DIVISION OF AIDS (DAIDS) TRIAL MASTER FILES (TMF) MANUAL

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1.0 ABBREVIATIONS

For additional definitions, see DAIDS glossary

Term	Abbreviation
AS	Authoritative Source
CBAR	Center for Biostatistics in AIDS Research
CRF	Case Report Form
CRO	Contract Research Organization
DAIDS	Division of Acquired Immunodeficiency Syndrome
DEV	Development
EDR	Essential Documents Repository
EDRMS	Electronic Document and Records Management System
ESM	Electronic Systems Mapping
eTMF	Electronic Trial Master File
FSTRF	Frontier Science & Technology Research Foundation
FAQ	Frequently Asked Questions
ICH	International Council for Harmonisation
MO	Medical Officer
NFG	Naming and Filing Guideline
NIAID	National Institute of Allergy and Infectious Diseases
OCICB CIB	Office of Cyber Infrastructure and Computational Biology Clinical Informatics Branch
OD	Office of the Director
OPCRO	Office for Policy in Clinical Research Operations
PC	Primary Contact
POS / PAC	Participants Off Study & Primary Analysis Completed
PROD	Production
RSC	Regulatory Support Center
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCORE	Site Clinical Operations and Research Essentials Manual
SOP	Standard Operating Procedure
TMF	Trial Master File

2.0 INTRODUCTION

The Division of AIDS (DAIDS) Trial Master File (TMF) Team in the Office for Policy in Clinical Research Operations (OPCRO) established this TMF Manual to outline the processes for the management of TMFs where DAIDS is the Sponsor. A TMF is the collection of essential documents used by Sponsors, clinical research organizations (CRO), and investigators to manage 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.

DAIDS uses a decentralized electronic TMF (eTMF) approach to allow the flexibility needed to support DAIDS business processes, operations, and research that DAIDS conducts.

This TMF Manual applies to all stakeholders (e.g., DAIDS staff, grantees, contractors, vendors, and any other group that is involved in the Sponsor TMF) conducting National Institute of Allergy and Infectious Disease (NIAID) / DAIDS-supported and / or -sponsored clinical trials where DAIDS has established a TMF.

The purpose of this Manual is to outline DAIDS processes and procedures related to DAIDS TMFs. This Manual supports the documentation, processes and procedures necessary to maintain the health of the DAIDS TMFs. Failure to follow the requirements outlined in this Manual may lead to findings during an inspection or audit. It is expected for all stakeholders to align with the most current DAIDS TMF processes and procedures as outlined in this TMF Manual.

3.0 TMF REQUIREMENTS

The TMF is the cornerstone of essential documentation for clinical trials, serving as the final deliverable for regulatory submissions to Regulatory Authorities for marketing approval. Documents within a TMF demonstrate Sponsor compliance with the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 and all applicable regulatory requirements. Given its critical role, the TMF is subject to scrutiny and inspection at any stage of a study, underscoring the collective responsibility of all clinical trial stakeholders to ensure its integrity and quality.

3.1 Establishing DAIDS TMFs

During the protocol development process, at the time of DAIDS Scientific Review but no later than DAIDS protocol regulatory review, DAIDS will determine if a study requires a TMF. As of September 2021, studies with a DAIDS Sponsor TMF, may not begin enrollment until DAIDS has initiated the TMF. A DAIDS Sponsor TMF is not considered initiated until the fundamental TMF documents are established, protocol specific TMF Process Training is completed, and DAIDS issues the official TMF initiation message.

Note: *Electronic System Owners may configure a study within their electronic system per timelines in their organizational processes; however, this does not indicate that the DAIDS Sponsor TMF has been initiated.*

3.2 The DAIDS Decentralized Approach

For each DAIDS study, there is one DAIDS Sponsor TMF, and DAIDS manages all TMF activities related to oversight, TMF initiation, TMF maintenance, and TMF archival. DAIDS- sponsored TMFs are stored individually across multiple electronic systems, a method known as the decentralized approach. Collectively, these electronic systems constitute DAIDS Sponsor TMFs.

As the Sponsor, DAIDS has chosen to use a decentralized approach for eTMFs. This approach allows flexibility to support the diverse research the Sponsor initiates. In the decentralized approach, TMF documents are stored in multiple eTMF and non-eTMF systems maintained by the Electronic System Owners.

An eTMF system is a commercial off-the-shelf product or other electronic system developed specifically to store TMF documents. An eTMF system is a regulatory compliant system configured to align with the specific structure of an eTMF, enabling eTMF features such as document versioning, tracking, access control, and audit trails.

A non-eTMF system is a regulatory compliant system that is used to store relevant clinical trial documentation, such as clinical study results, datasets, or analyses. A non-eTMF system may be used to house DAIDS TMF documents.

DAIDS collaborates with vendors, contractors, and grantees who provide support for the overall conduct of DAIDS-sponsored clinical trials. These collaborators, referred to as Electronic System Owners, are responsible for a portion of the documents in the DAIDS Sponsor TMF. Electronic System Owners must have a validated and regulatory-compliant electronic system qualified by DAIDS.

In the DAIDS decentralized eTMF approach, multiple electronic systems form the complete Sponsor TMF. To be a part of electronic system in a DAIDS decentralized eTMF, the system must be qualified and approved by the DAIDS QMS Team. Additionally, Electronic System Owners must have their own Standard Operating Procedures (SOP) for their electronic systems and those SOPs must align with DAIDS TMF procedures.

The following TMF operating procedures for DAIDS decentralized eTMFs apply to all stakeholders:

- There is only one TMF Plan, Electronic Systems Mapping (ESM) document, and Index for a study.
- Each TMF document is filed in a single location in one electronic system.
- Documents are filed based on the most current version of the TMF Index and TMF Plan.
- The TMF Index is used to determine the electronic system a TMF document is filed in and its location within that electronic system.
- Everyone has a responsibility to maintain access to electronic systems as needed to perform DAIDS TMF responsibilities.

4.0 ROLES AND RESPONSIBILITIES

Below are the responsibilities for specific DAIDS TMF stakeholders. Each role plays a vital part in ensuring the health of a DAIDS TMF throughout the clinical trial lifecycle.

4.1 DAIDS TMF Team

The DAIDS TMF Team is a team within the DAIDS OPCRO Office of the Director (OD).

The DAIDS TMF Team is responsible for:

- Overseeing DAIDS TMF process and procedures.
- Developing TMF Plan Template and network-specific Index Templates.
- Establishing protocol-specific TMF fundamental documents (TMF Index, TMF Plan, and ESM document).
- Informing Electronic System Owners about DAIDS staff needing access to an electronic system and approving access requests to DAIDS TMF documents within any electronic system that constitutes DAIDS TMFs.
- Conducting TMF system level reviews to ensure all documents filed in an electronic system are aligned with protocol-specific TMF fundamental documents.
- Conducting risk assessments on TMF documents included in the TMF Reference Model to evaluate the impact on study participants and data integrity if a document is missing from a TMF.
- Establishing the TMF risk assessment process and tools for DAIDS TMFs.
- Distributing protocol-specific TMF risk assessment tools to DAIDS Primary Contacts (PC) for DAIDS PCs to perform TMF document level QC.
- Maintaining the DAIDS TMF Risk Register.
- Collaborating with the Office of Cyber Infrastructure and Computational Biology Clinical Informatics Branch (OCICB CIB) and Electronic System Owners to complete the archival of DAIDS TMF.
- Completing final updates to the protocol-specific TMF fundamental documents and resolving TMF system-level issues before TMF archival.

4.2 Electronic System Owner

An Electronic System Owner is a person or organization responsible for the development, procurement, integration, modification, operation, access, maintenance, and/or final disposition of an electronic system including all applicable SOPs. Electronic System Owners must meet specific DAIDS-defined requirements to maintain DAIDS TMF documents in their electronic system. The requirements outlined below apply to electronic system Owners managing eTMF or non-eTMF systems.
An Electronic System Owner is responsible for:

- Establishing system-specific procedures for document submission, processing, quality control, access, training, and ensuring that these procedures are readily available for inspections and quality audits.
- Ensuring that, upon TMF initiation, the DAIDS TMF Team is immediately provided access to DAIDS TMF documents within each approved electronic system. *
- Requesting approval from the DAIDS TMF Team for any changes, updates, or new requests for access to DAIDS TMF documents within an approved electronic system that make up DAIDS Sponsor TMFs. *
- Maintaining DAIDS TMF documents within an electronic system in a confidential manner and in compliance with ICH GCP guidelines and local regulatory requirements.
- Providing TMF Metrics Reports and Summary Analysis documents twice a year to the DAIDS TMF Team and participating in TMF Oversight Meetings.
- Participating in audits and inspections of TMF electronic systems and procedures.
- At the time of archival or other DAIDS -approved transfer, preparing DAIDS TMF documents housed within their electronic system for transfer to another electronic system chosen by DAIDS, or transfer to long-term storage in the NIAID Electronic Document and Records Management System (EDRMS).
- Maintaining one email alias for each electronic system under their purview and sharing this email alias with the DAIDS TMF Team. Electronic System Owner email aliases are used by the DAIDS TMF Team to distribute documents, initiate access requests, send emails, and send invitations to meetings. Individual Electronic System Owner contact emails are used for document review (e.g., specific reviewers for SharePoint reviews).

** Note: Access to portions of the TMF stored in DAIDS-approved non-eTMF systems will be managed by the Electronic System Owner of the DAIDS-approved non-eTMF systems per the applicable Electronic System Owner's SOPs. The DAIDS TMF Team is provided guided access to maintain system level oversight of non-eTMF systems. Protocol-specific exceptions to access requirements are outlined in the protocol-specific TMF Plan for the study.*

4.3 Authoritative Source

An Authoritative Source (AS) is a person or group of people within DAIDS or outside of DAIDS (e.g., vendor, grantee, contractor) who has ownership of a document and/or is responsible for filing the document(s) in the DAIDS Sponsor TMF, per the most current version of the DAIDS protocol-specific TMF Index. The Authoritative Source may be called upon to speak about documents filed in a TMF during a regulatory inspection or audit.

Authoritative Sources are responsible for:

- Filing all documents expected for a study as defined by the most current version of the DAIDS protocol-specific TMF Index.
- Certifying documentation (when required).
- Reviewing, verifying, and providing feedback on DAIDS TMF fundamental documents.
- Maintaining access to electronic systems that make up DAIDS Sponsor TMFs to be able to file generated documents in a TMF.
- Attending required protocol-specific TMF Process Training at TMF initiation, and electronic system training prior to being granted access to DAIDS TMF documents.

4.4 DAIDS Primary Contact

A DAIDS Primary Contact (PC) is a DAIDS employee or group of people within DAIDS that ensures documents generated during the course of a study are filed in DAIDS Sponsor TMFs. Each DAIDS PC performs a document level Quality Control (QC) of the documents for which they are responsible for, per the most current version of a protocol-specific TMF Index, in all applicable electronic systems, per the DAIDS Work Instruction DAIDS-OPC-A15-WI-00002, and as outlined in TMF Document Level Oversight.

DAIDS PCs are responsible for:

- Using DAIDS protocol-specific Risk Assessment Tools to perform TMF document level QC.
- Following DAIDS PC review requirements and filing the completed DAIDS PC checklist in the TMF for that study.
- Working with the Authoritative Source and Electronic System Owner to resolve issues identified during QC reviews.
- Escalating any concerns to the DAIDS TMF Team.
- Reviewing, verifying, and providing feedback on DAIDS TMF fundamental documents and DAIDS' protocol-specific Risk Assessment Tools.
- Attending required protocol-specific TMF Process Training at TMF initiation, and Electronic System Training(s) prior to being granted access to any DAIDS TMF.

- Maintaining access to electronic systems that make up a DAIDS Sponsor TMF to be able to perform DAIDS PC oversight work.
- Ensuring that a DAIDS PC Delegation Memo is filed to TMFs when delegating all or a portion of their TMF oversight responsibilities to a DAIDS staff member.

4.5 DAIDS Clinical Research Site (CRS)

There are site-generated documents that are part of the DAIDS Sponsor decentralized TMF. These site-generated documents are housed at a CRS per the DAIDS protocol-specific TMF Index for a study.
A CRS must follow the Site Clinical Operations and Research Essentials (SCORE) Manual to ensure that any site-generated documents that are part of DAIDS Sponsor decentralized TMFs are maintained per DAIDS' requirements.

4.6 DAIDS Quality

DAIDS Quality is a group located within the DAIDS OD.

DAIDS Quality is responsible for:

- Performing initial quality assessments of DAIDS Vendors and periodic audits of their electronic systems to verify regulatory compliance.
- Performing ad hoc TMF audits of all electronic systems that make up a DAIDS TMF as necessary and requested by DAIDS staff.

5.0 TMF FUNDAMENTAL DOCUMENTS

DAIDS TMF activities are governed by processes and procedures documented in three DAIDS TMF Fundamental Documents: the TMF Index, the TMF Plan, and the ESM document. These TMF Fundamental Documents are protocol-specific and are developed and reviewed prior to each TMF initiation to ensure compliance for all stakeholders with DAIDS TMF processes during the course of a study. Subsequent reviews and revisions to TMF Fundamental Documents are based on study milestones outlined below; however, reviews/revisions may occur more frequently than these milestones if substantial changes have occurred (e.g., addition/ removal of electronic system, change in protocol study design, etc.).

- One year after first participant enrolled
- At study 'Closed to Accrual' milestone
- At study 'POS/PAC' milestone

DAIDS PCs and Authoritative Sources have the opportunity to review and provide comments on each DAIDS TMF Fundamental Document prior to finalization. After DAIDS TMF Fundamental Documents are finalized, the most current version of these documents must be utilized when filing documents in any electronic system that is part of a DAIDS decentralized Sponsor TMF. Deviating from the TMF Fundamental Documents for a study may result in an inspection/audit finding and/or CAPA. Any requests to modify or update protocol-specific TMF Fundamental Documents must be communicated to the DAIDS TMF Team. Before any electronic system can be used to house TMF documents, DAIDS TMF Fundamental Documents for a study must be updated.

5.1 TMF Index

The TMF Index identifies the expected documents for a given DAIDS-sponsored study and provides a list of Authoritative Sources, DAIDS PCs, and applicable electronic systems that comprise a DAIDS Sponsor TMF. The TMF Reference Model is used to develop the DAIDS TMF Index Templates based on DAIDS processes (e.g., addition of DAIDS PC, sub-artifacts, network-specific vendors, etc.) At the time of DAIDS Scientific Review and/or protocol regulatory review, the DAIDS TMF Index Template is customized to generate a protocol-specific TMF Index.

5.2 TMF Plan

The DAIDS TMF Plan is a protocol-specific document that defines the processes and procedures that will be followed to ensure a high-quality and complete TMF. The DAIDS TMF Plan provides information on how records will be managed and stored during and after the study, including protocol-specific processes and documentation for TMF archival, transfer, and destruction of records. DAIDS TMF Plans include a Responsible, Accountable, Consulted, Informed (RACI) table, Electronic Systems Contact Listing, timelines for filing, outline of all the electronic systems that make up a TMF and outline of the DAIDS PCs for that study. Electronic System Owners managing an electronic system outlined in DAIDS

TMF Plans may have an additional plan that explains how their electronic system is managed. However, this plan must align with the DAIDS TMF Plan for a DAIDS- sponsored study and should not be called a TMF Plan, but rather a Vendor Specific System Plan.

5.3 Electronic Systems Mapping (ESM) Document

The DAIDS ESM document provides a list of electronic systems used during the course of a study to maintain TMF documents. The ESM document is protocol specific and lists 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. The ESM only identifies electronic systems used to house TMF documents generated during the course of a study.

Electronic Systems that will house TMF documents for DAIDS studies must be qualified and approved by the DAIDS Quality Team. This includes verification that each Electronic System meets at a minimum (but not limited to) the following qualifications:

- Must be validated.
- Must have inspector access.
- Must provide audit trails.
- Must have applicable system related SOPs.
- A migration plan is in place (if migration activities were performed).

Electronic systems that do not meet the above qualifications cannot be used to house TMF documents as part of a DAIDS TMF and will not be included in the DAIDS ESM document.

Any requests from DAIDS PCs and/or Authoritative Sources to modify or update a protocol specific ESM (e.g., addition of a new system, migration of documents from one system to another) must be communicated to the DAIDS TMF Team for approval prior to the implementation of that electronic system.

If a new electronic system is identified or there are changes to current electronic system that is part of a DAIDS decentralized eTMF, the DAIDS TMF Team should be contacted to discuss and must approve the addition of any new electronic system and/or the changes to a current electronic system.

6.0 DAIDS TMF TRAINING REQUIREMENTS

DAIDS has established trainings sessions for both, the DAIDS TMF Process and the use of electronic systems. These sessions ensure that everyone involved in contributing to DAIDS TMFs receives the specific training required for their role, in lie with DAIDS procedures.

6.1 DAIDS TMF Process Training

Live protocol specific eTMF Process training is provided prior to TMF initiation. This training details the overall TMF process and outlines the roles and responsibilities for a study.

Completion of protocol specific DAIDS TMF Process Training is required each time a TMF is initiated. DAIDS PCs, AS, and Electronic System Owners are required to attend the DAIDS TMF Process Training to gain access to the DAIDS TMF documents for a study.

Upon completion of the DAIDS TMF Process Training, a training certificate is issued (or training is otherwise documented by DAIDS RSC TMF Team). To request protocol specific DAIDS TMF Process Training(s), contact the DAIDS TMF Team.

***NOTE**: DAIDS PCs, AS, and Electronic System Owners who cannot attend the live DAIDS TMF Process Training are responsible for following up with the DAIDS TMF Team to take the recorded training before access to a TMF is granted.*

6.2 Electronic System Training

Electronic System Training details the access procedures and document submission process for a specific electronic system that houses DAIDS TMF documents. DAIDS PCs, Authoritative Sources, Electronic System Owners (as applicable), inspectors, and auditors are required to complete electronic system training(s) to gain access to electronic systems housing DAIDS TMF documents. Electronic System Training is not protocol specific and may only need to be taken once.

Electronic System Owners are expected to establish and follow their own SOPs and procedures for electronic system access and training, and these procedures should be readily available for inspections and quality audits.

7.0 TMF DOCUMENT FILING REQUIREMENTS

7.1 TMF Procedures

Electronic System Owners must have TMF procedures for document submission, processing, and quality control, and those TMF procedures must be flexible enough to align with the DAIDS TMF processes. These Electronic System Owner SOPs may be reviewed by the DAIDS TMF Team and should be readily available for quality audits and inspections.

Electronic System Owners procedures must align with the following DAIDS TMF processes and procedures:

- DAIDS protocol specific TMF Plan and TMF Index
- DAIDS TMF system access requirements for Electronic System Owners, as outlined in this TMF Manual
- DAIDS contemporaneous filing requirements, as outlined in this TMF Manual
- DAIDS TMF System Oversight Metrics and Summary Analysis Requirements

If an Electronic System Owner has established procedures that require additional TMF filing in their electronic system (e.g., filing documents in their own system even though the DAIDS TMF Index indicates that these documents should be stored in a different system), then the Electronic System Owner must document that their process does not align with DAIDS expectations outlined in the DAIDS TMF Fundamental Documents. If an Electronic System Owner maintains DAIDS TMF documents within their system in a configuration that does not match the protocol specific TMF Index (e.g., customized sub-artifact names, etc.), a mapping document must be provided to outline how their filing aligns with the DAIDS TMF Index. This documentation will be reviewed by the DAIDS TMF Team and may be requested in vendor audits and inspections.

Failure to align with DAIDS TMF processes creates risks to DAIDS and may result in Electronic System Owner findings.

7.2 Filing DAIDS TMF Documents

Authoritative Sources must follow Electronic System Owner's document submission SOPs, the protocol specific TMF Plan, and the protocol specific TMF Index when filing documents in a DAIDS TMF. The DAIDS protocol specific TMF Index should be used to determine the electronic system a TMF document is filed in, and its location within that electronic system. Each TMF document should be filed in a single location within one electronic system per the TMF Index for the study. Documents should not be filed in multiple electronic systems. All expected documents for a study should be filed based on the most current version of the DAIDS protocol-specific Index and Plan.

7.3 TMF Maintenance

Electronic System Owners must maintain DAIDS TMF documents in an active state within their electronic system until the DAIDS TMF Team determines a TMF is eligible for long term archival or transfer to another electronic system.

Electronic System Owners provide TMF reports and summaries regularly for the DAIDS TMF per the TMF System Oversight Metrics and Summary Analysis Requirements document. This substantiates that each electronic system is properly maintained — i.e. documents are organized, complete, and readily accessible at all times - and allows the DAIDS TMF Team to review and address critical issues and confirm they are being addressed in a timely manner. This is one component to ensure DAIDS Sponsor TMFs are always inspection ready.

7.4 DAIDS Contemporaneous Filing Requirements

Effective July 1, 2024, the contemporaneous filing requirement, as defined by DAIDS, is that all DAIDS TMF documents housed in DAIDS-approved electronic systems must be filed within 30 calendar days from the date a document is finalized. Electronic System Owners should have processes in place that align with the DAIDS definition for contemporaneous filing for any DAIDS TMF documents filed into their electronic systems.

7.5 Naming, Filing & Metadata Conventions

Documents uploaded to a DAIDS -approved electronic system should use consistent naming and metadata conventions. DAIDS maintains a TMF Naming and Filing Guideline on the naming conventions for DAIDS TMFs. Electronic System Owners may establish their own naming and metadata conventions. These naming and metadata conventions will be provided to the DAIDS TMF Team during Bi-annual Electronic System Owner Oversight Meetings. If an Electronic System Owner does not have an established naming and filing convention, then the DAIDS TMF Naming and Filing Guideline must be followed. As part of quality assurance, Electronic System Owners will review the file naming and metadata entered by the Authoritative Source when documents are filed in a TMF and will update as needed, in accordance with the applicable Naming and Filing Guideline.

7.6 Certification of Documents

Documents filed in the DAIDS TMF are not expected to replace original documents in either 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 ICH GCP E6:

- 1.63. Certified Copy: A copy (irrespective of the type of media used) of the original record that has been verified (i.e., 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
- 8. Essential Documents for the Conduct of a Clinical Trial: When a copy is used to replace an original document (e.g., source documents, case report form (CRF)), the copy should fulfill the requirements for certified copies

Because documents filed in the DAIDS Sponsor TMF are not expected to replace the original documents, they are not required to be certified copies.

- If a document filed in the DAIDS Sponsor TMF will be used in place of the original document and/or the original document will be destroyed, the Authoritative Source must notify the DAIDS TMF Team.
- If replacement of an original document is approved by the DAIDS TMF Team, certification may be required in the electronic system prior to the original being destroyed.

All Electronic System Owners must have a process for certifying TMF documents either within or outside of their electronic system in the event that document certification is required.

Note: *Clinical Research Sites should refer to the SCORE Manual for instructions regarding identifying and creating certified copies.*

8.0 SPONSOR OVERSIGHT

8.1 Risk-Based Approach and Risk Assessment Tool

DAIDS utilizes a risk-based approach for the quality assessment of TMFs with the goal to assess what effect TMF documents would have if they were missing from a TMF on the safety, rights, and well-being of participants, as well as data integrity of a study. The DAIDS TMF Risk Assessment Tool allows DAIDS staff to perform Sponsor oversight activities without having to review the entire TMF. The DAIDS TMF Risk Assessment is integrated into each protocol specific TMF Index.

DAIDS assigns a risk ranking for each artifact type expected to be generated during a study. These risk assessments, defined by the DAIDS TMF Team, are recorded in the color-coded column of the DAIDS protocol specific TMF Index, which is filed in the DAIDS Sponsor TMF.
The four color-coded risk ranking categories are:

- Critical - Red: The document is deemed Critical as it will have a direct impact on the safety, rights, and well-being of participants, as well as data integrity if missing from the TMF.
- Major - Orange: The document is deemed Major as it will have a possible impact if missing.
- Minor - Yellow: The document is deemed Minor as it will have little impact if missing.
- N/A – No Color: The document is deemed Not applicable, as it was not generated or not required for a study.

DAIDS follows the DAIDS Risk Assessment Tool when performing oversight activities of TMF documents within an electronic system that comprises a DAIDS TMF. This assessment is not intended to be used or reviewed by Electronic System Owners and Authoritative Sources and does not require Electronic System Owners to update their business processes.

8.2 TMF System Level Oversight

The DAIDS TMF system level oversight process is the review carried out by the DAIDS TMF Team to assess the health of DAIDS TMFs in all DAIDS-approved electronic systems that make up a DAIDS Sponsor TMF. This system level oversight is critical to ensure that all electronic systems that comprise DAIDS Sponsor TMFs are aligned with DAIDS TMF Fundamental documents.

In support of this system level oversight, Electronic System Owners must provide TMF Metrics Reports and a summary analysis. This analysis should detail the metrics, critical findings, trends, pertinent issues, and proposed resolutions to be reviewed and discussed during biannual Electronic System Owner meetings.

The biannual meeting process and submission timeline requirements for metrics reports are outlined in the TMF System Oversight Metrics and Summary Analysis Requirements, located on the Regulatory Support Center (RSC) public website.

Key Elements of Electronic System Owner Biannual Meetings include discussion on the following topics:

- **TMF Metrics Reports**: Covering completeness, timeliness, and access.
- **Summary Analysis**: A document detailing any critical findings, trends, and pertinent issues should be summarized, and proposed resolutions provided.
- **Discussion:** Addressing issues and trends and completing a quality spot check of documents in electronic systems.

Documentation of all meetings is filed in DAIDS TMFs and distributed to Electronic System Owners.

8.3 TMF Document Level Oversight

Document level QC of DAIDS TMF documents is carried out by DAIDS PCs, as identified in the DAIDS protocol specific TMF Plan and TMF Index. This document level QC ensures that documents generated during a course of a study were filed by Authoritative Sources in the electronic systems that comprise DAIDS TMFs.

The document level QC will be done on a risk basis, as described in the Risk-Based Approach and Risk Assessment Tool section of this Manual. DAIDS PCs should refer to DAIDS WI DAIDS-OPC-A15-WI-00002 "*DAIDS Primary Contact (PC) Oversight of TMF Documents*" for detailed information regarding the requirements for document level QC.

DAIDS PC document level QC is required (at minimum) once per year per TMF. More frequent PC reviews may be performed but are not required. The initial DAIDS PC review must be completed within one year of the TMF initiation date. Subsequent DAIDS PC reviews must be completed within one year from the date of the previous DAIDS PC review. These subsequent reviews will include review of any new documents/document versions generated and filed in a TMF since the last DAIDS PC review.

In cases where no new documents are generated, a PC checklist must still be completed, with a note indicating that no new documents were produced during the review period.

DAIDS PCs will work with Authoritative Sources and/or Electronic System Owners to resolve issues identified during document level QC. If DAIDS PCs have questions during their document QC reviews, please contact the DAIDS TMF Team.

9.0 ACCESS

All DAIDS TMF stakeholders have a responsibility to maintain appropriate access to electronic systems that comprise DAIDS TMFs. To perform document level QCs, DAIDS PCs and/or their delegates are responsible for maintaining access to electronic systems that comprise DAIDS TMFs.

There are two levels of DAIDS TMF access:

- Access to electronic systems (e.g., system specific access)
- Access to TMF documents (e.g., study specific access)

Changes or new requests for access to electronic systems or TMF documents that comprise DAIDS TMFs require DAIDS TMF Team approval. Electronic System Owners are responsible for overseeing (e.g., granting, maintaining, and removing) access to any internal personnel per organizational procedures and DAIDS TMF Team approval is not required for such changes to internal personnel access that follows Electronic System Owner organizational procedures.

9.1 Access at TMF Initiation

At DAIDS TMF initiation, access will be granted as follows:

- All Electronic System Owners will grant immediate access to DAIDS TMF Team members.
- Within 30 business days of TMF initiation, the DAIDS TMF Team will inform Electronic System Owners of the specific DAIDS PCs that need access to an electronic system.

Additional details regarding access requirements for Electronic System Owners can be found in the protocol specific TMF Plans.

9.2 Individual Access Requests

If you believe you need access to an electronic system or to DAIDS TMF documents, contact the DAIDS TMF Team. Your request must include the following details:

- Name
- Email address
- Name of Electronic System
- Study specific TMF role (e.g., Medical Officer (MO) for study xx, delegate uploading on behalf of xx, etc.)
- List of TMFs for which access is being requested.

The DAIDS TMF Team will review the request, and if approved, the DAIDS TMF Team will confirm if protocol specific TMF Process Training was completed.

Approved requests for access will be sent to the Electronic System Owners who will follow their established access SOPs to assign applicable trainings and to grant access.
Note: *If existing system access is inactivated or issues are encountered on an active account, DAIDS PCs and Authoritative Sources may reach out to the Electronic System Owner directly and include the DAIDS TMF Team for awareness.*

9.3 Access Requirements for Electronic System Owners

Electronic System Owners are responsible for establishing and following their own SOPs and procedures for electronic system access. These Electronic System Owner SOPs are reviewed by the DAIDS TMF Team and should be readily available for quality audits and inspections.

Direct inspector access is a DAIDS requirement for Electronic System Owners to be able to house DAIDS TMF documents.

Note: *Electronic Systems maintained by DAIDS Data Management Centers such as FSTRF's and SCHARP's Medidata Rave, and CBAR's Research Computing Environment, are access limited due to advanced security controls and data sensitivity.*

The following access requirements apply to all DAIDS Electronic System Owners housing DAIDS TMF documents:

- Access is approved by the DAIDS TMF Team for any changes, updates, or new requests.
- Access is granted to DAIDS staff per Electronic System Owner procedures and confirmation of access being granted is sent to the DAIDS TMF Team.
- Access requests sent directly to the Electronic System Owners without DAIDS TMF Team awareness must be sent to the DAIDS TMF Team for approval.
- Access requests from the DAIDS TMF Team are fulfilled within 5 business days.
- Access Metrics Reports and a Summary Analysis documents are provided to the DAIDS TMF Team twice a year.

Note: *DAIDS TMF Team approval is not required for internal Electronic System Owner staff access requests when internal access SOPs are followed, and the Electronic System Owner verifies completion of required DAIDS TMF Process Training.*

The DAIDS TMF Team will review access reports provided by Electronic System Owners during biannual Electronic System Owner meetings. Electronic System Owners must ensure that access reports provided to the DAIDS TMF Team include a list of all DAIDS staff with access to DAIDS TMF documents within their system by study. Requirements for this report are outlined in the TMF System Oversight Metrics and Summary Analysis Requirements document.

9.4 System Outages

For planned or unplanned system outages, Electronic System Owners must have documented procedures that require notification to the DAIDS TMF Team. System Outages occurring outside of normal business hours are not reported to the DAIDS TMF Team.

9.5 Access Requirements during a TMF Audit or Inspection

For quality audits, DAIDS Quality contacts the DAIDS TMF Team to request access to the DAIDS TMF(s) being audited. Upon receiving the request from DAIDS Quality, the DAIDS TMF Team notifies Electronic System Owners of a TMF audit and asks them to initiate the process of granting temporary access to the auditors assigned to review electronic systems, as per established Electronic System Owner procedures. The DAIDS TMF Team ensures that auditor access is enabled and revoked for all electronic system(s) that make up a DAIDS TMF being audited. In addition, DAIDS TMF Team ensures appropriate access through the review of access reports provided by Electronic System Owners during biannual Electronic System Owner meetings.

For Sponsor inspections, the DAIDS TMF Team notifies Electronic System Owners of a Sponsor inspection and requests that Electronic System Owners initiate the process of granting temporary access to the inspectors assigned to review electronic systems, per established Electronic System Owner procedures. The DAIDS TMF Team will ensure that inspector access is enabled and revoked for all electronic systems that make up a TMF for the study being inspected through the review of access reports provided by Electronic System Owners during biannual Electronic System Owner meetings.

10.0 ARCHIVAL OF DAIDS TMF DOCUMENTS

Electronic System Owners are responsible for maintaining DAIDS TMF documents within their electronic systems until DAIDS initiates the TMF archival process and the migration of documents to another electronic system or transfer to the long-term storage in the NIAID EDRMS is confirmed by DAIDS to be complete.

The DAIDS TMF Team will monitor the status of all DAIDS TMFs to identify which TMFs have met the following criteria for archival:

1. The protocol has reached a POS/PAC study milestone.
2. There are no ongoing marketing applications.
3. All TMF documents have been filed into the DAIDS TMF per the protocol specific TMF Index.

Once the criteria 1 and 2 above have been met, the DAIDS TMF Team notifies all Electronic System Owners, Authoritative Sources, and DAIDS PCs of the last day to submit documents to the DAIDS TMF. After the filing deadline occurs, Electronic System Owners will not accept new documents into the DAIDS TMF and access to submit documents will be revoked. Completion of TMF document filing by the filing deadline fulfills criteria 3 above.

For TMFs that meet archival criteria, the DAIDS TMF Team and Electronic System Owners in collaboration with OCICB CIB will start preparation for the migration of documents into the DAIDS Essential Documents Repository (EDR) in the NIAID Validated EDRMS. OCICB CIB and Electronic System Owners will confirm system requirements and technical details regarding the transfer of DAIDS TMF documents from their electronic system(s) to NIAID EDRMS.

The Electronic System Owner is responsible for providing OCICB CIB access to all DAIDS TMF documents located within their electronic system, and for supporting the migration of these documents for long term archival by DAIDS. Electronic System Owners may not revoke DAIDS TMF Team and OCICB CIB access to their electronic systems until the DAIDS TMF Team confirms the migration is complete. Once the migration of all DAIDS TMF documents is confirmed, the DAIDS TMF Team will notify all Electronic System Owners. Upon receipt of that confirmation, Electronic System Owners may archive the DAIDS TMF documents in their systems as applicable per their organizational SOPs. The DAIDS TMF archival is complete once the documents are confirmed in the production environment of NIAID EDRMS.

Once a TMF has been archived, if Authoritative Sources need to file additional documents into a DAIDS TMF they should contact the DAIDS TMF Team for guidance.

The long-term storage and retention of the TMF documents must adhere to retention time periods defined by applicable regulation(s) and DAIDS Policies. In circumstances where multiple sets of requirements apply, the most stringent applicable retention requirement must be followed. These requirements include national, state, and local laws as well as institutional policies which may extend the record retention requirement.

11.0 TMF RESOURCES

The DAIDS RSC TMF Resources page is a public website that currently stores DAIDS TMF resources for DAIDS TMF Stakeholders. This website is managed by the DAIDS RSC. The following information is listed within the website include:

- **Relevant Communications Presentation** provides guidance on best practices for filing relevant communications, examples of TMF documents that qualify as relevant communications, recommendation on when to file, and filing location per DAIDS Indices.
- **DAIDS TMF Naming and Filing Guideline** is a document that is used to establish a baseline of how Authoritative Sources should name their documents when submitting into the DAIDS Sponsor TMF. The purpose of this guideline is to identify documents by study, site, person, and date, which will allow for easy retrieval from the eTMF during an inspection or audit. This will also allow adequate differentiation between similar documents.
- **Frequently Asked Questions (FAQs)** contain additional guidance and answers to commonly asked questions to help DAIDS TMF Stakeholders understand DAIDS TMF processes, requirements, and best practices.
- **Electronic System Contact Listing** contains the access links and email contacts of Electronic System Owners for all electronic systems that make up a DAIDS eTMF.
- **DAIDS TMF System Oversight Metrics and Summary Analysis Requirements Document** details DAIDS TMF system level oversight and standardizes the responsibilities of all Electronic System Owners maintaining DAIDS TMF Documents in their electronic systems.

- **DAIDS TMF Index Guiding Principles** provides a concise summary of the DAIDS TMF Index, covering its structure and content along with guidelines and best practices for reviewing the TMF Index.

12.0 REFERENCES

12.1 DAIDS-OPC-A15-SOP-00002 - Management and Oversight of Trial Master File (TMF) Procedures

12.2 DAIDS-OPC-A15-WI-00002 - DAIDS Primary Contact (PC) Oversight

12.3 DAIDS-OPC-A15-WI-00003 - DAIDS Protocol Specific Electronic Systems Mapping (ESM) Development and Management Process

12.4 DAIDS-OPC-A15-WI-00004 – DAIDS Trial Master File (TMF) Index

12.5 DAIDS-OPC-A15-WI-00005 – DAIDS Trial Master File (TMF) Plans

12.6 DAIDS-OPC-A15-WI-00006 – DAIDS TMF Team Oversight of TMF Documents and Systems

12.7 DAIDS-OPC-A15-SOP-00038-DAIDS Trial Master File (TMF) Risk Assessment

12.8 DAIDS-OPC-A15-SOP-00039-DAIDS Trial Master File (TMF) Archival Process

12.9 Division of AIDS (DAIDS) Site Clinical Operations and Research Essentials (SCORE) Manual

12.10 International Council for Harmonisation (ICH) E6, Guidelines for Good Clinical Practice E6

12.11 Hecht A, Busch-Heidger B, Gertzen H, Pfister H, Ruhfus B, Sanden PH, Schmidt GB. Quality expectations and tolerance limits of trial master files (TMF) - Developing a risk-based approach for quality assessments of TMFs. Ger Med Sci. 2015 Dec 10.

12.12 Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials. EMA/INS/GCP/636736/2012. 2015 Jun 15.

12.13 European Medicines Agency (EMA), Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). EMA/INS/GCP/856758/2018. 2018 Dec 06.

12.14 Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials. EMA/15975/2016. 2017 Mar 31.

12.15 DAIDS TMF System Oversight Metrics and Summary Analysis Requirements

12.16 DAIDS TMF System Owner Check-In Meeting #1. 2023 Jun 26.

12.17 DAIDS TMF System Owner Check-In Meeting #2. 2023 Aug 25.

12.18 DAIDS TMF System Owner Check-In Meeting #3. 2024 Feb 29.

13.0 REVISION SUMMARY

13.1 DAIDS-OPC-A15-MAN-00003 rev 01 is the original version of this Manual.