The Trial Master File and the TMF Reference Model

Presented by Karen Roy
Chair of the TMF Reference Model Steering Committee

Meet the Speaker

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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.*

- *I am employed by CDISC on a Consulting basis*

Agenda

1. What is the TMF and the TMF Reference Model
2. About the TMF Reference Model
3. The Move to CDISC
4. 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]

What are “Essential Documents”?

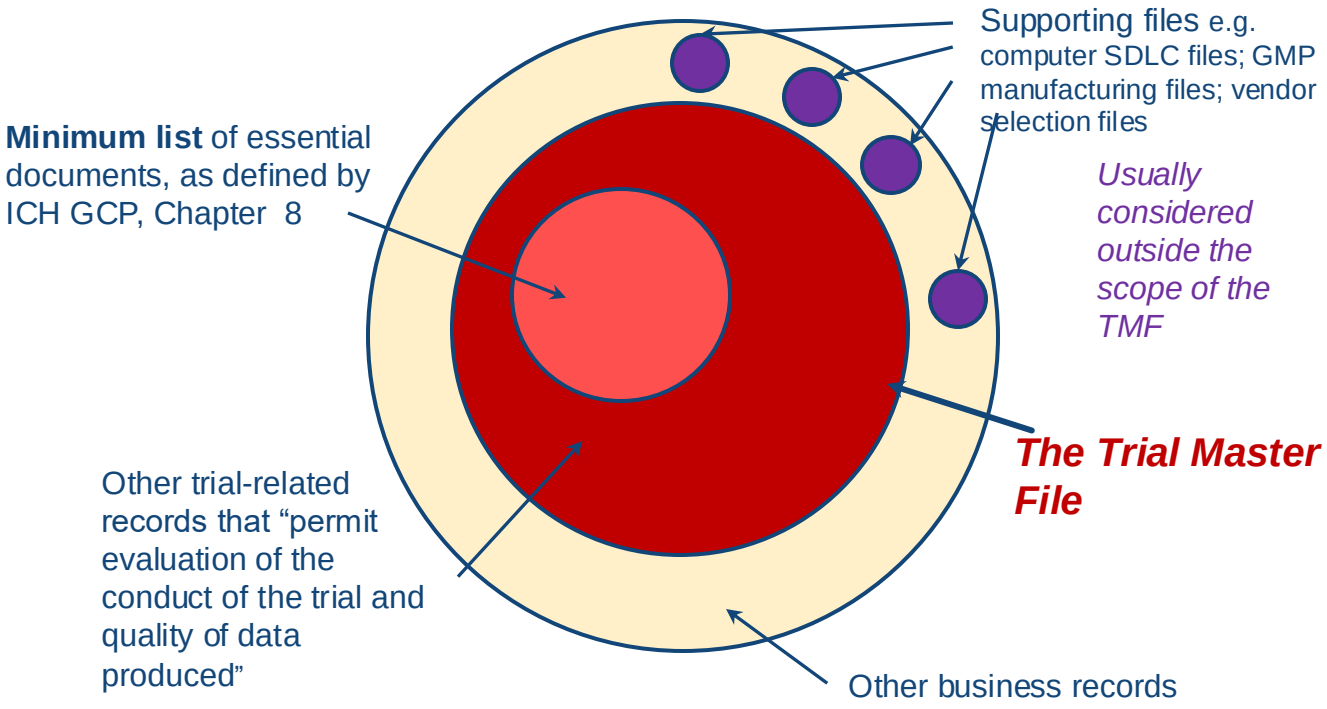
Essential documents are those documents that individually and collectively **permit evaluation of the conduct of a trial** and the **quality of the data** produced. These documents serve to demonstrate the **compliance** of the investigator, sponsor, and monitor with the standards of GCP and with **all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

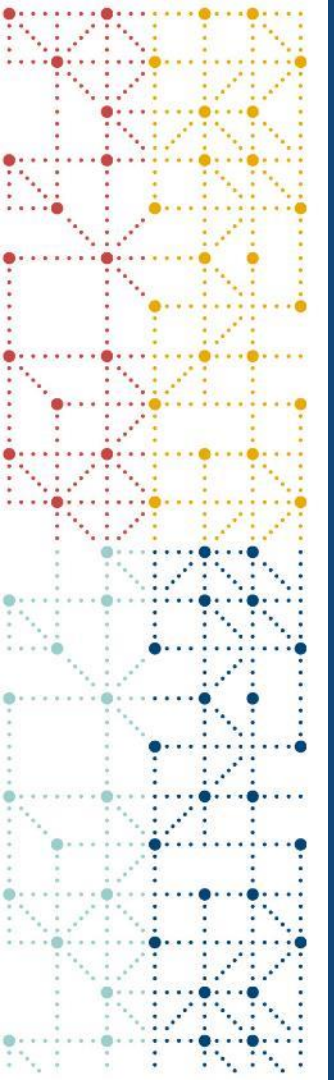
[ICH GCP, Section 8.1]

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

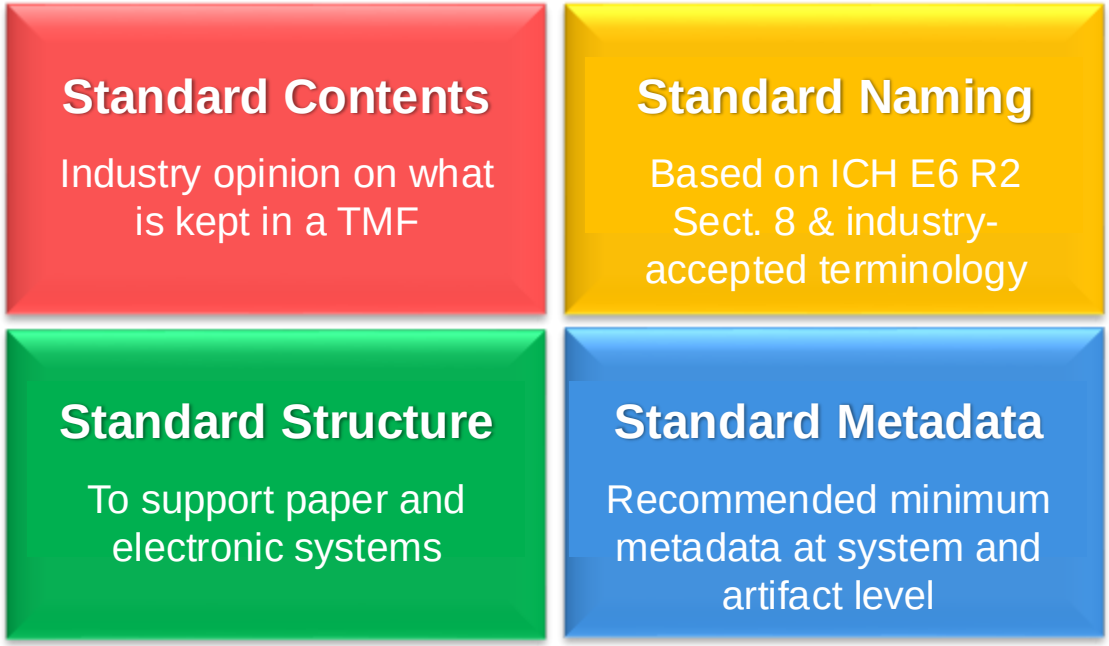
Defining the TMF Reference Model





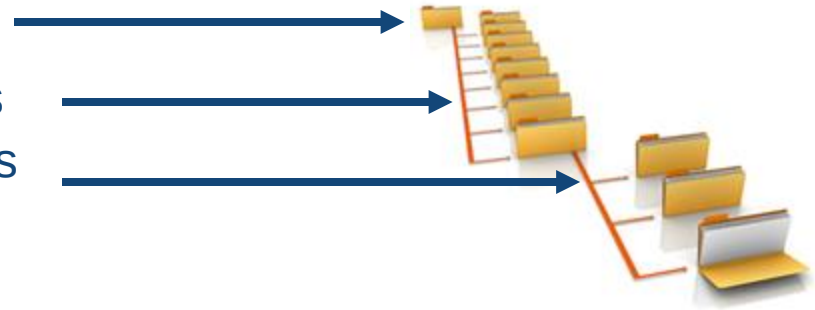
About the TMF Reference Model

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



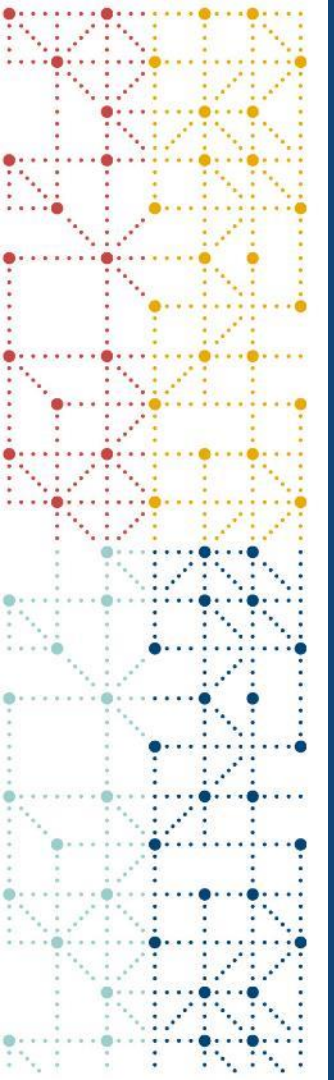
607 Sub-Artifacts

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 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



The Move to CDISC

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

2021 reassessment

CDISC TMF RM Strategy Pillars

Development of the TMF Reference Model

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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

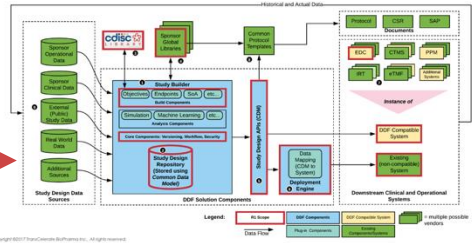
STANDARDS TO REMAIN FREELY AVAILABLE

CDISC Standards Development

- Consensus-based standards development
- Standards for clinical and translational research
- Standards are freely available at www.cdisc.org
- IP Policy ensures open standards
- Ongoing global research support in the Americas, Europe, Japan, China, India, China and other regions
- Standards and supporting documents available in English, Japanese, and Chinese.

CDISC Library

Community | Evolution | Expansion | Formalization



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*

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

Standards Sub-team update

Library Workstream

Version 4 will make us ready to move TMF RM to the CDISC library

Controlled Terminology

First pass of alignment/definition of Controlled Terminology almost complete

DDF – Data Driven Approach

White paper being developed around the participation of the TMF reference model in the digital data flow initiative as we move towards a more data driven approach

Education Team

- TMF Module 1: Introduction to the TMF Reference Model
  - Free
- Fundamentals of the TMF Reference Model
  - Scottsdale – 22 Oct 2024
  - Virtual – 3-5 September 2024 (2-5 pm CET)
- TMF QC Course – in development – On Demand
- TMF Reference Model for Biometric Professionals
  - Scottsdale – 25 Oct 2024

Risk Team

- Kicked off in Dec 2023
- Divided into 3 workstreams:
  - White Paper
  - Tools
  - Training
- White Paper is about to be released
- Have used AI to assist with writing

ISF Team

Goal:

- To develop an Investigator Site File (ISF) reference model for sites to use that supplements the TMF Reference Model with the intention of standardizing ISF structure, file naming conventions, and how/where site-level essential records are filed.
- To make it a standard, not reinvent, and to evaluate what is currently being used and how to bring it all together.

Progress:

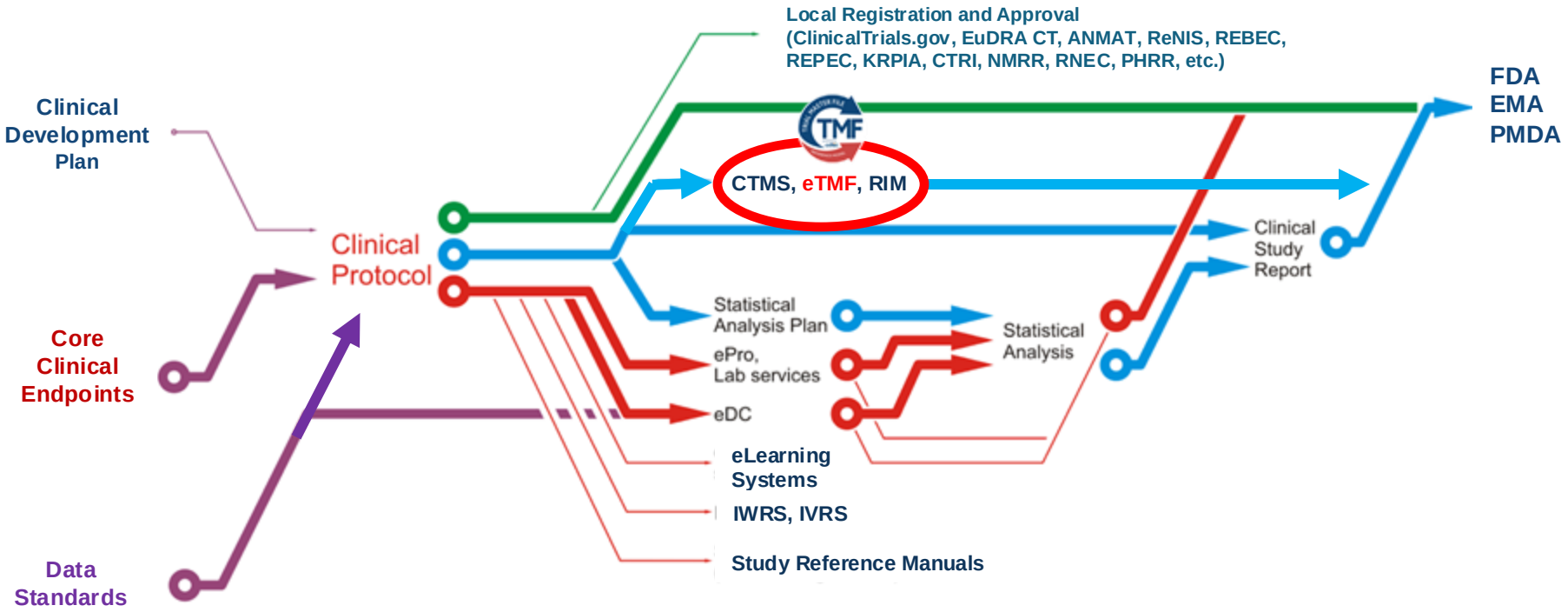
- ~50 volunteers!
- Kicked off 16-Apr-2024
- Subteams: Evaluation, Proofing, Standards, Outreach, Training.

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 ….

The Clinical Trial Information Flow



Using M11 and DDF to facilitate completeness and long-term retention

TMF RM Standard Structure, terms and metadata

CDISC Library

Many of these systems contain data and artifacts that are TMF relevant or that could drive TMF completeness

Key parameters about the clinical trial drives which artifacts we should expect i.e. Interim Analysis, randomization etc.

APIs

Clinical Systems

DDF
USDM
SDR

M11 Digital Protocol

Parameters

Artifacts

eTMF

Digital Dataflow leverages the Digital protocol to distribute protocol information to all downstream systems using Digital Data Flow and the Unified Study Definition Model (USDM) standard

By mapping the TMF RM artifacts to M11 we can navigate the TMF by digital protocol

+ Completeness
+ Timeliness
+ Quality

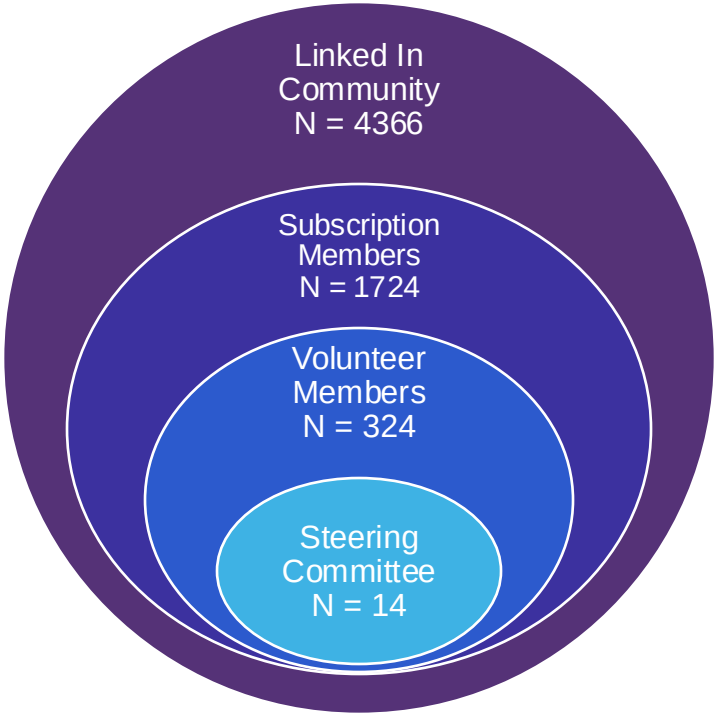
CDISC CT

TMF Specific
Metadata
Artifacts
Events / Milestones

EMS

Controlled Terminology across all standards facilitates understanding of terms and identification of artifacts

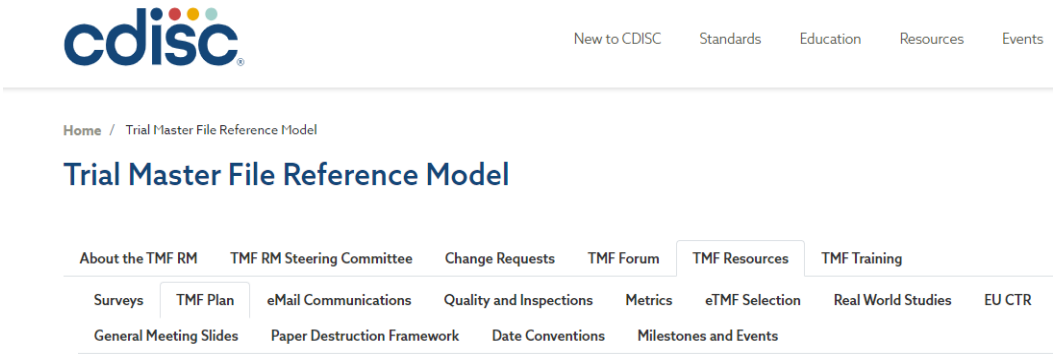
The TMF Reference Model Community



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)



What's Next?

- Survey 2024 300 respondents
- Next Version → 4.0 being started in September
- Next general meeting → 17th September

Thank You!