Back to the TMF: Managing Your Documents Across Time and Space

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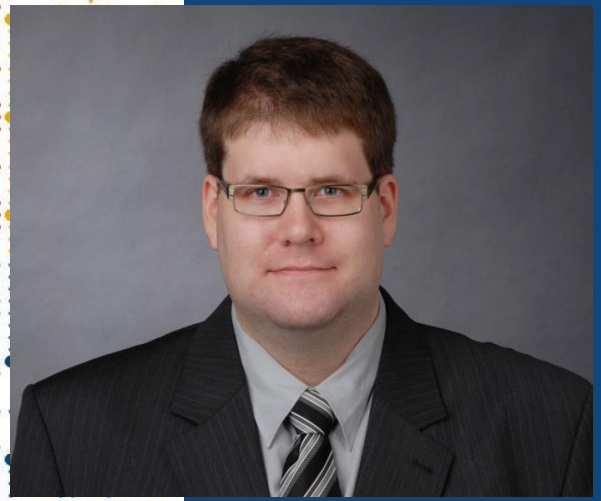

Meet the Speaker

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Dr Torsten Stemmler received his PhD in Biology (Neurobiology and Psychophysics) from the University of Bremen, Germany in 2011. He then moved to RWTH Aachen, where he worked as a post-doc on visual perception. He retrained as a Data Manager and developed database solutions at the University Hospital Aachen. In 2017, he joined the Federal Institute for Drugs and Medical Devices as a GCP Inspector.

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Introduction: Significance of the Trial Master File in Clinical Research

A Trial Master File is the 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 that the sponsor and the investigators/institutions have conducted the trial in accordance with the applicable regulatory requirement(s) and the principles and standards of GCP. *Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)**

The documents and records in the TMF should collectively permit confirmation of protocol and GCP compliance and the integrity of the data collected without the need for additional explanation by the sponsor, CRO or investigator/institution staff.

*Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)**

Key Point: All relevant trial events and decisions can be reconstructed with a well maintained TMF.

*Source: EMA Homepage: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-and-archiving-clinical-trial-master-file-paper-and/or-electronic_en.pdf

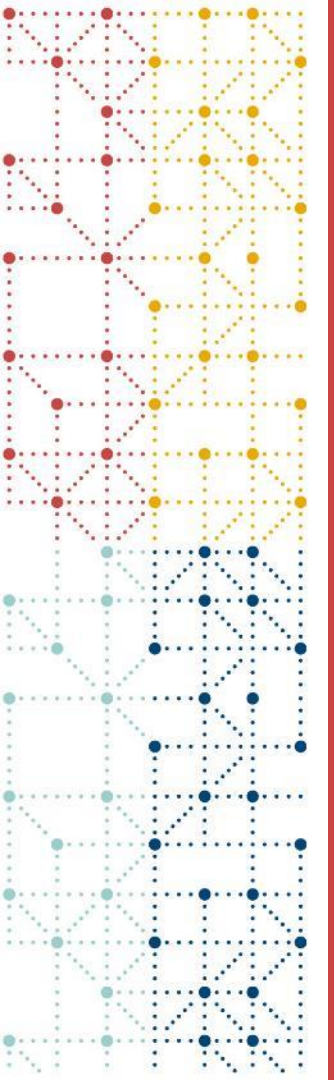
Importance of the TMF

An accurately maintained TMF ensures that the rights, safety, and well-being of trial participants are protected and that the clinical data generated are reliable and can be verifiable.

The TMF is a key tool for auditors and regulatory authorities, e.g. inspectors, to use to verify that a trial has been conducted according to the relevant laws and regulations and the trial protocol.

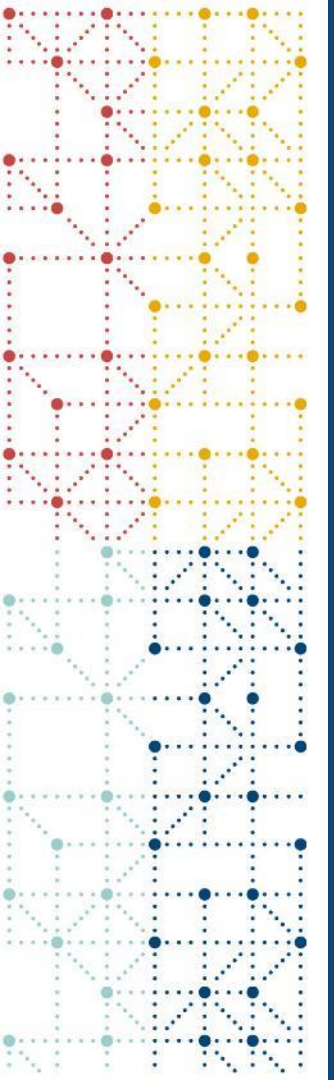
The interview will not correct missing or incomplete documentation; if it is not documented, it may as well not have happened.

The TMF is our DeLorean, taking us back to any point in the clinical trial to make sure everything is in order.



The goals of our journey

1. **Back to the TMF**: Some basic
2. **88 miles per hour**: ICH E6 R2 vs. R3
3. **Where we are going, we do not need roads**: Challenges
4. **The future is what you make it**: Smart use of information



Back to the TMF

Some fundamentals

Time Travel and the TMF: Parallels between time travel in sci-fi and TMFs role

Revisiting the events: This ensures that the events have taken place and have taken place in the correct order. Allows verification of trial the conduct and adherence to good clinical practice.

Confirming data: The data and metadata that are part of each record allow the integrity and quality of the data to be verified and validated. In particular, if the authorship and temporal reference are traceable and preserved.

Data traceability: Ensuring the traceability of changes and corrections also provides evidence of the authenticity and credibility of documents. The ability to reconstruct the life cycle of documents.

Well-preseved contemporary documents are a good substitute for first-hand experience.

TMF management is a complex undertaking that requires proper preparation and consideration

During inspections, we come across different filling strategies:

- Gravimetric filling: Documents are stacked as they are received and used. Rarely used documents are placed on the floor.

- Temporal filling: Documents are arranged according to a specific time in relation to the document (e.g. version date, last signature, postmark, etc.).

- Structured filing: Documents are classified according to their content and relationship to other documents. Documents are indexed for easy retrieval. [This is by now the norm.]

Keep in mind that a file that is not found is a file that is lost.

The Tale of the two TMFs

The TMF usually consists of a sponsor TMF, which is maintained by the sponsor organisation, and an investigator TMF, which is maintained by the investigator/institution.

*Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)**

The investigator TMF:

- Typically consists of paper or electronic records in a variety of file folders.
- Typically the monitor implements a filing structure at the site.
- Typically the monitor updates the TMF prior to inspection.

The sponsor´s TMF

- Usually consists of a dedicated TMF system
- Usually follows a reference model (e.g. CDISC)
- Typically has a peak of activity in the system prior to inspection

*Source: EMA Homepage: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-and-archiving-clinical-trial-master-file-paper-and/or-electronic_en.pdf

One TMF to Rule the Trial, One TMF to find the Data, One TMF to bring them all and in compliance bind them. In the Land of research were the Evidence lies

Forming a TMF can be compared to solving a puzzle with an unknown number of pieces and without edges. However, with careful consideration and attention to detail, it can be achieved with confidence.

- When starting a clinical trial, the sponsor and the investigator/institution should identify and maintain a record of the location(s) of all the potential documentation that is considered to form the TMF, even if multiple locations, departments, country organisations and systems are involved.
- There should be a primary TMF system for holding essential documents, which may be entirely electronic, entirely paper-based or a hybrid of both.
- There may be other systems, including central systems, that hold essential documents relevant to the trial and should therefore be part of the TMF.
  *Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)**

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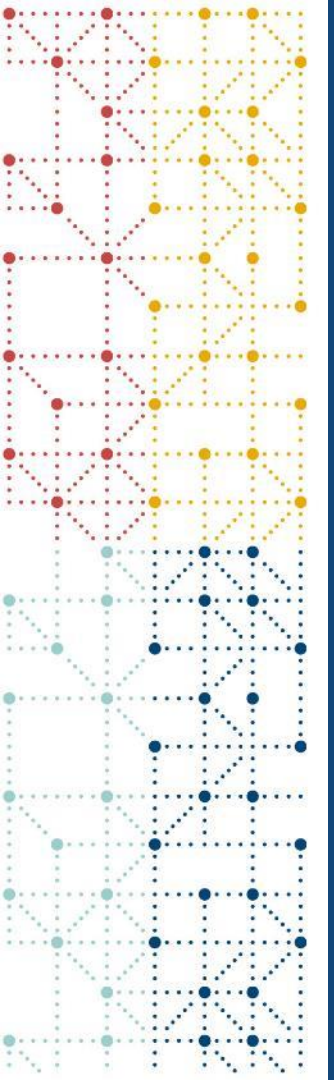

88 miles per hour

ICH E6 R2 vs. R3

Hitting 88 miles per hour: What is essential?

Documentation

All records, in any form ([…]) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken. ICH E6 R2*

Essential documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced […]. ICH E6 R2*

New: Essential Records

Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements […]. ICH E6 R3 Step 2b

*Source: EMA Homepage: https://www.ema.europa.eu/en/ich-e6r2-good-clinical-practice-scientific-guideline

ICH E6 R2 becomes R3

ICH E6 R2

Documents permit evaluation:

Conduct of a study

Quality of data

ICH E6 R3

Essential records are documents and data and metadata

Facilitate the ongoing management

Evaluation of the methods used,

Evaluation the factors affecting a trial,

Evaluation the actions taken during the trial,

- to determine the reliability of the trial results

The verification that the trial was conducted,

- in accordance with GCP

- in accordance with applicable regulatory requirements

The change in the definition is not only the merger of different definitions in ICH E6, but also emphasizes the living nature of records in a clinical trial landscape.

The Chapter 8 of ICH E6 R2

The various documents are grouped into three sections according to the stage of the trial at which they are normally generated:

1) before the start of the clinical phase of the trial,

2) during the clinical conduct of the trial, and

3) after completion or termination of the trial.

Trial master files should be established at the start of the trial, both at the investigator´s/institution’s site and at the sponsor's office.

[…] Essential documents for the trial should be supplemented or may be reduced if justified (prior to initiation of the trial) on the bases of the importance and relevance of the specific documents to the trial.

The following minimum list of essential documents has been developed.

Examples of documents that are considered essential when generated for a specific trial, but are not listed in section 8 of the ICH GCP guideline, include:

- completed trial-related forms, checklists, reports, etc. related to the trial, generated by the sponsor, investigator, or any third party performing trial activities on their behalf; quality system procedures;
- qualified person certification of the IMP;
- assay method validation report for the analysis of the IMP or metabolite(s) in clinical samples;
- advanced therapy investigational medicinal product (ATIMP) traceability documents;
- documentation demonstrating the validation of trial-specific computer system builds (e.g. electronic case report form (eCRF) and interactive response technologies (IRT) and electronic patient reported outcomes);
- data management documentation, e.g. data management plan, data validation plan and minutes of data review meetings;
- statistics documentation, e.g. SAS programme validation, statistical analysis plan and sample size estimates;
- delegation log as part of the investigator/institution TMF.

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Examples of documents on the minimum list of essential documents whose presence is a condition:

- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)
- INSURANCE STATEMENT (where required)
- REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)
- DECODING PROCEDURES FOR BLINDED TRIALS
- MASTER RANDOMISATION LIST
- RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)
- AUDIT CERTIFICATE (if available)

Others are required for paper-based processes:

- SIGNATURE SHEET

The concept that there is a minimum list of documents required has led to various problems in the past:

- Essential trial documents were not recognised as such and not maintained or available for inspection
- Essential trial procedures or trial conduct was not recorded, e.g. temperature log for IMP shipment
- Recruitment of trial participant was not documented as it was not considered to be trial-related
- Original trial data were not retained as the database was decommissioned and only flat file pdfs were filled
- Files were kept under a different name and were not made available during the inspection
- Documentation was created for the sole purpose of filling in the TMF.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.1.1 Many records are generated before and during the conduct of a clinical trial. The nature and extent of those records generated and maintained are dependent upon the trial design, its conduct, application of proportional approaches and the importance and relevance of that record to the trial.

C.1.2 Determining which records are essential will be based upon consideration of the guidance in this appendix.

C.1.3 The essential records permit and contribute to the evaluation of the conduct of a trial and the reliability of the results produced.

They are used to demonstrate the investigator's and sponsor's compliance with Good Clinical Practice (GCP) standards and applicable regulatory requirements.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

- The essential records are used as part of the sponsor´s oversight or investigator´s supervision of the trial.
- These records will be used by the sponsor's independent audit function and during inspections by the regulatory authority(ies) to assess the conduct of trial and the reliability of the trial results.
- The investigator/institution should have access to and the ability to maintain and retain, the essential records generated by the investigator/institution before, during, and after the trial.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.2 Management of Essential Records

C.2.1 Records should be identifiable and version controlled, and should include authors, reviewers and approvers as appropriate, along with date and signature (electronic or wet ink), where necessary.

C.2.2 For activities that are transferred or delegated to service providers by the sponsor or investigator/institution respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial.

C.2.3 These essential records should be maintained in or referred to from repositories, including, for example, the trial master file (TMF) or investigator site file (ISF). The TMF is held by the sponsor or by the investigator; in the latter case, it is often called the ISF.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.2 Management of Essential Records

C.2.4 The sponsor and investigator/institution should maintain a record of where essential records are located, including source records. The storage system(s) used during the trial and for archiving (irrespective of the type of media used) should provide for appropriate identification, version history, search and retrieval of trial records.

C.2.5 The sponsor and investigator/institution should ensure that the essential records are collected and filed in a timely manner, including those required to be in place prior to the trial start, which can greatly assist in the successful management of a trial.

C.2.6 The sponsor and investigator/institution should retain the essential records in a way that ensures that they remain complete, readable and readily available and are directly accessible upon request by regulatory authorities. Alteration to the essential records be traceable.

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.2 Management of Essential Records

C.2.7 The original version of the essential record should be retained by the responsible party (sponsor or investigator). When a copy is used to permanently replace the original essential record, the copy should fulfil the requirements for certified copies.

C.2.8 In order to fulfil their responsibilities in the conduct of the trial, the sponsor and investigator/institution may need access to or copies of one another's relevant essential records before, during and after the trial is completed. This will determine whether the record resides in the repositories of the sponsor, the investigator/institution, or both. There should be careful consideration of sharing of records subject to data protection legislation and blinding considerations in line with applicable regulatory requirements. For the sharing of essential records with service providers, see section C.2.2.

C.2.9 Certain essential records may not be specific to a trial but may be related to the systems and processes involved in running multiple trials and retained outside the trial-specific repositories (e.g., standard operating procedures validation records, master services agreements).

Appendix C. ESSENTIAL RECORDS FOR THE CONDUCT OF A CLINICAL TRIAL

C.3 Essentiality of Trial Records

C.3.1 Whether a specific clinical trial record generated before, during and after the trial is essential and needs to be retained should be based on the following criteria:

(a) Is a document that is submitted to or issued by the regulatory authority or IRB/IEC, including related correspondence and those documenting regulatory decisions or approvals/favourable opinions;

[…]

(n) Contains the data as well as relevant metadata that would be needed to be able to reconstruct the trial;

[…]

(z) Documents the recruitment, pre-trial screening and consenting process of trial participants and their identity and chronological enrolment as appropriate;

[…]

Let’s go back to the TMF

ICH E6 R2	**ICH E6** R3
The minimal list could still be reduced	The section list C3.1 can still be reduced
The lists are non-exhaustive	The lists are non-exhaustive
The list provide orientation	The list provide orientation
Document management	Detailed expectations on document management
Living system	Living system
Data quality	Data reliability

Higher emphasizes on Fit for purpose and proportionality

Where we are going, we do not need roads

Challenges

The never-ending TMF

My colleagues and I have learned over the years: What matters depends on your point of view.

Clinical Trial management

Monitor

Service Providers

Investigator

Auditor

Inspector

Ensure that you consider the needs of each stakeholder when setting up your TMF system and creating a reference model for structured filling. Involve stakeholders in the development. Ask the big question: **Is it fit for purpose?**

The inspectors' odyssey: Navigation a Universe of TMF Systems

What makes a system useful:

- all essential documents generated are available in the TMF;
- documents filed in the appropriate places;
- documents added to the TMF in a timely manner;
- documents are indexed correctly;
- relevant metadata is maintained (e.g. creation, modification, review, approval, transfer)
- Audit trail and metadata (for eTMF) can be reviewed.

What could possibly go wrong?

Minor:

The following observations were made about the documentation on site:

- Discrepancies in information due to redundant documentation
- Investigators summaries were often out of date or inconsistent with other source data
- The administration of study medication was not recorded in the electronic patient records (source data).

What could possibly go wrong?

Major:

The eTMF of the sponsor […] is part of […] software system and is based on […], which was released in […]. Primary support ended […] and End-of-Life was reached on […]. The sponsor only provided a […] as proof of support prolongation until […], the file has been created on […]. The support status of the […] system is unclear. System migration is planned for […]. Based on lack of evidence provided by the sponsor, the inspection team cannot confirm that the continued use of […] does not pose an imminent threat to essential document retention.

What could possibly go wrong?

Major:

The process of migrating the eTMF from […] to […] and to […] did not consider the audit trail information or the metadata of files migrated. The original audit trail was not migrated and file information was changed during staging by re-naming and conversion. Any modification in transit/staging by […] were not kept in an audit trail, which was part of the current eTMF. Hence, verification of document history in the current eTMF is not possible for documents created under […] sponsorship. This is problematic given that inspectors would not be able to directly access the complete audit trail and in a reasonable setting.

In addition, the access of the current sponsor […] to the eTMF was only granted to one […] member in […], nearly one year after eTMF transition was completed, making it questionable that the sponsor had uninterrupted access to the "primary" eTMF for the whole sponsorship duration.

- .

What could possibly go wrong?

Critical:

During the inspection, a file corruption issue was noted (inability to access a stored document). According to the explanations provided, this issue was related to the migration process from […] to […] and was known to the sponsor. It was decided not to take corrective action due to the limited number of issues (3360 files out of 7.8 million documents).

Although […] investigations during the inspection suggest that the number of relevant corrupted files is limited to 2290 documents […], migration from one system to another cannot result in loss of information.

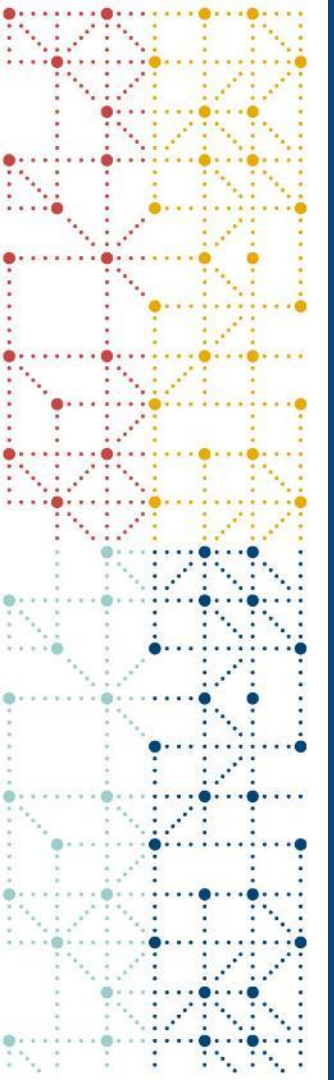
In addition, the inspectors noted that although the legacy audit trial was preserved during the migration, it cannot be considered intelligible to non-IT/database specialists.

What could possibly go wrong?

Strange:

- e) It was noted that the GCP inspectors did not have access to all eTMF documents prior to and at the beginning of the inspection. This was noted during the inspection of […] documents (paper vs. electronic). Note: The access was subsequently adjusted, whereby in return the UAT test access for the inspectors disappeared. The explanation provided by […] in the Clarification Form for Inspection Requests does not sufficiently clarify the matter.
- f) The [QA] has only had access to the eTMF ([…]) since […]. According to the [QA], she does not use this access as a matter of principle.
- g) In the eTMF, the user "[…] User" (status in the system: Approved and passed) was identified for a document (Doc: […]) as part of the audit trail. It is unclear who this user is.
- h) In the audit trail for a file in the eTMF (unblinded), the name of a user was found who was not listed on the user list provided by the sponsor. The reason for this was that her type of access (blanket) was not recorded.[…]: There was an unknown number of users with access to the eTMF part of the sponsor, which was not evident from the sponsor documents*.

It turned out **all** staff members of the service provider had access to the unblinded TMF



The future is what you make it

Smart use of information

Great Scott! The AI Document Evolution

A tier 1 smart TMF system

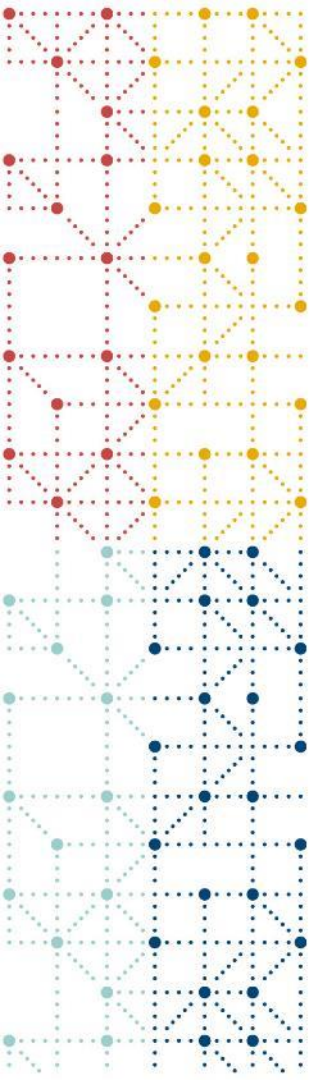
- is able to classify documents based on content
- is able to index documents accurately
- is able to infer whether Metadata is intact
- is able to predict the existence of documents and to provide a list of expected documents

A tier 2 smart TMF system

- is able to retrieve documents based on prompts, e.g. smart search
- is able to perform consistency checks between documents
- is able to answer questions about the trial

A tier 3 smart TMF system

- is able to create relevant documents based on the **information available** in the system at the time of the query.



Thank You!

If you have any questions, please do not hesitate to ask

cdisc