Summary, Critical Details, and FAQ for Your TMF Management

European Medicine Agency (EMA) Guideline on the content, management, and archiving of the clinical Trial Master File (paper and/or electronic), effective 30 June 2019

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Executive Summary

This overview summarizes and interprets the EMA's "Guideline on the content, management, and archiving of the clinical Trial Master File (paper and/or electronic)." This guidance was finalized at the end of 2018 and became effective in June of 2019.

The guidance was developed to assist clinical trial stakeholders in their compliance with current regulatory requirements (Directive 2001/20/EC and Directive 2005/28/EC) and the ICH E6 Good Clinical Practice (GCP) Guideline, as related to their use and management of the Trial Master File. The guidance was developed considering applicable requirements related to the pending Clinical Trials Regulation EU No 536/2014 and will continue to be relevant once the regulation is in effect.

Introduction

In the guidance, Trial Master File (TMF) is defined as a collection of essential documents that is used by sponsors, CROs, and investigators/institutions to manage the trial; and by monitors, auditors, and inspectors to review and verify whether those parties have conducted the trial in line with applicable regulatory requirements and the principles and standards of Good Clinical Practice (GCP).

The TMF is made up of two components: Sponsor TMF, which is held by and controlled by the Sponsor, and Investigator TMF, which is held by and controlled by the investigator or institution. The Investigator TMF is also known as the Investigator Site File (ISF). These two components should be segregated but collectively enable the trial's "story" to be told. The TMF may be managed in paper format, electronic format, or a combination of both (hybrid format). When utilizing electronic systems, primary and secondary systems may be used so long as the systems are validated as fit for purpose, and proper training and procedures are in place for their use. The use of multiple systems should be minimized when possible.

Essential Documents

The essential documents that make up the TMF are those documents that either individually or collectively enable trial conduct and data quality to be evaluated and measured.

- ICH/GCP defines a list of minimum essential documents required before, during, and after a trial is complete.
- The list should not be considered comprehensive.
- If the document is required to "tell the story" of the trial, it should be included in the TMF.
- Examples given of additional required documents not specifically called out in ICH/GCP guidelines include:
    - Completed checklists, reports, etc. related to the trial, generated from monitoring or review of quality management systems
    - Trial-specific computer system build validation (e.g., eCRF, IRT, eTMF room builds)
    - Data management documentation (DMP, data validation plan, data review meeting minutes)
    - Statistics documentation (SAS program validation, statistical analysis plan, sample size estimations)
    - Delegation log as part of the investigator/institution TMF
    - Documentation related to GMP activities
- Risk-based approaches may negate the need for certain types of documentation. Any reduced documentation requirements should have their justification documented and stored in the TMF.

TMF Trial Stakeholder Responsibilities

For both Sponsor TMF and Investigator TMF, TMF trial stakeholders include the sponsor and investigator(s) at a minimum and also may include contracted CROs and third parties. No matter the holder of the TMF, the Sponsor maintains overall responsibility for the trial and the Sponsor TMF; the investigator/institution maintains overall responsibility for the Investigator TMF.

Sponsors and investigators/institutions are responsible for ensuring that the TMF is established at the beginning of the trial. All documentation should be added in a timely manner throughout the trial. Timelines for document submission and periodic review should be established and documented as part of the TMF planning process.

QUALITY MANAGEMENT SYSTEM

A quality management system (QMS) is a formal mechanism for documenting relevant processes and procedures related to quality objectives and policies, as well as responsible parties. The guidance states that TMF trial stakeholders must have a QMS in place with procedures and processes for TMF management that ensure its completeness, quality, and accuracy.

AGREEMENTS BETWEEN STAKEHOLDERS

CROs and third parties need to be pre-qualified prior to contract signing, and their compliance with quality agreements should be evaluated and documented throughout the study, per the quality management system. The clinical trial agreement, TMF plan and/or other relevant

procedures should outline the plan for TMF management, in some level of detail, including:

WHO

- Holds the TMF or parts of the TMF
- Has access to the TMF
- Oversees the TMF

WHAT

- Structure and indexing of TMF
- Type of documents that each party should retain
- Scope of services between parties

WHEN

- Retention periods
- End of trial transfer
- Timelines for submission throughout trial

WHERE

- Record of the locations of all potential documentation that is planned to form the TMF, even if it is multiple locations, departments, countries, and/or systems

HOW

- Applicable TMF management procedures, including sponsor oversight
- Access arrangements
- Correspondence management
- System control
- Change management
- Archiving
- Multiple CRO interactions
- Procedures for involved party closedown
- Training requirements

OVERSIGHT

TMF trial stakeholders should ensure that the TMF is sufficient to reconstruct the activities for trial conduct and includes information about decisions and/or justifications made throughout the trial's duration. The TMF should be able to stand on its own to show compliance to the protocol, GCP, and data integrity, without need for additional explanation from TMF trial stakeholder staff.

TMF Structure

There should be an overall index or table of contents to facilitate finding essential documents, standardized across Sponsor and Investigator TMFs, regardless of responsible party. The plan for types of documents required, their location(s), and the structure(s) in which they are stored should be documented at the beginning of the trial and maintained throughout the trial.

PRIMARY AND SECONDARY TMF SYSTEMS

There should be a primary system for storing essential documents (paper, electronic, or hybrid format), but there can also be multiple secondary systems that store essential documents. Examples given include central email correspondence, SOPs and training records, and system software validation documentation. The guidance states that items that belong to multiple trials do **not** need to be duplicated across systems, and multiple systems should be minimized wherever possible.

SPECIFIC CONTENT GUIDANCE

Documents related to software validation may be retained by a CRO or third party when activities have been contracted by the Sponsor, but continued access to these documents should be included in the contract for the required archiving period. Evidence of the document review and approval process for documents requiring input from multiple parties (e.g., clinical trial protocol) should be maintained. Superseded versions of final documents should be retained in the TMF. Unblinded source documents that contain personal health information (PHI) or patient identifiable information (PII) should remain under sole control of the investigator/institution. If this type of document or information is uploaded into a sponsor/CRO electronic system, it must be *pseudonymized*.

RELEVANT CORRESPONDENCE

Relevant correspondence should be retained and is defined as correspondence that is necessary to reconstruct key trial activities and decisions. Electronic correspondence and attachments that are deemed to be relevant should be readily available and may be retained in their original format. Both sent and received correspondence should be filed in the TMF. Email chains and/or attachments should be carefully reviewed to ensure integrity and continuity in the chain of communication.

Security and Control of TMF

Regardless of format, the TMF should be managed securely at all times. Access to the TMF should be given and maintained based on role and/or permission and should be defined by sponsor and/or investigator/Institution and documented.

UNBLINDED CONTENT

Unblinded content should be appropriately controlled. Examples given:

- Storage of the unblinded documentation in another system or repository, OR
- By a role and permission description within the same system or repository

STORAGE AREAS

At all times, the storage area should be appropriate to maintain the documents in a manner in which they are legible and complete throughout the during of the trial and retention period. The storage area(s) should be able to be inspected upon request. Adequate and suitable space should be available to store essential documents from completed studies.

Facilities should be secure, with appropriate environmental controls, and provide protection from physical damage. Sponsors should make a documented assessment of storage areas at investigator/institution for storage of the investigator TMF and archiving. Sponsor should be notified if agreed arrangements are changed.

TMF Quality Oversight

Sponsor and/or investigator/institution should implement risk-based quality checks or review processes. Areas to consider to QC:

- All essential documents generated available in the TMF
- Documents filed in the appropriate locations
- Documents added in a timely manner
- Documents correctly indexed
- Documents only accessible according to assigned roles/permissions
- Review of the audit trail (for eTMF)

Additionally, the sponsor should:

- Perform routine QA measures on TMF-management processes
- Ensure TMF is readily available and directly accessible to the authorities for inspection purposes

CERTIFIED COPY REQUIREMENTS

A certified copy is defined as a paper or electronic copy of the original document that has been verified and/or generated through a validated process to produce an exact copy having all of the same information as the original, including data that describe the context, content, and structure. Certification is only required when the copy irreversibly replaces the original document.

Recommended quality checks when creating certified copies:

- Information is the same between copy and original
- Accuracy of metadata attributed to document (when applicable)
- Accuracy of file name, including version (when applicable)
- Quality of the image
    - Suitable resolution to allow the same readability as the original
    - Legibility and reproduction of color when color gives meaning and legibility of wet-ink signatures or annotations/handwriting (when applicable)
- eTMF audit trail associated with the document (when applicable)
- Approval of the certification process (when applicable)

NON-CERTIFIED COPY REQUIREMENTS

Some copies of documents don't irreversibly replace the original and therefore do not require certification. Procedural documents should state when certified copies are required, and regardless of certified copy status, the procedures should ensure that the copy is of sufficient quality for the intended purpose.

Electronic TMF (eTMF) Systems

Electronic Trial Master File (eTMF) systems should enable appropriate security and reliability, and ensure that no loss, alteration, or corruption of documents occurs throughout the document lifecycle and retention period(s).

eTMF CONTROLS

The primary eTMF should maintain the following controls:

- User accounts
- Secure passwords
- System for locking/protecting individual documents and/or the entire eTMF (at time of archiving) to prevent changes
- Backup
- Periodic restores/retrieval tests for data integrity
- Audit trail, including date/time/user details and uploading, deletion, and/or changes with explanation if necessary
- Role-based permissions
- Archiving capabilities

Secondary Systems

- Any secondary system defined as part of the TMF should follow the same principles (SOP management system, email central repository)

VALIDATION/VERIFICATION AND SYSTEM TRAINING REQUIREMENTS

All primary and secondary eTMF systems should be validated for fit for purpose, with formal procedures to guide the validation process. Where there are handoffs between TMF systems, the process for transfer should be robust and validated. Migration of data and documents to a new media or format should be verified for integrity. All staff using the system who are involved in the conduct of the trial should be trained on its use.

METADATA REQUIREMENTS

Special consideration should be given to defining dates for document filing, and this should be notated in the TMF planning documentation. Metadata applied to documents should be formally defined to ensure consistency. Metadata should include a predefined document date, and when appropriate, time (based on standard time zone) so that the files can be displayed chronologically. In instances where there are multiple versions of a document, this should be indicated in the file name as well as in the content of the document.

FILE FORMATS AND PDF CONVERSION REQUIREMENTS

The eTMF can include both dynamic (Excel spreadsheet with automatic calculation, eCRF) and

static (PDF scan of paper documents) types of files, as necessary and defined in the TMF plan. Appropriateness of the storage system should be evaluated based on the file format used (e.g., whether the eTMF system is appropriate for the storage of dynamic data files.)

- Dynamic data files do not need to be converted to PDF.
- When static files are made from dynamic files, the original should be maintained in its original system (e.g., eCRF exported to PDF)
- PDF files generated from other systems (e.g., monitoring visit reports, shipping reports may be uploaded to the eTMF, but should be maintained in their source system of record)
- Changes to images are acceptable only to increase legibility and should not add or remove material to the image (e.g., fax headers should remain)

DESTRUCTION OF ORIGINALS

Sponsors and investigators should ensure that essential documents are not destroyed before the end of the retention period. Creation of certified copies can enable earlier destruction of originals.

Low-risk destruction document types:

- Paper copy of electronic original can be destroyed as long as the original is maintained in the TMF
- Paper documents that do not have legally required wet-ink signatures

Archival and Retention of TMF

ARCHIVAL

The TMF and any associated audit trails should be archived appropriately to enable supervision after the trial has ended.

- Archiving should take place after investigator and sponsor have reviewed that their filed TMF is complete
- Access should be restricted via permissions or storage area access
- External archives may be used for paper or electronic media
- External vendors must be qualified by the sponsor
- Sponsor must be notified of locations of actual storage
- Overall log of TMF archives must be maintained, along with access logs
- When content is checked out, the person in charge of the archive needs to reconcile and ensure all content is returned
- Investigator TMF archival should be independent of the sponsor and determined to have no conflict of interest
- Sponsor is responsible for ensuring that the CRO has archived according to its procedures and the TMF plan
- Investigators should maintain a list of all trials being conducted and the archiving arrangements for each Investigator TMF

For eTMFs, there is additional guidance:

- When applicable and possible, the dynamic character of the audit trail should be preserved
- Any electronic system that holds trial data and/or metadata required for reconstruction should be archived so that the data/metadata can be retrieved as usable datasets
- Electronic documents and/or data that has been archived should be protected from unauthorized changes.
- Written procedures should help to ensure that future technology is able to read the archives and/or media
- In cases of eTMF, the audit trail will serve as the access log

RETENTION

The sponsor is responsible for determining the study retention period based on:

- Appropriate requirements/regulations
- Start and end dates
- Whether the trial is used or intended to be used to support a marketing authorization

These requirements also cover documents applicable to multiple TMFs, such as:

- Software validation documentation
- Training records, etc.

A subset of applicable retention period considerations is included in the table below.

Requirement/Regulation	Requirement/Regulation
2001/20/EC	At least 5 years after completion
Where used to support a marketing authorization	• At least 5 years after completion • At least 15 years after completion/discontinuation of trial • At least 2 years after last marketing authorization granted in EU • At least 2 years after formal discontinuation of clinical development of investigational product • Whichever is longest
2003/63/EC	• Data owners need to retain essential documents for as long as the product is authorized. • Final report shall be retained for 5 years after the product is no longer authorized.
Article 58	• Unless other law requires archiving for longer, sponsor and investigators will archive TMF content for at least 25 years after the end of the clinical trial. • This also applies to documents retained by CROs or third parties.
Documents relating to full traceability of the ATIMP	• 30 years after the expiry date of the product or longer if required by the clinical trial authorization • Includes Sponsor TMF, Investigator TMF, and trial subject medical files

Conclusion

The EMA's final "Guideline on the content, management, and archiving of the clinical Trial Master File (paper and/or electronic)" provides stakeholders with guidance on TMF creation, management, and archival. The main points of the guidance are summarized below.

1. The TMF consists of two separate and distinct components: Sponsor TMF and Investigator TMF. Its components may be housed in one or multiple controlled systems and/or locations and managed in paper format, electronic format, or a hybrid of both formats. The regulations apply equally, regardless of format.
2. The TMF should be established at the beginning of a trial, and its management and use should be planned out and documented clearly for all associated stakeholders.
3. Sponsors and investigators/institutions are responsible for qualifying any third-party providers or systems and should ensure quality management systems are in place and any applicable procedures followed.
4. The sponsor and investigator/institution are responsible for ensuring not only the quality and accuracy of individual documents and data contained in the TMF, but also the overall TMF quality, accuracy, and completeness.
5. Certified copies are required to be used only when a copy irreversibly replaces an original document and should be created using a formal and validated process.
6. Dynamic (Excel, datasets, etc.) and static (PDF) file types are permitted in the TMF. Final documents should be stored in a format that makes sense for the file type. Excel files are not required to be converted to PDF, for ease of use.
7. Studies should be archived once the sponsor and investigator/institution have verified that their TMFs are complete. The Sponsor TMF and Investigator TMF must be archived independently, and access should be restricted via permissions or storage area access.
8. Sponsors are responsible for determining retention period requirements based on regulations, study start and end dates, and whether the study will be used as part of a marketing application.
9. Original documents may be destroyed after retention periods are complete, or earlier if a certified copy process is validated and followed.

FAQ

Why do I need a TMF?

- Because the TMF tells the comprehensive story of the clinical trial
- Because the authorities and sponsors need a way to prove the data is sound, and they are compliant with relevant regulations

What is a TMF?

The TMF is a "collection of essential documents that is used by sponsors, CROs, and investigators/institutions for the management of the trial and by monitors, auditors, and inspectors to review and verify whether the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the principles and standards of GCP."

The guidance states that the regulations apply equally if the TMF format is paper, electronic, or a hybrid, which would be a combination of both formats. The TMF is made up of two separate and distinct components: Sponsor TMF and Investigator TMF, defined below.

What is a Sponsor TMF?

The Sponsor TMF is the portion of the TMF that is held by the sponsor or its contracted designees. It is related to but should be kept separate from the Investigator TMFs.

What is an Investigator TMF?

The Investigator TMF is the portion of the TMF that is held by the investigators and/or institutions that participate in the trial, or their contracted designees. The Investigator TMF should remain in the control of the investigator or institution at all times, even if housed electronically on a system that is in the control of the sponsor or designee.

What is considered to be an essential document?

Essential documents are defined as documents that enable monitors, inspectors, auditors, and sponsors to evaluate the conduct of a trial, determine compliance against applicable regulatory requirements, and verify the quality of data that is produced as a result of the trial. A minimum set of essential documents for both Sponsor and Investigator TMFs are detailed in ICH GCP guidelines, segmented by documents required at start of the trial, during the trial, and at trial close.

This should not be considered a definitive list, as various circumstances may necessitate either additional documentation or reduced documentation.

What are some examples of document types that are not specifically mentioned in the ICH GCP guidelines?

Completed forms, checklists, reports, etc. related to the trial

- Generated from monitoring or review of the QMS for CROs or third parties

Documents related to ATIMP

- Qualified Person Certification

- Assay method validation report

Trial-specific computer system build validation, e.g.,

- eCRF builds
- IRT builds
- eTMF room builds

Data management documentation, e.g.,

- Data management plan (DMP)
- Data validation plan
- Data review meeting minutes

Statistics documentation, e.g.,

- SAS program validation
- Statistical analysis plan
- Sample size estimations

Delegation log

- As part of the Investigator TMF

GMP-related documentation, e.g.,

- Related to the assembly and/or packaging of API

When should documentation be uploaded to the TMF?

All documentation should be added in a timely manner throughout the trial. Timelines for submission should be included in procedures or plans related to TMF content.

When should CRO or third-party vendors be qualified by sponsors?

Sponsors should pre-qualify CROs and/or third-party vendors prior to contracting and verify compliance to quality measures throughout the trial duration.

When should a record of TMF content locations be compiled?

The sponsor and investigator(s) should identify a record of the locations of all potential documentation that is planned to form the TMF, even if it is in multiple locations, departments, countries, and/or systems. This record should be updated and maintained throughout the duration of the trial. Plans for periodic review should be built into the TMF plan or relevant procedures so as to ensure compliance.

What is relevant correspondence?

Relevant correspondence is defined as correspondence necessary to reconstruct key conduct activities and decisions. Examples given in the guidance are ethics committee correspondence, DSMB correspondence, and correspondence with regulatory authorities.

Where should relevant correspondence be stored?

Relevant correspondence may be stored in the primary or a secondary repository so long as the secondary repository is clearly defined and documented as part of the TMF. It should be noted that any secondary electronic repository (such as shared email box) would be subject to the same system validation requirements as primary repositories.

When should relevant electronic correspondence be filed in the TMF?

While the guidance does not specifically call out timing for when correspondence should be filed in the TMF, it does state that electronic correspondence (and attachments) should be readily available.

In what format should electronic correspondence be stored?

Electronic correspondence and attachments may be retained electronically.

Does TMF mean one and only one repository?

No. TMF is an overarching term that covers both the Sponsor TMF and Investigator TMF. It can be made up of one or multiple electronic and/or physical repositories so long as the repositories are outlined in a TMF plan and an index of content locations is maintained. All electronic systems are subject to system access requirements and regulations. Physical/paper repositories are subject to records management storage requirements and regulations.

What controls are required for the primary eTMF?

In addition to the below controls, eTMF systems should be validated for fit-for-purpose, with formal procedures to guide the validation process.

- User accounts
- Secure passwords
- System for locking/protecting individual documents to prevent changes
- System for locking/protecting entire TMF (at time of archiving) to prevent changes
- Backup
- Periodic restores/retrieval tests for data integrity
- Audit trail, including date/time/user details and uploading, deletion, and/or changes with explanation if necessary
- Role-based permissions
- Archiving capabilities

What controls are required for Secondary eTMFs?

Any secondary system managed as part of the eTMF is subject to the same guidance. Examples given are SOP management systems and email repositories.

Do dynamic data files need to be converted to PDF when uploaded to the eTMF?

No. Certain types of files, such as Excel files or SAS datasets, are not readily usable in PDF format. These types of files are called “dynamic data files” and are not required to be converted to PDF. These dynamic data files may be stored in the eTMF in their native format.

When storing other-system-generated PDFs do I need to maintain the information in its source system?

Yes. PDF files generated by other systems, such as eCRFs, monitoring visit reports, shipping reports, etc. may be uploaded to the eTMF but should be maintained in the source system of record.

What is a certified copy?

A certified copy is defined as a paper or electronic copy of the original document that has been verified and/or generated through a validated process to produce an exact copy having all of the same information, including data that describe the context, content, and structure, as the original.

When is a certified copy required?

A certified copy is required only when the copy irreversibly replaces the original document. An example of irreversible replacement of an original document would be when a company has processes in place that allow them to shred original documents once the validated document capture process has been completed. Some copies (electronic or otherwise) do not replace the original and therefore are not required to have certified copies made.

Can investigators use sponsor systems for Investigator eTMF?

Yes, but documents containing PHI or PII should be maintained separately by and under the control of the investigator/institution at all times. Any source documents uploaded into sponsor or CRO eTMF systems should be *pseudonymized*.

How should investigators access sponsor systems for Investigator TMF?

Access can be given through a web portal or by the sponsor uploading directly into the Investigator eTMF. Procedures must be in place governing the system's use, and an audit trail must capture information about when the documents were accessed. Additionally, the investigator/institution must document when they implemented the processes.

What types of QC should be performed on eTMF Content?

- All essential documents that have been generated should be available in the TMF
- Documents should be filed in the appropriate locations, per the index
- Documents should be available in the TMF in a timely manner
- Documents should have the proper metadata applied
- Documents should be accessible according to assigned roles/permissions
- Audit trail should be available for review

What other QA measures should the sponsor perform?

The sponsor should perform routine QA measures on TMF-management processes and document the plan to do so at the beginning of the trial and maintain the plan throughout the duration of the trial.

If a document applies to multiple trials, does a copy need to be filed in each TMF?

Items that belong to multiple trials do not need to be duplicated for each TMF. However, the plans and overall index or table of contents must reference the central location as part of the TMF.

When can original documents be destroyed?

Original documents may be destroyed after the end of the retention period. Creation of certified copies can enable earlier destruction of originals if desired. Low-risk document types for destruction include those that are paper copies of original documents and paper documents that do not have legally required wet-ink signatures.

What is an archive?

An archive is a physical or electronic facility that securely stores and enables limited, controlled access to archived Sponsor and/or Investigator TMFs, as required. After trial completion, the TMF is required to be retained according to the applicable retention schedule, determined by the sponsor based on regulatory requirements and other considerations.

When should archiving take place?

Archiving should take place after the investigator(s)/institution(s) and sponsor have reviewed that their filed TMF is complete.

How should access to TMF archives be controlled?

Access to the TMF archive should be restricted via permissions or storage area access. Electronic documents and/or data that has been archived should be protected from unauthorized changes. An overall log of TMF archives must be maintained. In cases of paper TMF, an access log should be maintained, and the person in charge of the archive must reconcile the content upon its return to the archive. In cases of eTMF, the audit trail will serve as the access log.

What procedures should be in place related to archiving?

Written procedures should be in place to govern the management of TMF archives. In addition to archive management, the procedures should also ensure that future technology is able to read the archives and/or media.

Can external archives be used?

Yes. External archives may be used for paper or electronic media. External vendors must be qualified by the sponsor. Additionally, the sponsor must be notified of physical and electronic storage locations.

Can the Sponsor TMF and Investigator TMF be archived together?

No. The Investigator TMF archival should be independent of the sponsor and determined to have no conflict of interest.

Who determines the retention requirements for a clinical trial?

The sponsor is responsible for determining applicable requirements based on regulatory requirements, study start and end dates, and whether the trial is used or intended to be used in the future to support a marketing authorization.

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