

Trial Master File

Quality Control

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Version History

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# Overview and Objectives

Per the Trial Master File Reference Model Quality Group (TMF RM QG), TMF review is defined as a two-part process that consists of document quality control (QC) and TMF QC.

**Completeness definition:**

All documents that enable the reconstruction of the study are available in the TMF contemporaneously of milestones and events.

# Document Quality Control

In order to be considered "TMF Ready" a document should meet the following criteria:

* **Retrievable** - documents have appropriate metadata and appropriately filed as per TMF ref model or company's filing structure
* **Unique** - no duplicates exist
* **Translations** - all appropriate translation documentation is available as per country regulatory requirements and company policy/procedures
* **Original** - unaltered wet ink signature required when applicable as per regulatory agencies and/or company's policy
* **Legible** - Readable, clean and stamps/signatures identifiable
* **Applicable** - document that supports the story of a clinical trial and is required as per TMF Ref model and/or company's policy

# TMF Quality Control

The TMF is considered to be complete when all TMF documents that enable the reconstruction of the study are available in the TMF contemporaneously of milestones and events. In order to be considered "Inspection Ready" the TMF (in its entirety) should meet the following criteria:

* To assess TMF completeness it is imperative to know what is expected to be in the TMF and when (e.g. milestones).
* Completeness can be assessed against TMF specifications and also against regulatory requirements, company Standard Operating Procedures (SOPs) and business processes (e.g., business process requirements will help to determine number of versions or instances expected for a given artifact/document type).

Only after the expectations are clear is it possible to determine whether the TMF is complete.

# Considerations

| **Quality Considerations** | **Document QC** | **TMF QC** | **Comments** |
| --- | --- | --- | --- |
| Functional Line Engagement | Functional Lines are the Document Owners and should ensure TMF readiness prior to filing the document into the TMF. | Functional Lines should ensure that all expected documents (i.e. versions) are present in the TMF. | Education and engagement at the beginning of the study, and on an ongoing basis, is required to complete successful TMF QC. |
| Timeline | Upon receipt of document | Considerations should be given to study milestones/events (TMF content should be contemporaneous of the latest milestone and event) ensuring that the TMF is inspection ready at all times. Frequency should not exceed more than six months. |  |
| Scope | 100% of documents should be reviewed prior to filing into the TMF. | Risk based or full QC may be performed. | Scope of document QC could be risk-based or required for specific document types.  The tab specifying the document QC does not fit this sheet document QC description. It is not possible to do a 100% QC of the documents as described in the 'Document QC' tab (RUTOLA) prior to filing in the TMF.  A document QC is a document 'content' QC to ensure this is the required and expected document and that it is complete. The check for translations, originality and legibility (T, O and L in RUTOLA), must be performed by the document owner upon receipt of the document. This is only part of RUTOLA.  TMF QC must be a two-step activity. One for the single TMF where there is a check for completeness and no duplicates (unique and applicable - U and A in RUTOLA); and the second for TMF across trials where there is a risk based approach checking R (retrievable, in RUTOLA) and filing timeliness. |

| **Quality Considerations** | **Document QC** | **TMF QC** | **Comments** |
| --- | --- | --- | --- |
| Oversight QC |  | Must confirm the following:  Sponsor oversight of the CRO/vendors Written proof of QC from the CRO (in the contract) |  |
| List of TMF Repositories | Document (i.e. artifact) location of each document type (may be an appendix to the TMF Plan). Document (i.e. artifact) owner (may be an appendix to the TMF Plan) |  | All of the TMF documents may not reside in the same location. It is important to confirm document location as this positively impacts TMF quality. Document location should be confirmed as part of the TMF Plan, in an aforementioned appendix. |

# Tools

* **TMF Reference Model:** 
  + Ideally, is used in a modified version customized based on individual sponsor needs.
* **TMF Management Plan:** 
  + May include TMF Master List (i.e. TMF Specifications) or TMF Table of Contents (TOC).
  + Specifically defines which functional line is responsible for which sections of the TMF. This plan may also include the frequency of the TMF review.
  + TMF Master List may also include a link or reference to the Standard Operating Procedures where each TMF document is described. The TMF Master List may also include an indication of when each document is expected during trial conduct (i.e. prior first site initiation, FPFV, LPFV, DBL, study report or other relevant milestones as relevant per company.).
* **Corrective Action Plan:**
  + If discrepancies are identified, there should be a documented way to correct the discrepancies (including timeline, method (i.e. documentation) and responsible party).

**Summary**

In October 2016, the TMF RM QG defined TMF Quality as two processes, including both document QC and TMF QC, and delivered clear, realistic instructions to ensure TMF quality is attainable for any and every clinical trial.