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

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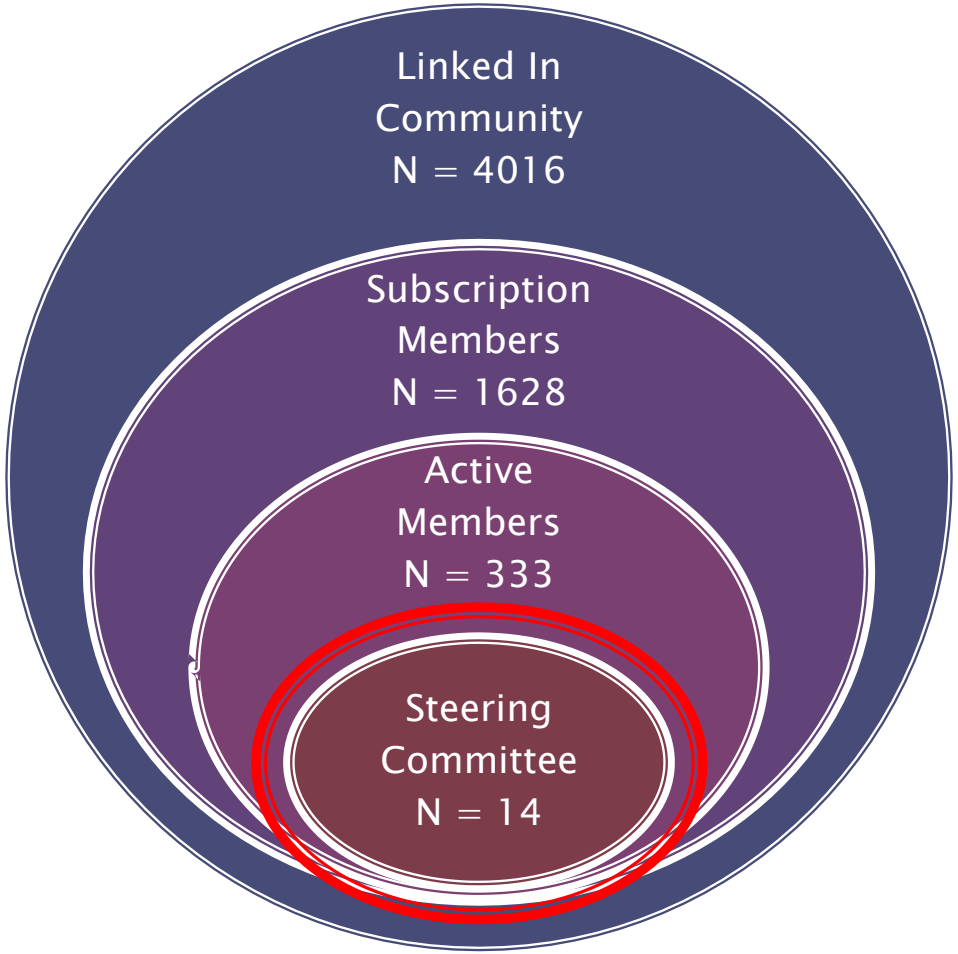
The TMF Reference Model Community



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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.

TAKE 2022 TMF SURVEY

https://tinyurl.com/3ea9hun9

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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

cdisc

phuse

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

PROMOTE 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

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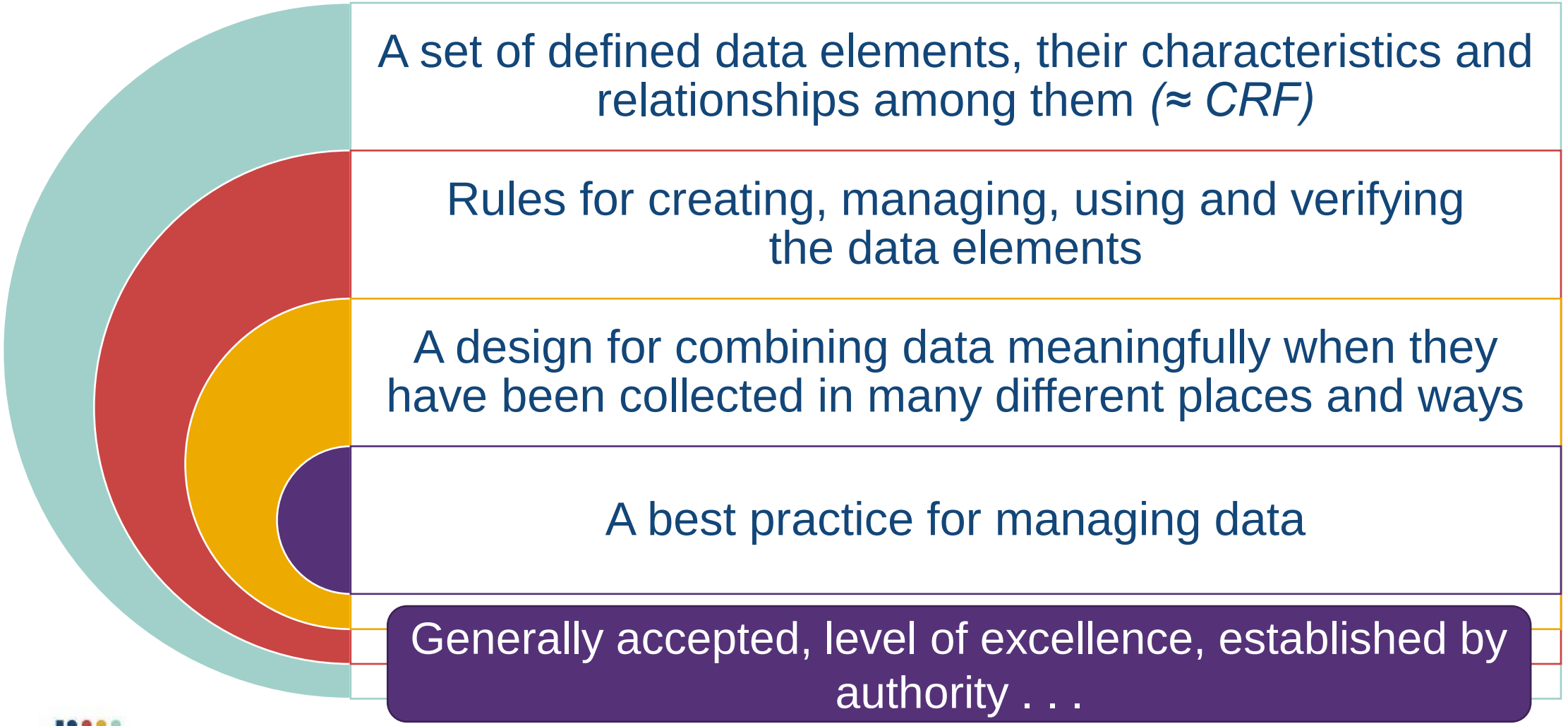
What is a Standard?

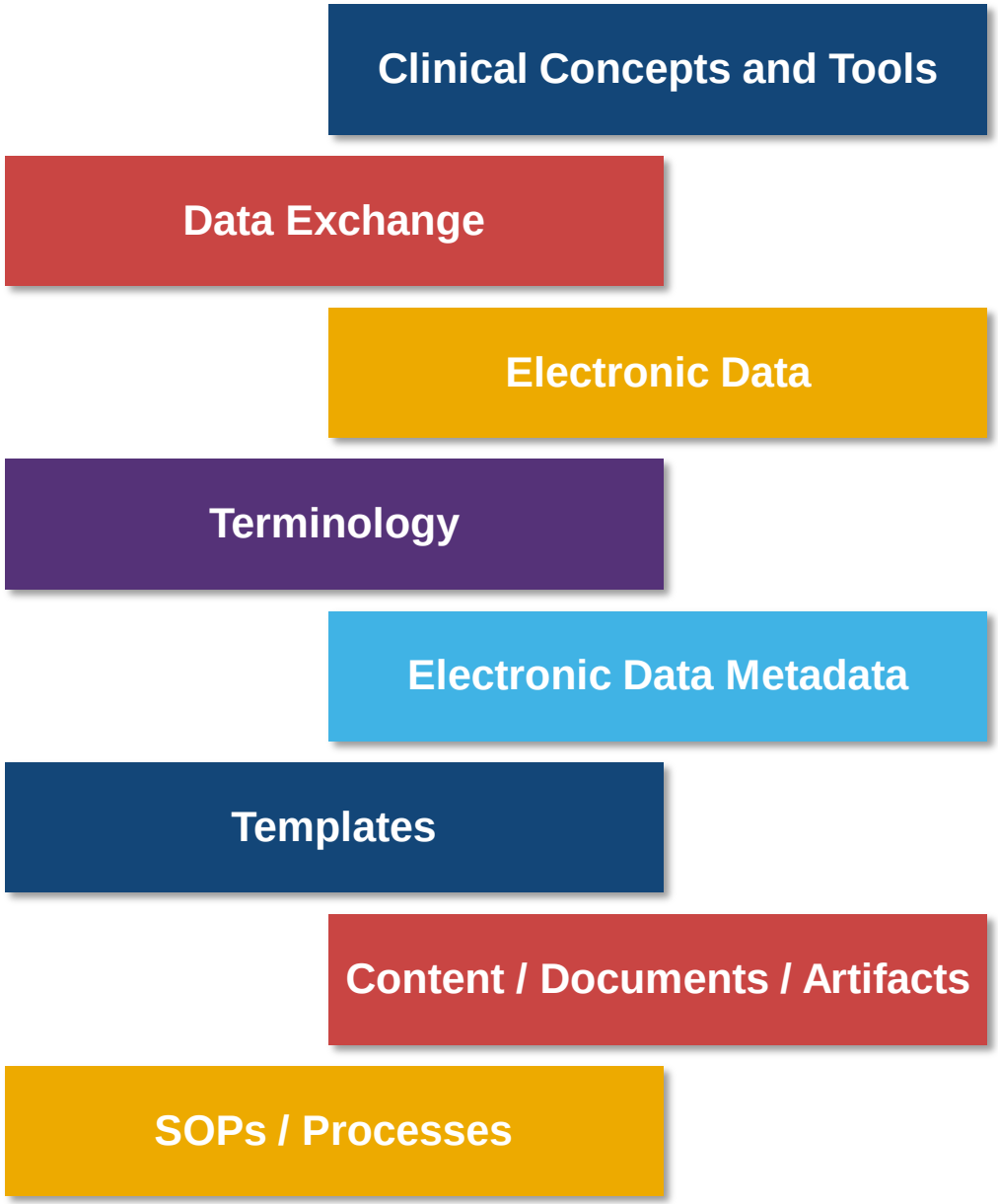
Webster's Dictionary

- "**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

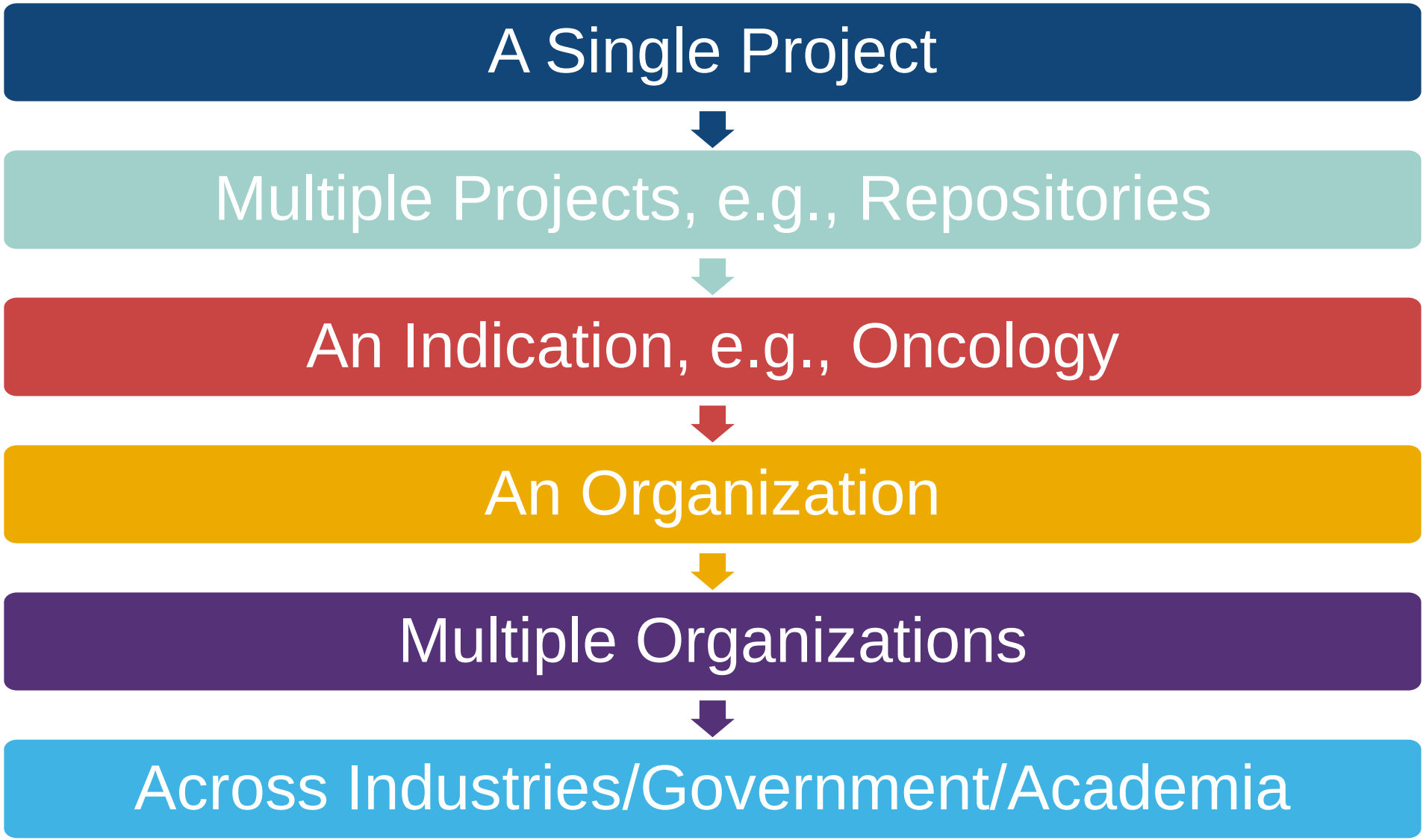
What is a Clinical Research Data Standard?



Flavors of "Standards" in Clinical Research



Where Can Clinical Research Use Data Standards?



Why Standards Are Needed (The Pillars of Misunderstanding)

USUBJID	SEX	SUBJID	SEX
0001	M	00011	0
0002	F	00012	1
0003	F	00013	1
0004	M	00014	0
0005	F	00015	1

caudate, adj. — having a tail, such as sperm cells, caudate lobe, etc.
chordate, adj. — having a notochord (in fetus).

HOMONYMS

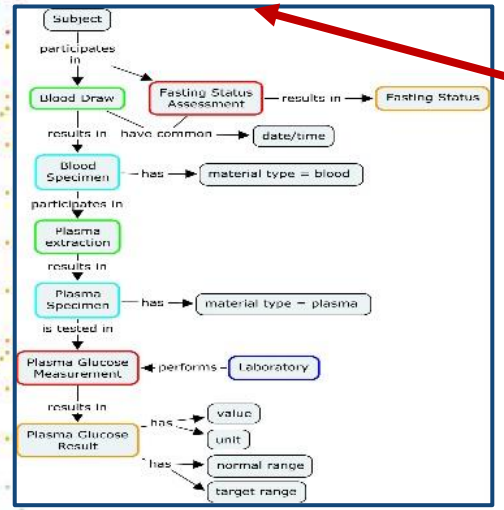
If you don't **understand what terms mean**, merging data to make meaningful connections is difficult.

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

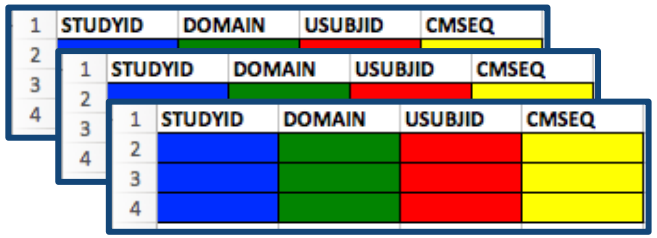
If you don't **see the relationships between and amongst data**, variability is created in how standards are understood & implemented.

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.



What Can Data Standards Do For You?

Efficiency

Interoperability

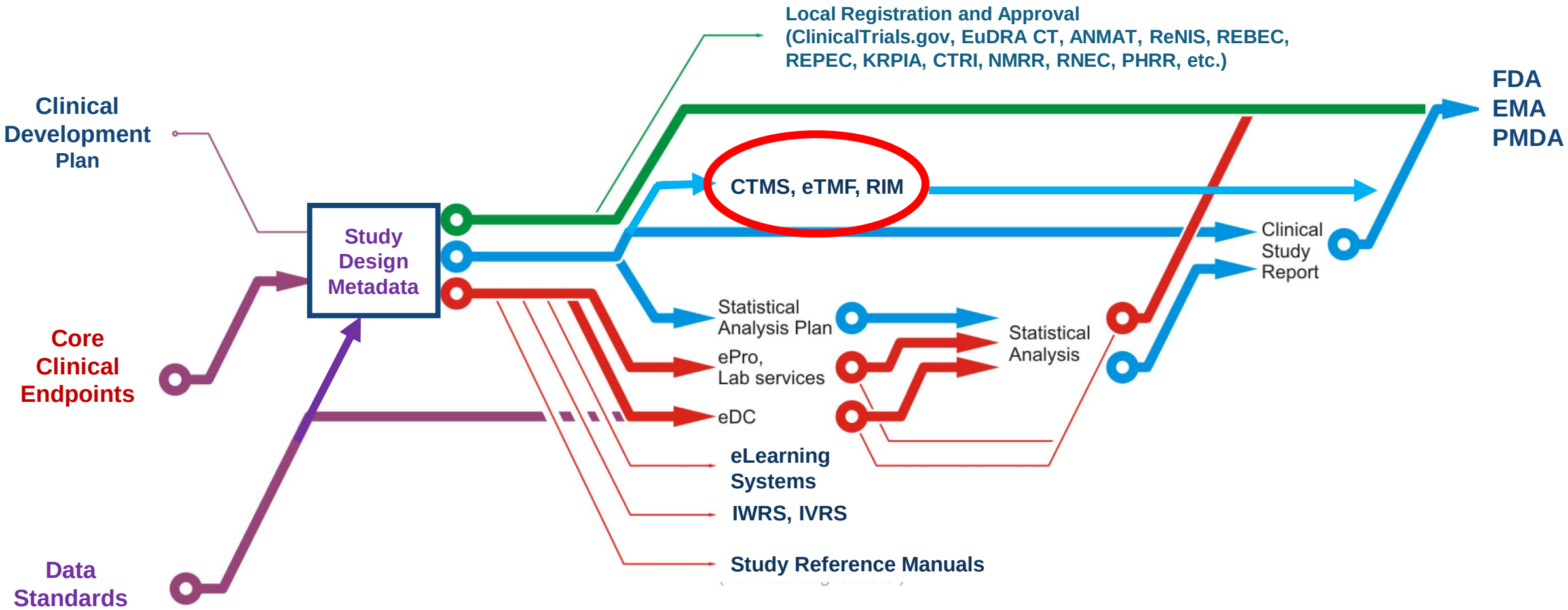
Data Reuse

Support New Science

Ethics & Safety

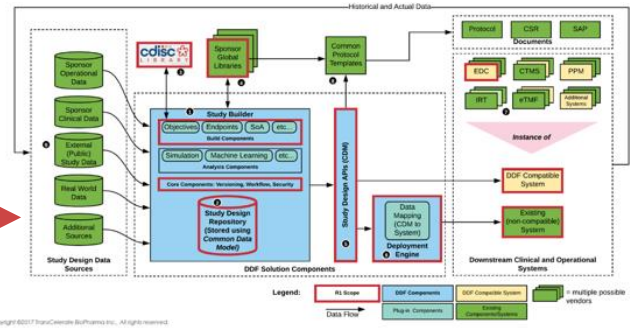
Quality

The Clinical Trial Information Flow



CDISC Library

Connect with Digital Data Processes through Open-API



Foundational Standards

Controlled Terminology

API

Machine-executable content

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	TRIAL MASTER FILE TMF REFERENCE MODEL	CRF Collection	Diff Content Between Versions

CDISC Standards

Informative Content

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We welcome the TMF RM Community to the CDISC Consortium of Clinical Research Standards

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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

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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

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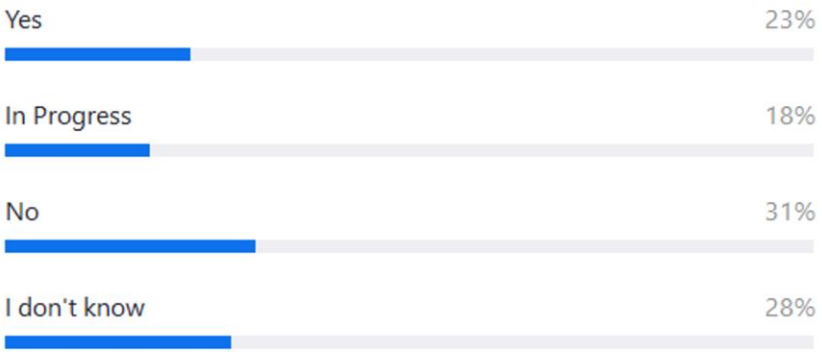
Trial Master File Reference Model

The Impact of the EU CTR on TMF Content

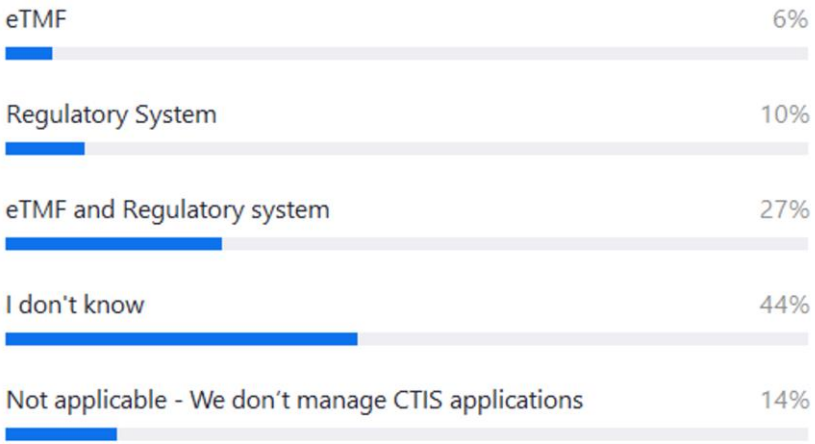
Karen Roy

Poll

1. Has your Company assessed the impact of EU CTR on TMF Content? (Single Choice) *



2. Where are tracking and collating all the documents required for CTIS? (Single Choice) *



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What does the EU CTR say about TMFs?

- 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.

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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.

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What does the EU CTR say about TMFs?

- **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.

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EU regulation 536/2014 largest change in legislative framework in EEA since decades

From current Directive 2001/20/EC…	… to new Regulation 536/2014
Directive with national interpretation	Regulation is binding and directly applicable in all EU Member States
Independent submission of clinical trial applications to EU member states	Single EU submission of clinical trial applications and approval via single Clinical Trial Information System (CTIS) – Event Reporting
FPFV (First Patient First Visit) concept	Near simultaneous approval / enrollment
Information submitted in the clinical trial application is treated confidential	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

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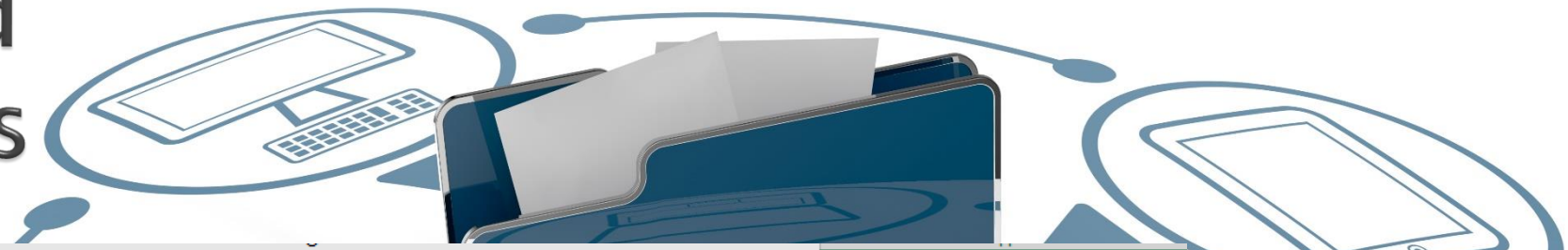
New or Changed Document Types



TMF Reference Model	TMF RM Website	Version 3.2.0

Zone	Zone Name	Section	Section Name	Artifact #	Artifact name	Definition / Purpose	Recommended Subartifacts – Documents/documentation recommended to be filed to the artifact.
03	Regulatory	03.01	Trial Approval	03.01.01	Regulatory Submission	A set of documents, along with required associated regulatory forms and correspondence, submitted to one or more regulatory agencies requesting approval to conduct the trial or for the purpose of notification, or requesting approval of changes to the trial documents or of any trial events that could adversely affect the safety of subjects, impact the conduct of the trial or alter the regulatory authority's approval/favorable opinion to continue the trial. Example Investigational New Drug Application (IND), Clinical Trial Application (CTA), Investigational Device Exemption (IDE) The submitted documents such as Investigator Brochure, Informed Consent Forms, etc. may or may not be filed as a complete Dossier within this Artifact, this is dependent on SOPs within your Organization.	Cover Letter List of Content Submitted Receipt of Acknowledgement Regulatory Submission Review and Approval of Regulatory Submission
03	Regulatory	03.01	Trial Approval	03.01.02	Regulatory Authority Decision	A documented notification received from a regulatory authority stating that the Submission has been received and approved.	Condition Approval List of Content Approved Regulatory Authority Decision
03	Regulatory	03.01	Trial Approval	03.01.03	Notification of Regulatory Identification	Document identifying unique Identification (ID) number used to uniquely identify the trial or the trial level in that region, assigned by a regulatory agency – e.g. EU = EudraCT Number, FDA = IND Number, US Device = IDE Number.	Notification of Regulatory Identification Number
03	Regulatory	03.01	Trial Approval	03.01.04	Public Registration	Documentation related to registration of clinical trials in public registries such as ClinicalTrials.gov and to submission of results periodically during the study and at study completion.	Public Registration Receipt of Acknowledgement
03	Regulatory	03.02	Investigational Medicinal Product	03.02.01	Import or Export License Application	An application made to one or more regulatory agencies requesting a license to import or export the investigational product and clinical supplies.	Import License Application Export License Application
03	Regulatory	03.02	Investigational Medicinal Product	03.02.02	Import or Export Documentation	A document issued by a national government authorizing the importation or exportation of certain goods into its territory.	Import License Export License
03	Regulatory	03.03	Trial Status Reporting	03.03.01	Notification of Safety or Trial Information	Notification to Regulatory Authorities of any trial events that could alter the regulatory authority's approval/favorable opinion to continue the trial. Notifications may include, but are not limited to: Quarterly line listings, suspected 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 Breaches, cover letters and/or country-specific reporting forms.	Evidence of Distribution of Safety Information Evidence of Distribution of Trial Information Notification of Safety Information Notification of Trial Information

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

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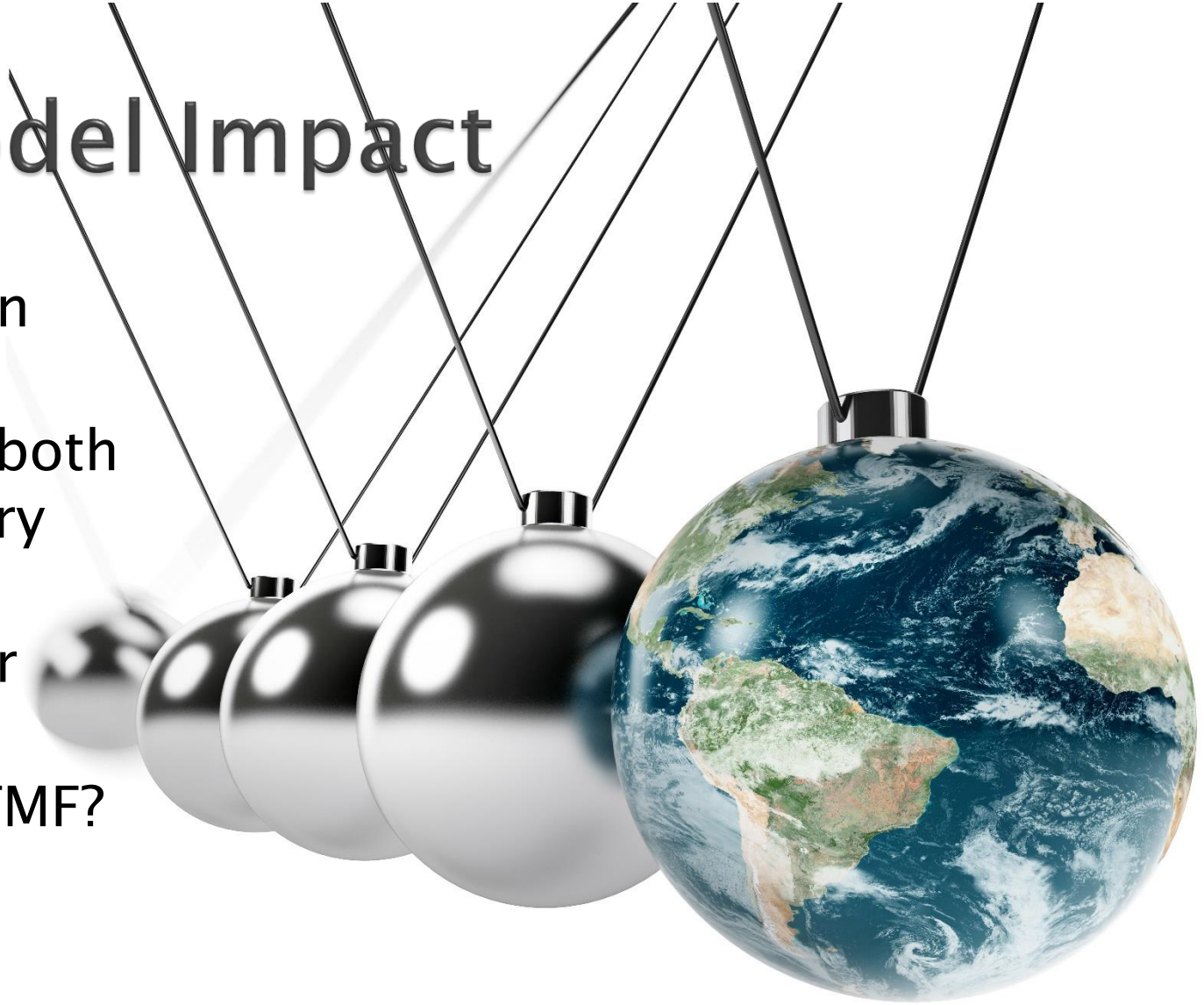
TMF Reference Model Impact

- 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?



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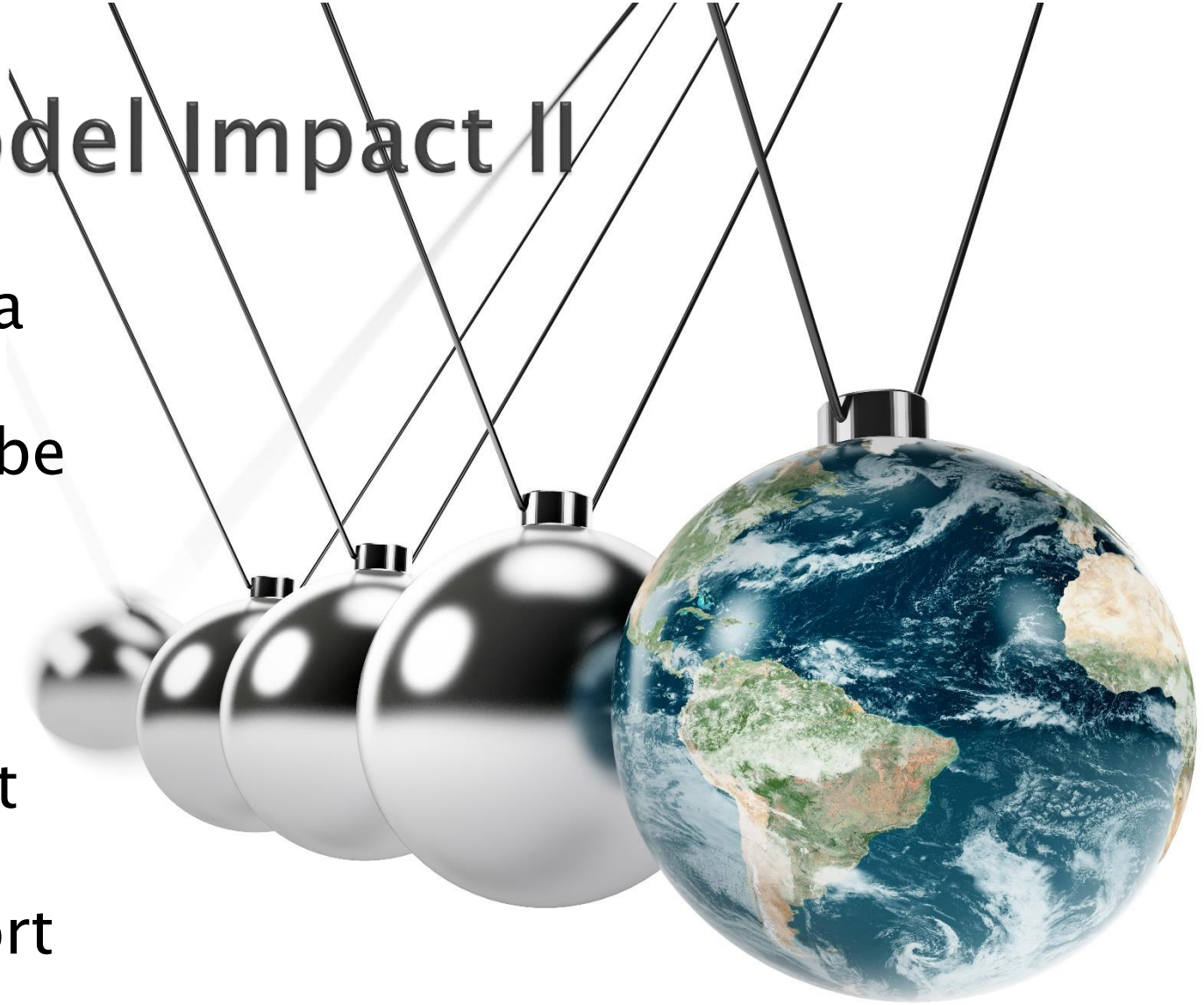
TMF Reference Model Impact II

- 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



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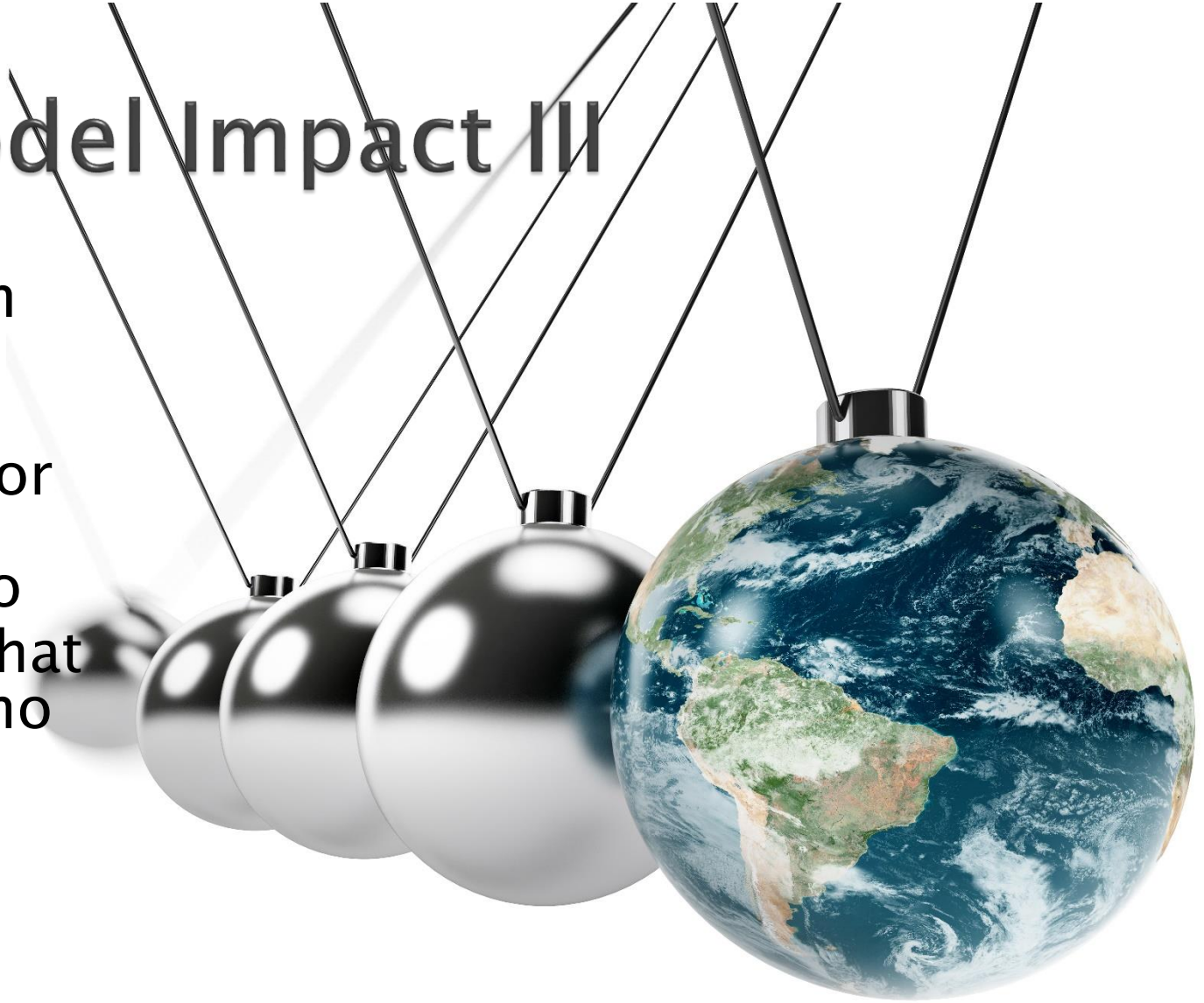
TMF Reference Model Impact III

- 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?



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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)*

Conference	When	Location
Hanson Wade Operationalize electronic Tral Master Files Summit	August 16- 18, 2022	Boston, MA, USA
HSRAA Conference	September 28-30, 2022	Manchester, UK
Fierce Pharma TMF Summit	November 14-16, 2022	London, UK

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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

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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

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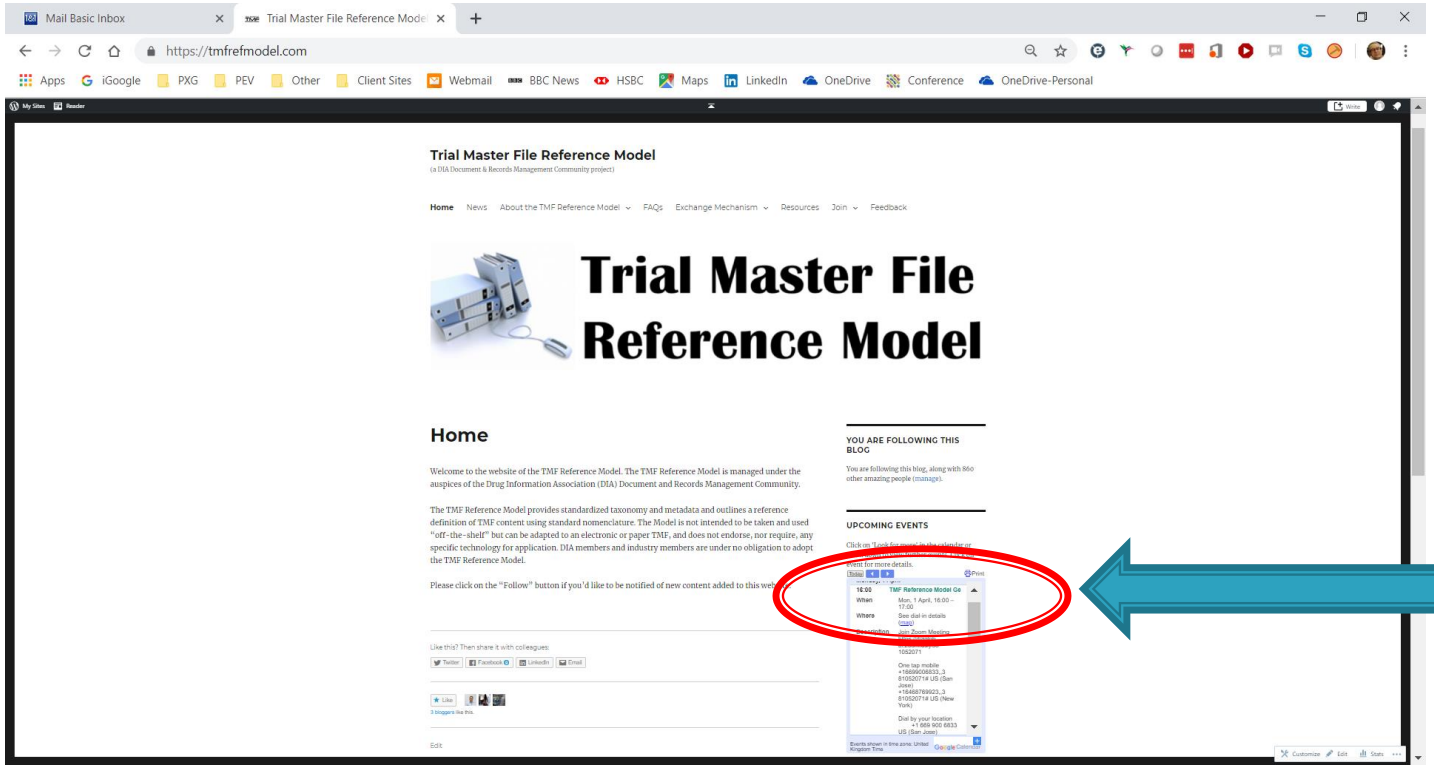
Meeting details

- 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.

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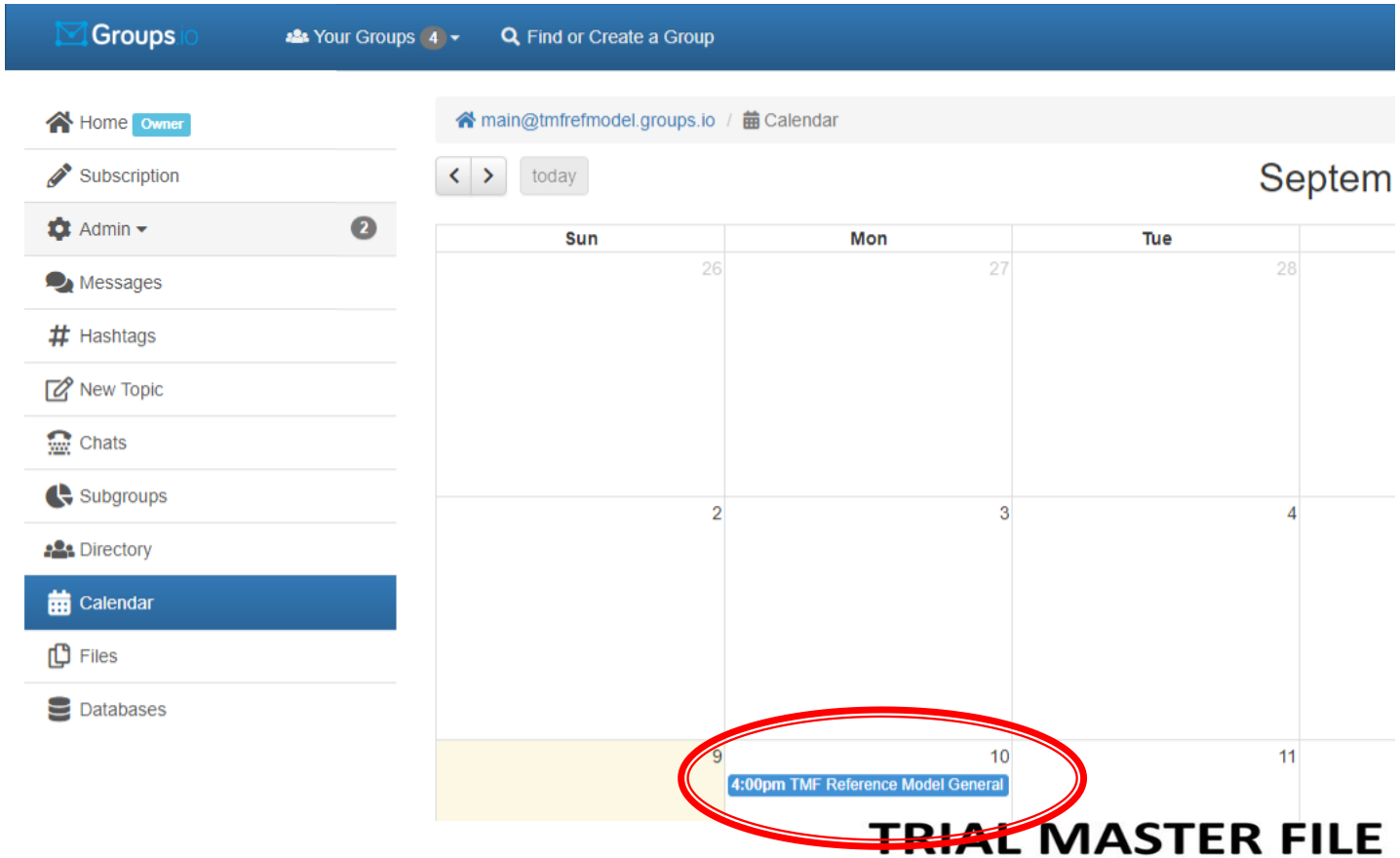
Meeting details

- 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**/



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