Trial Master File Reference Model

Trial Master File Reference Model User Guide

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1. Purpose of the Guide

The Trial Master File Reference Model (TMF RM) User Guide provides a framework for implementing the TMF RM in your organization. The information presented in this guide was created by industry volunteers responsible for designing, implementing, managing, maintaining, evolving, and otherwise working with Trial Master Files and the TMF RM. A history detailing the evolution of the TMF RM can be found in Appendix A.

The Model can be downloaded at: http://www.diahome.org/en/News-and-Publications/Publications-and-Research/EDM-Corner.aspx. This guide assumes knowledge of Trial Master Files and the TMF RM, including the organization and structure of the TMF RM. Appendix B provides a detailed description of the TMF RM.

This guide is not intended to provide step-by-step instructions for implementing the TMF RM, nor are the procedures in this guide required for implementation. This guide does present an organized overall process for an implementation approach which can be adjusted based on your company's specific needs. The guide also provides case studies which highlight key lessons learned.

This guide is intended to bring perspective to those involved such that knowledgeable decisions, those that leverage the benefits of the TMF RM, can be made. The intended audience for the TMF RM includes biopharmaceutical and device companies, CROs, and other vendors, all of whom are involved with managing study-specific TMFs. It also is applicable to investigators managing their Investigator Site Files and conducting Investigator Initiated Studies.

The TMF RM team has done extensive work detailing the results of the TMF RM through surveys focused on the use of the TMF RM, and its management processes. The results of those surveys can be found at: http://tmfrefmodel.com/resources/.

In addition the team has done extensive work to identify and capture metrics that can be used to determine the benefit and success of your implementation of the TMF RM. Details can be found at: http://tmfrefmodel.com/resources/.

2. Laying the Groundwork

Before implementation of the model, it is critical to have a thorough knowledge of the company's current TMF structure, Standard Operating Procedures (SOPs), and practices. It is important for those involved in the effort to come to agreement on the goal(s) and/or benefits of implementing the TMF RM. One benefit is to use a common industry model for defining the content of the TMF so that company is not at a competitive disadvantage to others in the area of comprehensive TMF content listing. Critical to success is ensuring acceptance and readiness for change taking into consideration the company's culture. Planning activities should take into account the potential obstacles which can include the number and size of artifacts in the TMF, length of trials, inspection readiness, integration requirements, and accessibility of individual documents/artifacts.

Implementing the TMF RM may expose deficits in good content management and stewardship, awareness of TMF management responsibilities, and gaps in inspection readiness of the TMF on an ongoing basis. Resistance to change may be encountered due to a perception that:

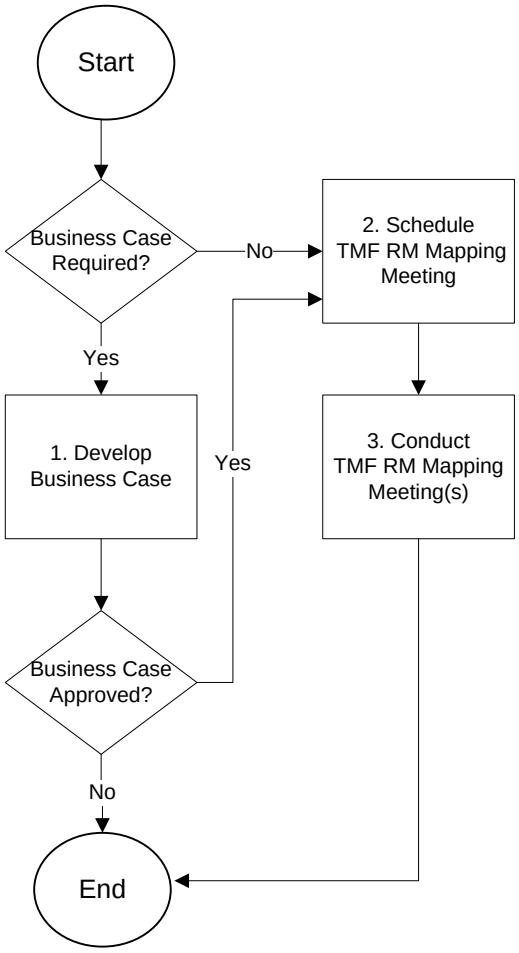
- No value is added since the organization's opinion might be that the current processes and TMF content listing and structure is acceptable;
- The workload or resource demands will increase;
- Implementing the TMF RM will result boundary breaches;
- Implementing the TMF RM will impact on current development timelines.

To successfully evaluate and adapt or adopt the TMF RM, your organization must be committed to change; agree on the value of making the change; have effective senior management support for the change; ensure global input during the project; and be willing to work through several iterations of detailed TMF content listing analysis.

Finally, as a result of using the TMF RM, it may become evident that necessary changes to existing processes or the development of new processes, which may include a review and/or modification of existing organizational roles and responsibilities, are required.

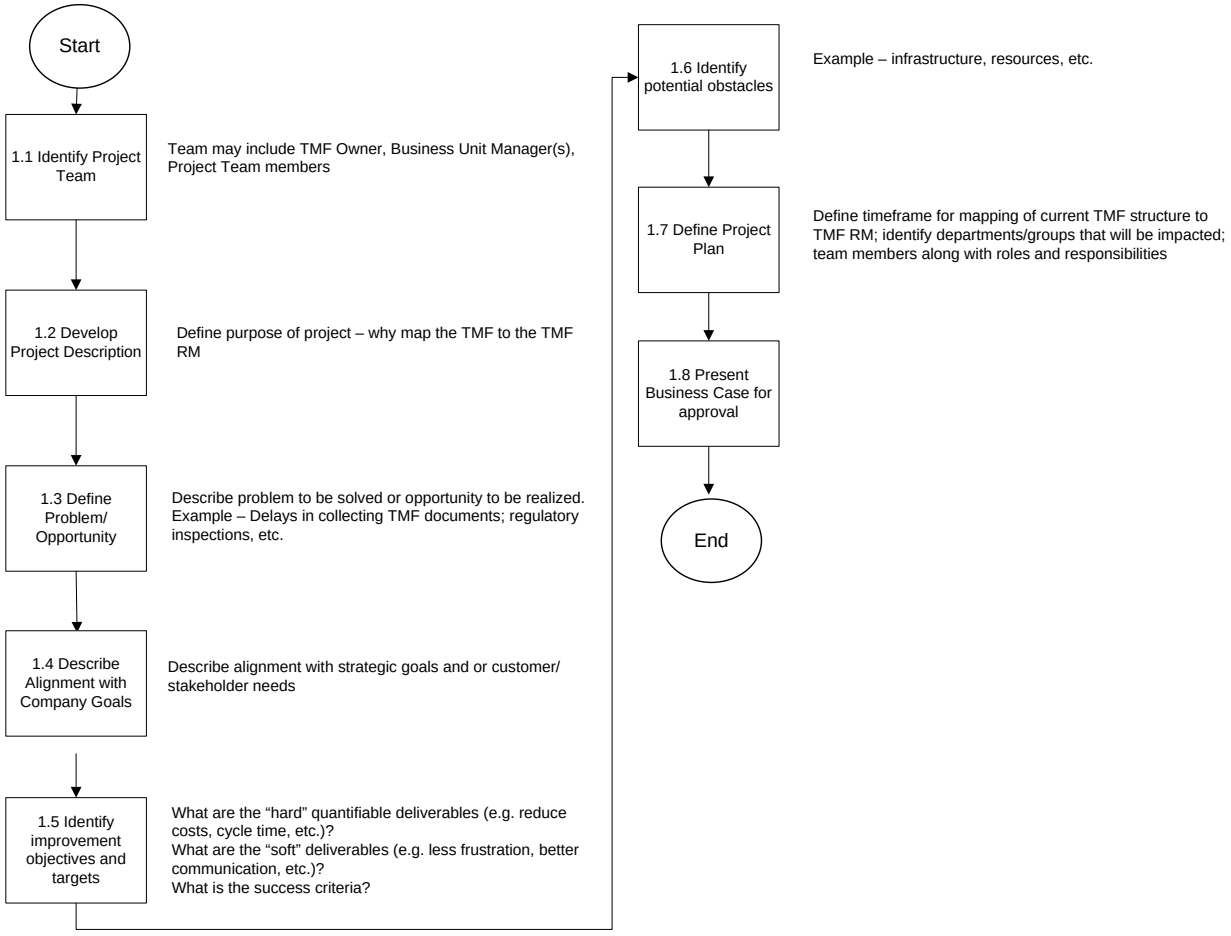
3. Process

Implementing Trial Master File Reference Model – Process Overview



3.1 Developing a Business Case

1. Develop Business Case



If you are required to present a business case for implementing the TMF RM it may include, but not be limited to, defining:

- The Implementation Team which may include the clinical documentation manager, Business Unit managers; Project Team members from the project to which the TMF RM is being mapped; individual(s) responsible for your company's TMFs, representation from Quality Assurance and/or Auditing, among others.

- The purpose for implementing the TMF RM should be clearly defined.

- Clear explanation of the problem that you expect to solve by implementing the TMF RM. Example – incomplete listing of the TMF, difficulty realizing "inspection readiness" due to incomplete listing, etc.

- Alignment with your organization's goals or responses to a health authority inspection finding.

- Improvement objectives – both hard and soft -- examples of metrics can be found in the survey results described in Section A above; as well as criteria to measure success.

- Potential obstacles and mitigation strategies – for example infrastructure constraints, organizational change, etc...

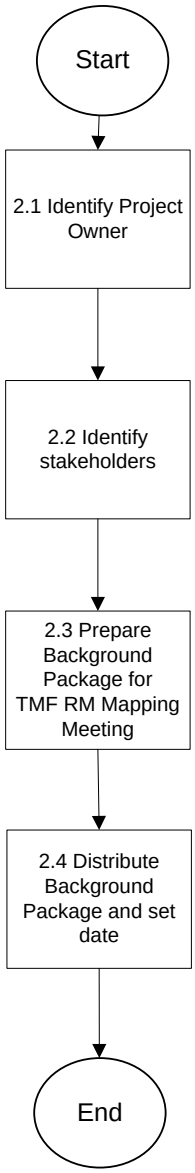
- Expected resourcing costs for the project.

- Timeline in the form of a Project Plan.

Once the Business Case has been developed, it should be presented to management for approval.

3.2 Plan TMF RM Mapping Meeting

2. Schedule TMF RM Mapping Meeting



Stakeholders may include representation from Quality Assurance, Regulatory, SOP Administration as well as members of the Clinical team, representative SME's from each of the 11 TMF RM Zones and any other group that creates or is responsible for TMF content.

Background Package should consist of the current Trial Master File Reference Model along with relevant description of the TMF RM; background on the current list to be mapped; Project Owner and List of TMF Stakeholders. If a Business Case was presented and approved, it should be included in the Background Package. The Background Package should also include a description of the process that will take place at the meeting(s).

The Mapping Meeting may be a series of meetings depending on the size and complexity of the project. It may be necessary to schedule mapping meetings for each Zone or group of Zones in the TMF RM

If not already done so, you should identify the Project Owner as well as all of the Stakeholders, which may include representatives from QA, Regulatory, SOP Administration, SMEs from each of the 11 TMF RM Zones, and any other group that creates content in support of a trial. A stakeholder should be identified for each part of the TMF (called Zones in the TMF RM). (Note – A stakeholder could very well be responsible for multiple zones).

A Background Package for the meeting should be distributed to members of the team and should include:

A. Current TMF RM (which can be downloaded at http://www.diahome.org/en/News-and-Publications/Publications-and-Research/EDM-Corner.aspx.

B. Description and background on the TMF RM.

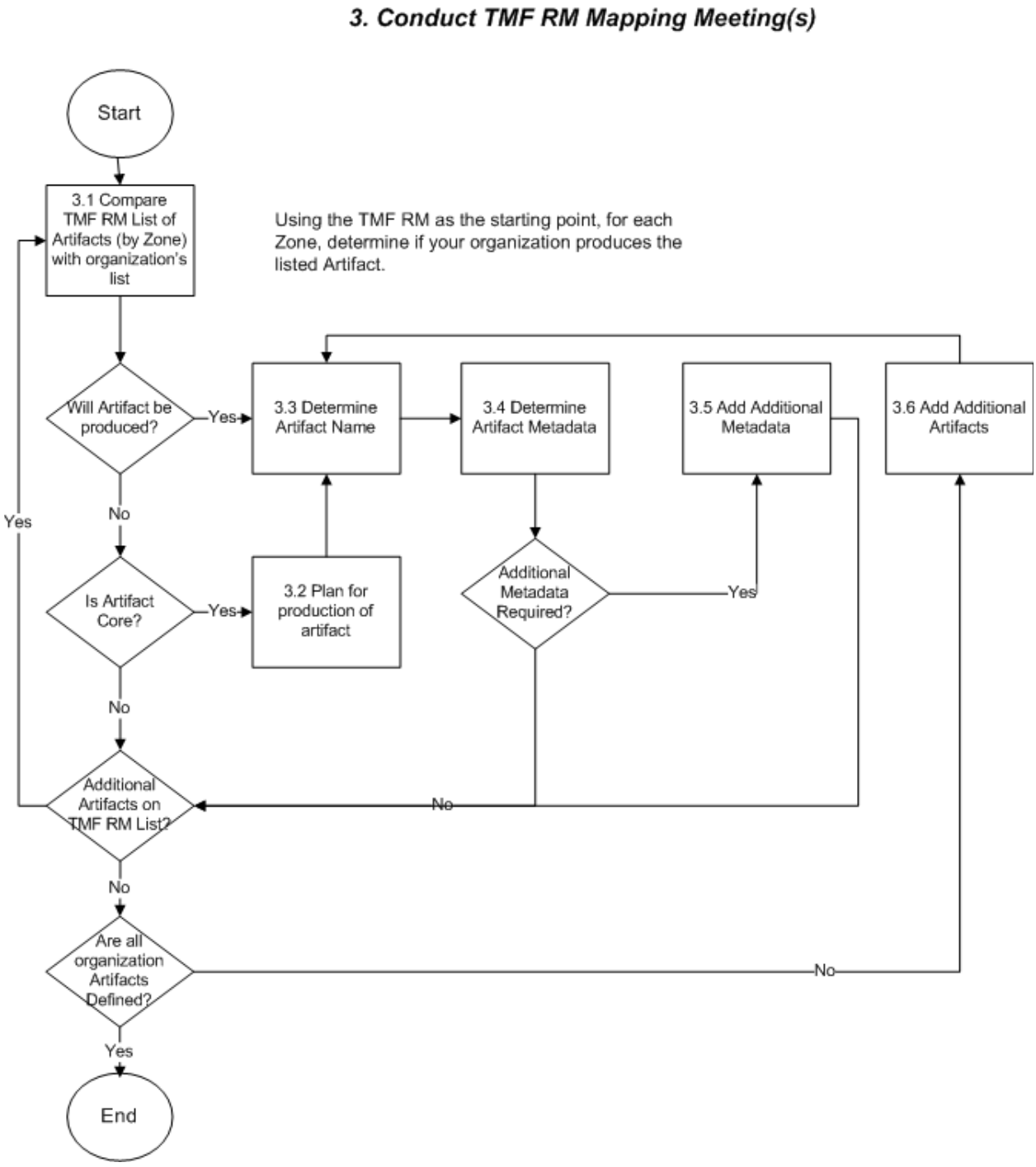
C. Description (or sample) of the organization's current TMF to which the TMF RM is being mapped.

D. List of Team Members including Project Owner and Stakeholders.

E. If a business case has been developed and approved, it should be included in the Background Package. If a business case was not required, the Background Package should include a summary of the anticipated benefits to be realized along with any known obstacles to implementation. Also important to provide the extended team is your organization's current TMF SOP and TMF List.

F. The Planning Meeting may be a series of meetings focusing on individual zones or groups of zones, depending on the size and complexity of the project.

3.3 Conduct TMF RM Mapping Meeting(s)



3.3.1 Compare the TMF RM list of artifacts with your organization's Master TMF List. The artifacts should be compared by zone and by individual artifacts within each zone.

3.3.2 As you consider each artifact, also consider any sub-artifacts. The TMF RM contains example artifacts, these need to be assessed for Company relevance compares to SOPs, business processes and workflow and outsourcing models.

3.3.3 If the artifact on the TMF RM is listed as "core" (required), the artifact must be in the TMF if it is created in support of the clinical study. If the artifact is not core, and it will not be produced, you may choose to delete the row from your Master TMF list. Make this determination for each artifact until all artifacts are considered. However, it is prudent to keep all, or almost all, artifacts on your Master TMF list in the event that any artifact will be required to be created in the future.

3.3.4 Determine the appropriate artifact name that you will use on your organization's Master TMF List. If you are using a name that is different from the name defined in the TMF RM, capture the name that you are using on your Master TMF List. The above process is iterative until you have considered all of the artifacts listed in the TMF RM.

3.3.4 Identify any artifacts required by your organization that are not in the TMF RM and consider if:

- They should be added to your Master TMF List in the respective zone and section;
- They can be combined with an already listed artifact; or
- Not necessary to be filed in the TMF at all.

For each artifact that you add to your Master TMF List, complete the steps outlined above until you have completed your organization's Master TMF List, including Aall artifacts and sub-artifacts.

Considerations:

- Review all of the material sent out in the Background Package.
- Review project plan and the resources required for the expected project.
- Answer any questions and address any resistance.
- Plan future mapping meetings.
- Review the TMF RM Zones and their descriptions as captured in the TMF RM and determine if they are appropriate for the company.
- The team should consider each artifact or groups of artifacts and how they have been organized in the Zones and Levels of the TMF RM.
  - The TMF RM is organized into 3 levels, trial, country, and site. Review the artifacts within the TMF RM to understand how they can be applicable at any or all of the 3 levels. Sort the TMF RM spreadsheet into the 3 distinct levels of trial,

country, and site to emphasize this point. Explain to the team members that they have to consider each of the artifacts at their multiple levels since responsibility for certain artifacts are different at the different levels. For example, the artifact called "IP Accountability Documentation" 6.1.5 in Zone 6 at the site level would likely be the responsibility of the site management function in your organization or a CRO or independent CRA delegate. However "Accountability Documentation" at the country and trial level would be the responsibility of the Clinical Supplies function.

- With exception of the repeating artifacts in the TMF RM, artifacts should appear only once in the TMF to ensure clarity in filing procedures and accountability for placement of the content into the TMF.

- Consider if the names of the artifacts in the TMF RM can be adopted by your organization. The industry is moving to accept the TMF RM artifact names instead of using the company's content names. Regardless, it is important to use consistent naming conventions for identifying Artifacts within your organization.

- It may help to create an excel spreadsheet from the downloaded TMF RM as an overall map to your organization's TMF RM. Artifact by artifact, determine if there is a comparable document listed in your organization's TMF Structure. As part of the evaluation, consider if the artifact is created at the trial, country, and site level. This spreadsheet will be updated at the Mapping Meetings and will eventually become the new finalized Master TMF List for your organization. This mapping might be initially attempted by one or a few person(s), and then the larger stakeholder group would validate or correct it.
  - NOTE: Once completed, the built-in spreadsheet functionality of the TMF RM template will allow you to sort and subset the TMF List by Zone, Section, Artifact Name, trial, country, and site level documents, etc.

- Multiple meetings may be required to complete the finalized Master TMF List and, as indicated previously, it may be efficient to conduct meetings for each Zone or groups of one or more Zones. Another option is to hold workshop type review sessions over the course of a few days to complete the review of the TMF RM to your organization's TMF List.

4. Use of the new Master TMF List based on the TMF RM

Your new Master TMF List may require changes or additions to existing processes. Some considerations may be:

- Add of new sub-artifacts to support changes in business processes, SOPs, business models etc.

- Identify new or modified roles and responsibilities based on the new TMF List and develop appropriate communications to ensure that those roles and responsibilities are clearly defined and understood.

- Evaluate your existing SOPs to ensure that they accurately reflect the new TMF Structure. If necessary, develop or modify the SOPs. Example – if you have added a new artifact to your TMF List, your SOPs should address the process for developing, capturing and managing that artifact.

- Current training should be evaluated to determine if additional or revised training is required based on new or modified roles and responsibilities. SOPs for capturing completion of required training should also be evaluated to assess if they need to be modified.

- The new TMF List should be created for each study. You may chose to start the creation for only future trials or it may be applied retrospectively, especially if the trial recently started and the amount of content created for that trial is minimal at that point in time.

5 Case Studies

Case Study #1 – Start-up Biotech

Section	Description	Example
Business Scenario	What was the purpose of your initiative?	To prepare for an upcoming NDA submission, the Sponsor needed to transform their existing paper based processes, collaboration models and technology architecture with a streamlined centralized electronic solution that would maximize limited resources by using a globally available web-based framework.
Format of TMF	In this initiative, is the model being applied to a paper TMF, eTMF, or hybrid?	eTMF implementation
Summary of Approach	Plan of approach or strategy. In what way did you leverage the TMF reference model? Factors for consideration implementing/adopting the model	1. eTMF structure, setup, and implementation 2. Ongoing clinical trial document processing 3. Legacy clinical trial document processing Software was implemented first, then the process was developed that included scanning, indexing, importing into document management system, reviewing, applying metadata and naming conventions, and QC. The TMF Reference Model was used as a starting point to determine the electronic file structure and metadata. The sponsor added a column for naming convention.
Team Members	What functional areas were involved in the project?	Representatives from Clinical Operations, Regulatory Affairs/QA, scanning vendor, and eTMF vendor.
Identification of Stakeholders	Who do you consider the major Stakeholders for using the Reference Model?	Clinical Operations, Regulatory Affairs, and Quality Assurance
Sponsorship	Did you secure Sr. Mgmt Sponsorship? If so, how?	The project was initiating by led Senior Management and executed by middle management so the project was fully supported.
Communication	How did you advertise your efforts and keep stakeholders and impacted parties aware of your progress?	The project team met on a weekly basis to deliver status reports and discuss issues.
Deliverables	What tools, templates, and/or documentation did you create as a result of the effort? What training was created/delivered	• Team will deliver a single mapping document that integrates the reference model with a complete inventory of Sponsor records with Sponsor file naming conventions. • SOPs/Methodologies/Working Practices for Scanning vendor, eTMF vendor, and Sponsor that cover each part of the process. • Appropriate and documented software and process training. • Validation documentation. • Fully searchable, reportable, 21CFR11 compliant eTMF for 1 legacy study and 1 ongoing study.

Section	Description	Example
Results Achieved	In short, how did this effort benefit your TMF practice?	• All study records are globally accessible, available and organized. • Time and cost associated with file requests, audits, and submissions has decreased while quality has increased.
Timeline	How long did this initiative take, from kickoff to closeout?	• 1 year
Lessons Learned	What parts of your approach worked well, and what would you do differently?	• Plan & Monitor are key actions to estimate and manage the program timeline • Establish paper document classification • Identify document naming conventions early • Recognize that changes impact timelines

Case Study #2 - Pharmaceutical Company

Section	Description	Example
Business Scenario	What was the purpose of your initiative?	Sponsor wanted to compare its current TMF structure and inventory to industry consensus to benchmark completeness and file management practices.
Format of TMF	In this initiative, is the model being applied to a paper TMF, eTMF, or hybrid?	Sponsor file is a hybrid of paper and electronic records stored in multiple physical and virtual locations.
Summary of Approach	Plan of approach or strategy. In what way did you leverage the TMF reference model? Factors for consideration implementing/adopting the model	The TMF Reference Model was used as a 'backbone' for identifying which Sponsor records meet the description of each artifact. As a result, Sponsor was able to assess the true completeness of expected TMF inventory, identify gaps, and implement new processes, standards, and controls to ensure total TMF quality. Sponsor used a two pass approach. The first pass was high level, with a single rep helping triage all artifacts in a given zone. The second pass was more granular, with individual artifact owners reviewing and updating the first pass.
Scope	Was this a global or regional implementation?	This was a global implementation with the first study using the model conducted in the US, Canada, Brazil and the UK.
Team Members	What functional areas and/or regions were involved in the project?	A primary representative for each TMF Zone was nominated, and secondary representatives were engaged to review the second pass. The TMF Zone leadership was responsible for including regional input were applicable.
Identification of Stakeholders	Who do you consider the major Stakeholders for using the Reference Model?	Internally, Clinical Operations and Regulatory. Externally our strategic CRO partners.
Sponsorship	Did you secure Sr. Mgmt Sponsorship? If so, how?	Sponsor engaged an Executive Committee and Sr. Executive Leadership Team to brief them on the approach, solicit participant nominations, and update them on progress.
Externalization	If an electronic format, was access to the TMF externalized to partners outside of your organization such as CROs, Pharma, IRBs, Centralized Testing?	This was an eTMF implementation for internal stakeholders only.
Communication	How did you advertise your efforts and keep stakeholders and impacted parties aware of your progress?	Core team put the mapping document in a public location on a SharePoint portal so that people could review progress and use information as it was confirmed.
Deliverables	What tools, templates, and/or documentation did you create as a result of the effort? What training was created/delivered	Team will deliver a single mapping document that integrates the reference model with a complete inventory of Sponsor records, classified by the internal Sponsor TMF Tab Structure.

Section	Description	Example
Results Achieved	In short, how did this effort benefit your TMF practice?	The final mapping allowed Sponsor to publish a set of standard TMF record owners and locations, to be put into practice as a central directory. This allows sponsor to focus on proper management and process improvement on a case-by-case basis instead of putting unnecessary urgency on consolidation.
Timeline	How long did this initiative take, from kickoff to closeout?	Sponsor is currently still in the finalization phase, but has been working on this effort as a secondary business priority for over a year.
Lessons Learned	What parts of your approach worked well, and what would you do differently?	By defining "Artifact ownership", Sponsor established the proper stakeholder for the information, which was learned to not always be the 'document owner'. By using an approach where every record ties back to the model, Sponsor cultivated better cross-study communication and consistency.

Case Study #3 – Mid-size pharmaceutical company

Section	Description	Example
Business Scenario	What was the purpose of your initiative?	To prepare for the implementation of an eTMF solution.
Format of TMF	In this initiative, is the model being applied to a paper TMF, eTMF, or hybrid?	Ultimately an eTMF implementation; however, the RM was used to ensure completeness of both historical paper and historical eTMFs.
Summary of Approach	Plan of approach or strategy. In what way did you leverage the TMF reference model? Factors for consideration implementing/adopting the model	1. Build US TMF structure based on TMF RM. 2. Map all active studies to this RM to track content owner, location during study, and location at archive. 3. Built TMF QC trackers based on the individual study maps. 4. Revised the US TMF structure to meet global needs of the organization. Used the RM as the basis for the company TMF Structure Needed to take into consideration the needs of the different functional areas. The initial map was reviewed after 18 months because how studies were filed had evolved. Each artifact included a list of expected content.
Team Members	What functional areas were involved in the project?	Representatives from Clinical Operations, Clinical Trial Materials Management, Biostatistics, Data Management, QA, and Bioanalytics.
Identification of Stakeholders	Who do you consider the major Stakeholders for using the Reference Model?	Clinical Operations, Clinical Trial Materials Management, Biostatistics, Data Management
Sponsorship	Did you secure Sr. Mgmt Sponsorship? If so, how?	The project was fully endorsed by executive management and managed at the Director level.
Communication	How did you advertise your efforts and keep stakeholders and impacted parties aware of your progress?	The project team members met with the individual functional areas to ensure that they were fully informed initially, and then on regular basis as necessary.
Deliverables	What tools, templates, and/or documentation did you create as a result of the effort? What training was created/delivered	• Template study specific TMF Map that was used to map each study. • Procedural documents for TMF Management, Managing TMF Structure, Adding content to the eTMF, and QC of TMF content. • Company template TMF Plan • Core content for CRO TMF Plan • Training was created initially to ensure all functional areas were fully informed.
Results Achieved	In short, how did this effort benefit your TMF practice?	• All studies have been mapped to identify location of content during the study and at archive • TMF QC for completeness, timeliness, and quality of content is performed for all studies on a quarterly basis by the sponsor. QC is risk based with expectation that CRO will perform 100% QC.

Section	Description	Example
		• TMF Map is used as a basis for ensuring TMF completeness at study completion. • As eTMF solution is implemented the TMF map is the foundation for the structural build.
Timeline	How long did this initiative take, from kickoff to closeout?	• TMF Map was fully implemented in 20 months. • Vendor selection took 14 months. • eTMF solution is now in implementation phase.
Lessons Learned	What parts of your approach worked well, and what would you do differently?	• Mapping was very successful in ensuring TMF Completeness, especially in situations where content was held in different locations for one study (i.e. CRO, sponsor, vendor). • Regular meetings with functional groups was helpful in identifying content that was being held outside of the TMF and ensuring security of that content. • Require CROs to use same structure. CROs using varying structures presented challenges.

Case Study #4 – Pharmaceutical Company

Section	Description	Example
Business Scenario	What was the purpose of your initiative?	To update current TMF structure and align with the industry standard to ensure a complete and compliant TMF.
Format of TMF	In this initiative, is the model being applied to a paper TMF, eTMF, or hybrid?	TMF is a hybrid of paper and electronic records stored in multiple physical and virtual locations.
Summary of Approach	Plan of approach or strategy. In what way did you leverage the TMF reference model? Factors for consideration implementing/adopting the model	The TMF Reference Model was used as the starting point and customized to reflect the company's TMF policies and practices. The first deliverable was a result of a working group made up of Clinical Operations and Clinical Quality Assurance and did not reflect the full TMF RM. The second deliverable was a result of input from 10+ functional areas and represented the full TMF RM.
Scope	Was this a global or regional implementation?	This was a global implementation.
Team Members	What functional areas and/or regions were involved in the project?	Clinical Operations, Clinical Quality Assurance, Data Management, Biostatistics, Clinical Trial Supplies, Pharmacovigilance, Regulatory Operations, Business Operations, Legal, Clinical, Medical Writing.
Identification of Stakeholders	Who do you consider the major Stakeholders for using the Reference Model?	Internally, Clinical Operations, Clinical Trial Supplies, Data Management and Biostatistics. Externally, our strategic partner CROs and eTMF Vendor.
Sponsorship	Did you secure Sr. Mgmt Sponsorship? If so, how?	Yes. Got buy-in and support from the Heads of functional areas for each Therapeutic Area and CQA.
Externalization	If an electronic format, was access to the TMF externalized to partners outside of your organization such as CROs, Pharma, IRBs, Centralized Testing?	Yes. We use an eTMF vendor so eTMF is accessed via the Web. CROs use our TMF file structure and eTMF.
Communication	How did you advertise your efforts and keep stakeholders and impacted parties aware of your progress?	Combination of emails, meetings, and presenting updates at various Functional Area Department meetings.
Deliverables	What tools, templates, and/or documentation did you create as a result of the effort? What training was created/delivered	TMF file structure based on the TMF RM, plus columns for Document Type Examples with guidance on how to submit documents to the eTMF (electronic upload vs paper), Document Location, Responsible Function, & Who Sends to eTMF; Template for TMF File Plan (study specific). Training specific to each functional area was created and delivered via WebEx. Slides included a summary of updates with a focus on the material each functional area would need to know.
Results Achieved	In short, how did this effort benefit your TMF practice?	The additional guidance resulted in more consistent TMF content across studies and regions, and less errors in what is submitted to the eTMF
Timeline	How long did this initiative take, from kickoff to closeout?	The first update took about 10 months; the second and more robust update took 18 months.

Section	Description	Example
Lessons Learned	What parts of your approach worked well, and what would you do differently?	The addition of columns to document Location (identifying what goes to the eTMF vs other locations), Responsible Function (who is responsible for what) and Who Sends (Sponsor vs CRO) have worked well to promote consistency and provide clarity. The comprehensive list of Document Type Examples ensures consistency with similar document types going to the correct section of the TMF across multiple document submitters. Also, getting the buy-in of Department Heads was critical to the success.

6 Glossary

Term	Definition
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.
Sub-artifact	When an artifact name does not explicitly refer to a single kind of record (Trial Management Plan, e.g.), sub-artifacts are intended to provide a means to list all company-specific records that a company would expect to file under a given artifact. Examples are provided in the model but expected to be overridden as part of adopting the Reference Model for your company.
Good Clinical Practice (GCP)	An international quality standard provided by the ICH with regulatory guidelines for the protection of human rights as a subject in clinical studies. It includes standards for the design, conduct, monitoring, auditing, analyses, and reporting of clinical studies. It defines the roles and responsibilities of the sponsor, investigators, and monitors in clinical research, and provides assurance of data integrity and patient safety is maintained.
International Committee on Harmonization (ICH)	An international body that defines standards, which governments can transpose into regulations for clinical research involving human subjects.
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation and management of a clinical study. **Per 21 CFR Part 50,** Sponsor means a person who initiates a clinical investigation, but who does not actually conduct the investigation, i.e., the test article is administered or dispensed to or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., corporation or agency) that uses one or more of its own employees to conduct a clinical investigation it has initiated is considered to be a Sponsor (not a Sponsor-Investigator), and the employees are considered to be Investigators.
Investigator	An individual responsible for the conduct of a clinical study at a site. If the study is conducted by a team of individuals at a site, the investigator is the responsible leader of the team, and is called the principal investigator. **Per 21 CFR Part 50,** Investigator means an individual who actually conducts a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.
Sponsor- Investigator	An individual who both initiates (plans and designs) and conducts a clinical study, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term refers to an individual, does not include a corporation or an agency. The obligations of a Sponsor-Investigator include both those of a Sponsor and those of an Investigator. **Per 21 CFR Part 50,** Sponsor-Investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does

Term	Definition
	not include any person other than an individual, e.g., corporation or agency.
Investigator Site File (ISF)	Set of artifacts expected to be maintained by the Investigator at the study site that permit the evaluation of the study conduct at the site. It serves to demonstrate site compliance to the protocol and standards of GCP and applicable regulatory requirements.
Investigator Initiated Studies (IIS)	This refers to studies with FDA-regulated products where the Investigator acts as a Sponsor-Investigator (SI). In addition to the standard investigator responsibilities, the SI will: plan, design, conduct, and monitor the study; manage data; prepare reports; and provide oversight, monitoring, and compliance with FDA-reporting requirements. There is a wide variation with respect to the complexity, size, and structure of IIS research.
Metadata	Data that serves to provide context or additional information about other data.
Wet-ink signature; Handwritten signature	Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate content in a permanent form.
Record	Records are documents [or more generally, information] created, received, processed and maintained as evidence and information assets by an organization or person, in pursuance of legal obligations or in the transaction of business.
Electronic Record; eRecord; Electronic Document	An electronic record is the combination of an electronic document plus additional metadata that defines the context and history of that content. An electronic document may be one or more document objects that as a collection represent the whole content and presentation of the document. Several examples of electronic documents that contain multiple objects are 1) SGML content and format files, or 2) compound documents that comprise many individual elements included in a structure. An electronic document may be a copy of a paper document that is an accurate representation or image of what content was contained on that original document.
Trial Master File (TMF)	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).

7 References

- ICH E6 Section 8.2 – 8.4

- Good Clinical Practice Guide, Medicines and Healthcare products Regulatory Agency (MHRA), 24 Sept 2012

- FDA Regulations 21 CFR Part 11

- FDA Regulations 21 CFR 312.57, 511.1(b)(7)(ii), and 812.140(d)
  Commission Directive 2005/28/EC (EU 2005/28/EC)

Appendix A - History Of Reference Model

Although ICH E6 Section 8 provides guidance regarding the 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. File structures have been created based on interpretation of ICH guidance, the results of audit findings, experiences and best practices from current organizational leadership. This approach can lead to inefficient TMF management practices, incomplete files, and files cluttered with extraneous documentation. Additionally, it has become increasingly difficult for organizations to effectively collaborate to create one final TMF whether within a global organization or across organizations such as the sponsor and the CRO.

The Trial Master File (TMF) is the trial sponsor's and investigator's document set 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. Creating and managing TMF content (referred to in the model as *artifacts)* in a standard format offers many benefits and many consider the Trial Master File Reference Model (TMF RM) to be a step forward in minimizing the administrative burden of clinical trial document management. The creation and publication of a set of industry wide generally recognized interpretations regarding the creation, maintenance and archival of TMFs in the current Reference Model format will benefit biopharmaceutical and device companies, Contract Research Companies (CROs), and investigators who conduct Investigator Initiated Studies in the successful and early adoption of the TMF RM. The term "company" will be used in this document to mean the owner.

The Trial Master File Reference Model Working Group was formed by co-chairs Lisa Mulcahy and Karen Roy in 2009 under the Document and Records Management Special Interest Area Community (SIAC) of the Drug Information Association (DIA), a neutral, nonprofit, global, professional association. The TMF RM team is a volunteer effort that includes bio-pharmaceutical and device companies, CROs, consultancies, technical vendors, industry groups, healthcare, academia, non-for-profit / non-governmental organizations and regulatory agencies. Membership has quickly grown and as of June 2015, there are approximately 450 representative members from @200 companies.

Although the activities of the TMF RM Working Group are managed by the rules and procedures of the DIA, the work product of the TMF RM Working Group – namely, the Trial Master File Reference Model – is owned and managed by the TMF RM Working Group.
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) refines the artifacts and Zones, introduces sub-artifact facilitation and provides an improved presentation layer. The TMF RM is free and available at: http://www.diahome.org/en/News-and-Publications/Publications-and-Research/EDM-Corner.aspx.

Appendix B - Organization And Structure Of The Reference Model

The TMF RM is organized by: Zones, Sections in each Zone and Artifacts (documents/components) in each section.

To organize the model, similar artifacts have been group together into eleven Zones, which are:

- Zone 1: Trial Management
- Zone 2: Central Trial Documents
- Zone 3: Regulatory
- Zone 4: IRB/IEC and other Approvals
- Zone 5: Site Management
- Zone 6: Investigational Product (IP) and Trial Supplies
- Zone 7: Safety Reporting
- Zone 8: Centralized and Local Testing
- Zone 9: Third Parties
- Zone 10: Data Management
- Zone 11: Statistics

The TMF RM indicates whether or not the artifact is to be included in the company TMF and/or maintained at the investigative site. The model provides a definition for each artifact, as well as a designation for inclusion in the TMF. "Core" artifacts are those artifacts identified as essential per ICH, regulations, or the TMF RM group; and "Recommended" artifacts are those that do not have to be created, but if created or collected, it is required to be in the TMF if not housed elsewhere.

Refer to the latest version of the model for the most current categories and definitions. The information below was extracted from version 3.0, dated 16-Jun-2105.

TMF Reference Model	TMF RM Website	Version 3.0	15-Jun-15

Zon	Zone Name	Sectio n #	Section Name	Artifact #	Artifact name	Alternate names (artifact also commonly known a	Definition / Purpose	Core or Recommended for inclusion	ICH Code	Artifact name in v1.3 EDM Reference Mode	Unique ID Numbe
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.	Recommended	5.5.7		001
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.	Recommended	2.2		002
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, checklists, etc.	Recommended	5.1		003
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	Core	5.1.1		004

TMF RM Headings

TMF Zone	Eleven categories / content buckets that group and structure the TMF RM.
Section	Subcategories within each Zone, used to add more granularity to TMF structure.
Artifact Name	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.
Alternate Names	A term equivalent to the Artifact Name, that may be commonly known in different facets or geographies of the clinical development industry.
Definition/Purpose	Explains the artifact's content and should help the reader understand why that artifact is TMF-related. TMF RM definitions are generic and so may need refinement for individual company's use.
Sub-Artifact	When an artifact name does not explicitly refer to a single kind of record (Trial Management Plan, e.g.), sub-artifacts are intended to provide a means to list all company-specific records that a company would expect to file under a given artifact. Examples are provided in the model but expected to be overridden as part of adopting the TMF RM for your company.
Core or Recommended	**Core** artifacts are required in the TMF as dictated by the ICH Guidelines, regulations, or by the TMF Ref Model Team; **Recommended** artifacts are not necessarily required, but if collected or created, it is required to be in the TMF if not housed elsewhere. Each company applying the RM should make their own determinations about core and recommended artifacts.
ICH Code	ICH GCP Guidelines code numbers; sections beyond just the ICH E6 Section 8 (TMF) are referenced.
Artifact Name in v1.0 EDM Reference Model	If the artifact is also referenced in the sister EDM model (content related to submissions / Common Technical Dossiers), the EDM RM name is listed here.
Unique ID Number	Three digit identifier that will remain constant throughout model updates. When using the model it is best practice to maintain a map to the unique ID codes; invaluable for working with vendors, outsourcing, and in partnerships.
Sponsor Document (non-Device)	Content applicable to drug/biologic (non-device) studies. Content required in the Sponsor TMF, or in both the Sponsor TMF and the Site ISF.
Investigator	Content applicable to medical device (device) studies. Content

Document (non-Device)	can be required in the Site ISF, or in both the Sponsor TMF and the Site ISF.
Sponsor Document (Device)	Content applicable to medical device (device) studies managed in the Sponsor files. Content can be required in the Sponsor TMF, or in both the Sponsor TMF and the Site ISF.
Investigator Document (Device)	Content applicable to medical device (device) studies managed in ISF. Content can be required in the Site ISF, or in both the Sponsor TMF and the Site ISF.
Investigator Initiated Study (IIS) Artifacts**	Content applicable to trials where the Investigator is also the trial Sponsor (aka IIS, IIT, IST, etc.) The many variables in the list reflect the wide variations in structure and sizes of IIS.
***For ISF:** X: applicable; NO : Not applicable - there may be some targeted exceptions based on local criteria (i.e. countries)	
****For IIS:** M is Mandatory, D is dependent upon the type of study being undertaken, R is recommended.	
Process Number & Process Name	The two process columns group TMF content collection in phases of a clinical trial lifecycle / by trial milestones. Process-based metadata is an especially useful consideration for electronic TMFs.
Trial Level Document	Indicates the artifact is managed at the trial level.
Country/Region Level Document	Indicates the artifact is managed at the country/region level.
Site Level Document	Indicates the artifact is managed at the site level.
Artifacts can be uniquely placed at one level and referenced in additional levels (e.g., 01.01.14 Audit Certificate can support trial, country/region, and site levels)	
Current Artifact Name	Identifies what an artifact is called at that particular company.
Artifact Owner	Identifies the person or department that creates and maintains a given artifact, regardless of its location.
Artifact Location	Identifies physical content storage locations, paper or electronic
Wet Ink Signature	Identifies the content that must, per ICH or company SOP, must be signed to be effective.
SOP Reference	Identifies any internal SOP related to the artifact
Translation Required	Identifies if per internal SOP, a translation requirement/standard is applicable to the artifact.
Dating Convention	Identifies the type of date field required for the artifact, especially useful for content that may expire.
Additional Metadata	Placeholder for company-specific metadata that may be required per SOP or business practice.

TMF RM Zones

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, Regulatory Filing and Registration Information, and Regulatory Notifications specific to the clinical trial.
04 - IRB / IEC and other Approvals	Official communications and exchanges with IRB's/IECs, including central, national, regional and local. Includes submissions, approvals, acknowledgments, as well as oversight information about the IRB/IEC.
05 - 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 level, this section 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.
06 - 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 fulfill the trial protocol requirements including shipping and returns – and any relevant communications.
07 - 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.
08 - 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).

09 - 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 study. (ex, delegation of responsibilities).
10 - Data Management	Records related to Data Management activity on the study. Includes subject data (completed CRFs or Final EDC Data). Database definition.
11 - Statistics	Records related to Biostatistics and Statistical Programming activity on the study.

Study Types

The TMF RM is reviewed on an ongoing basis to harmonize TMF related items in order to support a broad utilization across different study types and any changes in the regulatory environment. Version 1.0 focused primarily on bio-pharmaceutical company-sponsored interventional studies and artifacts maintained by the sponsor (or designee), based on ICH GCP, and industry best practices. The TMF RM has since been updated and expanded to consider application for device studies and Investigator Initiated Studies (IIS). Guidance regarding essential artifacts expected to be maintained by sites in the Investigator Site File (ISF) has also been added.

Interventional vs. Non-interventional: the current TMF RM does not delineate artifacts between interventional and non-interventional studies; although this will be considered for future versions. Companies who conduct non-interventional studies may note for themselves in the TMF RM those artifacts that not generated or collected for non-interventional studies.

See Glossary for definition of the following terms:

- Investigator Site File
- Investigator Initiated Study
- Sponsor/ Investigator/ Sponsor-Investigator