Overall Introduction of TMF

Tingting Wu, ICON

2024-12-06

Meet the Speaker

- Tingting Wu
- Title: Principle Statistical Programmer
- Organization: ICON

Tingting Wu is a principle statistical programmer with 9 years of experience in pharmaceutical industry. She worked as a statistical programmer at IQVIA for about 4 years. After that, she joined ICON and has been supporting the J&J Innovative Medicine FLEX program since 2019. She mainly supported oncology therapeutic projects, and has supported the NMPA submissions and inspections.

Disclaimer

- This presentation is for informational purposes only and does not represent professional guidance or advice. Any views and opinions expressed during this presentation are those of the presenters and do not necessarily reflect the views or policies of ICON.

Agenda

Introduction to CDISC TMF	Overview and Purpose
Components and Standards of TMF	TMF RM Structure and Compliance Standards
TMF Study Lifecycle	From Creation to Archiving
Case Sharing	Real-World Applications
Conclusion and Discussion	Key Takeaways and Q&A Session

Introduction to CDISC TMF

- What is TMF/TMF RM
- History of TMF RM
- Purpose of TMF RM

What is TMF

- The sponsor and the investigator shall keep a clinical **trial master file**. The clinical trial master file shall at all times contain the relating to that clinical trial which allow verification of the conduct of a clinical trial **essential documents** 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]

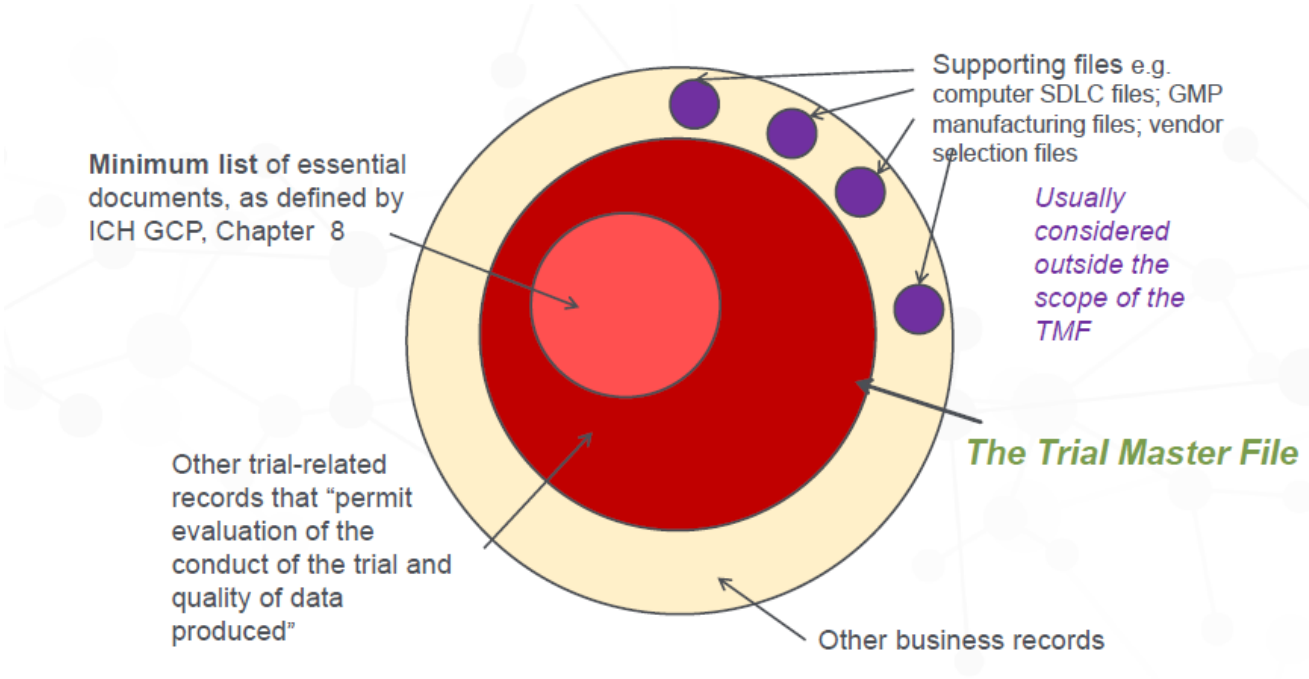
  - **Essential documents** are those documents that individually and collectively **permit evaluation of the conduct of a trial** and the **quality of the data produced**. These documents serve to demonstrate the **compliance** of the investigator, sponsor, and monitor with the standards of GCP and with **all applicable regulatory requirements**.

[ICH GCP, Section 8.1]

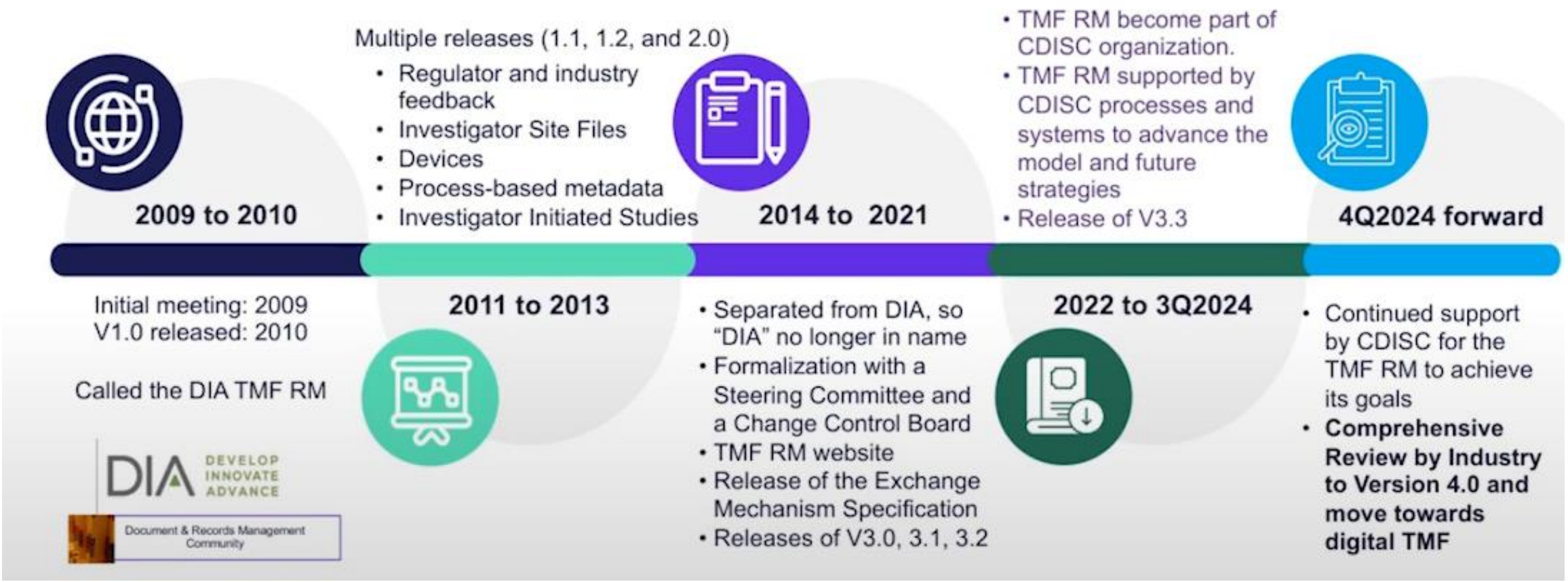
What is TMF Reference Model

A standardized structure, contents and naming of these Essential documents.

- 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.



History of the TMF Reference Model



New to CDISC - TMF Professiona

The Trial Master File Community joined CDISC in April 2022. The key de ster File Reference Model, which provides standardized taxonomy and metadata and outlines a reference definition of TMF content using star

The TMF Reference Model is maintained by a team of industry voluntee ties conducted by the project progress through a number of sub-groups, including maintenance and development of the Reference Mo

If you are interested in actively participating in this initiative and are prepared to contribute on a regular basis, you can volunteer on the CDISC website.

The TMF Initiative hosts General Meetings every quarter, the diary can be found **here**.

There is also an active **Forum** where questions can be posted and the community will respond. It is not a moderated Forum, and you need to **register** here to be part of the Forum

The TMF Reference Model **LinkedIn Group** is an active place for discussions and announcements. It is strictly monitored according to the following rules:

- No job postings
- No recruitment
- No company advertising, which includes company-specific 'advertorial' postings and promotions embedded in email signatures
- No vendor-specific conferences, webinars, or blog advertising, including links to these
- No advertising in responses to discussions

Learn More:

EDUCATE yourself on the TMF Reference Model, the management thereof and the deliverables.

VIEW The TMF Reference Model.

VIEW the Exchange Mechanism Specification.

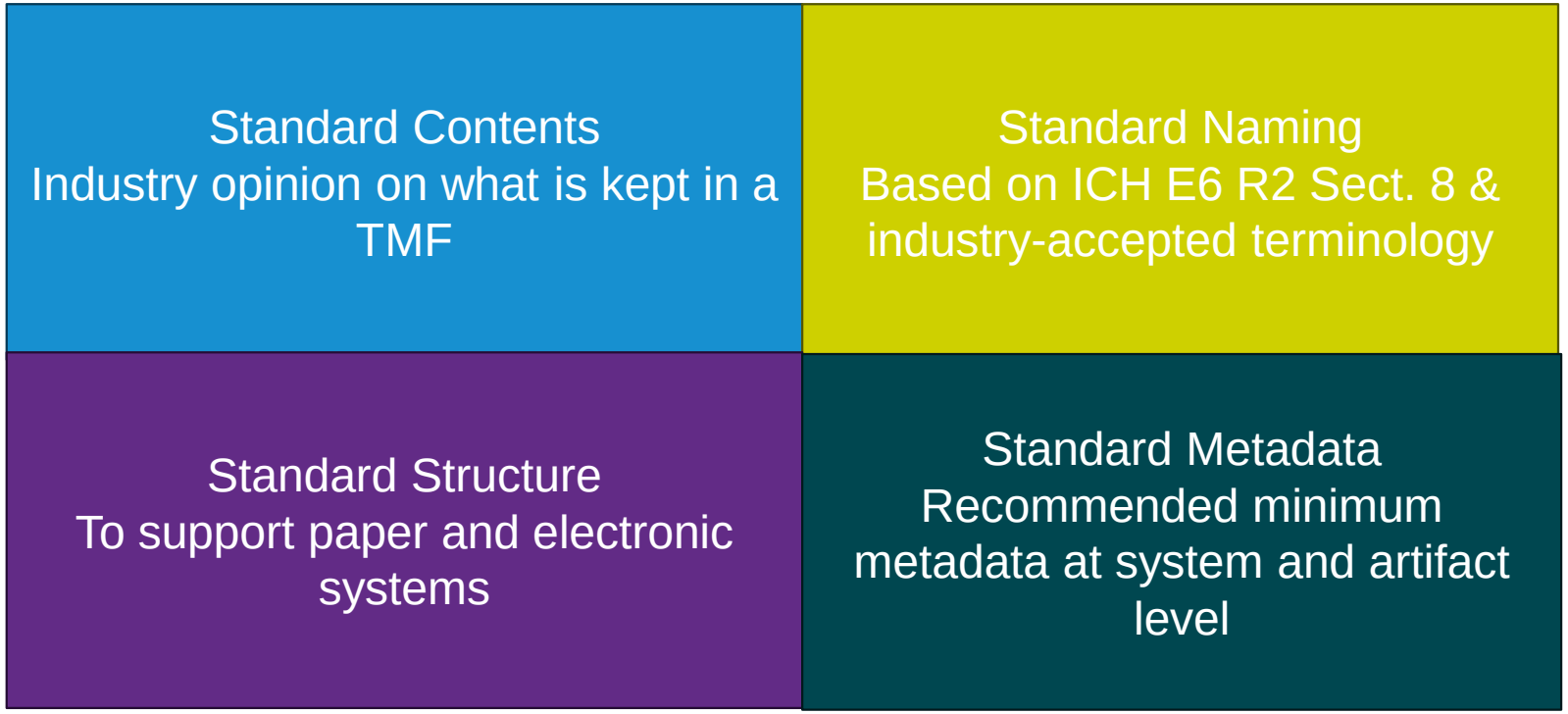
JOIN CDISC: Over 500 member organizations around the world comprise the CDISC Community.

VOLUNTEER: We rely on the subject matter expertise of volunteers to create our standards.

STAY INFORMED: Receive updates and announcements right to your inbox.

TAKE A COURSE: Public, Private, and Online Training (available 24 hours a day)

Purpose of TMF Reference Model



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
- Avoid scope creep for TMF

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
- Avoids company-specific terms

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

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

Components and Standards of TMF

- TMF RM Workbook
- Structure of TMF RM
- Benefits Gained by Implementation

TMF Reference Model Excel Spreadsheet

11-AUG-2023

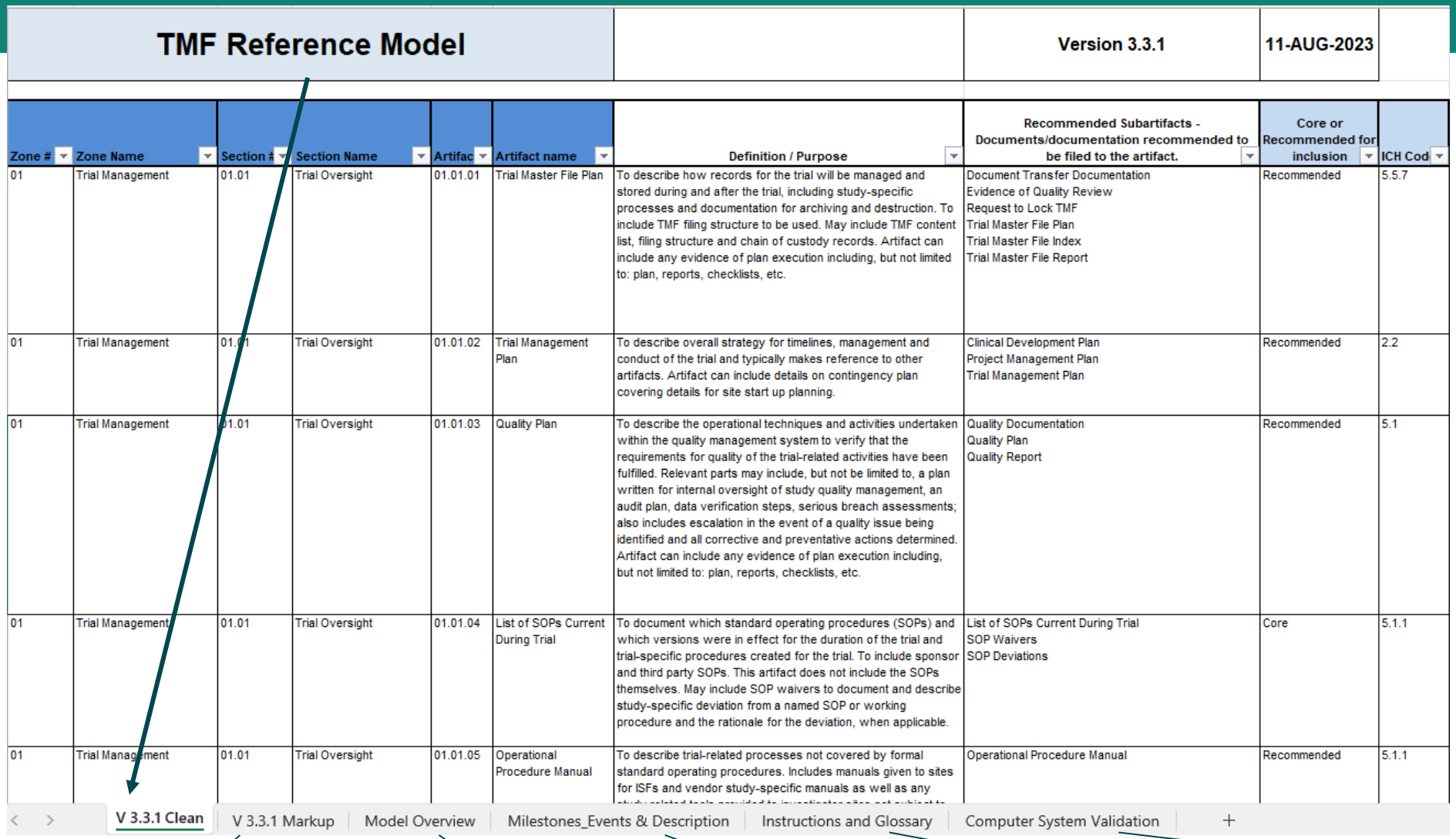
X: applicable; NO" : Not applicable
"There may be some targeted exceptions based on local criteria (i.e. countries)

					TMF Artifacts (Non-device)		TMF Artifacts (Device)		Investigator Initiated Study Artifacts	Metadata		TMF Level						Suggested Columns for Implementing the TMF Reference Model							
Core or Recommended for inclusio	ICH Code	ISO 14155 Reference (Device Studies)	Artifact name in v1.3 EDM Reference Mod	Unique ID Numb	Sponsor Docume	Investigator Documen	Sponsor Docume	Investigator Documen	M: mandatory, D: dependent upon the type of study, R: recommende	Process Numb	Process Name	Trial Level Documer	Trial Level MILESTONE/EVENT	Country/ Region Level Documen	Country Level MILESTONE/EVENT	Site Level Docume	Site Level MILESTONE/EVENT	Dating Convention	Artifact Owne	Artifact Locati	Wet Ink Signatur e	SOP Referenc e	Translation Requir	Current Artifact Name	Additional Metadata
Core	6.9	6.6	Statistical Analysis Plan	209	X	NO	X	NO	M	12	Develop Trial Management Strategy	X	03 Site Live / Ready / Open for Enrollment					Version Date							
Core		3.25 A7e A7e6 6.2.2 E.2		210	X	NO	X	NO	D	12	Develop Trial Management Strategy	X	01 First Country RA Approval					Document Date							
Core	4.7 6.4.2		Randomization Scheme	211	X	NO	X	NO	M	12	Develop Trial Management Strategy	X	03 Site Live / Ready / Open for Enrollment					Version Date							
Core				212	X	NO	X	NO	M	4	Develop Study Design / Document Development	X	03 Site Live / Ready / Open for Enrollment					Version Date							
Core	8.2.18	E.1.19 7.8.1		213	X	NO	X	NO	M	20	Manage Project	X	02 Clinical Infrastructure Ready	X	02 Clinical Infrastructure Ready			Version Date							
Core	5.4.1	A.7.E 7.8.3		214	X	NO	X	NO	D	12	Develop Trial Management Strategy	X	02 Clinical Infrastructure Ready					Version Date							
Core	5.1.1	A.7.E 7.8.3.		215	X	NO	X	NO	D	12	Develop Trial Management Strategy	X	02 Clinical Infrastructure Ready					Signature Date							
Core	5.1 5.5	7.8.1 10.7.e		216	X	X	X	X	D	30	Manage Subject Risk / Break Blind	X	10 Final Report / Clinical Study Report Approved					Signature Date							
Core	5.1 5.5			217	X	NO	X	NO	D	20	Manage Project	X	10 Final Report / Clinical Study Report Approved					Version Date							
Core	5.1 5.5			218	X	NO	X	NO	D	12	Develop Trial Management Strategy	X	10 Final Report / Clinical Study Report Approved					Document Date							

Newest version could be downloaded from CDISC website: https://www.cdisc.org/standards/trial-master-file-reference-model

Microsoft Excel Worksheet

TMF Reference Model Workbook



TMF Reference Model							Version 3.3.1	11-AUG-2023	
Zone #	Zone Name	Section #	Section Name	Artifac	Artifact name	Definition / Purpose	Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.	Core or Recommended for inclusion	ICH Cod
01	Trial Management	01.01	Trial Oversight	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	Recommended	5.5.7
01	Trial Management	01.01	Trial Oversight	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	Recommended	2.2
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, serious breach assessments; 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, checklists, etc.	Quality Documentation Quality Plan Quality Report	Recommended	5.1
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 applicable.	List of SOPs Current During Trial SOP Waivers SOP Deviations	Core	5.1.1
01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	To describe trial-related processes not covered by formal standard operating procedures. Includes manuals given to sites for ISFs and vendor study-specific manuals as well as any	Operational Procedure Manual	Recommended	5.1.1

V 3.3.1 Clean | V 3.3.1 Markup | Model Overview | Milestones_Events & Description | Instructions and Glossary | Computer System Validation | +

Mark-up Mapping of differences between two version

Model overview
Explanation of the history of the TMF reference Model and how artifacts work

Milestones Events and Description
Defines the latest point in time when an artifact is to be submitted / filed within the TMF

Instruction and Glossary
Provides a description of columns and abbreviations

Computer System Validation
Optional CSV artifacts

Structure of TMF Reference Model

- Hierarchical structure
  - 11 Zones
  - 48 Sections
  - 250 Artifacts

11 Zone
01 - Trial Management
02 - Central Trial Documents
03 - Regulatory
04 - IRB / IEC and other Approvals
05 - Site Management
06 - IP and Trial Supplies
07 - Safety Reporting
08 - Central and Local Testing
09 - Third Parties
10 - Data Management
11 - Statistics

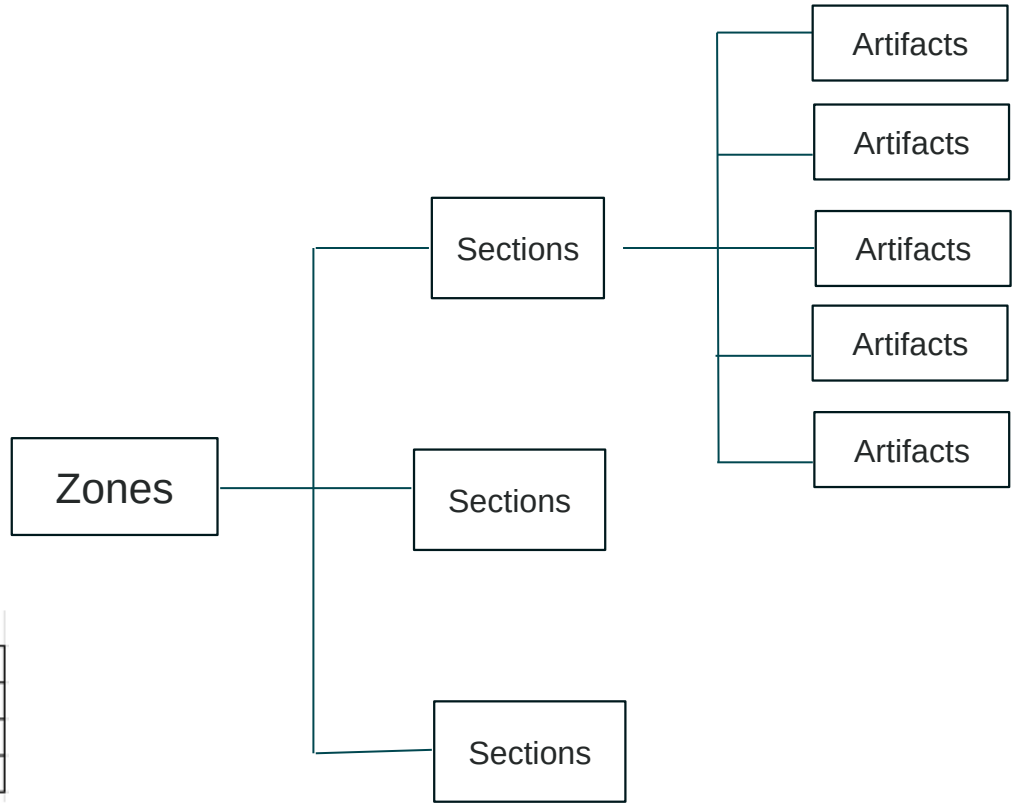
Each Zone lists Specific Sections

1.01	Trial Oversight
1.02	Trial Team
1.03	Trial Committee
1.04	Meetings
1.05	General

Each Sections lists Specific Artifacts

01.04.01	Kick-off Meeting Material
01.04.02	Trial Team Training Material
01.04.03	Investigators Meeting Material
01.04.04	Trial Team Evidence of Training

- **Organisation of the TMF RM in Zone, sections and artifacts**



TMF RM Zones

There are 11 Zones outlined in the TMF RM.

Zone	Definition of Zone Contents
01 - Trial Management	Records related to the general design, management and oversight of the s management and tracking; committees and charters, and training.
02 - Central Trial Documents	Includes the IB, Protocol, and Amendments, Sample CRF, ICF, and the C above. Capture study documents that are related to the protocol, key sub participation card and clinical study reports including pharmacokinetics in
03 - Regulatory	Records related to Regulatory Submissions and Approvals (to/from Health and Regulatory Notifications specific to the clinical trial.
04 - IRB / IEC and other Approvals	Official communications and exchanges with IRB's/IECs, including centra IRB/IEC submissions, approvals, acknowledgments, as well as oversight
05 - Site Management	Records related to selection, setup and management of investigational sit addition, documentation related to unselected sites.
	At the trial or country level, this section pertains to multi-site records and communications, etc. Site specific details will be managed in the Investig
06 - IP and Trial Supplies	Records related to the products under investigation including comparators and destruction, regulatory requirements, certificates, treatment allocatior needed to fulfill the trial protocol requirements including shipping and retu
07 - Safety Reporting	Records related to trial-specific Safety and Pharmacovigilance manageme database line listings, safety reports, and non-submission communicatior
08 - Central and Local Testing	Records related to all specialty testing vendors, including central and loca level. Records include certification (and expiration dates), procedure manu curriculum vitae (CV). The content should be modified based on the testin
09 - Third Parties	Records related to the establishment and maintenance of a relationship b Sponsors by contract on the study. (ex, delegation of responsibilities)
10 - Data Management	Records related to Data Management activity on the study. Includes subj definition
11 - Statistics	Records related to Biostatistics and Statistical Programming activity on t

TMF Reference Model

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01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	To describe trial-related processes not covered by formal standard operating procedures. Includes manuals given to sites for ISFs and vendor study-specific manuals as well as any

TMF RM Sections

48 Sections

- The contents of each Zone are grouped into sections
- Each Zone with 2+ sections within the TMF zone
- Each sections includes content that is relevant to a specified activity
- Sections are helpful for classification and searching

TMF Reference Model

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TMF RM Artifacts

As of now 250 Artifacts

- Could include data files, documents, media, digitized content
- Could be 1 document or multiple documents
- Includes associated records e.g. approvals, translations, checklists, QC records, amendments

Artifacts 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

TMF Reference Model

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TMF Reference Model — **Version 3.3.1**

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TMF RM Artifacts – cont.

Recommended 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. Assists with ensuring a common interpretation of the model
- Only examples are provided in the model but expected to be overridden as part of adopting the Reference Model for a company.

TMF Reference Model — Version 3.3.1

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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

Suggested Columns for Implementing the TMF Reference Model

Dating Convention	Artifact Owner	Artifact Location	Wet Ink Signature	SOP Reference	Translation Required	Current Artifact Name	Additional Metadata
Version Date							
Version Date							

TMF Inclusion – Core vs Recommended

- **Core:** meaning that if such a record exists, it must be in the TMF
- **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	Artifac	Artifact name	Recommended Subartifacts - Documents/documentation recommended to be filed to the artifact.	Core or Recommended for inclusion
01	Trial Management	01.01	Trial Oversight	01.01.04	List of SOPs Current During Trial	List of SOPs Current During Trial SOP Waivers SOP Deviations	Core
01	Trial Management	01.01	Trial Oversight	01.01.05	Operational Procedure Manual	Operational Procedure Manual	Recommended

TMF ICH Code

- Reference to the ICH E6 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	Artifact #	Artifact name	Core or Recommended for inclusion	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	Core	7.1 8.2.1 8.3.1	
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.02	Protocol	Core	1.44 8.2.2	Full Protocol (CSR component)
02	Central Trial Documents	02.01	Product and Trial Documentation	02.01.03	Protocol Synopsis	Core		Synopsis (CSR component)

TMF Filing Level

- ✓ Trial level
- ✓ Country level
- ✓ Site level

- It is important to note that artifacts should be filed at the most appropriate level, based on the content of the record.

								TMF Level					
Zone #	Zone Name	Section #	Section Name	Artifact #	Artifact name	Core or Recommended for inclusion	ICH Code	Trial Level Document	Trial Level MILESTONE/EVENT	Country/ Region Level Document	Country Level MILESTONE/EVENT	Site Level Document	Site Level MILESTONE/EVENT
01	Trial Management	01.01	Trial Oversight	01.01.06	Recruitment Plan	Recommended	5.6	X	03 Site Live / Ready / Open for Enrollment	X	03 Site Live / Ready / Open for Enrollment	X	03 Site Live / Ready / Open for Enrollment
01	Trial Management	01.01	Trial Oversight	01.01.07	Communication Plan	Recommended		X	01 First Country RA Approval	X	02 Clinical Infrastructure Ready		
01	Trial Management	01.01	Trial Oversight	01.01.08	Monitoring Plan	Core	5.18.3 5.18.7	X	02 Clinical Infrastructure Ready	X	02 Clinical Infrastructure Ready	X	

Benefits Gained by Implementation of TMF RM

- 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 Study Lifecycle

Start-up phase

Conduct phase

Closure phase

TMF RM
Milestones / Events lists

- Serve as a guide

- From Creation to Archiving
- Version Control and Audit Trails
- Key milestones and Timelines

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	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.	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
#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	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	
#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	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	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.
		Study Conduct		
#4	First Monitoring Visit	This is the first monitoring visit to occur within the study after enrollment	This is the first monitoring visit to occur within the specified country after	This is the first monitoring visit to occur at the site after enrollment has
#5	Significant Study Event	Any key event within a study that indicates a significant change. Examples include but are not limited to: a protocol amendment, safety issue that results in system changes, management of study Committee (such as committee output), an IP	Any key event within a country that indicates a significant change. Examples include but are not limited to: a protocol amendment, a change impacting the IRB/IEC, an IP process (such as IP relabeling), change in country coordinator, etc.	Any key event within a site that indicates a significant change. Examples include but are not limited to: a safety issue that results in system changes, a change in Principal Investigator, an IP process (such as IP relabeling) etc.
#6	Annual IRB / IEC Renewal		Documentation received from IRB/IEC in response to a renewal submission indicating an approved trial can continue in the specified country.	Documentation received from IRB/IEC in response to a renewal submission indicating an approved trial can continue at the site.
#7	Last Subject Last Visit	Completion of the last subject's last visit across the study and will include collection of all samples and data.	Completion of the last subject's last visit within the specified country and will include collection of all samples and	Completion of the last subject's last visit at the site and will include collection of all samples and data.
		Close Out		
#8	Database Lock	Confirmation that all of the requirements for database lock have		
#9	Close Out Monitoring Visit / Site Closed	Completion of the final monitoring visit across the study, confirming that all trial activities are complete, and the site is closed, which should occur prior to trial completion. Includes completion and filing of the Site Close Out Visit	Completion of all final monitoring visits within the specified country, confirming that all trial activities are complete, and all sites are closed, which should occur prior to trial completion. Includes completion and filing of all Site Close	Completion of the final monitoring visit for the specified site, confirming that all trial activities are complete, and the site is closed, which should occur prior to trial completion. Includes completion and filing of the Site Close Out Visit
#10	Final Report / Clinical Study Report Approved	Sign off of the final study report, which summarizes all findings and includes the relevant back up documentation to support the findings.	Sign off of the final study report, which summarizes all findings and includes the relevant back up documentation to support the findings.	Sign off of the final study report, which summarizes all findings and includes the relevant back up documentation to support the findings.
			Other	
#11	Ongoing	Artifacts may be updated / collected as needed and should be filed	Artifacts may be updated / collected as needed and should be filed	Artifacts may be updated / collected as needed and should be filed

及时持续追踪TMF 完整性

前
- 实验开始前必须生成并存档的文件

中
- 试验过程中所有新产生的相关信息的文件

后
- 试验结束时所有试验文件必须集中存档

研究开始阶段:
- ✓ 研究项目特定的文件列表，在系统中为所需的期望文件建立对应的文件夹;
- ✓ 为每个文件夹所对应的文件设置定稿的期望时间节点

研究进行阶段:
- ✓ 持续追踪超过时间节点的文件是否已上传归档;
- ✓ 维护更新研究所需的文件夹

研究结束阶段:
- ✓ 核查临床研究项目所有的期望文件是否存放在对应的文件夹;
- ✓ 追踪所有文件夹对应的文件是否上传

Case Sharing

- Real World Application from Johnson&Johnson Innovative Medicine
- Only focus on programming involvements in the TMF process
- Best Practice – Quality Control of TMF

Programming Responsibilities in TMF Process

Make sure that the location(s) of Programming deliverables are filed in V-TMF and on time

Refer to the TMF Content Map which contains the Programming required classifications, and determine if they are required or not required

Complete or review the programming section in Filing and Archiving Plan (FAP)

Received by Email from GTL

Review and/or complete it, and send back to GTL via the same Email

Perform Annual quality review of content and file the quality review confirmation form in vTMF.

Note: programming activities in vTMF begin at study start and continue throughout the study.

Milestone

At Study Start Up

- Set the Expected Document List (EDL) with Requiredness within 30 days of Study Start
- If Requiredenss is YES, then content or Placeholder with External system must be uploaded before the **first milestone. Note that the first milestone is critical as it triggers the AQR. First milestone can be official interim/Primary analysis or final database lock.**
- Verify the “managed by” field, if your FA
- Provide input for FAP

During the study

- Update EDL as needed
- Enter reference to external Link in vTMF
- Complete and document Quality Review Confirmation Form (AQR) within the annual interval **unless there is no milestone**
- Upload AQR into vTMF

Milestone (continue)

End of Clinical Activity – Study Completion

- Complete Final Quality review of vTMF content
- Complete Quality Review Confirmation Form
- Upload AQR into vTMF if needed

Locking of vTMF

- Update the EDL in vTMF to ensure FAP is current prior to locking

Detailed Programming Activities

vTMF Content Map: 11 Items + AQR/FQR

Type/ Zone #	Type/Zone	SubType/ Section #	SubType/Section	Classification/Artifact	Alternative Document Name(s)
11	Statistics	11.3	Analysis	Data Definitions for Analysis Datasets	Data Presentation Specification (DPS) and Update including Post Hoc Analysis Specifications Post Hoc Analysis Request Form
11	Statistics	11.3	Analysis	Interim Analysis Programs	Interim Analysis Programs and Macros
11	Statistics	11.3	Analysis	Interim Analysis Datasets	Interim ADAM Datasets
11	Statistics	11.3	Analysis	Interim Analysis Output	Tables Listings Graphs
11	Statistics	11.3	Analysis	Final Analysis Datasets	Final ADAM Datasets
11	Statistics	11.3	Analysis	Final Analysis Programs	Final Analysis Programs and Macros
11	Statistics	11.3	Analysis	Subject Evaluability Criteria and Subject Classification	Population Definition Criteria Protocol Violations Deviations and Exemptions Protocol Deviation Listing (Programming) Final Protocol Deviation Report with signature (includes secure MAc - NPP Deviation Memo Request EV Datasets (C-SC)
11	Statistics	11.3	Analysis	Interim Analysis Raw Datasets	Interim Submission Ready SDTM Product Janssen Standard Studies IDAR J&J Pharma studies (Programming) Interim Submission-ready SDTM datasets
11	Statistics	11.3	Analysis	Final Analysis Raw Datasets	Final Submission Ready SDTM Product
11	Statistics	11.3	Analysis	Analysis QC Documentation	RBQR Communication Tracker RBQR Plan
11	Statistics	11.3	Analysis	Final Analysis Output	Top Line Results Document Template (Biostats) Tables, Listings and Graphs (Programming)

	Biostats, Programming	Study	Ready for TMF Lock	TMF RM
	Biostats, GD MAO, Programming	Study	Ready for TMF Lock	TMF RM

Zone 11 Example from TMF RM Workbook

11 Zones
01 - Trial Management
02 - Central Trial Documents
03 - Regulatory
04 - IRB / IEC and other Approvals
05 - Site Management
06 - IP and Trial Supplies
07 - Safety Reporting
08 - Central and Local Testing
09 - Third Parties
10 - Data Management
11 - Statistics

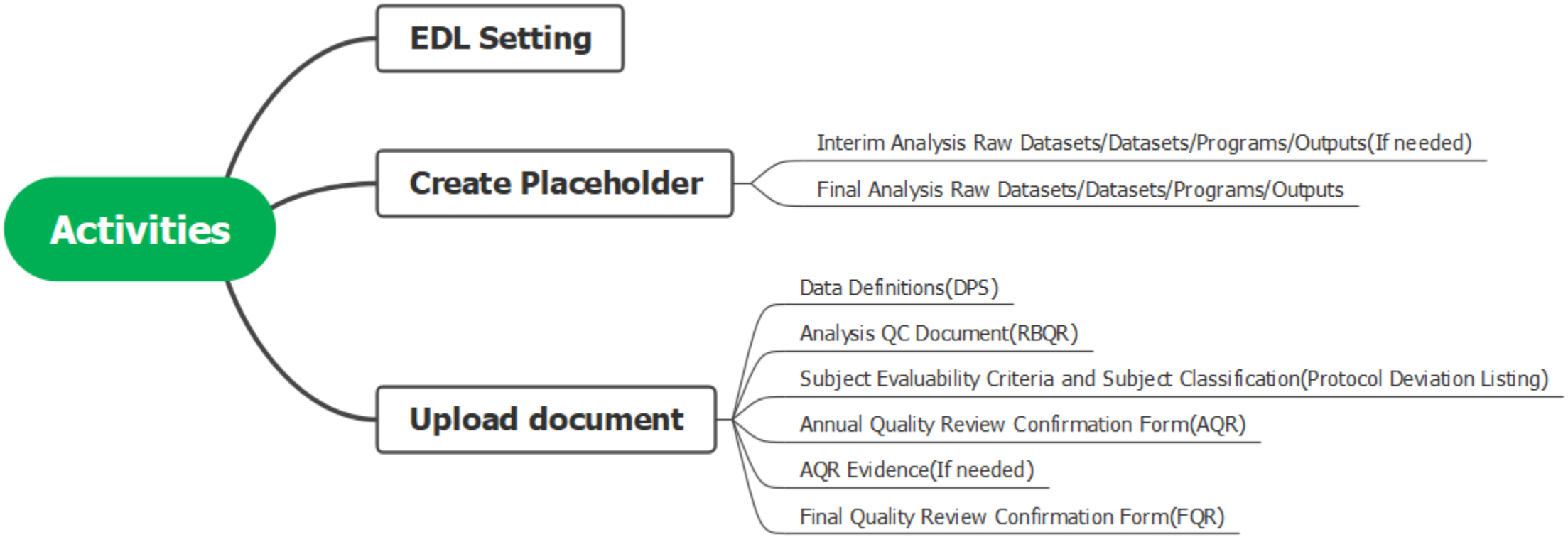
Each Zone lists Specific Sections

11.01	Statistics Oversight
11.02	Randomization
11.03	Analysis
11.04	Report
11.05	General

Each Section lists Specific Artifacts

11.03.01	Data Definitions for Analysis Datasets
11.03.02	Analysis QC Documentation
11.03.03	Interim Analysis Raw Datasets
11.03.04	Interim Analysis Programs
11.03.05	Interim Analysis Datasets
11.03.06	Interim Analysis Output
11.03.07	Final Analysis Raw Datasets
11.03.08	Final Analysis Programs
11.03.09	Final Analysis Datasets
11.03.10	Final Analysis Output
11.03.11	Subject Evaluability Criteria and Subject Classification

Detailed Programming Activities



Best Practice

To ensure the quality and the integrity of the TMF, the following steps need to be taken:

- ✓ Quality checks and review processes to ensure that the TMF is kept up-to-date and that all the essential documents have been added to the TMF.
- ✓ Documents are filed in the correct locations.
- ✓ Documents added to the TMF promptly.
- ✓ Documents are correctly indexed.
- ✓ Documents are only accessible to those with the correct permissions and roles.
- ✓ The Sponsor needs to ensure that the TMF is available and accessible to regulatory authorities for inspection.

Conclusion and Discussion

- Key Takeaways and Q&A

Key Takeaways on TMF

- **Definition & Purpose**
  - The TMF is a compilation of all documents, both paper and electronic, related to a clinical trial.
  - Purpose: To demonstrate that the clinical trial was conducted in accordance with regulatory requirements, ensuring data integrity and quality.
- **Regulatory Compliance**
  - Adherence to guidelines from ICH GCP, EMA, FDA and NMPA.
  - Ensuring all documents meet GCP standards and relevant legal regulations.
- **Structure & Composition**
  - Comprises both Sponsor TMF and Investigator TMF (ISF).
  - Covers all necessary documents from pre-trial to post-trial phases.
- **Management Process (Storage & Archiving)**
  - Ongoing maintenance of the TMF from trial design to conclusion.
  - Ensuring timely updates and archiving of documents.
  - Ensuring the integrity and readability of the TMF during and after the trial period.
- **Quality Assurance**
  - Implementing quality management processes to ensure the integrity and accuracy of the TMF.
  - Regular auditing and monitoring of TMF management processes.
- **Action Items**
  - Clarify key action points and responsibility assignments in the clinical trial.
  - Ensure all team members understand their roles in TMF management.

TMF Resources

- CDISC TMF website: Trial Master File Reference Model | CDISC
- Trial Master File Reference Model Discussion Forum – (a Community Group now part of CDISC)
- ICH E6(R2): https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf

Q&A

Thank you