines for all electronic systems that are used to house TMF documents will be made available for review by the Sponsor (DAIDS), auditors and inspectors.

3.5 Standard Operating Procedures (SOPs)

All Electronic System Owners must have SOPs in place regarding TMF-related processes. SOPs for all electronic systems and organizational specific procedures related to TMF processes will be made available for review by the Sponsor (DAIDS), auditors and inspectors.

4 Roles and Responsibilities

Role	Responsibilities
DAIDS PC	• In collaboration with the AS, identifies documentation for the eTMF • Completes the DAIDS PC Oversight Review of documents in electronic systems per DAIDS Work Instruction DAIDS-OPC-A15-WI-00002 • 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 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	• Assesses the health of DAIDS TMFs, establishing protocol-specific TMF management documents, and collaborating with DAIDS staff and vendors to ensure DAIDS TMF compliance per DAIDS Work Instruction DAIDS-OPC-A15-WI-00006

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, 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, HPTN 084, HPTN 083-01, HPTN 084-01, MTN-034, MTN-042, MTN-043, 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 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. Documentation Identification and Submission of Documents to the eTMF

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

6.1.2 TMF documentation is submitted by the AS or designee, throughout the clinical trial, as defined in the DAIDS protocol-specific 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.

Note: Correspondence documentation may be submitted as batched files.

6.1.3 Electronic System Owners must have, and follow, an established process for defining what information is provided by the AS when submitting documents.

6.1.4 The AS or designee utilizes the naming conventions per the DAIDS TMF Naming and Filing Guidelines. If Electronic System Owners do not have an established Naming and Filing Guideline, they must follow the DAIDS TMF Naming and Filing Guidelines.

6.2 Receipt, Upload, and Processing of TMF Documents

6.2.1 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.

6.2.2 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.

6.2.3 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.

6.3 DAIDS PC Oversight of TMF Documents

6.3.1 The DAIDS PC or designee is responsible for performing a document level QC of the documents that they are responsible for, as outlined in the DAIDS protocol-specific TMF Index, that are housed in applicable electronic systems that make up the Sponsor TMF, per DAIDS Work Instruction DAIDS-OPC-A15-WI-00002.

6.4 DAIDS TMF Team Review of the eTMF

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

6.4.2 The DAIDS TMF Team is tasked with assessing the health of TMFs housed within DAIDS- approved electronic systems, by comparing what has been filed against TMF specifications (i.e., TMF Index and TMF Plan), regulatory requirements, Standard Operation Procedures (SOPs) and Work Instructions (Wis) and applicable DAIDS operational procedures per DAIDS Work Instruction DAIDS-OPC-A15-WI-00006.

7 Glossary

Term	Abbreviation
AS	Authoritative Source
DAIDS	Division of Acquired Immunodeficiency Syndrome
ESM	Electronic Systems Mapping
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 Contact
RSC	Regulatory Support Center
SOP	Standard Operating Procedure
TMF	Trial Master File
VV	Veeva Vault eTMF System

8 Sponsor Approvals

Name	Title	Signature and Date
Melissa Kin, M.S., M.B.A.	Associate Director and TMF Team Leader, OPCRO, DAIDS, NIAID	

9 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
6.0	Updated to reflect updates to definitions, procedures (removal of email submissions) and processes in workflow.	March 27, 2023

10 Appendix

10.1 RSC VV eTMF System 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**