# TRIAL MASTER FILE
# TMF
# REFERENCE MODEL

# User Guide
# Version 2

18-Nov-2020

This document is freely distributable

# Identification

## Authors

| Name | Organization | Title |
|------|--------------|-------|
| TMF User Guide and Implementation Guide Sub-Team | | |

# Version History

| Version | Steering Committee Approval Date | Changes |
|---------|----------------------------------|---------|
| 1.0 | 16-Mar-2018 | This is a new document, replacing the original User's Guide from June 2015. |
| 2.0 | 18-Nov-2020 | Updated to reflect changes in v3.2.0 |

# Table of Contents

# 1 Introduction to the TMF Reference Model

## 1.1 Goal of TMF Reference Model

The Trial Master File (TMF) is the trial sponsor's and investigator's collection of records (artifacts) that allows the reconstruction of the trial. It is part of the evidence for regulatory inspection that verifies that the project teams ensured subject protection, were compliant with regulations/Good Clinical Practice (GCP), and produced scientifically robust benefit-risk data.

The TMF can also greatly assist in the successful management of the trial by the investigator, sponsor and monitor. Although ICH E6 Section 8 provides guidance regarding the minimum essential documents required to be on file during the various phases of the trial, there are many additional documents, datasets, and data that are generated during a trial that are not defined in Section 8. This has left each organization with the task of defining their own structure/inventory of files that they were going to maintain to comply with applicable regulatory requirements.

Unfortunately, this approach led to inefficient TMF management practices, incomplete files, and files cluttered with extraneous documentation. These outcomes helped to contribute to inspections that resulted with findings for the Sponsors and Investigators.

Additionally, it has become increasingly difficult for organizations to effectively collaborate to create one final TMF filing structure whether within a global organization or across organizations such as the sponsor and the CRO. These two drivers helped the industry recognize that there needs to be a model/structure the industry can coalesce around.

## 1.2 History of TMF Reference Model

The Trial Master File Reference Model (TMF RM) Working Group was formed in 2009 by the Drug Information Association (DIA) Document and Records Management Community. The TMF RM team is a volunteer effort that includes biopharmaceutical and device companies, CROs, consultancies, technical vendors, industry groups, healthcare, academia, non-for-profit / non-governmental organizations and regulatory agencies. Since the inception of the TMF RM working group, membership as quickly grown and continues to grow over the years.

The first version of the TMF RM was published in 2010 as a single unified interpretation of the regulations and best practices. Version 2 (released June 2012) includes additional details for Investigator Site Files, Investigator Initiated Studies, Process-based Metadata, and Device Studies. Version 3 (released June 2015) refined the artifacts and Zones, introduced sub-artifact facilitation and provided an improved presentation layer. Version 3.2.0 (released November 2nd 2020) added "recommended sub-artifacts" and features a super-set of 612 customizable sub-artifacts to replace the previous "Sub-artifact" and "Alternate name" columns. The TMF RM is free and available at: https://tmfrefmodel.com/

## 1.3 How to contribute to the TMF Reference Model

The TMF RM is always evolving in response to industry trends and regulatory agency expectations. We value the input of all Industry colleagues and welcome you to participate in maintaining/growing the Reference Model. Go to https://tmfrefmodel.com/ to learn more about the group and to join in the work. In addition, comments or change requests can be submitted for consideration by the Reference Model Change Control Board via the website.

# 2 Introduction to the User Guide

## 2.1 Goal of the User Guide

The Trial Master File Reference Model (TMF RM) User Guide is a simple to use resource for introducing the TMF RM, understanding its structure, and how to use it. A separate guide describes how to implement the TMF RM. These two guides replace the original User Guide which was release in June 2015. The information presented was created by industry volunteers responsible for designing, implementing, managing, maintaining, evolving, and otherwise working with Trial Master Files and the TMF RM. The User Guide can be downloaded at: https://tmfrefmodel.com/.

# 3  Structure of the TMF Reference Model

## 3.1  TMF Zones, Sections and Artifacts

Defined in the model are record types, called artifacts, which one would expect to find in a TMF. The term artifact is used because the TMF can contain information recorded in a variety of different ways, including records, documents and data. An artifact is therefore any information that is captured during a clinical trial that meets the purpose or definition described in the Reference Model. In some cases, the artifact is a single document, data set or piece of information but in other cases it could be represented by multiple document types or data types.

The artifacts listed in the model are organised in zones; each zone is divided into sections and each section lists a number artifacts or document types.

Figure 2: Organisation of the TMF RM in zones, sections and artifacts
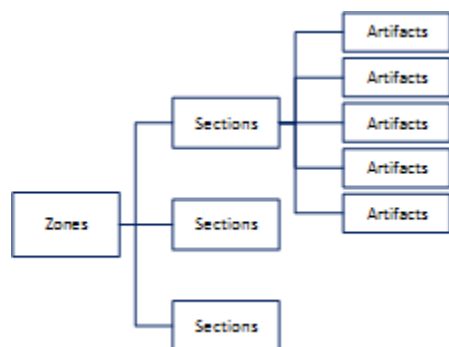


### 3.1.1 Zones and Sections

There are eleven categories/content Zones that group and structure the TMF RM.

- Zone 1: Trial Management – Records related to the general design, management and oversight of the trial; includes information about the trial team; project management and tracking; committees and charters, and training.

- Zone 2: Central Trial Documents – Core reference documents for the trial, including the Investigator Brochure, Protocol, and Amendments, Sample Case Report Form, Informed Consent Form (ICF), and the Clinical Study Report, as well as any ancillary documents directly related to the above. Capture trial documents that are related to the protocol, key subject documentation such as the ICF, questionnaire, diary, participation card and clinical study reports including pharmacokinetics in accordance with applicable regulatory standards.

- Zone 3: Regulatory – Records related to Regulatory Submissions and Approvals (to/from Health Authorities), Regulatory Filing and Registration Information, and Regulatory Notifications specific to the clinical trial.

- Zone 4: IRB/IEC and other Approvals – Official communications and exchanges with IRB's/IECs and other equivalent committees, including central, national, regional and local. Includes records related to IRB/IEC submissions, approvals, acknowledgments, as well as oversight information about the IRB/IEC.

- Zone 5: Site Management – Records related to selection, setup and management of investigational sites. Includes central site training and central monitor training. In addition, documentation related to unselected sites.

  – At the trial or country level, this Zone pertains to multi-site records and communications, such as newsletters, "all-sites" communications, etc. Site specific details will be managed in the Investigator Site Specific File. Also note that other zones also contain artifacts that are specific to an individual site; refer to the Filing Levels columns in the Reference Model to identify the recommended filing level for an artifact (see section 4.1.9).
  – Refer to Section 4 for guidance on filtering the model to show a trial-level structure, a country-level structure or a site-level structure and to show the structure for an Investigator Site File (also known as a Regulatory Binder).

- Zone 6: Investigational Product (IP) and Trial Supplies – Records related to the products under investigation including comparators - including instructions for shipping, storage, handling, returns and destruction, regulatory requirements, certificates, treatment allocation and decoding, inventory information - also includes supplies needed to fulfil the trial protocol requirements including shipping and returns – and any relevant communications. In the case of trials on devices and diagnostic tools, these records relate to the item under investigation.

- Zone 7: Safety Reporting – Records related to trial-specific Safety and Pharmacovigilance management:  This includes the safety management plan, safety database line listings, safety reports, and non-submission communications/documentation. Safety notifications to IEC/IRBs are found in Zone 4 and safety notification to regulatory authorities are fond in Zone 3.

- Zone 8: Centralized and Local Testing - Records related to central and local laboratory's SOPs, certification (and expiration dates), procedure manuals, current normal value ranges and the Laboratory Director's curriculum vitae (CV).

- Zone 9: Third Parties – Records related to the establishment and maintenance of a relationship between Sponsors and the Vendors / 3rd-Parties serving Sponsors by contract on the trial.  (ex, delegation of responsibilities)

  – It should be noted that this zone concerns the establishment and management of third party relationship and is not intended as the filing location for artifacts that are generated by a third party. These artifacts should be filed in the zone that is relevant for their content.

- Zone 10: Data Management – Records related to Data Management activity on the trial. Includes subject data (completed CRFs or Final EDC Data) and the design and establishment of databases.
- Zone 11: Statistics - Records related to Biostatistics and Statistical Programming activity on the trial.

## 3.1.2 Artifacts

Artifacts are collections of information presented in records, documents or data that one would expect to find in a TMF, at both Sponsor and Investigator site. In most cases, the term artifact should not be considered a single document but rather a collection of records, documents and data that fulfil a specific purpose. It is important to note that records that are associated with the named record/document, such as approval/signature pages, amended records, translation documentation, quality control records are not listed independently in the TMF RM as they belong filed with their related artifact. These are recommended sub-artifacts (see below).

- Recommended Sub Artifact – When an artifact name does not explicitly refer to a single kind of record (e.g. FDA 1572 Form.), recommended sub-artifacts are intended to provide a deeper level of granularity for records that a company would expect to file for a given artifact. Examples are provided in the model but expected to be replaced or supplemented by your own records as part of adopting the TMF RM for your company (refer to the Implementation Guide).
- Artifact Owner – Identifies the person or department or vendor that creates and maintains a given artifact, regardless of its location.
- Artifact Location – Identifies content storage system/locations for paper or electronic.

# 4 Navigating the TMF Reference Model Excel Spreadsheet

## 4.1 TMF Reference Model Workbook

The TMF RM is presented as a Microsoft Excel Workbook with content split into five different spreadsheets. The TMF RM itself is found in the first spreadsheet.

Figure 1: Overview of the content of the tabs



| Model overview | Explanation of the history of the TMF Reference Model and how artifacts work |
| Mark-up | Mapping of differences between two versions |
| Milestones Events and Description | Defines the latest point in time when an artifact is to be submitted / filed within the TMF |
| Instructions and Glossary | Provides a description of columns and abbreviations |
| Computer System Validation | Optional CSV artifacts |

## 4.1.1 TMF Numbering – Zones, Section & Artifacts

The TMF RM Workbook is organized to provide detailed information regarding each TMF artifact per row, and information related to each artifact in the vertical columns. The information in each column is as follows:

- **Zone #** - (1.0, 2.0, etc.) There are 11 TMF Zones outlined in the TMF RM
- **Zone Name** – Title of TMF Zone providing a high-level organization for TMF
- **Section #** (2.1, 2.2, etc.) Each TMF Zone with 2+ sections within the TMF Zone
- **Section Name** – Title of the TMF Section providing a breakdown of the TMF Zone
- **Artifact #** (2.1.1, 2.2.2, etc.) Each TMF Artifact defines a content level (record)
- **Artifact Name** – Common title of record generated to represent that artifact

| Zone # | Zone Name | Section # | Section Name | Artifac | Artifact name |
|--------|-----------|-----------|--------------|---------|---------------|
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.03 | Protocol Synopsis |

## 4.1.2 TMF Descriptions –Definition & Recommended Sub-artifacts

The TMF RM Workbook also provides informative details to provide guidance on what content is referenced by an artifact such as, definition/purpose, and recommended sub-artifacts.

| Artifact | Artifact name | Definition / Purpose | Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact. |
|----------|---------------|----------------------|---------------------------------------------------------------------------------------------|
| 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 |
| 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 |

**Definition/Purpose:**

To assist in the understanding of each artifact, a definition or regulatory purpose of each artifact is provided. Where applicable, the text is based on published regulations, including ICH E6. In the case of difficulty understanding where a company record matches an artifact in the Reference Model, the definition/purpose can be extremely useful to identify the most appropriate mapping.

**Recommended Sub-artifacts:**

The "Recommended Sub-Artifacts" column includes a fully-customizable list of company-specific types of records/documents that a company might expect to file under a given artifact. This provides flexibility to help ensure the TMF Reference Model is aligned with a company's procedural documents and compliance needs.

## 4.1.3 TMF Inclusion – Core vs. Recommended

The artifacts are labelled with the artifact inclusion recommendations as dictated by either the ICH Guidelines, regulations, or by consensus of the TMF RM group (ONLY if applicable for the trial) with either:

- **Core -** meaning that if such a record exists, it must be in the TMF, or
- **Recommended** - meaning the artifact does not have to be produced but if it is created or collected, it is recommended to be in the TMF

| Zone # | Zone Name | Section # | Section Name | Artifact # | Artifact name | Core or Recommended for inclusion |
|--------|-----------|-----------|--------------|------------|---------------|-----------------------------------|
| 02 | Central Trial Documents | 02,01 | Product and Trial Documentation | 02.01.04 | Protocol Amendment | Core |
| 02 | Central Trial Documents | 02,01 | Product and Trial Documentation | 02.01.05 | Financial Disclosure Summary | Recommended |

Organizations should only omit Core artifacts from their TMF index with extreme caution. If an artifact is not applicable to a trial, it may be omitted. For example, in an open-label trial, artifacts related to blinding may be excluded. In addition, if the information related to more than one artifact is recorded in a single artifact, the redundant artifact may be omitted to avoid duplication. For example, medical surveillance procedures may be described in the Safety Management Plan (artifact 07.01.01) rather than in a separate Medical Monitoring Plan (artifact 01.01.09).

## 4.1.4 ICH Code and EDM RM Artifact

The purpose of the **ICH Code** column is to cross reference the requirement of that content per ICH guidance. Many of the artifacts are mentioned either explicitly or implicitly in ICH E6 Good Clinical Practice Guidelines. These references are included in the model and include artifacts included in the minimum list of essential documents (Chapter 8) and throughout the remaining text of the guideline.

The purpose of the **EDM RM Artifact** name field is to provide a cross reference to the possible use of that TMF artifact for inclusion in a regulatory marketing submission. The Electronic Document Management (EDM) Reference Model is an associated taxonomy for regulatory submission content. Where a TMF RM artifact is also included in the EDM Reference Model (v1.3), the EDM Artifact name is identified to provide a cross-reference.

| Zone # | Zone Name | Section # | Section Name | Artifact # | Artifact name | ICH Code | Artifact name in v1.3 EDM Reference Model |
|---|---|---|---|---|---|---|---|
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure | 7.1 8.2.1 8.3.1 | |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol | 1.4.4 8.2.2 | Full Protocol (CSR component) |

## 4.1.5  Unique ID Number

Each artifact has been given a **unique ID Number**, which will allow for the tracking of the artifacts and their changes through future updates to the model. As the structure and content of the Reference Model changes over time, the artifact reference numbers (e.g. 02.03.04) may change or the artifact name and other details may change. However, the Unique ID Number that is associated with an artifact will always remain the same. This may be useful to facilitate sharing of content between organizations. For example, two organizations may use different names for a Subject Identification Card" but the Unique ID Number in both organizations will be 042 for this artifact.

| Zone # | Zone Name | Section # | Section Name | Artifact # | Artifact name | Unique ID Number |
|---|---|---|---|---|---|---|
| 02 | Central Trial Documents | 02,02 | Subject Documentation | 02.02.04 | Subject Information Sheet | 041 |
| 02 | Central Trial Documents | 02,02 | Subject Documentation | 02.02.05 | Subject Participation Card | 042 |

## 4.1.6 Sponsor/Investigator Filing Accountability

TMF artifacts are initiated and maintained by various stakeholder or parties on a clinical trial, including sponsors, partners (e.g., CROs) and investigational sites. The TMF RM includes the capturing of information for defining whether content should be filed in the **Sponsor** TMF, in the **Investigator** TMF or in both TMF files.

| Zone # | Zone Name | Section | Section Name | Artifact # | Artifact name | Sponsor Document | Investigator Document |
|---|---|---|---|---|---|---|---|
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure | X | X |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol | X | X |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.03 | Protocol Synopsis | X | NO |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.04 | Protocol Amendment | X | X |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.05 | Financial Disclosure Summary | X | NO |

## 4.1.7 Investigator Initiated Studies

It is recognized that some artifacts included in the TMF RM may not be relevant in the context of an investigator-initiated trial. The Investigator Initiated Study Artifacts column includes information to define which artifacts are mandatory, recommended or suggested depending on the trial design.

| Zone # | Zone Name | Section | Section Name | Artifact # | Artifact name | Investigator Initiated Study Artifacts M: mandatory, D: dependent upon the type of study, R: recommended |
|---|---|---|---|---|---|---|
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure | M |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol | M |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.03 | Protocol Synopsis | M |

## 4.1.8 Process Based Metadata

The classification of artifacts into zones provides a useful means of grouping related records. However, the records that are generated by a specific trial process may be filed across multiple zones, depending on how those records are subsequently used. The TMF RM therefore includes process metadata to align each artifact with a trial process; each process also has an associated process number for reference purposes. This metadata can be particularly useful in electronic filing systems to search for all records that are related to a specific process but are spread across multiple artifacts e.g. Process 22 – Management of IMP. The full list of processes can be downloaded as a process map from the TMF RM website (https://tmfrefmodel.com/resources/). A Process Number and Name are assigned to each artifact in the Reference Model.

| | | | | | | | Process Based Metadata | |
| Zone # | Zone Name | Section | Section Name | Artifact # | Artifact name | Process Number | Process Name |
|---|---|---|---|---|---|---|---|
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure | 2 | Develop Study Design / Study Conduct |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol | 2 | Develop Study Design / Study Conduct |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.03 | Protocol Synopsis | 4 | Develop Study Design / Document Development |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.04 | Protocol Amendment | 4 | Develop Study Design / Document Development |

## 4.1.9 TMF (Filing) Levels

TMFs are typically maintained as three sets of files (for paper-based filing) or in a three-level hierarchy (for electronic filing): trial-level, country-level or site-level. The model (see Columns U, V and W) shows which level each artifact is typically filed at.

It is important to note that artifacts should be filed at the most appropriate level, based on the content of the record. For example, if an artifact that is shown in the model as a trial-level artifact has been customized for an individual site, the filing level recommendation in the model should be ignored; the artifact should be filed as a site-level artifact.

It should also be noted that Zone 5 Site Management artifacts are not all site-level artifacts. Zone 5 artifacts may be filed at the country-level or trial-level if they are relevant to all sites within a country or all sites/countries within a trial respectively.

| Zone # | Zone Name | Section # | Section Name | Artifact # | Artifact name | TMF Level | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Trial Level Document | Country/ Region Level Docume | Site Level Documen |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.01 | Investigator's Brochure | X | X | |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.02 | Protocol | X | X | X |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.03 | Protocol Synopsis | X | X | |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.04 | Protocol Amendment | X | X | X |
| 02 | Central Trial Documents | 02.01 | Product and Trial Documentation | 02.01.05 | Financial Disclosure Summary | X | X | X |

## 4.2 TMF Mark-up Tab

The TMF RM Mark-up tab contains a red-lined version of the changes which were implemented since the preceding version.

| TMF Reference Model | | | TMF RM Website | Version 3.2.0 | 02-Nov-20 | |
|---|---|---|---|---|---|---|
| **Zone** | **Zone Name** | **Section #** | **Section Name** | **Artifact #** | **Artifact name** | **Alternate names (artifact also commonly known as)** | **Definition / Purpose** | **Recommended Subartifacts - (examples of document tes different from the artifact provided, overwrite with your company-specific records) Documents/documentation recommended to be filed to the artifact** | **Core or Recommended for inclusion** |

| 01 | Trial Management | 01.01 | Trial Oversight | 01.01.01 | Trial Master File Plan | Records Management Plan Central File Maintenance Plan Filing instructions Filing and archive 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 Core Document List TMF Report TMF Transmittal Form TMF Setup Request | Recommended |
| 01 | Trial Management | 01.01 | Trial Oversight | 01.01.02 | Trial Management Plan | Project Management Plan Clinical Development 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 Site Selection Strategy | Recommended |
| 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; 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... | Quality Documentation Quality Plan Quality Report | Recommended |
| 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 procedure and the rationale for the deviation, when... | List of SOPs Current During Trial SOP Waivers SOP Deviations | Core |
| 01 | Trial | 01.01 | Trial Oversight | 01.01.05 | Operational | Study Reference | To describe trial-related processes not covered by formal | Operational Procedure Manual | Recommended |

Ver 3.2.0 | **Ver 3.2.0 Markup** | Model Overview | Milestones_Events & Description | Instructions and Glossary | Computer System Validation | ...

## 4.3 TMF Model Overview Tab

The TMF RM Overview tab contains background information regarding the development and purpose of the TMF RM in general as well as links to the website where a variety of additional resources can be found.  An email address is provided if you have questions about the development of TMF RM and its management/oversight. Queries or comments regarding the implementation or interpretation of the RM can be raised on the Working Group's online discussion board or LinkedIn group.

**The Trial Master File Reference Model**
**Version 3.2.0 02 November 2020**
http://tmfrefmodel.com

feedback@tmfrefmodel.com

The TMF Reference Model team was initially formed in 2009 to develop a standardized taxonomy that outlines the clear definition and organization of TMF content using standard nomenclature. The Document and Records Management SIAC of the Drug Information Association (DIA) supported this initiative, and their support continues as the Reference Model evolves and expands today.

Since its inception, the TMF Reference Model has been developed by a pan-industry, global project team comprising in excess of 800 representatives from more than 300 bio-pharmaceutical and medical device companies, contract research organizations (CROs), consultancies, technical vendors, industry groups, healthcare, academia, not-for-profit / NGO and regulatory agencies.  The TMF Reference Model is a consensus of the TMF Reference Model Team that includes all essential documents that individually and/or collectively permit the evaluation of the conduct of a study and the quality of the data produced, in accordance with industry opinion and best practices. The model is a reference for the industry and should not be considered mandatory, but rather an opportunity for standardization across the industry. The TMF Reference Model can be adapted to an electronic or paper TMF.  It does not endorse, nor, require, any specific technology for application.  The model can be downloaded from the DIA website at:  http://www.diahome.org/en/News-and-Publications/Publications-and-Research/EDM-Corner.aspx

V1.0 of the TMF Reference Model, first released in June of 2010, was updated in February, 2011 (V1.1) and again in December, 2011 (V1.2), based on feedback provided (including Regulator feedback) as the model was widely implemented. V2.0 was released on 25th June 2012, at the DIA Annual Meeting and included additional details for Investigator Site Files, Device Studies, Investigator Initiated Studies, and Process-based metadata. Version 3 was released mid June 2015, at the annual DIA meeting and includes a complete review of the content, with a specific focus on standard artifacts, device artifacts and investigator site file artifacts.

**Rationale for the creation of a model**
The TMF contains those essential documents that individually and collectively permit the 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 Guideline for Good Clinical Practice, E6, Section 8).

All companies and investigators conducting clinical trials in the pharmaceutical/biotech and medical device industries maintain documentation for each clinical trial. Each company has their own unique TMF structure as defined by their SOPs. No comprehensive common model exists for managing TMF documents. Over the conduct of a trial many functions contribute to the TMF, although oversight of the content is usually not one function's responsibility – resulting in a highly inefficient work processes including but not limited to:

* All drug and medical device development companies and CROs expend considerable resources defining the content of the trial master file for each clinical trial.  Consequently,
* Investigators have the challenge of adapting to different formats and TMF content organization with each clinical trial.

| ▶ | Ver 3.2.0 | Ver 3.2.0 Markup | **Model Overview** | Milestones_Events & Description | Instructions and Glossary | Computer System Validation | ... ⊕ ⋮ ◀ |

## 4.4 Milestone Events and Descriptions Tab

There is a regulatory expectation that artifacts are filed contemporaneously so this tab defines what the TMF Reference Model considers to be the reasonable latest point in time when an artifact is to be submitted or filed within the TMF. Only one Milestone/Event has been assigned to each artifact for each level. As this is a guide, each company should modify the Milestone/Event list according to their own practices, including rolling up to fewer or expanding to more Milestones/Events. The intention is to ensure maintenance of the TMF on an ongoing basis.

| TMF Study Milestones / Events | | TMF Level | | |
|---|---|---|---|---|
| | | **Trial** | **Country** | **Site** |
| **Start Up** | | | | |
| #1 | First Country RA approval | The first notification (written or silent) across the study received from a regulatory authority stating that the Submission has been received and approved, indicating the trial is open for enrollment. In some instances, this may be an IEC approval. | The first notification (written or silent) received from a regulatory authority within the applicable country stating that the Submission has been received and approved, indicating the trial is open for enrollment within that country. In some instances, this may be an IEC approval. | The first notification (written or silent) received from a regulatory authority for the site stating that the Submission has been received and approved, indicating the trial is open for enrollment within that site. In some instances, this may be an IEC approval. |
| #2 | Clinical Infrastructure Ready | The necessary systems and processes required to support a study are ready for use. Examples include but are not limited to: study manuals describing critical study processes, the case report form (if paper) or a live EDC system, a live interactive web / voice response system, a live safety database, establishing a required study Committee, completing team training and an active trial master file. This milestone should occur just PRIOR TO opening the first site. Public registrations should be complete, as required. | The necessary systems and processes required to support a study are ready for use. Examples include but are not limited to: study manuals describing critical study processes, the case report form (if paper) or a live EDC system, a live interactive web / voice response system, a live safety database, establishing a required study Committee, completing team training and an active trial master file. This milestone should occur just PRIOR TO opening the first site. Public registrations should be complete, as required. | |
| #3 | Site Live / Ready / Open for Enrollment | The first site in the study has been approved / activated, IP shipment has been authorized, the site initiation visit and / or all training of site personnel is complete and the site is ready to begin screening / enrollment. | The first site within the specified country has been approved / activated, IP shipment has been authorized, the site initiation visit and / or all training of site personnel is complete and the site is ready to begin screening / enrollment. | The site has been approved / activated, IP shipment has been authorized, the site initiation visit and / or all training of site personnel is complete and the site is ready to begin screening / enrollment. |

... | Ver 3.2.0 Markup | Model Overview | **Milestones_Events & Description** | Instructions and Glossary | Computer System Validation

## 4.5 Introductions and Glossary Tab

The TMF RM Introductions and Glossary tab describes common terms used in the Reference Model.

| Item | Description |
|---|---|
| Artifact | Records or documents which one would expect to find in a TMF, at both Sponsor and Investigator site. It is important to note that artifact "progeny records" such as approval/signature pages, amended records or translation documentation are not typically called out uniquely as they belong filed with their related artifact. |
| Recommended Sub-artifact | A fully-customisable list of company-specific records that an organization might expect to file under a given artifact |
| Paper TMF / eTMF | Paper TMF usually presented according to Trial, Country and Site levels. Electronic TMFs denote level using metadata. For single country, combine Trial and Country. |
| Core | If created or collected, the artifact must be in the TMF as dictated by either the ICH Guidelines, regulations, or by consensus of the TMF Reference Model group. |
| Recommended | The artifact does not have to be produced, but if it is created or collected, it is required to be in the TMF if not housed elsewhere. |
| Drafts | Drafts to be excluded unless specifically submitted for approval |
| Central and Local Testing | Centralized and local testing zone is intended for all specialty testing vendors, on a global study level, a country level or a site level and should be modified based on the testing utilized. |
| ISF | X refers to an artifact that is always part of the ISF; NO refers to one that usually is not - please note there may be some targeted exceptions based on local criteria (i.e. countries). |
| IIS | For IIS, M is Mandatory, D is dependant upon the type of study being undertaken, R is recommended |

| Zone | Definition of Zone Contents |
|---|---|
| 01 - Trial Management | Records related to the general design, management and oversight of the study; includes information about the trial team; project management and tracking; committees and charters, and training. |
| 02 - Central Trial Documents | Includes the IB, Protocol, and Amendments, Sample CRF, ICF, and the CSR, as well as any ancillary documents directly related to the above. Capture study documents that are related to the protocol, key subject documentation such as the ICF, questionnaire, diary, participation card and clinical study reports including pharmacokinetics in accordance with applicable regulatory standards |
| 03 - Regulatory | Records related to Regulatory Submissions and Approvals (to/from Health Authorities), Regulatory Filing and Registration Information, and Regulatory Notifications specific to the clinical trial. |
| 04 - IRB / IEC and other | Official communications and exchanges with IRB's/IECs, including central, national, regional and local. Includes records related to IRB/IEC |

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## 4.6 Computer System Validation Tab

The TMF RM Computer System Validation tab contains information to consider for computer system validation records. These computer systems may be associated with TMF records across all of the zones and so have been listed separately. A trial -specific specification and trial -specific sign-off is usually considered part of the TMF but other CSV artifacts are typically held in an IT validation file, separately from TMF records described in zones 01-11. They must all nonetheless be readily available upon request in a GCP inspection.

### Computer System Validation

The variety of computer systems utilized in execution of clinical studies continues to grow, and includes both 'core' systems that are used for many studies and systems that are developed and/or configured for specific studies. ICH 5.5.3 suggests that when study data handling systems are utilized, sponsors should complete computer systems validation (CSV) processes to "Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance."

The TMF Reference Model includes artifacts for IRT systems (Zone 6) and CDM/EDC systems (Zone 10). The CSV artifacts are not consistent between these two zones. In anticipation of new types of clinical study data systems and in order to more consistently account for CSV artifacts, a TMF Reference Model CSV tab has been included. This list is intended to include in scope only those computer systems which are specifically developed or configured to handle data and electronic records for a specific clinical study (for example, the computer systems development of most Clinical Trial Management Systems is not study-specific thus CTMS computer systems validation documentation would not be expected to be in scope).

Use of these artifacts is strictly optional for the TMF Reference Model, either within zones or as a new zone - Zone 12 . An assessment has been completed and these artifacts will be maintained outside of the official TMF Reference Model. Your ongoing feedback & experience related to the classification of CSV artifacts is welcomed by the TMF Reference Model team.

| Artifact name | Alternate names | Definition/Purpose | Core or Recommended for inclusion | ICH Code |
|---|---|---|---|---|
| Specification | Requirements | Define the baseline for computer systems validation - what the computer system should do. Common documents for this artifact include (based on scope and magnitude of the computer system): Business/User Requirements, Functional Requirements, Technical Requirements, Performance Requirements, and Configuration Specifications. | Core (if applicable) | 5.5.3 |
| Signoff | Summary Report (Computer System) Validation Report | Record the results of a completed CSV project, including the conclusion that the computer system has been validated for its intended use. Document decision to release the computer system to a production environment. | Core (if applicable) | 5.5.3 |
| Computer System Validation Packet | Validation Package Validation Documentation | All other relevant computer systems validation documentation for the associated project. Specific documents to be included will vary based on company SOPs for computer systems validation, but may include | Recommended | |

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# 5 Navigate the TMF RM filter and sort functions

## 5.1 Filtering the TMF Workbook

The TMF RM Excel document has filters turned on for all columns. To filter a column, click the small arrow at the right side of that column header, and choose which data to display. Examples:

1. Filter by Zone Number/Name, Section Number/Name, or Artifact Number/Name to narrow down your view to only those selected zones, sections or artifacts.

| Zone | Zone Name | Section # | Section Name | Artifact # | Artifact name | |
|---|---|---|---|---|---|---|
| 01 | Trial Management | 01.01 | Trial Oversight | 01.01.01 | Trial Master File Plan | |

2. Filter by Column J "Core or Recommended for Inclusion" to see which artifacts are considered Core (always include) or Recommended (should include if produced during the trial)

| Core or Recommended for inclusion |
|---|
| Recommended |
| Recommended |
| Recommended |
| Core |

3. Filter by Columns N/O TMF Artifacts (Non-Device) or P/Q TMF Artifacts (Device) to see which artifacts are Sponsor or Investigator records.

| N | O | P | Q |
|---|---|---|---|
| X: applicable; NO* : Not applicable | | | |
| *There may be some targeted exceptions based on local criteria (i.e. countries) | | | |
| **TMF Artifacts (Non-device)** | | **TMF Artifacts (Device)** | |
| Sponsor Document ▼ | Investigator Document ▼ | Sponsor Document ▼ | Investigator Document ▼ |
| X | NO | X | NO |

For example, if you are running a non-device clinical trial and want to see just the artifacts that are expected in the Investigator Site File (also known as a Regulatory Binder), filter on Column O to select only those artifacts identified with an "X".

4.  Filter by Columns U/V/W TMF Level to see which artifacts are Trial, Country, and/or Site level artifacts.

| U | V | W | |
|---|---|---|---|
| **TMF Level** | | | |
| Trial Level Document ▼ | Country/ Region Level Docume ▼ | Site Level Docume ▼ | |
| X | | | |
| X | X | | |

For example, if you want to see just the artifacts that are expected in the Sponsor Site File, filter on Column W to select only those artifacts identified with an "X". Similarly, a country-level index can be generated by filtering on Column V (select artifacts identified with an "X") or a trial-level index by filtering on Column U (select artifacts identified with an "X").

## 5.2 Sorting

The Reference Model can be sorted by any column to organize data in a certain order. To sort by a column, click the small arrow at the right side of that column header, and select the sorting order (ascending or descending). Examples:

1. Sort by Zone Number/Name to quickly identify a specific zone.

| Zone # | Zone Name | Section # | Section Name | Artifact # | Artifact name | |
|---|---|---|---|---|---|---|
| 01 | Trial Management | 01.01 | Trial Oversight | 01.01.01 | Trial Master File Plan | |

Additional methods of sorting also include sorting by color if people choose to highlight specific cells within the TMF RM and the ability to Custom Sort.  Examples of how to use Custom Sort:

1. To custom sort, select the Sort & Filter button.
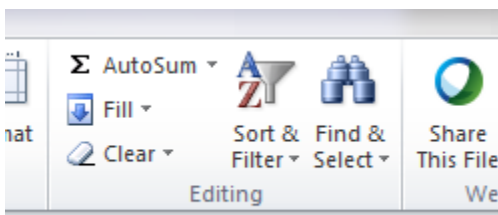
2. A Sort dialog box will appear.
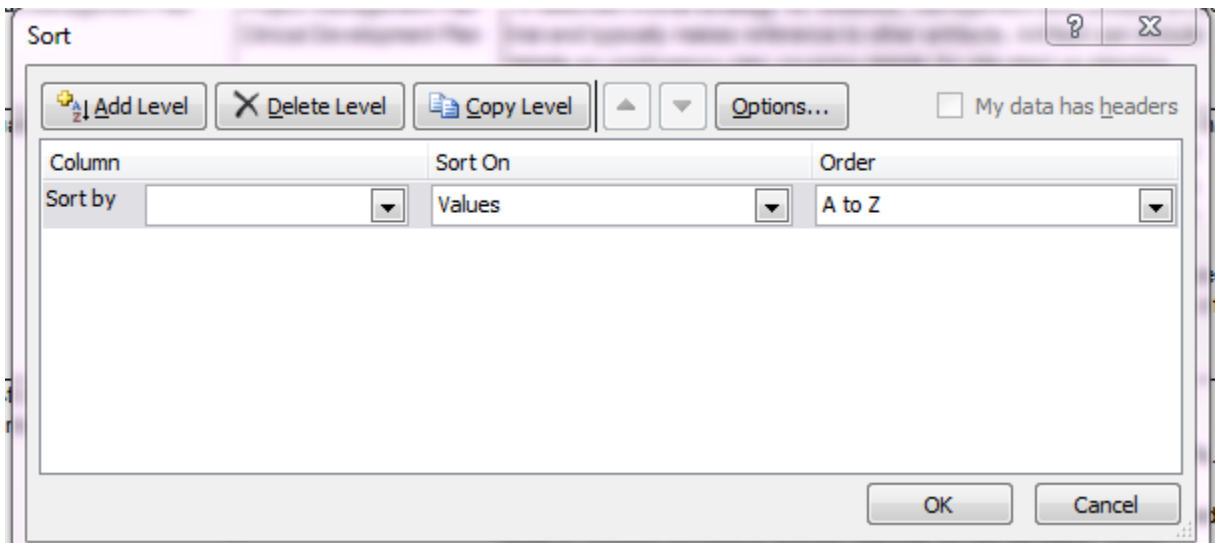
3. Select the columns you'd like to Sort by.
   a.     To see data values, select the checkbox "My data has headers".
   b.  To sort by more than one column, select Add Level