Nachvollziehbarkeit der Studiendurchführung – Trial Master File

BfArM im Dialog
Aktuelle GCP Anforderungen in klinischen Prüfungen

Bonn
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Agenda

- Einführung
- Arrangements für den Trial Master File in laufenden klinischen Prüfungen bei der Involvierung multipler Dienstleister
  - Nachvollziehbarkeit des Studienmanagements und der Aufgabenabgrenzungen zwischen Sponsor und Auftragsforschungsunternehmen / Serviceerbringern
- Arrangements zur Archivierung von Unterlagen und Daten nach Studienende
  - Archivierungsfristen: Sponsor / Investigator und Marketing Authorisation Holder (MAH)
  - Archivierung dynamischer Daten
- Häufige Fragen
- Zusammenfassung
- Anhang: Fragebogen zur BVMA-Umfrage

Einführung

Wichtige Dokumente für den Vortrag

ICH-GCP (R2)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 December 2016
EMA/CHMP/ICH/135/1995
Committee for Human Medicinal Products

Guideline for good clinical practice E6(R2)
Step 5

Adopted by CHMP for release for consultation	23 July 2015
Start of public consultation	4 August 2015
End of consultation (deadline for comments)	3 February 2016
Final adoption by CHMP	15 December 2016
Date for coming into effect	14 June 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

06 December 2018
EMA/INS/GCP/856758/2018
Good Clinical Practice Inspectors Working Group (GCP IWG)

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

Draft adopted by GCP Inspectors Working Group (GCP IWG)	30 January 2017
Start of public consultation	12 April 2017
End of consultation (deadline for comments)	11 July 2017
Final revised document after comments received from public consultation adopted by GCP Inspectors Working Group (GCP IWG)	06 December 2018
Date of coming into effect	6 months after publication

06 June 2019

EU (e)TMF Guideline

Essential Documents / (e)TMF

1.23 Essential Documents (ICH – GCP (R2))

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

2. Introduction (EU (e)TMF Guideline)

A TMF is the 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.

Essential Documents = (e)TMF

Investigator and Sponsor Responsibilities according to ICH-GCP (R2)

2. The Principles of ICH-GCP

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. This principle applies to all records referenced in this guideline, irrespective of the type of media used.

4. Investigator

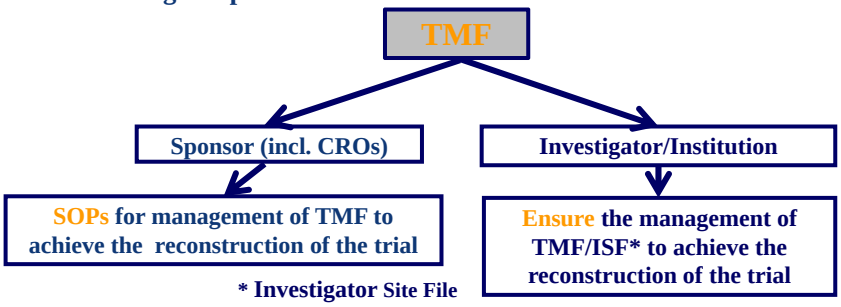
4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

5. Sponsor

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

EU (e)TMF Guideline

3.1 Sponsor and Investigator Trial Master File
There should only be one TMF for a clinical trial, comprising the sponsor and investigator parts.



*** Investigator Site File**

2. Introduction
The legislation does not differentiate between paper and electronic TMFs (eTMFs). Therefore, all basic requirements are the same for both formats or when used in combination as a hybrid TMF.

Digitalisierter Paper TMF vs eTMF

Ein digitalisierter Papier TMF ist
NICHT
äquivalent zu einem eTMF

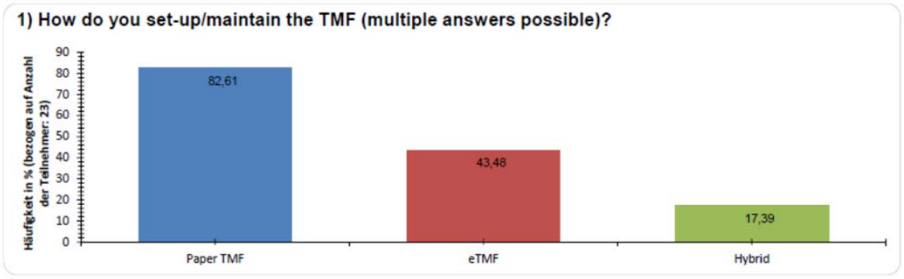
➔ **Ein eTMF muss die ICH-GCP Anforderungen an elektronische Systeme erfüllen, u.a. Implementierung eines audit trails**

(siehe ICH-GCP 5.5.3 und EU (e)TMF Guideline 4.1.2)

BVMA Umfrage

Ergebnisse

Optionen	Anzahl	Häufigkeit nach Teilnehmer	Häufigkeit nach Antworten
Paper TMF	19	82.61%	57.58%
eTMF	10	43.48%	30.30%
Hybrid	4	17.39%	12.12%
Gesamt	33 Antworten	23 Teilnehmer	



ICH – GCP (R2)

8. Essential Documents for the Conduct of a Clinical Trial

Introduction

…

The minimum list of essential documents which has been developed follows. (Text in R1 (and R2))

Addendum

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial. (Text in R2)

ICH – GCP (R2)

Introduction (ICH-GCP (R2))

….

In the event of any conflict between the E6(R1) text and the E6(R2) addendum text, the E6(R2) addendum text should take priority.

Risk-based approach with respect to TMF content (not with respect to retention period!)

4.2. Quality of trial master file (EU (e)TMF Guideline)

Article 57 of the Regulation states *"The clinical trial master file shall at all times contain the essential documents"*.

….

In addition, the sponsor should ensure the TMF is readily available and directly accessible to the competent authority, e.g. for inspection purposes.

Risk-based Content of the (e)TMF

3.5.1 Essential Documents (EU (e)TMF Guideline)

Article 57 of the Regulation states that the TMF essential documents' content shall take into account "all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial". Therefore, some documentation specified in the ICH GCP guideline may not be necessary due to the implementation of a risk proportionate approach. The justification for reducing documentation should be documented in the TMF.

EU (e)TMF Guideline

3.5.1. Essential documents (cont.)

…

The documentation listed in the ICH GCP guideline section 8 defines the documents that are considered essential (as appropriate to the trial) … ; however, this list should not be used as a definitive checklist for TMF content. It is not an exhaustive list. Depending on the activities being carried out, many trials require additional documents not specifically mentioned, therefore the sponsor and/or investigator/ institution should include any documentation that facilitates reconstructing and evaluating the trial conduct, as part of the TMF.

Essential Documents according to ICH-GCP (R2)

ICH-GCP Section 8 (Auszug)
ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.18	MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

Additional Essential Documents to be considered according to EU Guideline on (e)TMF

- completed forms, checklists and reports etc. related to the trial, generated from following quality system procedures of the sponsor, investigator or any third-party performing trial activities on their behalf;
- qualified person certification of the IMP;
- assay method validation report for analysis of IMP or metabolite(s) in clinical samples;
- advanced therapy investigational medicinal product (ATIMP) traceability documents;

Additional Essential Documents to be considered according to EU Guideline on (e)TMF

- documentation to demonstrate validation of trial-specific builds of computer systems (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 data-review meeting minutes;
- statistics documentation, e.g. SAS program validation, statistical analysis plan and sample size estimations;
- delegation log as part of the investigator/institution TMF.

DIA TMF Reference Model

Trial Master File Reference Model

TRIAL MASTER FILE TMF REFERENCE MODEL

User Guide

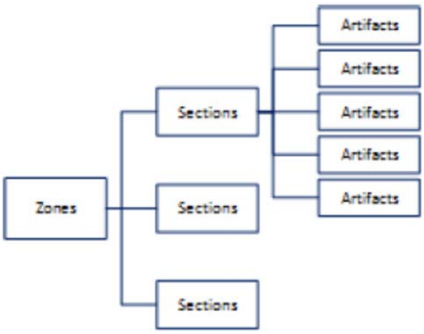
16-Mar-2018

DIA TMF Reference Mod

Trial Master File Reference Model

11 Zones

1. **Trial Management**
2. **Central Trial Documents**
3. **Regulatory**
4. **IRB/IEC and other approvals**
5. **Site Management**
6. **Investigational Product (IP) and Trial Supplies**
7. **Safety Reporting**
8. **Centralized and local Testing**
9. **Third Parties**
10. **Data Management**
11. **Statistics**



Audit Trail

1.9 Audit Trail (ICH – GCP (R2))

Documentation that allows reconstruction of the course of events.

- ➔ **Data Trail / Edit Trail (➔ (e)CRF, (e)Source)**
- ➔ **System Access Trail (➔ log-on, log-off, by whom, when)**
- ➔ **Decisions (➔ situation, reasoned grounds/rationale for decision making)**
- ➔ **Trial Activities (➔ what, when, by whom, why (e.g., based on SOPs, based on decisions)**

Die Gesamtheit der in Dokumenten enthaltenen Information, die die Rekonstruktion der klinischen Prüfung unterstützt.

MHRA
GCP Inspections Metrics Report, 11 May 2018

Data Integrity

It was found during the site inspection that the Electronic Health Records (EHRs) and the paper source data used on the trial had several significant deficiencies, for example; it was not possible to verify who completed them, when they were completed, who had been making changes and why. Entries into the EHRs could be deleted and amended. The EHR audit trails had not been reviewed by the monitor or sponsor prior to the trial start and there was only evidence that the monitor had logged onto the EHR on one date. The audit trail provided for the EHR was limited and deficient as it did not show what type of changes were being made, i.e. if the entries were new, deletions or amendments. Due to these deficiencies integrity of the data could not be confirmed.

Audit Trail of Trial Documents

Beispiel:

3.5.2. Superseded documents (EU (e)TMF Guideline)

…

During a document's development (e.g. clinical trial protocol development and release), the sponsor's/CRO's procedures may require input and review by various functions. The documentation to demonstrate that the process was followed should be retained.

Input der verschiedenen "functions" muss ebenfalls nachvollziehbar sein

MHRA
GCP Inspections Metrics Report, 11 May 2018

A critical finding was given to a commercial sponsor for Record Keeping/Essential Documents as the Trial Master File (TMF) had a number of issues with finding and accessing documents in the eTMF, as evidenced below:

- The inspector requested documents that could not be located in the eTMF. Despite the assistance of the study team and the eTMF experts, not all these documents could be found over the 4-day inspection, and those that were provided took two days to locate.

.....

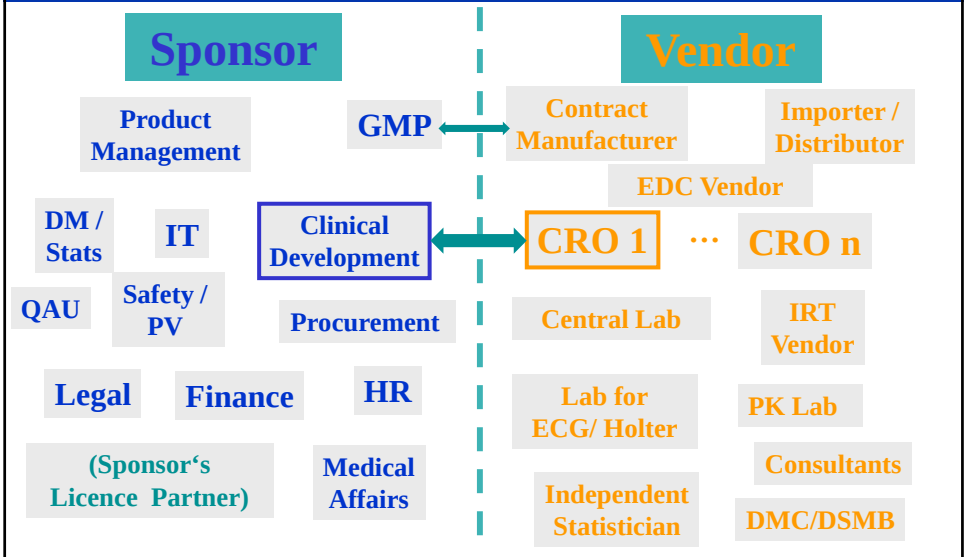
- There were many documents missing from the eTMF, for example, signature sheets, correspondence, emails and previous versions of documents.

.....

Arrangements für den Trial Master File in laufenden klinischen Prüfungen bei der Involvierung multipler Dienstleister

Sponsor und Dienstleister / Vendor

Szenario



ICH – GCP (R2)

8. Essential Documents for the Conduct of a Clinical Trial

Introduction

The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

EU (e)TMF Guideline

3.4. Trial master file structure

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 several locations, departments, country organisations and systems are involved. There should be a primary TMF system for holding essential documents, ...

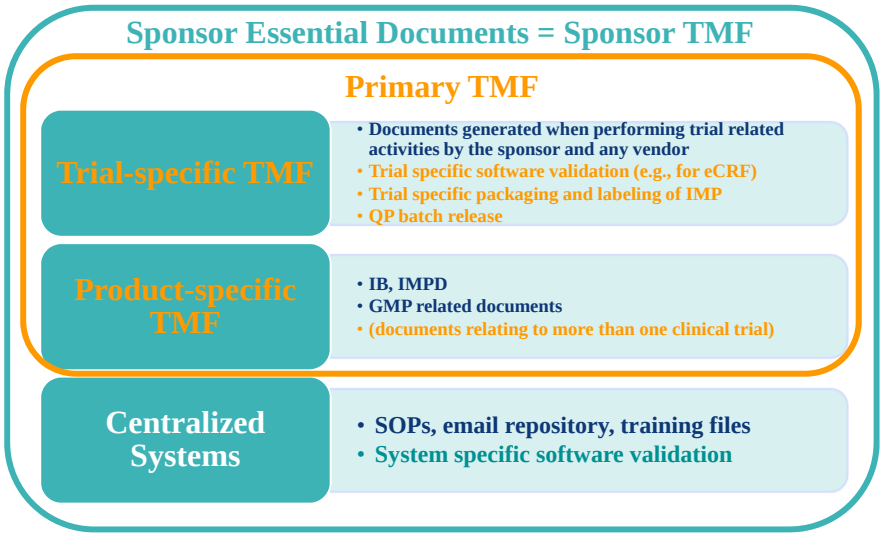
EU (e)TMF Guideline

3.4. Trial master file structure (cont.)

…..

Other systems including central systems may exist that hold essential documents (e.g. a central e-mail repository, SOP-management system, central training records, delegation logs, software validation records and records concerning more than one trial, e.g. investigator's brochures (IB)) relevant to the trial and should therefore be part of the TMF. The number of these other systems should be minimised with the priority focused on placing documents in the primary TMF system. Documents applicable to multiple trials do not need to be duplicated in several TMFs.

Decentralized Sponsor TMF



MHRA
GCP Inspections Metrics Report, 11 May 2018

Record Keeping/Essential Documents

The TMF was presented as a paper TMF for inspection. However, the TMF did not contain all the essential documents required to enable the reconstruction of trial events and demonstrate compliance with the regulations and the organisation's own quality system. Several essential documents were retained within different electronic systems which were not defined to be part of the TMF and to which inspectors were not provided direct access (even with a guide user). The TMF had not been fully defined to include all the ancillary systems and the documents located within them. Where the TMF maintenance had been contracted out to a third-party contractor, there was limited information available in the organisation's own files to demonstrate effective oversight of clinical trial activities to fulfil its obligations as a sponsor.

Nachvollziehbarkeit des Studienmanagements und der Aufgabenabgrenzungen zwischen Sponsor und Auftragsforschungsunternehmen / Serviceerbringern

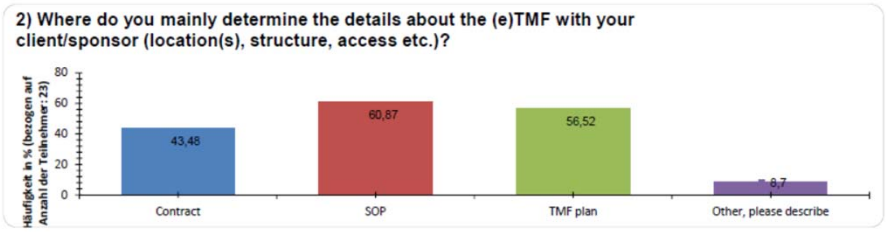
Schnittstellenmanagement

- ➔ **Aufgabenabgrenzung**
  (Task Allocation List (TAL), FDA: Transfer of Obligations)
- ➔ **Verträge**
- ➔ **SOPs**
- ➔ **Studienspezifische Pläne (Functional Plans)**

BVMA Umfrage

Ergebnisse

Optionen	Anzahl	Häufigkeit nach Teilnehmer	Häufigkeit nach Antworten
Contract	10	43.48%	25.64%
SOP	14	60.87%	35.90%
TMF plan	13	56.52%	33.33%
Other, please describe	2	8.70%	5.13%
Gesamt	39 Antworten	23 Teilnehmer	



Task Allocation List - Beispiel

TASK Allocation List for Clinical Trial: <Title>

Task	Task of (✓)				Comments
	Sponsor	CRO	Other Vendor (please specify)	NA	
Trial Document Preparation and Maintenance					
1. Design protocol	✓				Co-operation, joint task
2. Write protocol (English language) including protocol synopsis		✓			Relevant literature and guidelines to be provided by Sponsor
3. Review, comment on and approve protocol	✓				Two Review Cycles
4. Translate protocol synopsis into German language		✓			For Ethics Committee
5. Write protocol amendments		✓			Assumption: A total of 5 protocol amendments
6. Review, comment on and approve protocol amendments	✓				Two Review Cycles each
7. Design eCRFs (incl. questionnaire for QoL, e.g., xxx Index) and CRF completion guidelines		✓			
8. Review, comment on and approve CRF (User Acceptance Test)	✓				Two Review Cycles
9. Develop Informed Consent Form (German Language)		✓			Only sites in Germany planned at this stage
10. Review and comment on and approve Informed Consent Form	✓				Two Review Cycles
11. Prepare and maintain Paper Trial Master File according to DIA Reference Model		✓			
12. Prepare and maintain Investigator Site File according to DIA Reference Model		✓			

Reicht nicht aus!

Verträge - Beispiel

➔ **Beispiel 1**

All relevant files are expected to be returned to <Sponsor> at the conclusion of the study. Costs for off-site long-term storage or archiving by <CRO> have not been included.

Reicht nicht aus!

Verträge - Beispiel

- **Beispiel 2**

  Das CRO erlaubt <Sponsor> oder einem durch <Sponsor> benannten Beauftragten die Durchführung von Audits in allen Einrichtungen der CRO, welche an der Erfüllung der Aufgaben gemäß der Verantwortungsabgrenzung beteiligt sind. <Sponsor> und/oder dessen Beauftragter ist berechtigt, Einsicht in alle mit der Durchführung der klinischen Prüfung in Zusammenhang stehenden Daten und Aufzeichnungen, auf welchem Speichermedium auch immer, zu nehmen.

  Besser, aber reicht immer noch nicht aus!

  ….

  Für den Fall, dass die zuständigen Behörden eine Inspektion bei <Sponsor> ankündigen bzw. durchführen, wird das CRO nach entsprechender Anfrage durch <Sponsor> bei einer solchen Inspektion anwesend sein und <Sponsor> in allen Belangen bei der Durchführung der Inspektion unterstützen. Insbesondere sind die erforderlichen Studienunterlagen zur Verfügung zu stellen .

  ….

EU (e)TMF Guideline

3.2 Contract Research Organizations

The sponsor may choose to outsource duties and functions of the sponsor to a CRO. The sponsor remains responsible for the trial and will need to maintain oversight. Therefore, access to the CRO maintained part of the sponsor TMF (e.g. by remote access to an eTMF) or at least regular access to relevant documents from it will be necessary to fulfil these responsibilities effectively. ….

The clinical trial contract/agreement and other documents and procedures agreed between all parties should outline the arrangements for the TMF in some detail, such as:

EU (e)TMF Guideline

- ➔ which party holds the TMF (or which party holds which parts of the TMF when this is divided);
- ➔ the structure and indexing of the TMF;
- ➔ the access arrangements for the involved parties;
- ➔ when an eTMF is being used, the details of the system and change control management;
- ➔ lists of applicable procedures to be followed and training requirements;
- ➔ type of documents that each party should retain;
- ➔ arrangements for managing correspondence;

EU (e)TMF Guideline

- ➔ how the TMF would be made available to the competent authorities;
- ➔ arrangements for when the trial is completed (the CRO may archive the TMF [or parts thereof] on behalf of the sponsor); if there is a contractual arrangement for the CRO to transfer all essential documents they have generated to the sponsor for archiving, the arrangement should ensure the sponsor retains the full set of documents and makes it readily available and accessible for inspections (including inspections related to the CRO's duties and functions);

EU (e)TMF Guideline

- ➔ **arrangements for oversight of the TMF performed by the sponsor and how this would be achieved (e.g. audit reports and/or monitoring);**
- ➔ **retention times;**
- ➔ **arrangements regarding the archiving of and access to data/documents held in centralised systems (such as central training documents and central e-mail repository);**
- ➔ **procedures in case of an involved party closing down its business for any reason.**

MHRA
GCP Inspections Metrics Report, 11 May 2018

- It was not clearly defined in agreements with the trial Sponsors the scope of the Trial Master File (TMF) that was required to be held by the CRO i.e. the whole TMF or parts of the TMF in relation to the activities delegated to the CRO.

MHRA
GCP Inspections Metrics Report, 11 May 2018

A critical finding was given to a commercial sponsor for Record Keeping/Essential Documents as the Trial Master File (TMF) had a number of issues with finding and accessing documents in the eTMF, as evidenced below:

- Documents were not filed consistently or correctly with documents at the inappropriate level of the TMF (e.g. Product Level vs Study Level.)

- The eTMF was incomplete and unreliable with emails incomplete, duplicate documents, blank/incomplete documents, the same name for many different documents, same document under different names and in different locations and missing documents.
- The eTMF management SOP required that there be monthly QC of all eTMFs at a study level, but this was not occurring.
- The audit trails for all 5 eTMFs reviewed during the inspection showed there was a large number of documents uploaded following the inspection notice prior to the inspection showing the eTMFs were not being updated regularly and therefore were not being kept in an inspection ready state.

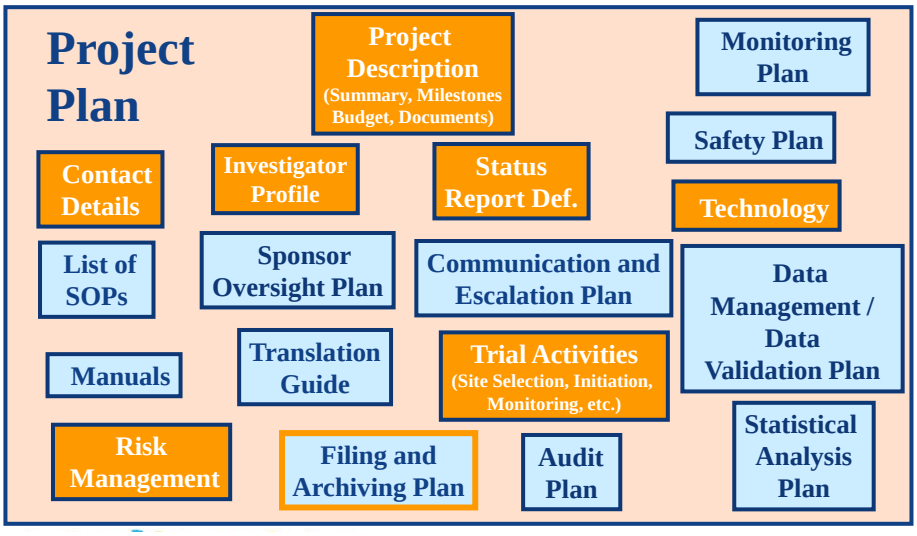
BVMA Umfrage
Which areas of the (e)TMF are determined with your client/sponsor?

Optionen	Anzahl	Häufigkeit nach Teilnehmer
Party that holds the TMF (or party that holds part of the TMF when it is divided)	22	95,7%
Structure and indexing of the (e)TMF	17	73,9%
Access arrangements of the involved parties	13	56,5%
Details of the system (validation, required functionalities like audit trail, ...) and change control management (for eTMF only)	9	39,1%
Lists of applicable procedures to be followed	14	60,9%
Training requirements	11	47,8%
Type of documents that each party should retain	17	73,9%
Arrangements for managing correspondence	16	69,6%
How the (e)TMF is made available to auditors and authorities for inspections	15	65,2%
Arrangements regarding archiving when the trial is completed	20	87,0%
Arrangements for (e)TMF oversight (e.g., who/what/how often/documentation) by client/sponsor and how this is achieved	16	69,6%
Retention times	12	52,2%
Procedures in case an involved party is closing down its business for any reason	7	30,4%
Other, please describe all further items:	3	13,0%
Gesamt	192 Antworten	23 Teilnehmer

Functional Plans

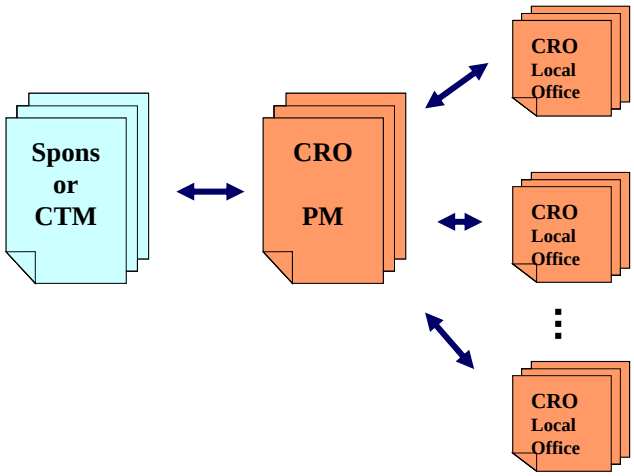
- Project Plan, including
  - List of SOPs
  - Communication and Escalation Plan
  - Monitoring Plan
  - Data Management Plan / Data Validation Plan
  - Safety Plan
  - Statistical Analysis Plan
  - Translation Guide
  - Filing and Archiving Plan
  - Sponsor Oversight Plan
  - Audit Plan
  - Manuals, z.B. IMP Manual, Lab Manual

Project Plan as Frame for all Trial Specifications and Functional Plans



xxx Preferably administered as stand alone document

Filing Plan - Beispiel



Filing Plan – Beispiel

- ➔ **Sponsor to keep original documents that were generated under sponsor responsibility, e.g. trial medication order, label approval, batch release, CoA, Site Approval documentation**
  (copies to CRO Project Manager (PM) as needed)
- ➔ **Main part of TMF to be kept at CRO PM during the trial**
- ➔ **Country specific Trial Master File / Investigator File: originals to be kept by CRO Local Office during the trial and to be shipped to CRO PM at end of trial. Copies will be sent to CRO PM on a monthly basis in order to build a shadow file**
  (➔ eTMF might be the better solution)

Filing Plan – Beispiel

➔ **End of trial: After all originals of CRO Local Offices are at CRO PM, QC/QA by CRO before shipment of total files to sponsor**

➔ **Audit of files at CRO advisable before shipment to sponsor**

➔ **Sponsor: Consolidation of sponsor and CRO TMF**

Filing Plan – Beispiel

➔ **Sponsor to be provided with originals as they become available for:**

- ❑ **Documentation pertaining to Regulatory Authorities (RAs) and IRBs/IECs**
  - **Submission documents (initial and any amendments)**
  - **Authorization/approval**
  - **Any correspondence with RAs / IRBs/IECs**
- ❑ **Any contractual agreements**
  - **With third parties/vendors/contractors**
  - **With investigators/coordinating investigators**
- ❑ **Any documentation pertaining to SAEs**

BVMA Umfrage

Do you see any issues with the following areas of (e)TMF handling?

	Paper TMF (n=23)		eTMF (n=15)	
Häufigkeit in %	No Issue	Some Issues	No Issue	Some Issues
Handling of certified copies	52,2%	47,8%	40,0%	60,0%
Filing of correspondence	21,7%	78,3%	20,0%	80,0%
Translation of documents	56,5%	43,5%	60,0%	40,0%
Integration of third parties	21,7%	78,3%	6,7%	93,3%
Prompt / continuous filing	21,7%	78,3%	40,00%	60,0%
Regular quality control	34,8%	65,2%	60,00%	40,0%
Communication/agreements with all parties	50,0%	50,0%	46,7%	53,3%
Access control	78,3%	21,7%	40,00%	60,0%
Archiving	68,2%	31,8%	66,7%	33,3%
Handover to client/sponsor	65,2%	34,8%	53,3%	46,7%
Structure and indexing	82,6%	17,4%	60,00%	40,0%
Validation of eTMF	na	na	26,7%	73,3%
eSignature	na	na	35,7%	64,3%
Handling of originals/paper signed documents	na	na	6,7%	93,3%
Note to files	73,9%	26,1%	80,0%	20,0%
Identification of missing documents	17,4%	82,6%	60,0%%	40,0%
Differentiation and handling of cross-project documents (e.g., validation documentation, full training records)	21,7%	78,3%	40,0%	60,0%
Sponsor and CRO separate TMF maintenance	21,7%	78,3%	40,0%	60,0%
Availability of documents during audits/inspections	39,1%	60,9%	57,1%	42,9%

Arrangements zur Archivierung von Unterlagen und Daten nach Studienende

Arrangements zur Archivierung Sponsor - CRO

Szenarien

1. **Sponsor archiviert den gesamten TMF, d.h. die CRO liefert den TMF (die Teile des TMF, die sich bei der CRO befinden) nach Studienende an den Sponsor**
   (in Gänze gar nicht möglich ➔ zentrale Systeme der CRO werden bei der CRO verbleiben)

2. **Die CRO wird beauftragt nach Studienende die Archivierung des (gesamten) TMF zu übernehmen**
   (in Gänze gar nicht möglich ➔ zentrale Systeme des Sponsors werden beim Sponsor verbleiben)

3. **Die CRO wird beauftragt nach Studienende Teile des TMF zu archivieren**

Frage zu Szenario 1

Situation: Eine CRO ist der Meinung, dass ein "serious GCP breach", z.B. Datenmanipulation, an einer Prüfstelle vorgekommen ist. Der Sponsor folgt der CRO Empfehlung, den Fall der Behörde zu melden, nicht. Vertraglich ist vereinbart, dass der Sponsor für die Meldung von "serious GCP breaches" zuständig ist.

Frage: Darf die CRO die Unterlagen behalten, die im Falle einer Inspektion aufzeigen würden, dass sich die CRO regelkonform verhalten hat? Darf eine CRO Dokumentation zur eigenen Absicherung behalten, auch wenn vertraglich vereinbart ist, dass der TMF nach Studienende in Gänze an den Sponsor übergeben wird?

Antwort
EU (e)TMF Guideline

6.1 Archiving of sponsor trial master file

…..

In the case that a sponsor has subcontracted a CRO for certain duties, the sponsor is responsible for ensuring the archiving of the documentation generated by the CRO from following its internal procedures. The contract between the sponsor and CRO should specify whether the CRO wants to retain original documents of their part of the TMF or certified copies thereof, after the certified copies or the original documents respectively were handed over to the sponsor for archiving, in order to retain evidence of compliance with their (CRO) internal procedures.

EU (e)TMF Guideline

6.1 Archiving of sponsor trial master file

…..

The sponsor's TMF may be transferred to a CRO for archiving (e.g. an external archive), but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor.

EU (e)TMF Guideline

3.2 Contract Research Organizations

The clinical trial contract/agreement and other documents and procedures agreed between all parties should outline the arrangements for the TMF in some detail, such as:

…..

- ➔ **arrangements for when the trial is completed (…); if there is a contractual arrangement for the CRO to transfer all essential documents they have generated to the sponsor for archiving, the arrangement should ensure the sponsor retains the full set of documents and makes it readily available and accessible for inspections (including inspections related to the CRO's duties and functions);**

Arrangements zur Archivierung von Unterlagen und Daten nach Studienende

Archivierungsfristen: Sponsor / Investigator und Marketing Authorisation Holder (MAH)

GLP vs GCP

- **GLP is a quality system concerned with the organizational process and conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported. (OECD: ENV/MC/CHEM(98)17 part two)**

- **GCP is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected. (ICH-GCP, 1.24)**

No archiving !

Regulatory Framework for Archiving

Sponsors and Investigators

- **ICH-GCP (R2)**
- **EU Commission Directive 2005/28/EC (GCP Directive)**
- **(Recommendation on the content of the trial master file and archiving)**
- **EU (e)TMF Guideline**
- **Local Law**
- **EU Regulation (EU) No 536/2014**

Marketing Authorisation Holders

- **EU Commission Directive 2003/63/EC, Annex I (amending EU Directive 2001/83/EC)**

Governance for Archiving in the EU

Dir 2001/20/EC / Dir 2005/28/EC now EU Reg 536/2014 in future

Dir 2001/83/EC as amended by Dir 2003/63/EC

Archiving for Sponsors, Investigators and MAHs

- **Sponsors and Investigators: EU GCP Directive: 5 years**
- **Caveat: National regulations for sponsors and investigators might differ (e.g. Germany: 10 years)**
- **MAHs: Commission Directive 2003/63/EC, Annex I**
  - **Investigators: 15 years or at least two years after the granting of the last marketing authorisation in the European Union …**
  - **Sponsors:**
    - **As long as the product is authorised**
    - **Final report for 5 years after the MP is no longer authorised**
- **Sponsors and Investigators: EU Regulation 536/2014: 25 years**
- **ATMPs: Regulation (EC) No 1394/2007: 30 years after the expiry date of the product …**
- **Exposure to ionizing radiation: Council Dir. 96/29/EURATOM: at least 30 years**

Retention Times
EU (e)TMF Guideline

6.3. Retention Times of Trial Master File

….

MAH ???

Directive 2003/63/EC (amending Directive 2001/83/EC) also states that "the sponsor or other owner of the data shall retain some of the documentation pertaining to the trial for as long as the product is authorised. This documentation shall include the protocol (…), standard operating procedures, all written opinions on the protocol and procedures, the investigator's brochure, case report forms on each trial subject, final report and audit certificate(s), if available. The final report shall also be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised."

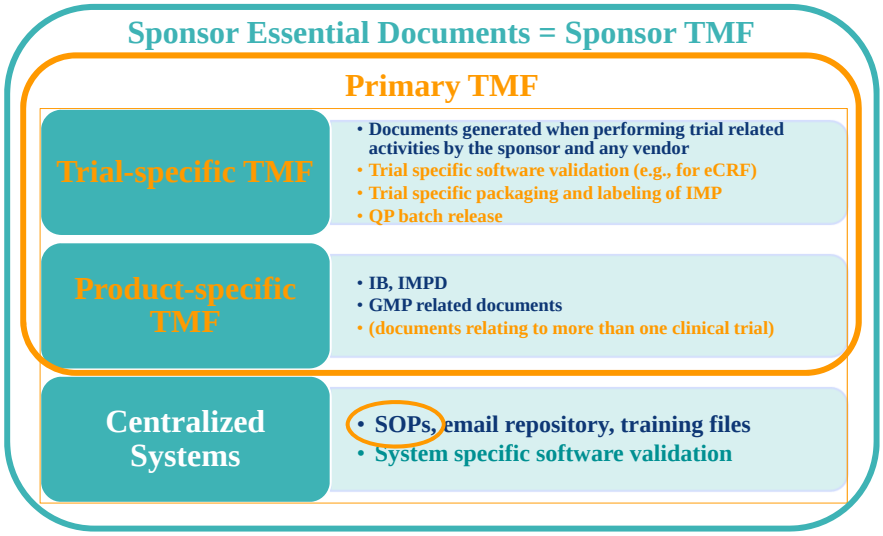
Retention Times
EU (e)TMF Guideline

6.3 Retention times of trial master files

Retention times, as laid down in Article 58 of the Regulation, Directive 2005/28/EC and Directive 2003/63/EC for sponsors' documents also apply to the documents retained by CROs or other agents of the sponsor under agreement with the sponsor.

CRO SOPs used in a clinical trial and archived in a central system by the CRO have to be retained as long as the product is authorized (in case the trial supported a MA)

Decentralized Sponsor TMF



Arrangements zur Archivierung von Unterlagen und Daten nach Studienende

Archivierung dynamischer Daten

Was sind dynamische Daten?

➔ **Daten, die in einer dynamischen Umgebung entstehen, z.B.**

- **Berechnete Daten**
  - **Excel**
  - **SAS**

Es dürfen nicht nur die Ergebnisse der Berechnungen als statische Daten archiviert werden, sondern die einzelnen Berechnungsschritte müssen nachvollziehbar bleiben.

- **Durch Interaktion (Dialogfelder) entstehende Daten**
  - **eCRF Eingaben (system audit trail, data audit trail)**
  - **eTMF Aktionen (system audit trail, document audit trail)**

Es dürfen nicht nur die zuletzt gespeicherten Daten / Dokumente als statische "Elemente" abgespeichert werden, sondern die Dynamik der Systemnutzung sowie die Entstehungsgeschichte der Daten bzw. Speicherung der Dokumente muss nachvollziehbar bleiben.

EU (e)TMF Guideline - eTMF

➔ **4.1.2 Sponsor/CRO electronic trial master file (cont)**

…

Any electronic system that holds trial data and metadata (e.g. audit trails) required for reconstruction should be archived so that the contained trial data and metadata can be retrieved as usable datasets.

….

The appropriateness of the storage system should be evaluated based on the file format used, e.g. whether the eTMF-document-management system is appropriate for the storage of dynamic data files (e.g. Excel files and SAS datasets), where needed and does not require such files to be rendered as a PDF. Within the eTMF-document-management system, PDF files generated from dynamic data files in other systems (e.g. IMP shipping reports generated from IRT datasets and monitoring visit reports generated from the clinical-trial-management system (CTMS) datasets) might be uploaded to the primary TMF system; if so, the original dynamic file should be retained in the original system.

EU (e)TMF Guideline

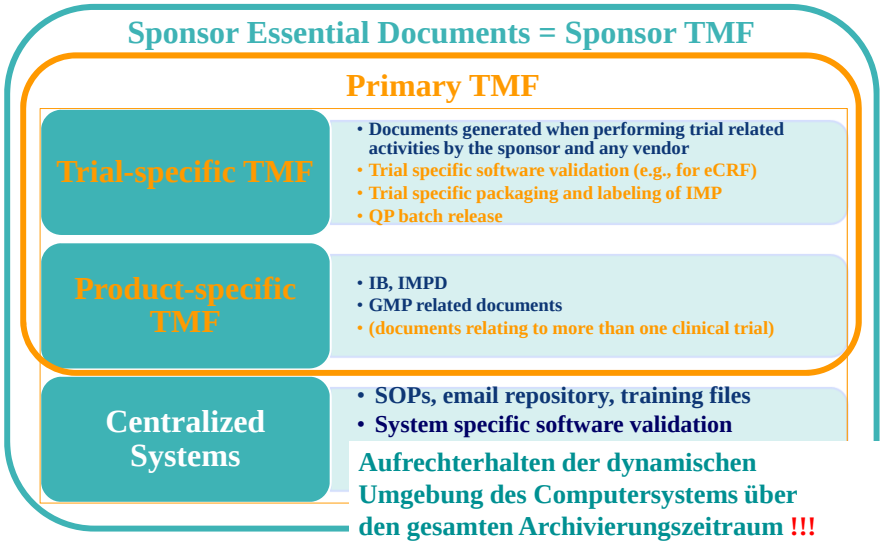
6. Archiving and retention of trial master file

It is important that access to documents and data is maintained for the entire archiving period. This could include maintaining the system (hardware and software) to access the data in its original archived format, or the use of a new system to emulate the old software or migration of the data into a new format to ensure continual access with new software. This issue should be addressed by the organisation by written procedures.

Emulator

➔ **In computing, an emulator is hardware or software that enables one computer system (called the host) to behave like another computer system (called the guest). An emulator typically enables the host system to run software or use peripheral devices designed for the guest system**

Decentralized Sponsor TMF



Aufrechterhalten der dynamischen Umgebung des Computersystems über den gesamten Archivierungszeitraum !!!

Häufige Fragen

Häufige Fragen

- **Gelten die 25 Jahre Archivierungszeitraum auch für Rohdaten in Laboren?**
  - **Lokales Routinelabor**
  - **Zentrallabor**
- **Welche Daten(-mengen) von „Wearables“ müssen archiviert werden?**
- **Recht auf Vergessen nach der DSGVO versus Archivierung von Daten aus klinischen Prüfungen nach der CT Reg 536/2014?**
- **CT Reg 536/2014, Art. 35 (3), Klinische Prüfungen in Notfällen:**
  “Erteilt der Prüfungsteilnehmer oder gegebenenfalls sein gesetzlicher Vertreter seine Einwilligung nicht, wird er davon in Kenntnis gesetzt, dass er das Recht hat, der Nutzung von Daten, die im Rahmen der klinischen Prüfung gewonnen wurden, zu widersprechen.“

Zusammenfassung

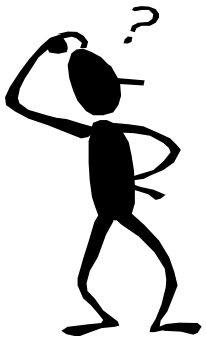
Zusammenfassung

- ➔ **Unser Bewusstsein für die Wichtigkeit der Dokumentation (essential documents / TMF) ist in den letzten > 20 Jahren deutlich gestiegen und wir haben viel dazugelernt**
- ➔ **Arzneimittelentwicklung ist deutlich globaler geworden**
  - ❑ **Höhere Fragmentierung**
  - ❑ **Mehr Schnittstellen**
  - ❑ **Mehr Anforderungen, dadurch mehr Dokumentation**
- ➔ **Komplexere (e)TMFs**
- ➔ **Höhere Fehleranfälligkeit, deshalb mehr QC/QA erforderlich**

Zusammenfassung

- ➔ **EU Guideline zu (e)TMF ist sehr hilfreich aber nicht ohne Herausforderungen**
  - ❑ **Ein TMF ist nichts „Zentrales“, sondern immer dezentral aufgebaut**
  - ❑ **Ein Index muss den Weg zu den verschiedenen TMF Teilen eindeutig aufzeigen**
  - ❑ **Auch Dokumente aus zugrundeliegenden zentralen Systemen gehören zum TMF (SOPs, Training Records, nicht prüfungs-spezifische Softwarevalidierungen) und unterliegen den zutreffenden Archivierungszeiträumen**
  - ❑ **Die dynamische Umgebung von interaktiven Systemen muss über den Archivierungszeitraum erhalten bleiben**
- ➔ **Fazit: Filing und Archiving benötigen mehr Aufmerksamkeit!**

Noch Fragen?



Vielen Dank für Ihre Aufmerksamkeit!

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Questionnaire to support BVMA presentation for BfArM im Dialog, May 7th, 2019 Topic: "Trial Master File (TMF)"

1) How do you set-up/maintain the TMF (multiple answers possible)?

- ☐ Paper TMF
- ☐ eTMF
- ☐ Hybrid

2) Where do you mainly determine the details about the (e)TMF with your client/sponsor (location(s), structure, access etc.)?

- ☐ Contract
- ☐ SOP
- ☐ TMF plan
- ☐ Other, please describe:_____

3) Which areas of the (e)TMF are determined with your client/sponsor (check all that apply)?

- ☐ Party that holds the TMF (or party that holds part of the TMF when it is divided)
- ☐ Structure and indexing of the **(e)**TMF
- ☐ Access arrangements of the involved parties
- ☐ Details of the system (validation, required functionalities like audit trail, ….) and change control management (for eTMF only)
- ☐ Lists of applicable procedures to be followed
- ☐ Training requirements
- ☐ Type of documents that each party should retain
- ☐ Arrangements for managing correspondence
- ☐ How the **(e)**TMF is made available to auditors and authorities for inspections
- ☐ Arrangements regarding archiving when the trial is completed
- ☐ Arrangements for **(e)**TMF oversight (e.g., who/what/how often/documentation) by client/sponsor and how this is achieved
- ☐ Retention times

- ☐ Procedures in case an involved party is closing down its business for any reason
- ☐ Other, please describe all further items:_____

4) Do you see any issues with the following areas of (e)TMF handling?
0 = no problem
1 = little problem
2 = larger problem

Area	Paper TMF			eTMF		
	0	1	2	0	1	2
Handling of certified copies	☐	☐	☐	☐	☐	☐
Filing of correspondence	☐	☐	☐	☐	☐	☐
Translation of documents	☐	☐	☐	☐	☐	☐
Integration of third parties	☐	☐	☐	☐	☐	☐
Prompt / continuous filing	☐	☐	☐	☐	☐	☐
Regular quality control	☐	☐	☐	☐	☐	☐
Communication/agreements with all parties	☐	☐	☐	☐	☐	☐
Access control	☐	☐	☐	☐	☐	☐
Archiving	☐	☐	☐	☐	☐	☐
Handover to client/sponsor	☐	☐	☐	☐	☐	☐
Structure and indexing	☐	☐	☐	☐	☐	☐
Validation of eTMF	n/a			☐	☐	☐
eSignature	n/a			☐	☐	☐
Handling of originals/ paper signed documents	n/a			☐	☐	☐
Note to files	☐	☐	☐	☐	☐	☐
Identification of missing documents	☐	☐	☐	☐	☐	☐
Differentiation and handling of cross-project documents (e.g., validation documentation, full training records)	☐	☐	☐	☐	☐	☐
Sponsor and CRO separate TMF maintenance	☐	☐	☐	☐	☐	☐
Availability of documents during audits/inspections	☐	☐	☐	☐	☐	☐
Other, please describe_____	☐	☐	☐	☐	☐	☐
Other, please describe_____	☐	☐	☐	☐	☐	☐
Other, please describe_____	☐	☐	☐	☐	☐	☐

5) **Correspondence: if you have identified the filing of correspondence as an issue in the previous question, which difficulties do you see in particular?**

Free text: _____

6) **Do you have any feedback from audits/inspections that are related to (e)TMF? If yes, please specify:**

Free text:_____

7) **If applicable, please give a short description of case studies regarding difficulties with (e)TMF?**

Free text:_____

8) **Any other comment that you would like to add?**

9) Free text:_____