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Nature of a Distributed Trial Master File - Practical Aspects

A white paper written by a joint task force from
the European CRO Federation and the eClinical Forum

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1 Executive Summary

Involved organizations (i.e., sponsor, investigator sites, Contract Research organization (CRO) and Third-Party Vendors (TPVs[1])), before and during the conduct of a clinical trial, are naturally focusing on trial design, conduct, and data collection. Their focus is not records retention. This lack of attention given to records formatting, ownership, storing management, legibility, retrievability, as well as (e-)archiving locations, could lead to the distributed Trial Master File (TMF)[2] being uncontrolled at the time of trial closure. This could lead to situations where retrievability is impacted during a need to examine the distributed TMF in its retention period.

2 Introduction

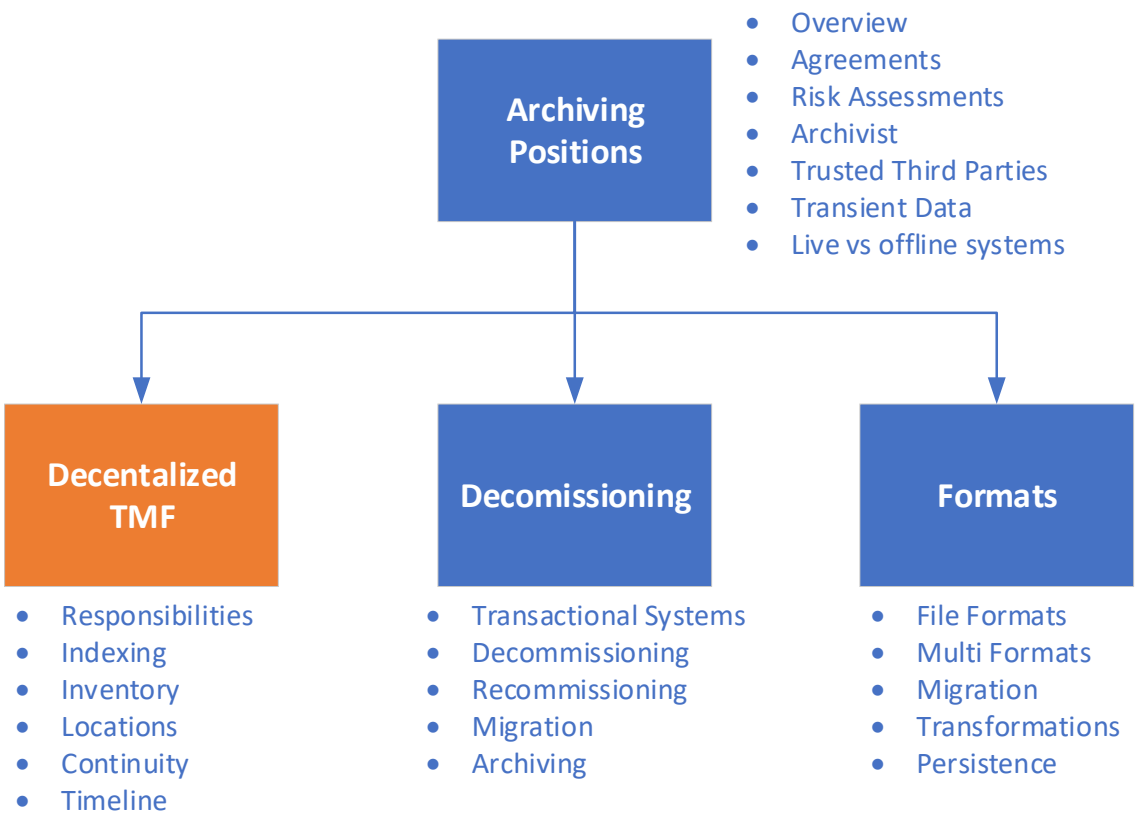
Essential Documents (including data) per International Conference Harmonization- Good Clinical Practice (ICH-GCP) E6, §8 Revision 2 are those that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. They collectively make up the TMF. These are retained and archived by the sponsor, the investigator and, in some cases, sub-contractors to the sponsor and/or investigator. These essential records consist of data, trial specific, and non-trial specific documentation. The non-trial specific essential records may be retained separately and signposted in the sponsor TMF. The location of these records will vary depending on the type and source of the records in question and over time. Consequently, the whole TMF will span across multiple locations and be distributed among multiple parties.

The trial and non-trial specific essential records must allow for the seamless reconstruction of clinical development activities, must be open to audits and inspections, and must fulfil all regulatory and legal purposes for the applicable full retention periods.

This document is a TMF focus to the position paper '*Trial Master File Archiving and the Decommissioning of Computerised Systems Used in Clinical Trials*' written by a joint task force from the European CRO Federation and the eClinical Forum and published on 24FEB2021. It is intended to provide hands-on practical guidance on TMF implementation by describing examples of risks in practice with proposed recommendation(s).

[1] TPV: Third-Party Vendors shall be understood as "any vendors and service providers to the extent of their assumed sponsor trial-related duties and functions" [EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic), 2018]

[2] TMF shall be understood as paper and/or electronic; the legislation does not differentiate between paper and electronic TMFs (eTMFs) [EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic), 2018]



3 Definition of a distributed TMF

One specific TMF is the amalgamation of evidence records (including at a trial-specific level and non-trial-specific level) held and maintained by multiple parties with respect to their duties during the trial. Together, these records constitute the *distributed TMF.* The distributed TMF is analogous to an encyclopedia with many volumes linked to each-other. Each volume can be in a different location. To make it whole, there needs to be an index linking those different parties' volumes. The sponsor remains responsible for oversight of all parts per ICH-GCP 5.2.2.

The purpose of the TMF, as per the European Medicine Agency (EMA) *Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)* dated 08DEC2019, is to collect materials that facilitate the reconstruction of the activities during the lifecycle of a clinical trial. Clinical trial related records shall be retained for a defined and formalized period in compliance with regulatory requirements (based on local and/or medicinal product-related requirements).

The retention periods may vary based on the sponsor intended use of the data and responsibility as marketing authorization holder. These also need to be implemented in third parties' agreements.

These records at each distributed location must be retained in a way that protects the records from risk of destruction and ensures their long-term legibility. They must also be accessible upon request from regulatory authorities.

The combination of archived records, which might be paper or electronic, allows the evaluation of the conduct of a trial. They must demonstrate the quality of the trial data produced and support reconstruction of the trial conduct during the full retention period.

A viable records' format is also of importance to be able to open and review the records.

The 'final fate and location' of electronic/paper, essential/non-essential records must be understood by all contributing entities, whether acting as sponsor's partner, Electronic Data Capture (EDC) or archiving TPV.

4 Frequent Risks, and Recommendations

4.1 Responsibilities of the parties involved in a distributed TMF

The clinical trial sponsor is ultimately accountable for the distributed TMF. Sponsor has a duty to perform continued oversight of all other parties involved with the TMF. TPVs performing duties with respect to a clinical trial should be conducting risk-based reviews of the TMF documentation they manage in compliance with the appropriate regulatory requirements, directives, and guidance. The sponsor must establish communication channels and regularly communicate with each remote party to get sufficient advanced notice of, and act upon, any risk to TMF records.

The investigator is responsible for essential records generated at the investigator site and should always maintain control of them.

The processes – along with duties and responsibilities - for storing, managing, and retrieving these materials must be defined before, during and after the trial, and, importantly, contractually agreed between the respective parties for the full retention duration as the trial sponsor remains responsible for its oversight and content.

4.1.1 Risks in practice

Responsibilities for storing and archiving may not be fully assigned and/or are not maintained over time. Changes will occur over time that may impact the established record management responsibilities. The risks related to these changes must be periodically assessed for their overall impact on the integrity of paper and electronic archives.

4.1.2 Recommendations

Practical operating recommendations that could be made to improve the process and ensure compliance to the requirements of *EMA Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic*):

- Define before the trial start the roles and responsibilities for records management of each involved party, including detailed split of responsibilities and the defined retention period.
- Nominate a sponsor coordinating and dedicated tasks/role(s) (this is the sponsor records management responsible / archivist role) whose responsibilities are to ensure:
  - An overview, oversight, and regular contact with contributing entities,
  - That archiving contractual agreements are in place and maintained for the full retention period,
  - That the overall TMF Inventory is maintained current,
  - That traceability, security and timely retrievability of archives is maintained over time through documented periodic restore testing,
  - A periodic risk-based assessment of the sponsor ability to demonstrate oversight and maintenance of the complete TMF archives.
- Ensure contracting aspects with all TPVs who are delegated task(s) related to records management are maintained.

It has been identified that contracts between the contributors are often showing gaps regarding (e-)archiving requirements. The requirements exist but are typically not well defined at the time of the contract set-up. The risk being not anticipating this need, due to activities focusing then on the trial conduct.

Nevertheless, these requirements need to be defined with sufficient level of details before the archiving period starts. Long term access to the TMF records needs to be covered in the contracts between parties. This includes:

- Clarity around storage formats, retention times,
- Agreements regarding the provisioning of requests for TMF content in case of inspection,
- catering for scenarios where parties may cease or change their operations and/or transfer their duties to another party (e.g., via mergers and/or acquisitions or going out of business).

As part of its oversight, the sponsor should assess risk for the foreseen sub-contracting, including, when deemed necessary, the conduct of a pre-contractual qualification audit. This process should be adapted based on predefined risk levels (e.g., criteria for low/medium/high risk profile services/tasks).

After selecting one TPV, the contractual agreement should ensure the right for the sponsor to audit and assess their record management mechanisms during and after the trial. The sponsor shall ensure adequate TPV support to deliver relevant documentation in case of inspection during the whole archiving period.

4.2 Procedure to manage non-trial specific records

The non-trials specific records are those not specifically produced for the trial. These are held within non-trial paper or electronic storage areas. These records can apply to many trials but are mandatory components of the TMF. These records are company or computer system related records, for example:

> Staff qualifications, operating procedures, equipment calibration, computing platform and/or application validation, log files, and TPV qualification.

4.2.1 Risks in practice

The non-trial-specific level documentation are held across multiple parties. Despite being essential to support the quality of the trial activities, such records may be insufficiently considered as part of the sponsor oversight. Checks should exist and be included as part of the trial-level TMF quality control activities. Without defining unique reference locations that are known, the risk is to have multiple co-existing versions. Contracted TPV may be unaware of their retention duties (even when contractually agreed which might lead to issues and finally potential mistakenly destruction before the retention period is lapsed). The TPV may experience difficulties to reach the sponsor archivist to provide guidance and arbitration on records desirable fate at the end of retention period.

4.2.2 Recommendations

Mechanisms to manage non-trial specific records shall be explicitly stated in written procedures, contractual agreements, or any other archiving management plan from the start of a trial and must state who is responsible. Such non-trial archiving management plan should be including the applicable documentation for each party and define their storage location, maintenance activity, and retrieval instructions. The sponsors must reconcile and maintain the continuity of all parties' knowledge about the TMF records. This is an essential part of the sponsor oversight.

For example, the TPV trial operating procedures relevant for the activities conducted by them during the trial, are part of the trial essential documentation. These records being the intellectual property of each company, are typically kept by each TPV. The sponsor must verify that each party can retrieve and deliver records in a timely manner, in case of inspection during the full retention period. According to ICH-GCP E6 (R2) this also applies to any sub-contractors of the TPV delivering GxP relevant services. This means the sponsor should periodically check, via audits or other mechanisms, that the contracts are sufficiently covering this aspect, and the sub-contracting oversight ensures this availability.

4.3 Overall TMF Inventory

4.3.1 Risks in practice

Some contributing entities involved in the archiving[3] may not be listed, nor documented in the Overall TMF Inventory which is guiding the archiving maintenance over time.

This may lead to the inability of the sponsor to retrieve the needed records without knowing where or how to find them.

4.3.2 Recommendation

An Overall TMF Inventory documenting all involved parties, their roles and responsibilities, records inventory, specific contact details, and locations shall be in place. This document should describe what are the specific records that are applicable to the trial at each legal entity.

The Overall TMF Inventory is paramount to manage the records. Each change in the trial should be evaluated for its risk impact to archiving and mitigated where relevant.

4.4 Change Management

4.4.1 Risks in Practice

Changes happening after the initial contract agreements during or after the trial, may not be assessed for their impact on TMF files/archives maintenance and accessibility. This can happen due to company merger, acquisition, going out of business, new/updated version of equipment/computerized system introduced, or major organizational changes. This may result in lack of detection in a timely manner that trial essential records access may be compromised.

4.4.2 Recommendations

The occurrence of the following list of sample events can lead to archives risk re-assessment for their potential impact on the archiving responsibilities and maintenance:

- Any change in contributing entities ownership e.g., acquisition or merger,
- Any change in contributing entities archiving responsibilities,
- Any change in the initial strategy for a specific clinical trial in the overall sponsor plan for registration dossier,
- Any change in the eTMF computerised system that requires migration of the records,
- Any reorganization or platform changes that affect archiving activities.

Such major trial operational changes, need to be implemented in a controlled manner by redefining the roles and responsibilities and adapting the trial plans/contracts accordingly.

Periodic document retrieval testing (e.g., mock-inspections and/or audits) are recommended to be conducted and documented:

- As part of the routine inspection readiness checks during the trial
- At time of active trial phase moving to trial archiving retention
- Regularly during the archiving phase
- At time of an inspection announcement/preparation
- At time of archives supporting media expected decommissioning.

It is essential to also review the record formats to confirm their continued suitability for future retrieval.

[3] Archiving shall be understood as paper and/or electronic.

4.5 Documenting decisions

During the clinical trial, decisions and associated rationales for those decisions must also be recorded and retained within the TMF. This can take many forms. Whilst stand-alone records are preferred, it is well known that emails, although not preferred, are used for documenting clinical trial decisions.

4.5.1 Risks in practice

The volume of records generated during a trial creates a risk of a specific decision being lost 'in the mass' of communications, and not easily and timely retrievable when not regularly maintained and when there is no specific template in place.

When managing unplanned events that call for unscheduled decision making, it is quite often that decision is not being documented adequately (i.e., in emails only). At the time of taking a decision, email may be the adequate method to ensure immediate notification to all involved parties, and quick implementation of a change. However, it may not be possible to retrieve such email when trying to re-construct the trial from evidence after some time has elapsed and the involved staff have changed.

4.5.2 Recommendations

Considerations must therefore be given by the various parties engaged in the clinical trial as to how such records for essential decisions must be retained within a TMF.

Archiving email correspondence could provide insight in the decision-making process. However, it needs to be considered whether an email can be attributed to its author without alterations, how to index emails to ensure easy and timely retrieval and whether the proprietary email format could be opened after a long period of time.

It is therefore recommended to maintain a decision log during the trial to document the main decisions and related rationale, which may cross-reference to additional source record if necessary (i.e., the email or meeting minutes); when the decision was made and distributed. Major decisions should evoke formal documentation with binding approvals to forestall any ambiguity.

4.6 Electronic devices

The clinical trial environment and conduct has tremendously changed over the past years due to an increased use of instruments, software, devices, and services in the creation, capture, or management of electronic clinical data.
These systems include but may not be limited to:

- Electronic Health Records (EHR),
- tools supplied to investigators/trial participants for recording clinical data by data entry (e.g., electronic Case Report Forms (eCRFs), Clinical Outcome Assessments (eCOAs)),
- tools for electronic files maintenance (e.g., eTMFs),
- site medical equipment's (e.g., Magnetic Resonance Imaging (MRIs) and Computerized Tomography (CT) scan,
- instruments supplied for automatic capture of events such as biometric measures (e.g., blood pressure),
- respiratory measures or Electrocardiograms (ECG) monitoring,
- and other tools such as genetic sequencing, e-Consent, Bring Your Own Device (BYOD) etc…

These systems can generate massive amounts of data which can be a more common risk. For example, wearable activity tracking devices normally measure hundreds of data points per seconds in all three axes, which is later 'translated' into a step or activity count by an algorithm. In addition, the documentation related to the set-up, maintenance, and usage of these systems (e.g., medical device calibration, computerized system validation, user access rights and training…) requires them to be part of the trial essential records, and to demonstrate the reliability of the data they produce.

4.6.1 Risks in practice

This is raising multiple "new" challenges to remain compliant to the applicable regulations as well as to evidence the integrity, confidentiality, and availability of relevant clinical information.
These include (but may not be limited to) risks with the ability to:

- Maintain dynamic formats over time,
- Ensure secure transfer of trial data and metadata from various sources in and between systems for analysis,
- Ensure consistency of data and metadata from various source,
- Ensure qualification and validation, including BYOD, and quality of the analysed datasets,
- Evidence data attributability and ALCOA + rules application,
- Determine the suitable raw data required for retention as well as the acceptability of the clinically meaningful instrument data[4],
- Ensure reliance of data integrity on existing medical device authorization(s).

4.6.2 Recommendations

It is recommended that only the clinically meaningful data is transferred for long-term archiving in the database. This will constitute the reference datasets used for trial analysis. There should be a documented assessment, to support the rationale of what derived data was assessed and defined as being source or relevant raw data with sufficient quality, versus what raw data was assessed as not relevant for analysis.

A thorough and regular risk analysis shall be performed to assess changes that might impact the data lifecycle. Not only the most recent data points or documents (static data/documents) should be retained, but the entire history as to the development of those data and documents needs to be available along with any changes. It is recommended to create a source data plan which describe the flow of data from the assessed source record to the dataset used for analysis including the transformational steps. The relevant metadata such as user roles and privileges, audit trail of users assigned to the trial, relevant access logs should be available to support reconstructing the data flow.

4.7 Archives management

The trial archives are the composite of many pieces being geographically and contractually distributed. Therefore, it is necessary to keep the control of each piece as part of the sponsor oversight.

4.7.1 Risks in practice

With the TMF being archived in a distributed manner at various involved parties may bare the risk that these are not managed in a controlled way. Multiple events may happen during the retention period, such as change happening at local affiliate may lead to records being managed in a siloed approach without sufficiently considering the impact.

Also, companies, including archiving facilities, may disappear from one day to the next, with critical data pieces from the registration dossier disappearing without the sponsor becoming aware or noticing in a timely manner.

4.7.2 Recommendations

It is recommended to select and maintain one supporting tool for the maintenance and continuous inventory of clinical trial archives, including TMF and non-trial specific records. A set of useful archives characteristics could be maintained:

[4] Position paper: §5.1, Trial Master File Archiving and the Decommissioning of Computerised Systems Used in Clinical Trials, version A, 08th February 2021.

- Map the information/materials that are maintained at the various archives contributing entities with clinical trial(s) referencing and indexing,
- Define a coordinating responsible role for each entity, with sufficient back-up,
- Map the contractual requirements at each archive location (including potential archives country-specific requirements), and plan for regular checks or transition during the retention period,
- Verify the contract states that the TPV will contact the sponsor in the event of demise or merger,
- Assign an archive risk score, apply mitigations, and monitor residual risk,
- Register the electronic archives media/supporting systems used to be able to proactively identify need for constraints based on format expiry date and anticipate upgrade/changes before records becoming unreadable,
- Most importantly, ensure that the inventory supporting tool remains viable for the retention period.

4.8 Legacy trials / Due Diligence

Sponsor and/or TPV(s) may be impacted by company changes such as merger/acquisition or reorganization events during the records archiving period. In such circumstances, staff responsible of the archived trials may not be aware of the above changes.

4.8.1 Risks in practice

Old clinical trials files may be inherited without sufficient information or evidence of their quality. It can also be that the party responsible for the records are not adequately taking care of their archiving duties. It also happens when clinical trials which were closed or discontinued at a time where not of relevance anymore, may later suddenly become relevant. Without staff historical knowledge of the trial, some TPV record parts may be unidentified/forgotten e.g., biomarker laboratory or technology provider.

The retrieval of the records created by TPV who were involved in these areas, especially for the non-trial specific records (i.e., TPV SOPs or staff qualification) may be difficult after years, especially if there were no adequate contractual requirements.

Another issue may be that legacy files which were not regularly checked during their retention period may no longer be readable.

4.8.2 Recommendations

At time of merger/acquisition or identification that legacy files may be of relevance, the **Overall TMF Inventory** should be assessed for completeness. In case of gaps, the review of the existing archives' structure should be considered for identifying all involved parties, roles and responsibilities, records, materials, contacts, and locations. This should be the basis to start assessing the content and consider additional mechanisms such as quality controls and/or audits. In case the **Overall TMF Inventory** or similar overview is not in place, this will need to be created to assess the completeness of the files, and risk-assessed their use in a regulatory submission for marketing application.

In case of legacy data format issues, a new viewer system may be needed.

The Archivist role is responsible to make sure that the data remains viable during the whole archives' retention period to address any inspection need.

4.9 Final destructions

The final decision for destruction of the complete trial archived records is complex considering the distributed nature of the content. All archive parties need to be notified with subsequent confirmation of destruction. When a TPV is needing to prematurely destroy their archive for business or other reasons, this needs to be a known activity with any remediation discussed upfront with the sponsor.

4.9.1 Risks in practice

Archives which are located at TPV are outsourced with an expiry date as per the contract signed with the sponsor. When unable to contact the known sponsor representative who can arbitrate the final fate of the archives upon expected termination of archiving period, this will definitively result in destroyed trial/ non-trial specific records located at the TPV.

TVPs need to maintain their designated essential records that may or may not be part of essential trial records. If this is not delineated in contract and subject to financial compensation, essential records located at the TPV may be destroyed right after contract period termination.

When there is insufficient control of the archiving activities, it is difficult to reconcile the various pieces of archives spread across locations and third parties. It allows TPVs to take the decision to finally destroy trial records, instead of being under sponsor oversight. In the case of non-trial specific records, these shall be maintained as remaining relevant for other sponsor purposes.

4.9.2 Recommendations

The '**Overall TMF Inventory'** should be considered for identifying **all** the TMF non-trial specific records that may be supporting any potential future regulatory submission.

The sponsor shall work with each TPV to define what records are globally needed for multiple trials so that there is adequate understanding what can and cannot be destroyed for any given trial.

The sponsor must maintain a way for an archivist to be reachable to address TPVs' questions during the archiving phase. Furthermore, the sponsor archivist must maintain the oversight and perform periodic checks of archives completeness and retrievability.

Understand that the sponsor may propose a contract succinctly stating that all their trial records must be maintained for 25 years. These contract clauses need to be refined to delineate specific requirements and compensation in concert with the here-in recommendations.

The overall implementation of the adequate archives oversight by the sponsor represents cost and resources which should not be neglected.

5 Conclusions

As largely demonstrated in this position paper, some principles shall be applied to managed clinical trial records while ensuring compliance with the current applicable guidelines for archiving and the current context of distributed TMF (involving multiples third parties) and digitalization of clinical trials records:

- Establish contractual terms for records management,
- Anticipate archives already since in-life trial retention period,
- Nominate sponsor coordinating and dedicated role(s) (archivist) and maintain those roles,
- Assess regularly and mitigate risk(s) that may impact records,
- Enforce the **overall TMF inventory** as the central governing document to manage records,
- Trace documented trial decisions and maintain their retrievability during the whole records lifecycle,
- Actively coordinate and communicate with archiving TPV.

To summarize, archives should be actively managed on a regular basis to ensure their permanent compliance and inspection readiness status.

This position paper was authored by the EUCROF and eClinical Forum Joint Task Force on Archiving and Decommissioning.

You can contact the task force via the EUCROF and eClinical Forum websites (www.eucrof.eu and www.eclinicalforum.org) if you would like more information or if you have any comments on the contents of this position paper.

Although the Task Force was initiated as a joint effort by EUCROF and the eClinical Forum, team members representing the following organisations have also participated in the authoring of this position paper:

- ECRIN - https://ecrin.org/
- The ePRO Consortium - https://c-path.org/programs/eproc/
- Medicines for Europe - https://www.medicinesforeurope.com/
- RQA - https://www.therqa.com/

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