Trial Master File Reference Model

Overview and Version 3.1

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”?

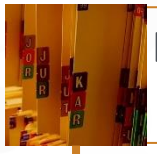
Essential documents are those documents that individually and collectively **permit evaluation of the conduct of a trial** and the **quality of the data** produced. These documents serve to demonstrate the **compliance** of the investigator, sponsor, and monitor with the standards of GCP and with **all 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 does **NOT** provide a comprehensive contents list for the TMF
  - Examples of missing documentation:
    - Electronic systems
    - Data management and statistical methodology
    - Safety monitoring

Origins of the TMF Reference Model Concept



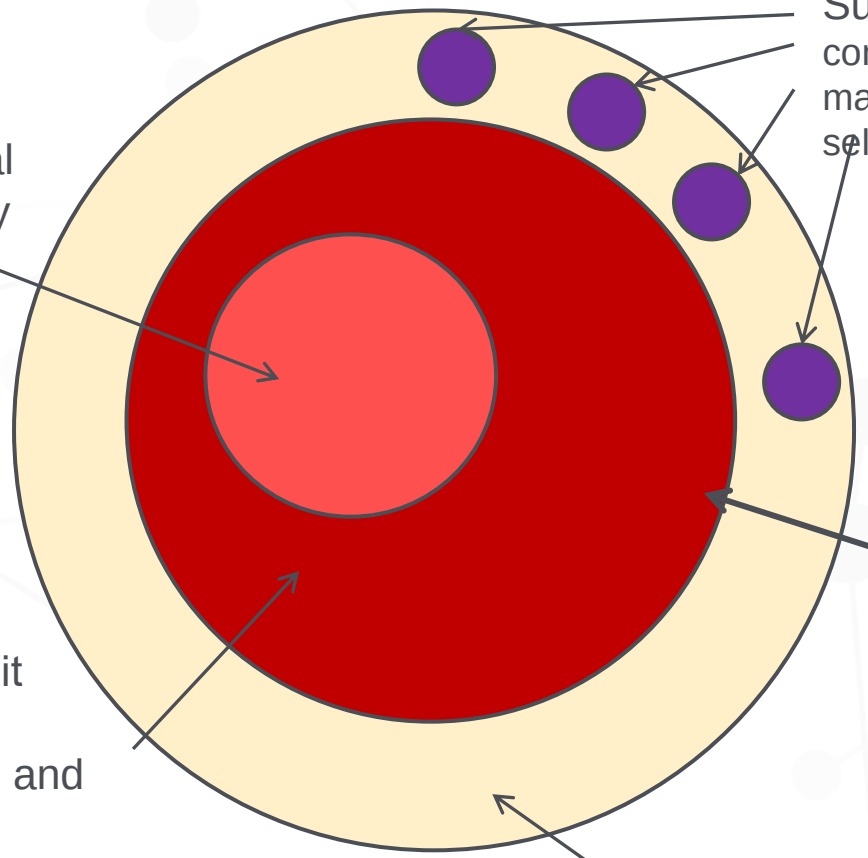
DIA Communities

Document & Records Management Community

- EDM Reference Model

- 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
  - Hence the creation of the TMF Reference Model

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"

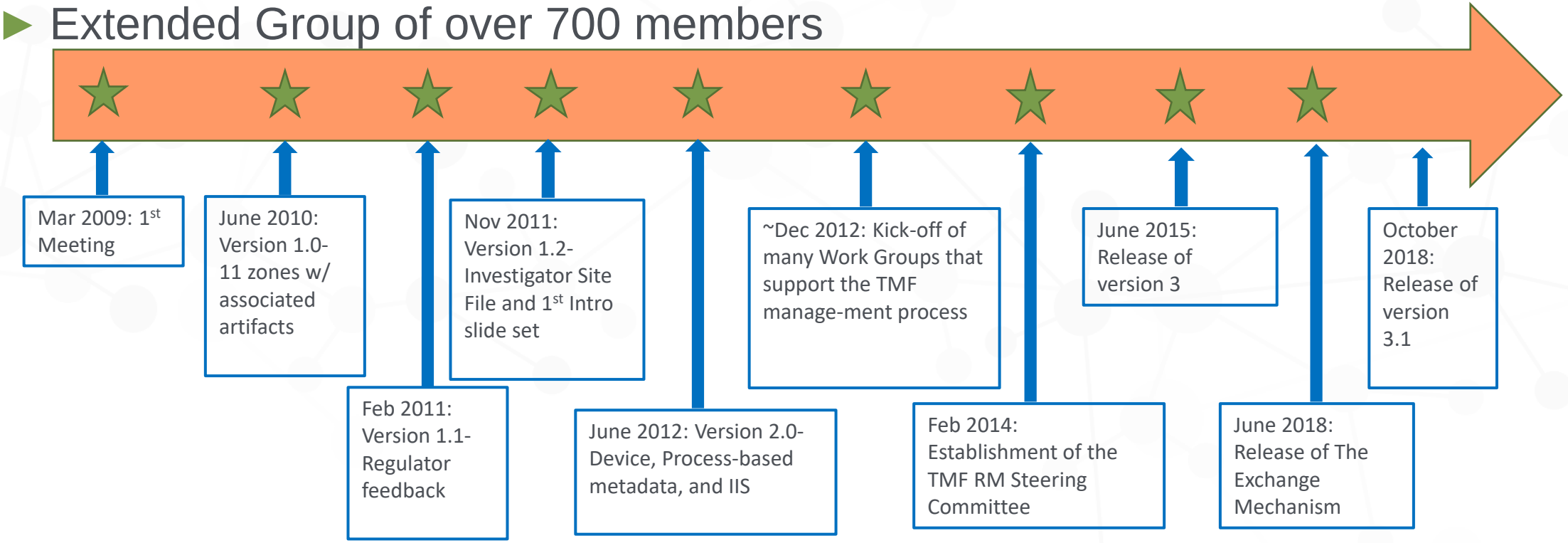
Other business records

Benefits Gained by Implementation

- Standardizes company content and structure and limits company customization
  - 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)

TMF RM History and Management

- Managed by a Steering Committee of 14 members
- Change Control Board
- Extended Group of over 700 members



Purpose of the TMF Reference Model

Standard Contents

Industry opinion on what is kept in a TMF

Standard Naming

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

Standard Structure

To support paper and electronic systems

Standard Metadata

For eTMFs, minimum metadata at system and artifact level

Purpose – Standard Contents

Standard Contents

Industry opinion on what is kept in a TMF

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

Purpose – Standard Naming

Standard Naming

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

- Avoids one artifact being referred to using different terms within an organisation and between organisations
- Avoids 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

Purpose – Standard Metadata

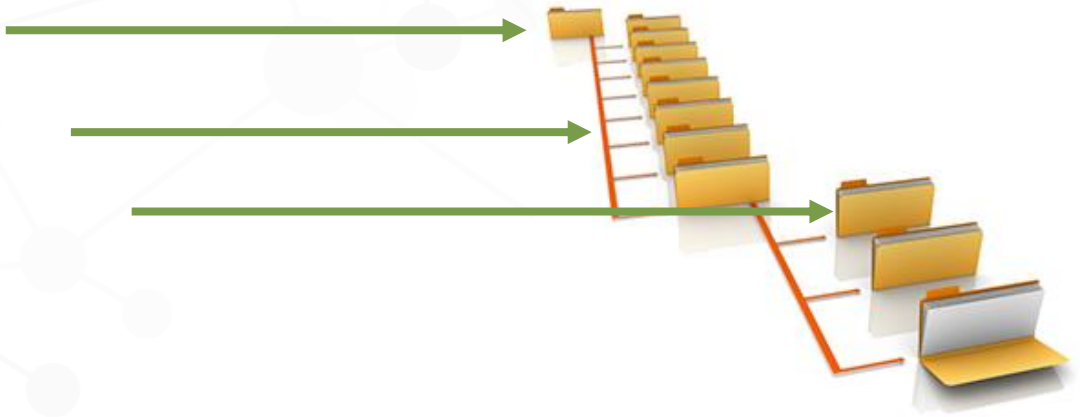
Standard Metadata

For eTMFs, 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***



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

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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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

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

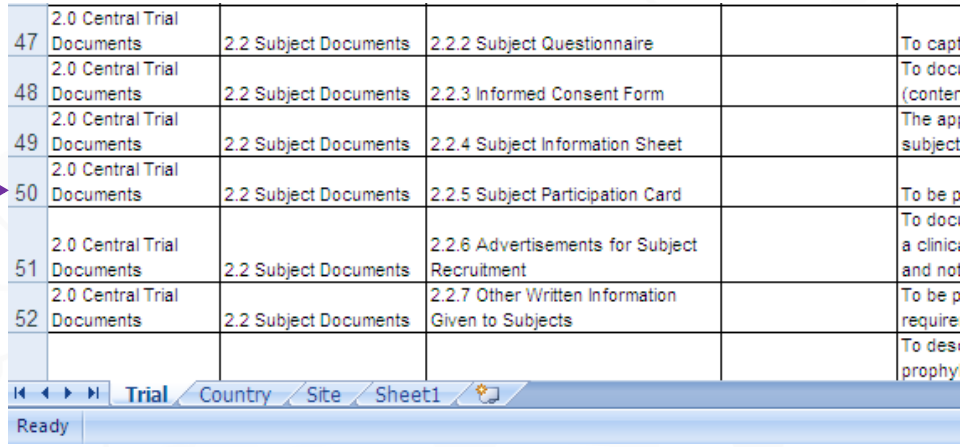
Sub-artifacts

- 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.
- Current subgroup activity to refine

Zone #	Zone Name	Section #	Section Name	Artifact	Artifact name	Sub-artifacts (examples of document types different from the artifact provided, overwrite with your company-specific record
01	Trial Management	01.03	Trial Committee	01.03.03	Committee Output	Committee Correspondence Committee Data Package Committee Minutes Committee Report
01	Trial Management	01.04	Meetings	01.04.01	Kick-off Meeting Material	Agenda Minutes Attendance Sheet Presentation Materials Questions and Answers Recording
01	Trial Management	01.04	Meetings	01.04.04	Trial Team Evidence of Training	Attendance Sheet Training Report Recording

Paper TMF Application

		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 doc (conter
49	2.0 Central Trial Documents	2.2 Subject Documents	2.2.4 Subject Information Sheet		The ap 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 doc a clinic 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 des prophy

Trial | Country | Site | Sheet1

Ready

To create a paper TMF, split the Model out to 3 spreadsheets, filtering for trial, country and site on each

Version Control

- 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

TMF Reference Model 3.1.0

- **Documentation Delivered**
  - TMF Reference Model Version 3.1.0
  - TMF Reference Model Version 3.1.0 Release Notes
    - Released on 10-Sep-2018 for preview
    - Effective as of 10-Oct-2018
    - https://tmfrefmodel.com/resources/
- **Change Requests ‘By the Numbers’**
  - Total of 64 Change Requests Submitted since October 2015
    - 23 Approved and included in release 3.1.0
    - 18 Rejected
    - 21 Deferred
      - Deferred to sub-teams, Steering Committee or next release

TMF Reference Model 3.1.0

- Added deliverables already approved
  - Suggested dating conventions for each artifact (Feb 2017)
  - Recommended milestones/events (Jan 2018)
    - Also scheduled for assessment during 2019 to take account of industry feedback

TMF Reference Model 3.1.0

- Four minor changes to artifact name
  - 03.01.02 Regulatory Approval Notification…. Regulatory Approval Decision
  - 03.02.02 Import or Export License…. Import or Export Documentation
  - 03.03.01 Notification to Regulatory Authority of Safety or Trial Information…. Notification of Safety or Trial Information
  - 10.03.10 Data QC or QA Plan and Results…. Data Review Documentation

TMF Reference Model 3.1.0

- Eight minor changes to artifact definition/purpose
  - 01.05.04 Filenote
  - 02.01.01 Investigator's Brochure
  - 03.01.01 Regulatory Submission
  - 03.03.01 Notification of Safety or Study Information
  - 06.01.06 IP Transfer Documentation
  - 08.02.05 Record of Retained Samples
  - 11.03.02 Analysis QC Documentation
  - 11.03.09 Final Analysis Datasets

TMF Reference Model 3.1.0

- Sub-artifacts added for three artifacts
  - 10.03.09 Dictionary Coding
  - 10.03.10 Data QC or QA Plan and Results
  - 02.03.01 Clinical Study Report

- Further sub-artifacts currently under development by sub-artifact team…. for release in 2019

TMF Reference Model 3.1.0

- Two artifacts with revised ICH codes
  - To correct a typographical error
  - 02.01.02 Protocol
  - 02.01.04 Protocol Amendment

TMF Reference Model 3.1.0

- Three artifacts with additional filing level
  - Added study-level:
    - 03.01.01 Regulatory Submission
    - 03.01.02 Regulatory Approval Notification
  - Added site level:
    - 06.03.02 IP Unblinding Plan

TMF Reference Model 3.1.0

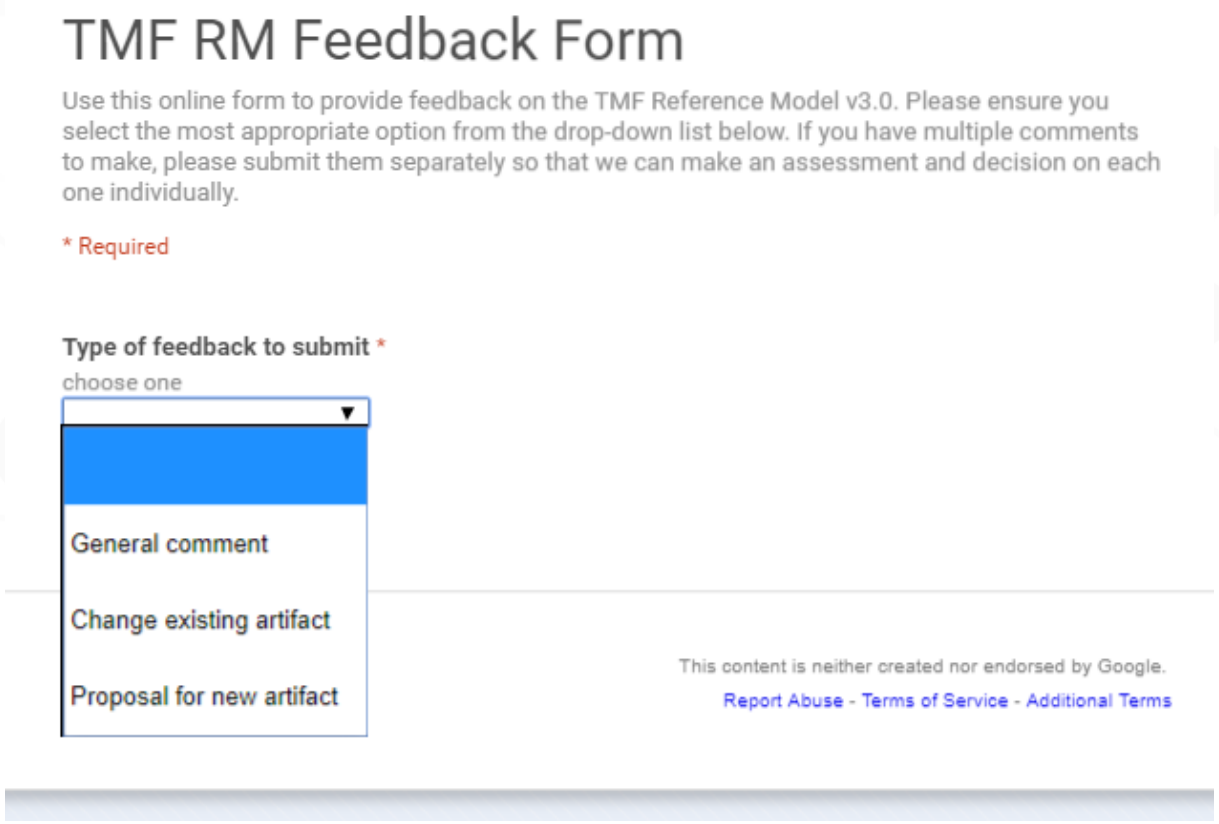
- Two artifacts with additional alternate names
  - To correct a typographical error
  - 03.01.02 Regulatory Authority Decision
  - 03.02.02 Import or Export Documentation

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/

Feedback and Change Requests



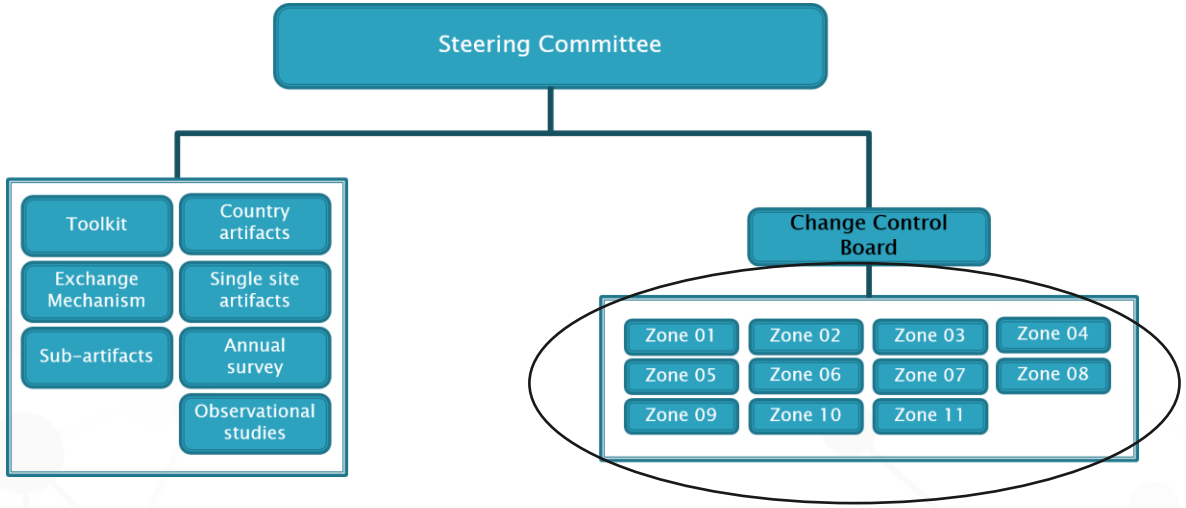
Use online form for:

- 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.

Get Involved!



- Have a passion for the TMF? Are you an expert in a particular area? We are always looking for new members to join the zone teams!

- Follow the instructions on the Join page or contact any member of the CCB team

TMF RM Version 3.1.0

What is the Impact?

- Release notes give all details to assess impact
- Minor release so minimal impact on overall structure
- Artifact names may change BUT the artifact numbers do not change
- Includes process aspects such as milestones and dating conventions – very customised by Sponsors / CROs

Future Releases

- Minor/Maintenance release anticipated in 1Q 2019
- Major release anticipated later in 2019 to incorporate deliverables from the following sub-teams:
  - Sub-artifact
  - Observational and Device

Deliverables to Date

TMF Tools:

- TMF Reference Model User Guide: Introduction to the model, understanding its structure, and how to use it (v1.0 Approved 16-March-2018) **NEW**
- TMF Reference Model Implementation Guidance: Provides a framework for implementing the model in your organization (v1.0 Approved 14-March-2018) **NEW**
- TMF Plan Template: Suggested structure and outline for a Trial Master File Plan (v1.0 Approved 23-February 2018) **NEW**
- TMF Plan Template Feedback: Click on LINK to provide feedback on the TMF Plan **NEW**
- Milestones / Events: Suggested latest milestones or events by which each artifact should be filed (v1.1 Approved 31-January-2018) **REVISED**
- Date Conventions: Suggested date convention to use for each artifact (Approved 15-Feb-2017)
- Date Conventions Guidance: Guidance notes to be used with Date Conventions spreadsheet (Approved 15-Feb-2017)
- TMF Quality Control: Toolkit to help prepare a TMF quality control programme (Approved 12-Oct-2016)
- TMF Quality Control Presentation: Powerpoint slides presented to group meeting November 7, 2016
- Inspection Readiness: Toolkit to help prepare TMF for regulatory inspections (Approved 09-Nov-2016)
- Inspection Readiness Presentation: Powerpoint slides presented to group meeting January 9, 2017
- eTMF Selection – Request for Proposal Template (co-authored by Scientific Archivists Group, TMF Reference Model and Pocket EDMS, March 2017
- Inspection FAQs: Common inspection questions with answers, and regulatory resource list (Approved 15-Mar-2017)

- Metrics 101 – How to Implement a TMF Metrics Program (PDF File)
- Metrics 101 – How to Implement a TMF Metrics Program (PPT File)
- Metrics Definitions – Recommended Metrics for your TMF Metrics Program (XLS File)

DIA

Ongoing Subgroup Activities

Group	Aim
Metadata	To standardise the metadata collected – integrated into the Exchange Mechanism
Sub-artifacts	To standardise the subartifacts in the TMF RM
Country specific artifacts	Guide for country specific artifacts required (with links to relevant websites)
Device Studies	Device specific artifacts
JGCP	Mapping to Japanese GCP documents

QUESTIONS?

Join the Trial Master File Reference Model Discussion Forum

https://tmfrefmodel.com/

- Knowledge sharing
- Networking
- Too Much Fun!

Join the TMF Reference Model Project Team

http://tmfrefmodel.com/join