Trial Master File
Reference Model

Trial Master File Reference Model

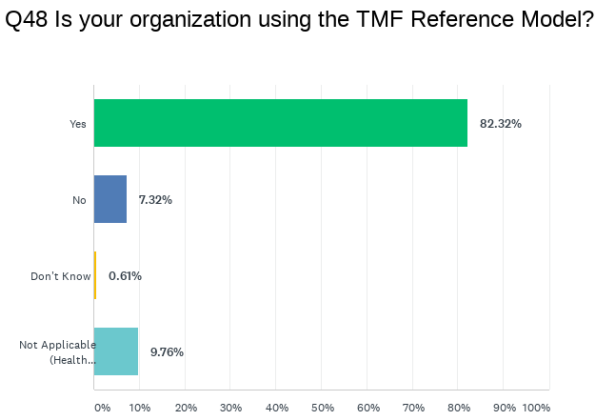
History and Current Status

What *is* the Trial Master File?

Essential documents relating to that clinical trial which allow verification of the conduct of a clinical trial and the quality of the data generated.

What *is* the Trial Master File Reference Model?

A Standardised structure, contents and naming of these Essential documents



Source: Annual TMF Ref Model Survey 2019
From 247 Respondents

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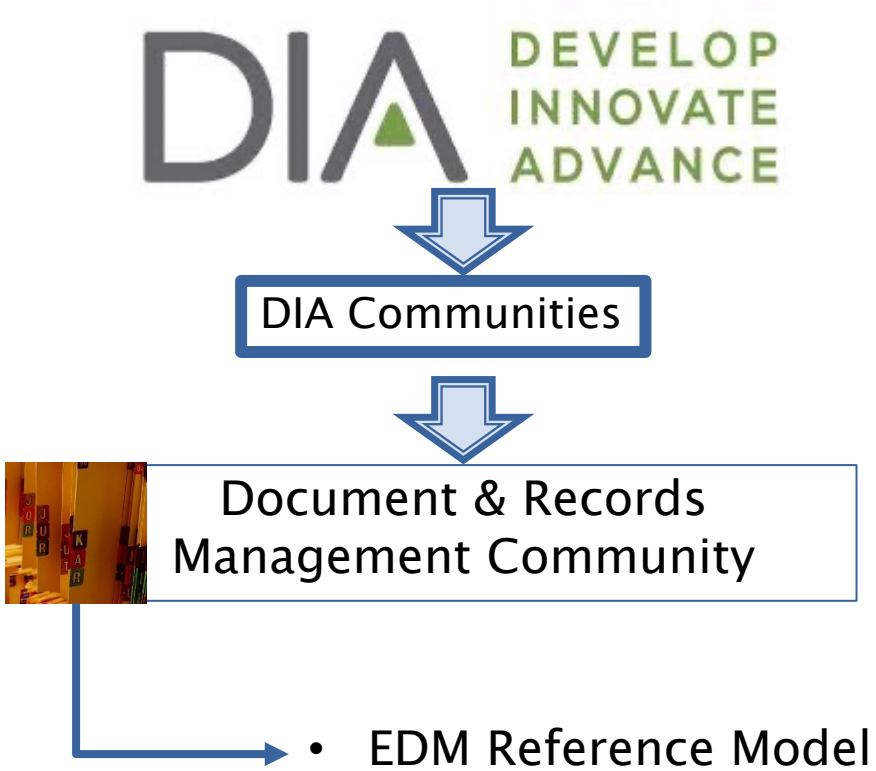
REFERENCE MODEL

Origins of the TMF Reference Model Concept



- Gap in Electronic Document Management (EDM) Reference Model identified for non-submission TMF documents
- EDM scope is regulatory submissions:
  - Significant input to the EDM Reference Model is TMF Documents

TRIAL MASTER FILE TMF REFERENCE MODEL

Why a TMF Reference Model?

- ICH GCP Section 8.2 – 8.4
- "The **minimum** list of essential documents that has been developed....."
- ICH GCP does **NOT** provide a comprehensive contents list for the TMF
  - Examples of missing documentation:
    - Electronic systems
    - Data management and statistical methodology
    - Safety monitoring

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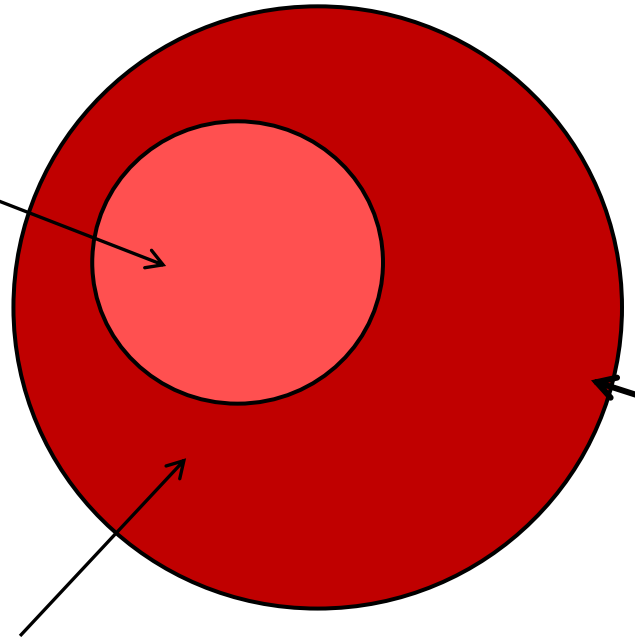
Defining the TMF Reference Model

Minimum list of essential documents, as defined by ICH GCP, Chapter 8



The Trial Master File

Other trial-related records that "permit evaluation of the conduct of the trial and quality of data produced"

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REFERENCE MODEL

Development of the TMF Reference Model

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

The Future as a Standard

TRIAL MASTER FILE TMF REFERENCE MODEL

How is the TMF Reference Model Managed?

- Governed under a formal charter
- 14 member Steering Committee
  - Chair
  - Meeting secretary
  - SC Charter – open for general review
- Independent website www.tmfrefmodel.com
  - Resources include Charter, deliverables, meeting slides, educational links, useful information and links
- Change Control Board

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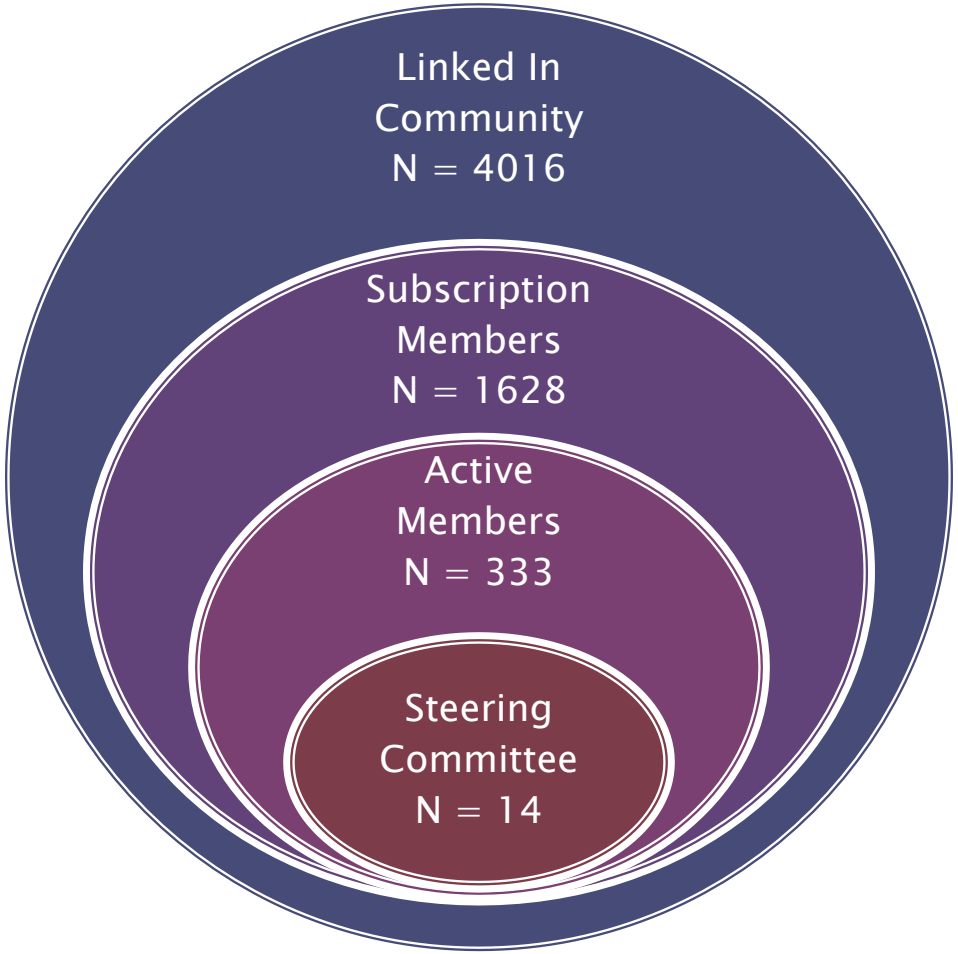
Who Manages the TMF Reference Model? (Jun-22)

- Karen Roy, Phlexglobal, Chairperson of SC, Co-chair of the TMF RM
- Lisa Mulcahy, Mulcahy Consulting – Co-chair of the TMF RM
- Allison Varjavandi, Astellas, Meeting secretary
- Mary Emanoil, Pfizer
- Jamie Toth, BeiGene
- Kathy Clark, Ennov
- Todd Tullis, Veeva
- Paul Fenton, Montrium
- Donna Dorozinsky, Just in Time GCP
- Joanne Malia, Regeneron
- Gillian Gittens, TransPerfect
- JP Miceli, Advanced Clinical
- Dawn Niccum, Inseption
- Wendy Trimboli, Acadia

The TMF Reference Model Community



For details on these different groups and how to get involved, see http://tmfrefmodel.com/join

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REFERENCE MODEL

…With many Deliverables!

Resources

- + TMF Reference Model
- + Project Team All-Hands Meetings
- + Resources for Current Versions of the Model
- + eTMF Exchange Mechanism Standard (eTMF-EMS)
- + TMF Tools
- + Annual TMF Reference Model Survey
- + Miscellaneous Resources
- + Published Articles
- + Prior Versions of the TMF Reference Model

Trial Master File Reference Model

(a Community Group affiliated to CDISC)

Current version: TMF Reference Model V3.2.1

Home

Welcome to the website of the TMF Reference Model. The TMF Reference Model was developed under the auspices of the Drug Information Association (DIA) Document and Records Management Community and is now affiliated to the **Clinical Data Interchange Standards Consortium** (CDISC).

The TMF Reference Model provides standardized taxonomy and metadata and outlines a reference definition of TMF content using standard nomenclature. The Model is not intended to be taken and used "off-the-shelf" but can be adapted to an electronic or paper TMF, and does not endorse, nor require, any specific technology for application. Organizations are under no obligation to adopt the TMF Reference Model.

Latest News:

TMF Reference Model Group Officially Affiliates with CDISC April 28, 2022

Upcoming Events

JUN **27** 4:00 pm - 5:00 pm UTC+0
TMF Reference Model General Meeting / Webinar

AUG **16** August 16 @ 8:00 am - August 18 @ 5:00 pm UTC+0
Operationalize: Electronic Trial Master Files Summit

SEP **28** September 28 @ 8:00 am - September 30 @ 5:00 pm UTC+0
HSRAA Annual Conference

NOV **14** November 14 @ 8:00 am - November 16 @ 5:00 pm UTC+0
Fierce European TMF Summit

View Calendar

Recent Discussion Topics

Translation Plan
1 week, 2 days ago

Digital Health – implications for records and data

TRIAL MASTER FILE TMF REFERENCE MODEL

Feedback and Change Requests

- If you have any feedback on the TMF Reference Model, including comments on existing artifacts, milestones, suggestions for additional artifacts or general comments about the TMF Reference Model, please use the link below to submit your feedback:

https://tmfrefmodel.com/feedback/

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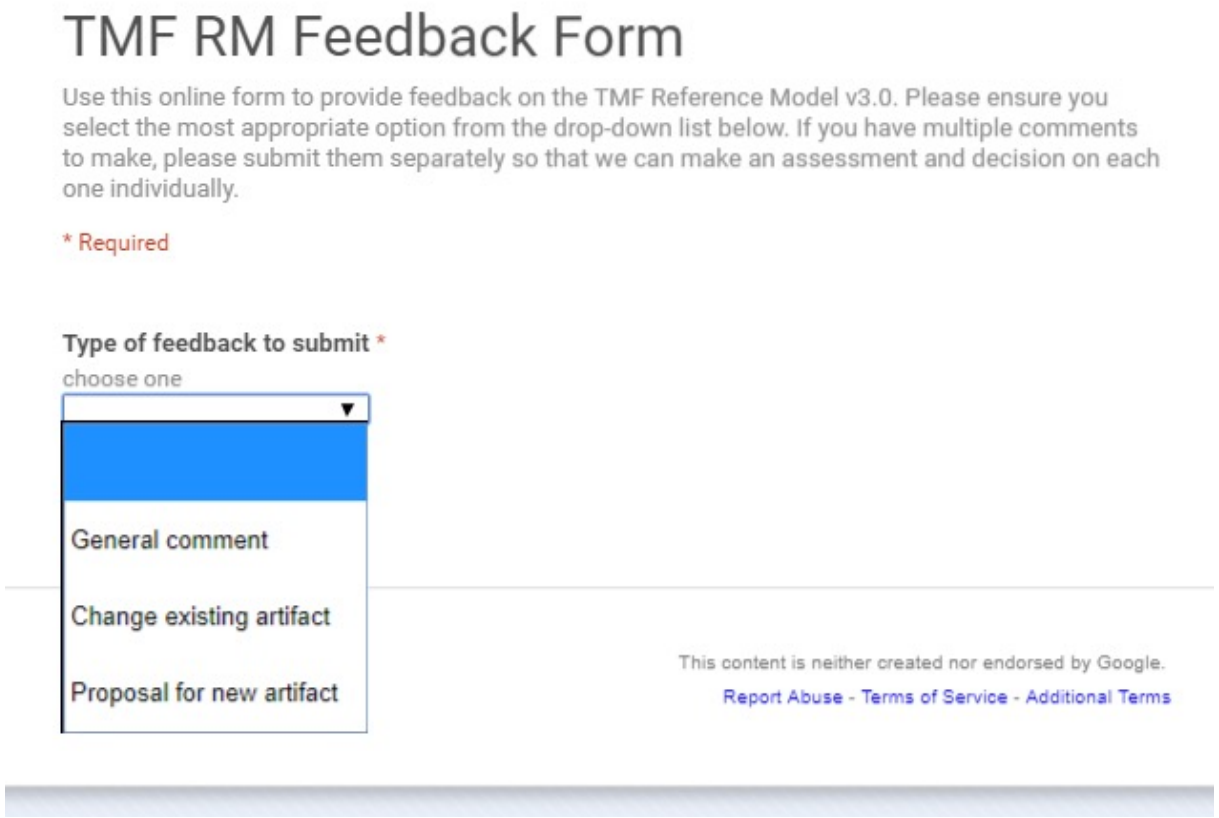
REFERENCE MODEL

Feedback and Change Requests



Use online form for:

- Making a suggestion for a general enhancement to the Reference Model
- Suggesting a change to any metadata for an existing artifact
- Suggesting a new artifact

Select the appropriate option and only make ONE suggestion per form submitted please.

Do not send general queries using this form.

TRIAL MASTER FILE TMF REFERENCE MODEL

Trial Master File
Reference Model

Trial Master File Reference Model

Defining the 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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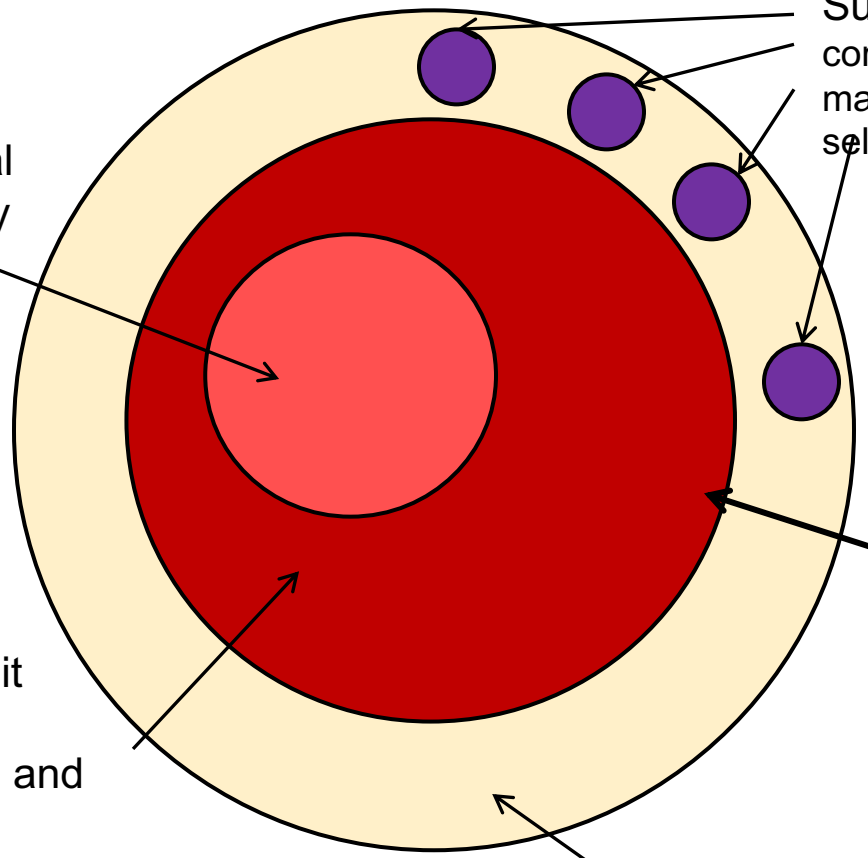
Defining the TMF Reference Model



Supporting files e.g. computer SDLC files; GMP manufacturing files; vendor selection files

Usually considered outside the scope of the TMF

Minimum list of essential documents, as defined by ICH GCP, Chapter 8

The Trial Master File

Other trial-related records that "permit evaluation of the conduct of the trial and quality of data produced"

Other business records

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Purpose of the TMF Reference Model

Standard Contents

Industry opinion on what is kept in a TMF

Standard Naming

Based on ICH E6 R2 Sect. 8 & industry-accepted terminology

Standard Structure

To support paper and electronic systems

Standard Metadata

Recommended minimum metadata at system and artifact level

TRIAL MASTER FILE TMF REFERENCE MODEL

Purpose – Standard Contents

Standard Contents

Industry opinion on what is kept in a TMF

- Expands minimum list of documents found in ICH E6 R2
- Consistent interpretation, based on peer opinion and regulator feedback
- Avoids scope creep for TMF

TRIAL MASTER FILE TMF REFERENCE MODEL

Purpose – Standard Naming

Standard Naming

Based on ICH E6 R2 Sect. 8 & industry-accepted terminology

- Avoids one artifact being referred to using different terms within an organisation and between organisations
- Potential for avoiding company-specific terms

Purpose – Standard Structure

Standard Structure

To support paper and electronic systems

- Facilitates consistent filing and rapid retrieval
- Helpful when responsibility for maintaining different sections of the TMF is distributed across several parties e.g. sponsor, CRO, consultants

TRIAL MASTER FILE TMF REFERENCE MODEL

Purpose – Standard Metadata

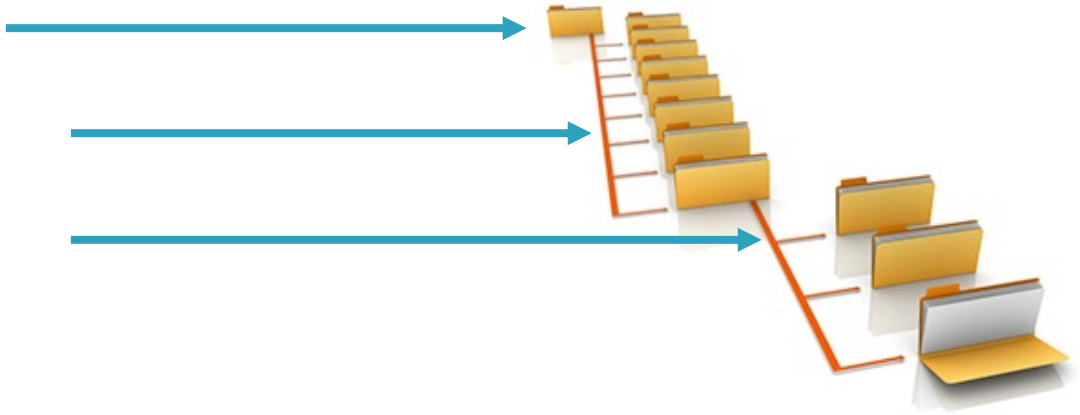
Standard Metadata

Recommended minimum metadata at system and artifact level

- Encourages adoption of good practices to facilitate document retrieval
- Encourages consistency across the industry for exchange of content

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

TRIAL MASTER FILE TMF REFERENCE MODEL

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 selectic
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 docu that del obligati descrip
09	Third parties	09.03	General	09.03.01	Relevant Communications	Correspondence	Zone-sp not spe include
09	Third parties	09.03	General	09.03.02	Tracking Information		Zone-sp 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 docu
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 compila limited Databa
10	Data Management	10.02	Data Capture	10.02.01	CRF Completion Requirements	CRF Completion Guidelines	To prov comple

TRIAL MASTER FILE TMF REFERENCE MODEL

TMF Reference Model Sections

- The contents of each zone are grouped into sections
- Each section includes content that is relevant to a specified activity
- Sections are helpful for classification and searching

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
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10	Data Management	10.02	Data Capture	10.02.01	CRF Completion Requirements	CRF Completion Guidelines	To prov comple

TRIAL MASTER FILE TMF REFERENCE MODEL

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

TRIAL MASTER FILE TMF REFERENCE MODEL

Artifact Definition

- A description to explain the content of an artifact and/or the use and purpose of the artifact
- Assists with ensuring a common interpretation of the model
- Aligned with ICH definitions

Artifact name	Alternate names (artifact also commonly known	Definition / Purpose
Filenote	Note to File	To document any decision or to clarify any information relating to this zone.
Data Management Plan	Data Management Operational Plan Data Handling Manual Data Processing Plan Technology Plan	To identify the overall strategy for data management process for the study; a compilation of documents that may include amendments/appendices but are not limited to: Completion Guidelines, Data Quality Plan, CRF Design Document, Database (build) Specification, Entry Guidelines, Database Testing..
CRF Completion Requirements	CRF Completion Guidelines	To provide detailed instructions on how data points on each CRF are to be completed; how to enter on paper and if EDC, how to enter data into the system.
Annotated CRF		To assign variable names and attributes to the fields on the CRF and to link the

ICH Code

- Reference to the ICH GCP Guidelines
- Notice that other sections beyond E6 Section 8 are quoted
- Includes indirect as well as direct references

Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Core or Recommended for inclusion	ICH Coc
08	Central and Local Testing	08.02	Sample Documentation	08.02.02	Shipment Records	Recommended	8.2.15 8.3.8
08	Central and Local Testing	08.02	Sample Documentation	08.02.03	Sample Storage Condition Log	Recommended	8.2.14
08	Central and Local Testing	08.02	Sample Documentation	08.02.04	Sample Import or Export Documentation	Core	8.2.15 8.3.8
08	Central and Local Testing	08.02	Sample Documentation	08.02.05	Record of Retained Samples	Core	8.3.25
08	Central and Local Testing	08.03	General	08.03.01	Relevant Communications	Core	8.3.11

TRIAL MASTER FILE TMF REFERENCE MODEL

Sub-artifacts

- When an artifact name does not explicitly refer to a single kind of record (e.g. Meeting Material), sub-artifacts provide a means to list all company-specific records that are expected for a given artifact.
- Only examples are provided in the model but expected to be overridden as part of adopting the Reference Model for a company.
- 3.2 includes a comprehensive list

Zone	Zone Name	Section	Section Name	Artifact #	Artifact name	Recommended Subartifacts – Documents/documentation recommended to be filed to the artifact.
01	Trial Management	01.01	Trial Oversight	01.01.14	Audit Certificate	Audit Certificate List of Audits
01	Trial Management	01.01	Trial Oversight	01.01.15	Filenote Master List	Filenote Master List
01	Trial Management	01.01	Trial Oversight	01.01.16	Risk Management Plan	Risk Management Plan Risk Assessment Risk Log

TRIAL MASTER FILE TMF REFERENCE MODEL

How does this correlate to a paper TMF?

- Trial level files
- Country level files per Country
- Site level files per Site

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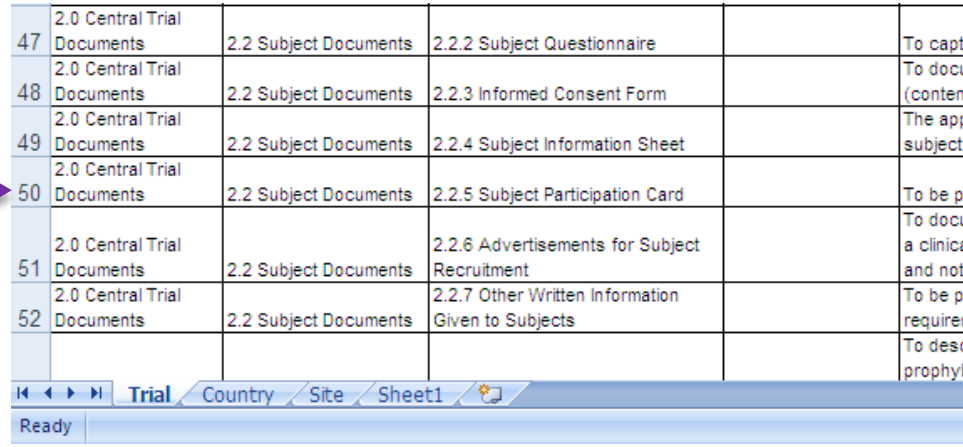
Application of the TMF Reference Model

		TMF Level		
Artifact #	Artifact name	Trial Level Document	Country/ Region Level Docume	Site Level Documer
01.01.01	Trial Master File Plan	X		
01.01.02	Trial Management Plan	X	X	
01.01.03	Quality Plan	X	X	
01.01.04	List of SOPs Current During Trial	X	X	



47	2.0 Central Trial Documents	2.2 Subject Documents	2.2.2 Subject Questionnaire		To capt
48	2.0 Central Trial Documents	2.2 Subject Documents	2.2.3 Informed Consent Form		To docu (conten
49	2.0 Central Trial Documents	2.2 Subject Documents	2.2.4 Subject Information Sheet		The app subject
50	2.0 Central Trial Documents	2.2 Subject Documents	2.2.5 Subject Participation Card		To be p
51	2.0 Central Trial Documents	2.2 Subject Documents	2.2.6 Advertisements for Subject Recruitment		To docu a clinica and not
52	2.0 Central Trial Documents	2.2 Subject Documents	2.2.7 Other Written Information Given to Subjects		To be p require
					To desc prophyl

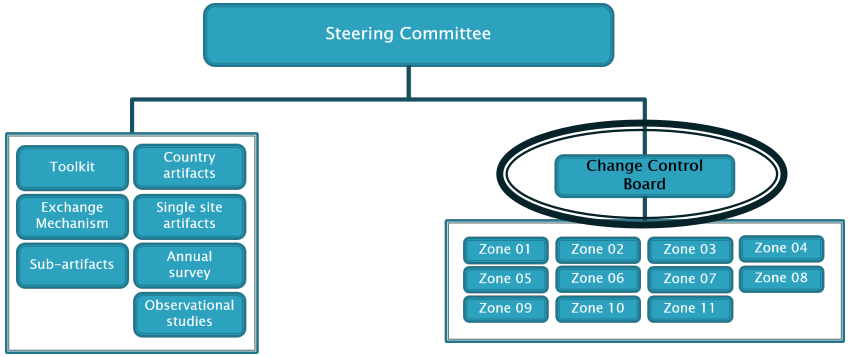
Trial | Country | Site | Sheet1

Ready

To create a paper TMF, filter for trial, country and site

TRIAL MASTER FILE TMF REFERENCE MODEL

Who Controls the Versions?



- **Change Control Board Structure (Sep-21)**
  - Kelley Robinson, Odonate: Chair
  - Leila Ponce, Seattle Genetics: Deputy Chair
  - JP Miceli: Zone Team Liaison
- **Deliverables**
  - Meeting twice a month
  - Change Control Procedure, RACI and CR Tracker
  - Reviewing and categorising all current change requests
  - Triaging all change requests to Zone Teams
  - Delivery of new versions

TRIAL MASTER FILE TMF REFERENCE MODEL

Version Definition

- Maintenance release e.g. v3.0.1
  - e.g. minor typographic changes, clarification, sub-artifacts
- Minor release e.g. v3.1
  - Substantial change in content but no compatibility issues e.g. additional optional column (milestones)
- Major release e.g. v4.0
  - Change likely to have compatibility issues with prior version e.g. addition/removal of artifacts

- You don't need to be on the latest version!

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)

TRIAL MASTER FILE TMF REFERENCE MODEL

QUESTIONS?

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

- Knowledge sharing
- Networking
- Too Much Fun!

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