Trial Master File Reference Model

General Meeting

9th May 2022
Agenda

- TMF Reference Model Community
- The TMF RM Annual Survey
- Introduction to CDISC and Standards in Clinical Trials – Dave Evans
- CDISC Implementation Update – Mary Emanoil
- Impact of EU CTR on TMF content and process – Karen Roy
- Upcoming TMF Meetings
- Next TMF RM Meeting
The TMF Reference Model Community

Linked In Community
N = 4016

Subscription Members
N = 1628

Active Members
N = 333

Steering Committee
N = 14
TMF Reference Model Survey

Make sure your perspective is heard and get valuable insights and data!

The survey closes June 30, 2022

Important: Apologies but questions asking to submit multiple answers is not working in the survey. If you have multiple answers to select for these questions, then please select Other and specify those items in the comments field.
Introduction to CDISC and Standards in Clinical Trials

Dave Evans – President & CEO, CDISC
Mission: To develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare

- Global Non-profit Consensus-based Standards Development Organization
- 20 Years of Regulatory Clinical Data Standards Development and Implementation
- Experienced Leadership Team and Dedicated Staff of 40+ Professionals and SMEs
- Volunteer Network of 1000+ Industry Experts
- 540+ Member Organizations
- Widely Adopted and Freely Available Clinical Research Data Standards
- Mature Standard Governance Processes
- Innovative Open-Source Technology for Standards Library and Metadata Management
- Involved in a wide range of emerging Industry Initiatives and Projects
- Collaborative Ecosystem of Relationships and Partnerships
  - Members, Regulators, Patient Foundations, Academia, SDOs and Industry
Alliances and Collaborations

CFAST & Therapeutic Area Partnerships
CDISC collaborates with many organizations to develop Therapeutic Area (TA) standards for multiple disease areas through the Coalition for Accelerating Standards and Therapies (CFAST) initiative, as well as other partnerships.

Regulatory Collaborations
CDISC works closely with regulators around the world to ensure that CDISC standards will 1) streamline research from protocol/study design and trial registration through analysis and reporting; 2) facilitate the eSubmission review process; 3) ensure that clinical research is high quality; and 4) support the approvals of safe and efficacious medicines for patients.

Regulators also contribute to TA standards development

Standards Development Organizations (SDO) Collaborations
CDISC collaborates with other SDOs to develop standards that are synergistic to support a learning health system based upon high quality research.

CDISC and PhUSE partner to further the mission of each organization collectively, with CDISC focusing on the development of global, platform-independent data standards, and PhUSE focusing on the implementation and use of the CDISC standards. The two organizations work to combine efforts on key initiatives around end-to-end standards, TA standards, and semantics, strengthening an interdependent process.
Why Affiliate with CDISC?

- Global non-profit clinical research standards development organization
- Promotes interoperability
- Ability to extend the TMF metadata and provide in machine-readable format
- Develops guidance and implementation documents
- Standards education on implementation
- Standards to remain freely available
What is a Standard?

Webster’s Dictionary

• “something established by authority, custom, or general consent as a model or example”
• “the type, model, or example commonly or generally accepted or adhered to; criterion set for usages or practices: moral standards”
• “a level of excellence, attainment, etc. regarded as a measure of adequacy”, e.g., the standard of care
What is a Clinical Research Data Standard?

A set of defined data elements, their characteristics and relationships among them (≈ CRF)

Rules for creating, managing, using and verifying the data elements

A design for combining data meaningfully when they have been collected in many different places and ways

A best practice for managing data

Generally accepted, level of excellence, established by authority . . .
Flavors of “Standards” in Clinical Research
Where Can Clinical Research Use Data Standards?

- A Single Project
- Multiple Projects, e.g., Repositories
- An Indication, e.g., Oncology
- An Organization
- Multiple Organizations
- Across Industries/Government/Academia

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Why Standards Are Needed
(The Pillars of Misunderstanding)

- **Homonyms**
  If you don’t understand what terms mean, merging data to make meaningful connections is difficult.

- **Terminology**
  If you don’t agree on which terms to use, merging data to make meaningful connections is difficult.

- **Definitions**
  If you don’t agree on what terms mean, merging data to make meaningful connections is difficult.

- **Relationships**
  If you don’t see the relationships between and amongst data, variability is created in how standards are understood & implemented.

- **Organization**
  If you can’t find the data consistently, you waste time & resources. Using standards models, stakeholders can consistently find data within a submission.

- **Standards**
  Facilitate semantic clarity and organization of clinical data so it can be shared efficiently.

**Caudate, adj.** — having a tail, such as sperm cells, caudate lobe, etc.

**Chordate, adj.** — having a notochord (in fetus).
What Can Data Standards Do For You?

- Efficiency
- Interoperability
- Data Reuse
- Support New Science
- Ethics & Safety
- Quality
The Clinical Trial Information Flow

Local Registration and Approval
(ClinicalTrials.gov, EuDRA CT, ANMAT, ReNIS, REBEC, REPEC, KRPIA, CTRI, NMRR, RNEC, PHRR, etc.)

FDA
EMA
PMDA

Clinical Development Plan

Core Clinical Endpoints

Data Standards

Study Design Metadata

CTMS, eTMF, RIM

Statistical Analysis Plan
ePro, Lab services
eDC
eLearning Systems
IWRS, IVRS
Study Reference Manuals

Clinical Study Report
We welcome the TMF RM Community to the CDISC Consortium of Clinical Research Standards
Trial Master File
Reference Model

CDISC Transition Update

Mary Emanoil
CDISC Implementation Areas

- Membership – Karen Roy
- Communications – Kathie Clark
- Events – Mary Emanoil
- Standards – Joanne Malia
- Technology – Paul Fenton
CDISC Implementation Progress

**Completed**

- Member of Understanding signed on 6-Apr-2022
- Presented at CDISC Board Meeting on 8-Apr-2022
- [CDISC Press Release](#) 27-Apr-2022
- TMF Summit Keynote

**Upcoming**

- Membership transition
- Governance approach
- Finalize schedule for
  - Standards
  - Technology
  - Events
The Impact of the EU CTR on TMF Content

Karen Roy
### Poll

1. **Has your Company assessed the impact of EU CTR on TMF Content?** *(Single Choice)*
   - Yes: 23%
   - In Progress: 18%
   - No: 31%
   - I don’t know: 28%

2. **Where are tracking and collating all the documents required for CTIS?** *(Single Choice)*
   - eTMF: 6%
   - Regulatory System: 10%
   - eTMF and Regulatory system: 27%
   - I don’t know: 44%
   - Not applicable - We don’t manage CTIS applications: 14%
In order to be able to demonstrate compliance with the protocol and with this Regulation, a clinical trial master file, containing relevant documentation to allow effective supervision (monitoring by the sponsor and inspection by Member States), should be kept by the sponsor and by the investigator. The clinical trial master file should be archived appropriately to allow for supervision after the clinical trial has ended.
What does the EU CTR say about TMFs?

- Article 57
  - **Clinical 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, taking into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial. **It shall be readily available, and directly accessible upon request,** to the Member States.
    - The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.
Archiving of the clinical trial master file

Unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law.

The content of the clinical trial master file shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities.

Any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article.

The sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals.

The media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible throughout the period referred to in the first paragraph.

Any alteration to the content of the clinical trial master file shall be traceable.
EU regulation 536/2014 largest change in legislative framework in EEA since decades

From current Directive 2001/20/EC...

- Directive with national interpretation
- Independent submission of clinical trial applications to EU member states
- FPFV (First Patient First Visit) concept
- Information submitted in the clinical trial application is treated confidential

... to new Regulation 536/2014

- Regulation is binding and directly applicable in all EU Member States
- Single EU submission of clinical trial applications and approval via single Clinical Trial Information System (CTIS) – Event Reporting
- Near simultaneous approval / enrollment
- Most information submitted via CTIS will be published (Redacted)

HARMONISATION

A clinical trial sponsor must define and establish mechanisms to

// Comply with the new requirements
// Protect commercial confidential information
// Protect personal data

TRIAL MASTER FILE REFERENCE MODEL
## New or Changed Document Types

### TMF Reference Model

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<thead>
<tr>
<th>Zone</th>
<th>Zone Name</th>
<th>Group</th>
<th>Section Name</th>
<th>Artifact Name</th>
<th>Definition / Purpose</th>
<th>Recommended Submittals</th>
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<td>Regulatory</td>
<td>03.01</td>
<td>Trial Approval</td>
<td>03.01.01</td>
<td>Regulatory Submission</td>
<td>- Certificate of Current Submitted Receipt of Acknowledgement Regulatory Submission Review and Approval of Regulatory Submission -</td>
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<td>- Condition Approval List of Content Approved Regulatory Authority Decision -</td>
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<td>- Notification of Regulatory Identification Number -</td>
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<td>03.01.04</td>
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<td>- Public Registration Receipt of Acknowledgement -</td>
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<td>03.02.01</td>
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<td>- Import License Application Export License Application -</td>
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<td>03.03.03</td>
<td>Notification of Safety Trial Information</td>
<td>- Notification of Distribution of Safety Information Evidence of Distribution of Trial Information Notification of Safety Information Notification of Trial Information -</td>
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</tbody>
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*Note: The table above outlines the new or changed document types based on the TMF Reference Model Version 3.2.0.*

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*Example: Notification of Safety Trial Information includes notifications of serious adverse events that could alter the regulatory authority's approval decision, including unexpected serious adverse reactions (SUSARs), Unexpected Serious Adverse Device Events (USADE), Council for International Organizations of Medical Sciences (CIOMS) MedWatch, Analysis of Similar Events, Serious Breach, country-specific reporting forms.*
New or Changed Document Types?

- Process may have changed but outcome is similar
- The ‘new’ document types can be mapped to the TMF RM artifacts
- New sub-artifacts were suggested
- Duplication of documents may be a concern
- Data field information collation sheet – kept in TMF?
- Redacted and Not Redacted – both in TMF? Redacted not necessary for TMF but for Organisation
- Tagging of CTR documents for tracking purposes
- Is the whole CTA filed in the TMF?
Submission Evidence – add a new sub-artifact to 3.1.1

Multiple notifications – maybe new subartifact
  - From CTIS in 3.1.2
  - To CTIS in 3.1.1

Protocol synopsis for laypersons – new subartifact in 2.1.3

Clinical Trial Summary Report for Laypersons – new subartifact in 2.3.1
Batch certificate – stored with batch records or QP certification
IMPD – one for Quality, one for Safety and Efficacy – ? Split sub-artifact? Consensus = no
Safety – Unexpected events that affect benefit risk balance – no change
Annual Safety Report – Trial level 7.1.2
Compliance with Biological samples? New Artifact?
Relevant Links

- [DRAFT] Guidance document on how to approach the protection of personal data and commercially confidential information in documents uploaded and published in the Clinical Trial Information System (CTIS)  7 April 2022, 56 pages

- Guidance to pharmaceutical industry on redacting commercially confidential information (CCI) in clinical reports & Process  6 July 2015, 18 pages
## TMF–related events coming up*

*Events page on website (under Resources menu)*

<table>
<thead>
<tr>
<th>Conference</th>
<th>When</th>
<th>Location</th>
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<td>Hanson Wade Operationalize electronic Tral Master Files Summit</td>
<td>August 16–18, 2022</td>
<td>Boston, MA, USA</td>
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<tr>
<td>HSRAA Conference</td>
<td>September 28–30, 2022</td>
<td>Manchester, UK</td>
</tr>
<tr>
<td>Fierce Pharma TMF Summit</td>
<td>November 14–16, 2022</td>
<td>London, UK</td>
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TMF RM General Meetings

- 27th June 22 – Webinar with CDISC
- Add to your calendar NOW or download the calendar file (.ics file) from our homepage
- Outlook Meeting Request no longer distributed
QUESTIONS?

Join the TMF Reference Model Discussion Group
https://tmfrefmodel.com/register

- Knowledge sharing
- Networking
- Too Much Fun!

Join the TMF Reference Model Project Team
(be prepared to work! – we can’t do this without YOU)
https://tmfrefmodel.groups.io/g/main
Meeting details

Wondering where to find details of the next meeting?

On TMF Reference Model website, click on calendar to see meeting details. Click 'Copy to my calendar' to add to your Outlook / Google calendar.
Meeting details

- Wondering where to find details of the next meeting?

On Groups.io, click on Calendar to show group calendar. Click on an event to see dial-in details.

https://tmfrefmodel.groups.io/g/main/