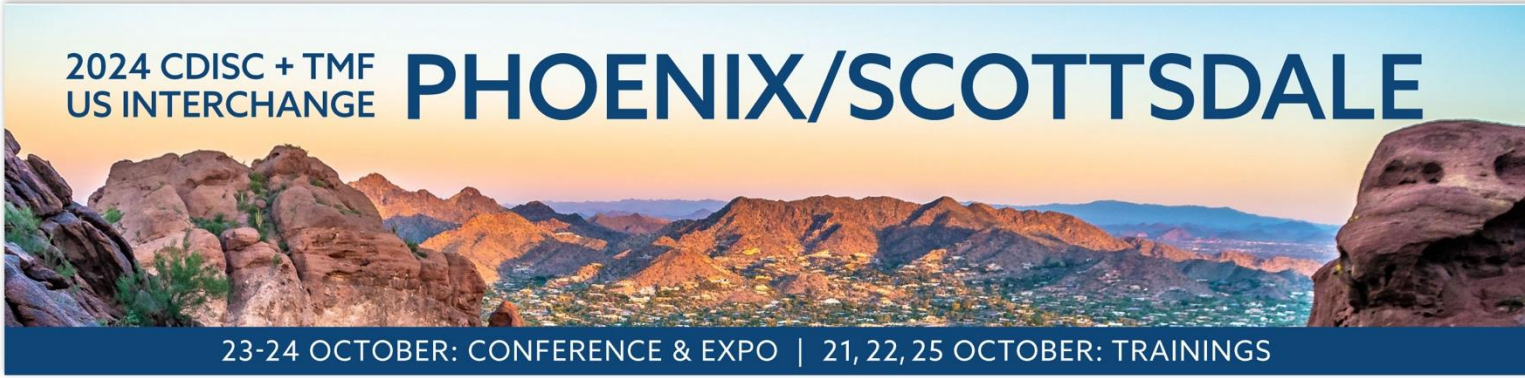

Introduction to the TMF Reference Model and the TMF Plan

Presented by Karen Roy, Consultant, CDISC

Meet the Speaker

Karen Roy

Title: Co-Founder and Chair of the TMF Reference Model Steering Committee
CDISC Consultant

Organizations: TMF Reference Model and CDISC

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

- *The presenter is a CDISC consultant*

Agenda

1. What is the TMF and the TMF Reference Model
2. About the TMF Reference Model
3. The TMF Plan
4. The Move to CDISC
5. The Future of TMF

What is the TMF and the TMF Reference Model

What *is* the Trial Master File?

The sponsor and the investigator shall keep a clinical **trial master file**. The clinical trial master file shall at all times contain the **essential documents** relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated […]. It shall be readily available, and directly accessible upon request, to the Member States.

[EU Regulation 536/2014]

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What are “Essential Documents”?

Essential documents are those documents that individually and collectively **permit evaluation of the conduct of a trial** and the **quality of the data** produced. These documents serve to demonstrate the **compliance** of the investigator, sponsor, and monitor with the standards of GCP and with **all applicable regulatory requirements**.

[ICH GCP, Section 8.1]

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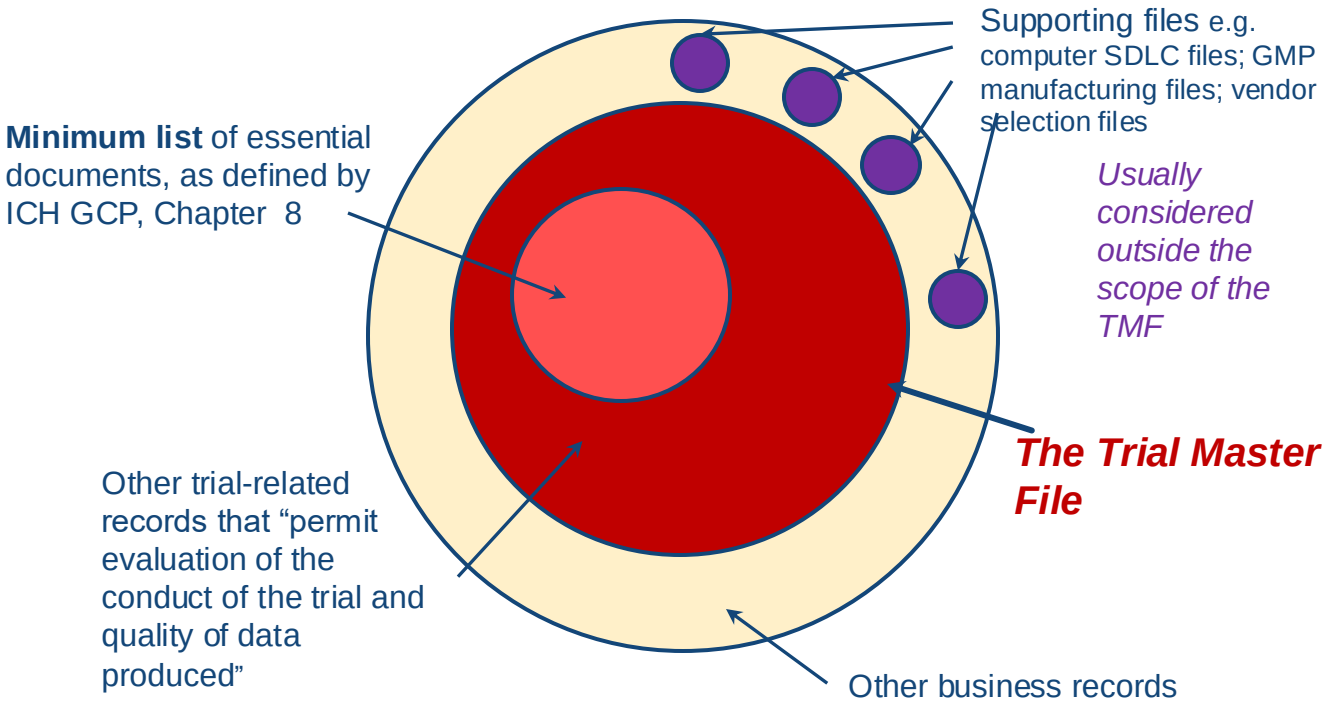
Why a TMF Reference Model?

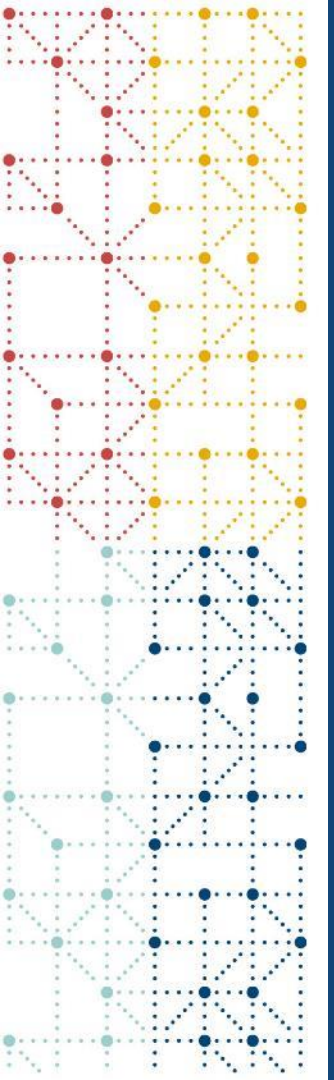
- ICH GCP Section 8.2 – 8.4
- “The **minimum** list of essential documents that has been developed.....”
- ICH GCP did **NOT** provide a comprehensive contents list for the TMF
  - Examples of missing documentation:
    - Electronic systems
    - Data management and statistical methodology
    - Safety monitoring
- Everyone had their own customised structure – Sponsors, CROs and third parties

Defining the TMF Reference Model



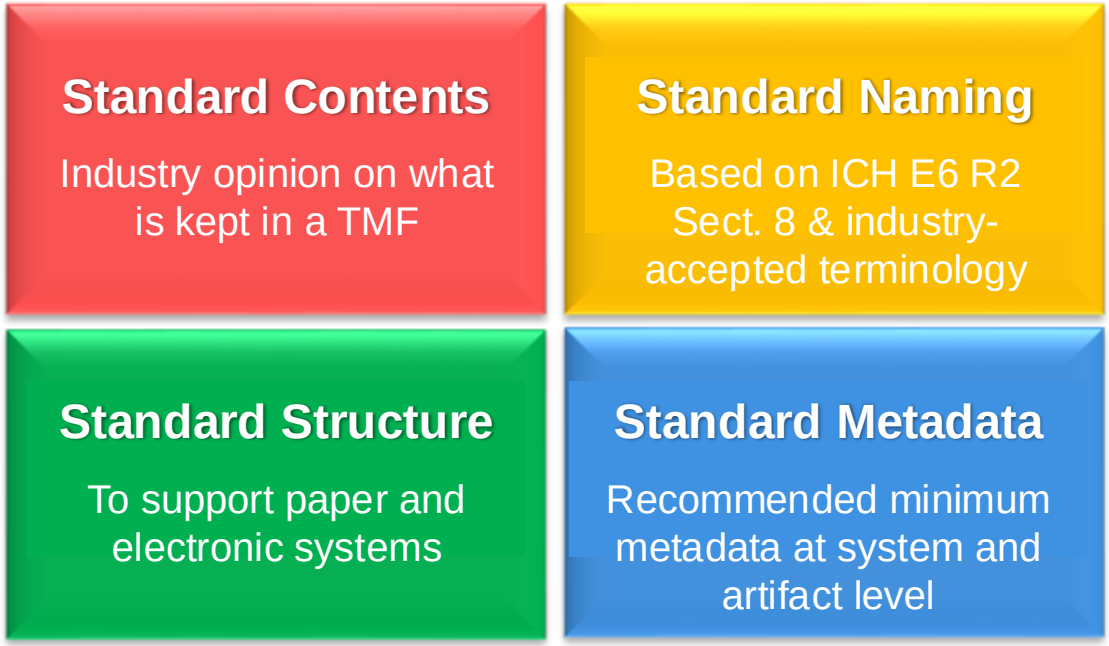
Benefits Gained by Implementation

- Standardises company content and structure and limits company customisation
  - We all follow the same regulatory requirements
  - Inspectors are the same across companies
  - Company-specific requirements are often driven by tradition, legacy or personal opinion
- Simplifies engagement of CROs and other third parties
- Simplifies consolidation of disparate documents into a single TMF structure (in real time, at defined trial events and/or at study end)



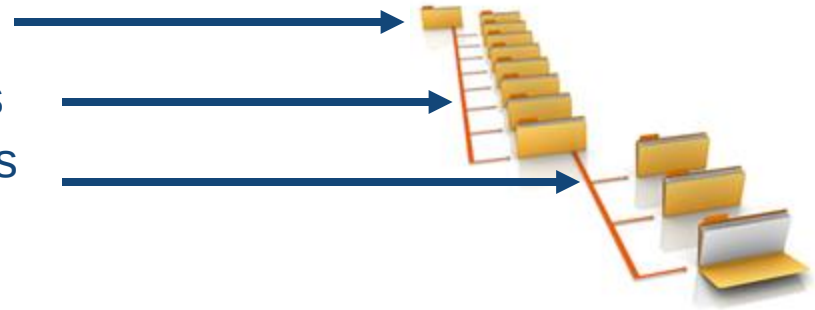
About the TMF Reference Model

Purpose of the TMF Reference Model



Structure and Content of the Model

- Data held in a simple Excel spreadsheet
  - Easy for non-technical people to use!
- Hierarchical structure
  - 11 Zones
  - 48 Sections
  - 249 Artifacts



607 Sub-Artifacts

ZONES:

1. Trial Management
2. Central Trial Documents
3. Regulatory
4. IRB or IEC and Other Approvals
5. Site Management
6. IP and Trial Supplies
7. Safety Reporting
8. Central and Local Testing
9. Third Parties
10. Data Management
11. Statistics

TMF Reference Model Zones

11 Zones
Trial Management
Central Trial Documents
Regulatory
IRB or IEC and other Approvals
Site Management
IP and Trial Supplies
Safety Reporting
Central and Local Testing
Third Parties
Data Management
Statistics

TMF Reference Model — TMF RM Website

Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Alternate names (artifact also commonly known	
09	Third parties	09.01	Third Party Oversight	09.01.03	Ongoing Third Party Oversight		To conf meet al
09	Third parties	09.02	Third Party Set-up	09.02.01	Confidentiality Agreement		To conf be prev contrac
09	Third parties	09.02	Third Party Set-up	09.02.02	Vendor Selection		To iden parties selectio
09	Third parties	09.02	Third Party Set-up	09.02.03	Contractual Agreement	Scope of Work Project Work Order(s) Change Order(s) Financial Agreement Contract Service Agreement Letter of Agreement Letter of Intent Authorization to Proceed	To doc that del obligati descrip
09	Third parties	09.03	General	09.03.01	Relevant Communications	Correspondence	Zone-s not spe include
09	Third parties	09.03	General	09.03.02	Tracking Information		Zone-s the cou
09	Third parties	09.03	General	09.03.03	Meeting Material		Agenda internal signific and any
09	Third parties	09.03	General	09.03.04	Filenote	Note to File	To doc
10	Data Management	10.01	Data Management Oversight	10.01.01	Data Management Plan	Data Management Operational Plan Data Handling Manual Data Processing Plan Technology Plan	To iden compil limited Databa
10	Data Management	10.02	Data Capture	10.02.01	CRF Completion Requirements	CRF Completion Guidelines	To prov comple

TMF Artifacts

- Could include data files, documents, media, digitised content
- Could be 1 document or multiple documents
- Includes associated records e.g. approvals, translations, checklists, QC records, amendments

Artifac	Artifact name	Alternate names (artifact also commonly known	Definition / Purpose
09.01.03	Ongoing Third Party Oversight		To confirm throughout the duration of a study that a third party continues to meet all relevant criteria to fulfill a contractual obligation.
09.02.01	Confidentiality Agreement		To confirm by written legal agreement that key information between parties will be prevented from being inappropriately disclosed. May be included in another contractual agreement.
09.02.02	Vendor Selection		To identify how a third party was selected. May include details of other third parties short-listed, master vendor list and any assessments carried out prior to selection.
09.02.03	Contractual Agreement	Scope of Work Project Work Order(s) Change Order(s)	To document by a written dated signed agreement between two or more parties that defines any arrangements on delegation and distribution of tasks and obligations (including financial obligations); critical components include service

TMF Reference Model Snapshot

TMF Reference Model							Version 3.3.1	11-AUG-2023					X: applicable; NO* : Not applicable *There may be some targeted exceptions based on local cr (i.e. countries)			
													TMF Artifacts (Non-device)		TMF Artifacts (Device	
Zone	Zone Name	Section I	Section Name	Artifac	Artifact name	Definition / Purpose	Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.	Core or Recommended for inclusion	ICH Cod	ISO 14155 Reference (Device Studies	Artifact name in v1.3 EDM Reference Mod	Unique ID Numbe	Sponsor Documen	Investigator Document	Sponsor Documen	Investiga Docume
01	Trial Management	01.01	Trial Oversight	01.01.01	Trial Master File Plan	To describe how records for the trial will be managed and stored during and after the trial, including study-specific processes and documentation for archiving and destruction. To include TMF filing structure to be used. May include TMF content list, filing structure and chain of custody records. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists, etc.	Document Transfer Documentation Evidence of Quality Review Request to Lock TMF Trial Master File Plan Trial Master File Index Trial Master File Report	Recommended	5.5.7			001	X	NO	X	NO
01	Trial Management	01.01	Trial Oversight	01.01.02	Trial Management Plan	To describe overall strategy for timelines, management and conduct of the trial and typically makes reference to other artifacts. Artifact can include details on contingency plan covering details for site start up planning.	Clinical Development Plan Project Management Plan Trial Management Plan	Recommended	2.2			002	X	NO	X	NO
01	Trial Management	01.01	Trial Oversight	01.01.03	Quality Plan	To describe the operational techniques and activities undertaken within the quality management system to verify that the requirements for quality of the trial-related activities have been fulfilled. Relevant parts may include, but not be limited to, a plan written for internal oversight of study quality management, an audit plan, data verification steps, serious breach assessments; also includes escalation in the event of a quality issue being identified and all corrective and preventative actions determined. Artifact can include any evidence of plan execution including, but not limited to: plan, reports, checklists, etc.	Quality Documentation Quality Plan Quality Report	Recommended	5.1	7.11 9.1 a		003	X	NO	X	NO
01	Trial Management	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial	To document which standard operating procedures (SOPs) and which versions were in effect for the duration of the trial and trial-specific procedures created for the trial. To include sponsor and third party SOPs. This artifact does not include the SOPs themselves. May include SOP waivers to document and describe study-specific deviation from a named SOP or working	List of SOPs Current During Trial SOP Waivers SOP Deviations	Core	5.1.1			004	X	NO	X	NO

History of the TMF Reference Model

2009 to 2010

Initial meeting: 2009
V1.0 released: 2010

Called the DIA TMF RM

DIA DEVELOP INNOVATE ADVANCE

Document & Records Management Community

2011 to 2013

Multiple releases (1.1, 1.2, and 2.0)

- Regulator and industry feedback
- Investigator Site Files
- Devices
- Process-based metadata
- Investigator Initiated Studies

2014 to 2021

- Separated from DIA, so "DIA" no longer in name
- Formalization with a Steering Committee and a Change Control Board
- TMF RM website
- Release of the Exchange Mechanism Specification
- Releases of V3.0, 3.1, 3.2

2022 to 3Q2024

- TMF RM become part of CDISC organization.
- TMF RM supported by CDISC processes and systems to advance the model and future strategies
- Release of V3.3

4Q2024 forward

- Continued support by CDISC for the TMF RM to achieve its goals
- **Comprehensive Review by Industry to Version 4.0 and move towards digital TMF**

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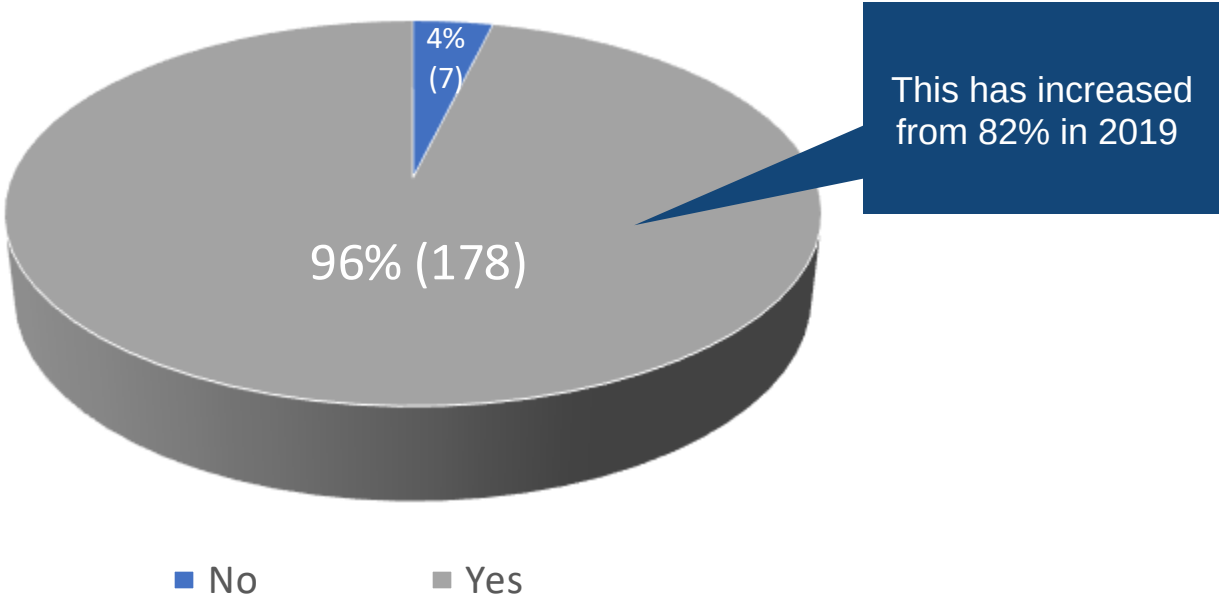
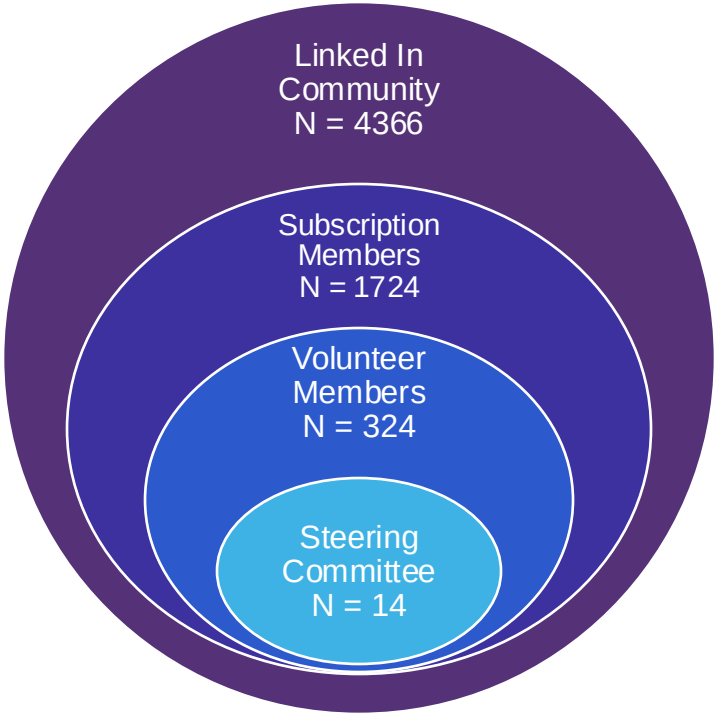
Organizations using TMF Reference Model



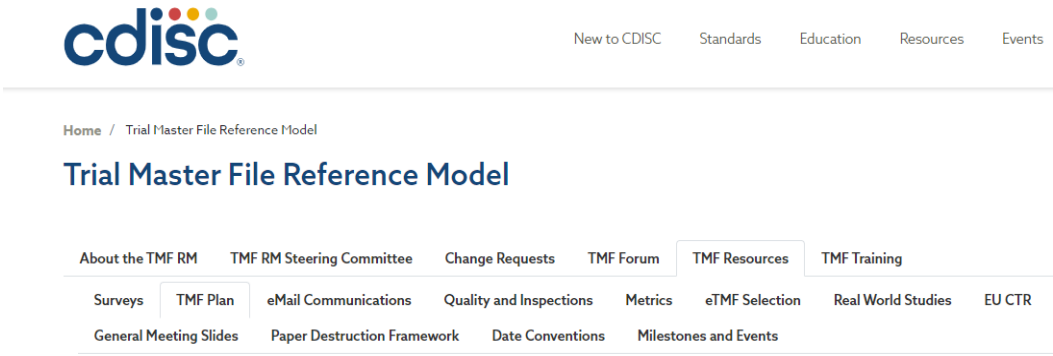
The TMF Reference Model Community



Many tools created over the years….

https://www.cdisc.org/tmf

- Industry Guidance for Email Communications
- RWE study index
- Document date conventions
- TMF Quality
- Metrics
- Inspection Readiness
- RFP template
- TMF Plan Template
- Framework for the Destruction of Paper (Covers certified copies)



The TMF Plan

Need for a TMF Plan

Multiple regulatory bodies have outlined the need to have documentation that describes how the TMF is managed for clinical trials. Both the EMA and MHRA have defined the minimum requirements along with suggested areas to cover to ensure roles and responsibilities as well as expectations on document management for all parties involved. Below are just some of the bullet points from the guidances.

The content of such a plan could typically address:

- **which party holds the TMF** (or which parts each party holds when this is divided)
- **the process for filing documentation in the TMF during the live phase of a trial**
- **the access arrangements for both parties to enable trial management and oversight**
- **the structure and indexing of the TMF**
- where an electronic TMF (**eTMF**) is being used, **the details of the system, processes to be followed, training requirements etc**.
- **documents that both parties must retain**
- **arrangements for managing correspondence, so that there is not a huge amount of duplication**
- **how the TMF would be made available if either party was inspected**
- **arrangements for when the trial is completed (long term access especially if the CRO is maintaining any of the documents)**
- **lists/attachments of applicable written procedures and training**."

Source:
MHRA GCP Guide, March 2013, Chapter 10, Section 10.2.6
1 Regulations 31A (4) of SI 2004/1031
EMA/INS/GCP/856758/2018

TMF Plan Template – Objective/Scope & Details

Objective: Review the template published in 2018 and incorporate changes due to regulations, technology, pandemic needs. Template must still be: a *cross-industry usable, simplistic TMF Management Plan template. Guidance provided on how to deal with variations depending on study size, phase, type.*

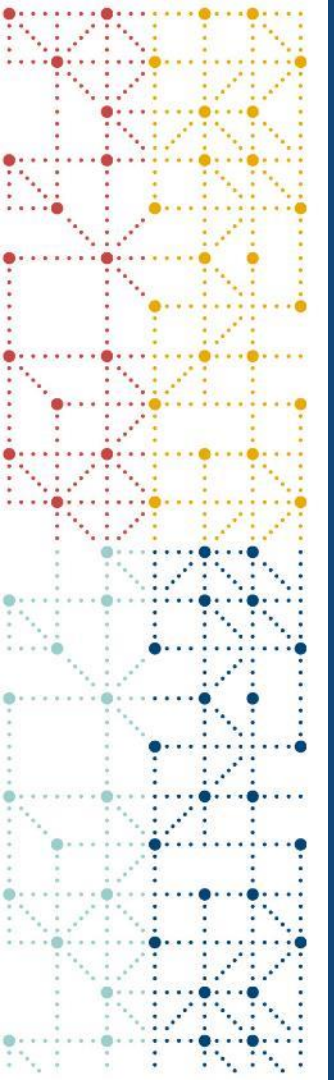
Scope: Template to be used for all clinical research study/trial types.

Details:

- Collaborative effort from March 2022-October 2022 with members from Sponsors, vendors, and consultants.
- Published and available to the industry on 21-Oct-2022!
- Available to download from the CDISC website
- Includes **green** guidance text and **blue** insertion prompt text.
- Comprehensive! Still only 12 sections and ~23 pages (less when **green** text is removed).

Summary of Revisions Oct 22 – High Level

- Updated instructions, added additional instructions throughout.
- Re-arranged the order of the sections, i.e. archive is section 10 from 7 now for better end to end flow.
- Added in tables for SOPs, training, vendor responsibilities.
- Created activities table, removed RACI.
- Created subsections for TMF Review documentation, Archiving at Sponsor or CRO/Vendor and Retention and Destruction.
- Created table for Legal Holds section.
- Added Transfer Agreement language into section 11.



The Move to CDISC

CDISC TMF RM Strategy Pillars

Development of the TMF Reference Model

DIA DEVELOP INNOVATE ADVANCE

Document & Records Management Community

2009 to 2010

Initial meeting in 2009 with first version being released in 2010

2011 to 2013

Multiple releases including Regulator feedback, Investigator Site Files, Devices, Process based metadata. Workgroups established

Separated from DIA

2014 to 2021

Formalization with a Steering Committee. **Release of the Exchange Mechanism Specification** and Version 3

2022 onwards

Forward to Compliance

Why the TMF RM is now part of CDISC

GLOBAL NON-PROFIT CLINICAL RESEARCH STANDARDS DEVELOPMENT ORGANIZATION WITH 40+ STAFF

RECOGNITION BY REGULATORY AGENCIES

ABILITY TO EXTEND THE TMF METADATA AND PROVIDE IN MACHINE READABLE FORMAT

FRAMEWORK FOR STANDARDS DEVELOPMENT LIFECYCLE

EDUCATION TEAM FOR CERTIFIED TRAINING

MARKETING AND EVENTS

STANDARDS TO REMAIN FREELY AVAILABLE

Where is the TMF Reference Model at today?

- The reference model itself is an Excel spreadsheet
- We need to be able to better map the TMF RM to other standard and models
- We need to expand the reference model in terms of metadata
- We have developed an initial standard for eTMF Interchange: the EMS (Exchange Mechanism Standard)
- We are already embarking on our CDISC journey to standardisation!

TMF Standards Team

- Established in December 2022
- Overseeing the move of the TMF Reference Model from a de-facto standard to a formal standard
- 4 Initiatives:
  1. Migration of TMF RM to CDISC Library
  2. Evolution of EMS/Interoperability
  3. TMF RM Standard Alignment and Management
  4. Development of Controlled Terminology and alignment with ICH M11

CDISC Library

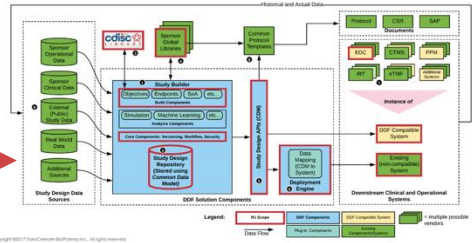
Community | Evolution | Expansion | Formalization

cdisc LIBRARY

Foundational Standards

Controlled Terminology

API



Machine-executable content

Connect with Digital Data Processes through Open-API

Executable Conformance Rules

Biomedical Concepts	Codelist Subsets	Tables, Listings, and Figures	Implementation Guide Text	FHIR to CDISC Mappings
Analysis Concepts	TAUG Metadata	Derivations and Mappings	Machine-readable Examples	LOINC Code Mappings
Templates	Study Design Metadata		CRF Collection	Diff Content Between Versions

TRIAL MASTER FILE TMF powered by cdisc REFERENCE MODEL

CDISC Standards

Informative Content

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The Future of TMF

Align & Engage with Regulators

- EMA Stakeholder database
- CDISC has multiple touchpoints with Regulators
  - FDA board member
  - Regular FDA / EMA / PMDA meetings
- Recognition from Industry bodies e.g. Transcelerate
- CDISC standards have been made mandatory by the FDA ….

Thank You!