Advanced Clinical

WHITE PAPER

Achieving Inspection-Ready, TMF Quality: The Four Cornerstones

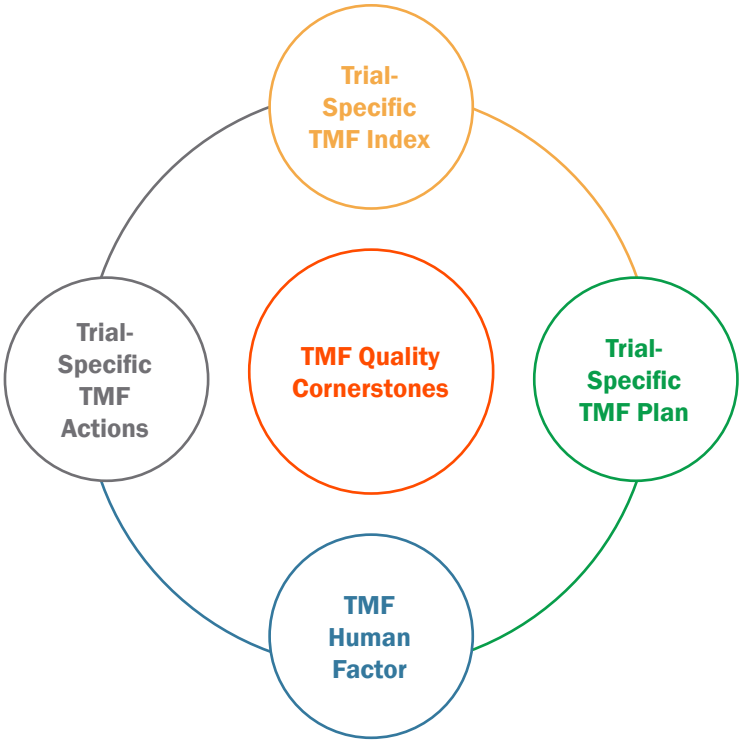
JP Miceli
Director, Document Management

Introduction

The TMF (Trial Master File) Reference Model achieved a significant milestone in 2020, having celebrated its 10th anniversary in June. Much has changed in TMF management over the decade since publication of version 1, including the explosive growth of eTMF (electronic Trial Master File systems. In the five-year period between 2015 and 2020, an industry clinical survey reports the use of eTMF systems has increased from 27% to 68%. There has also been a heightened awareness of TMF criticality to trial operations, with increased attention by health authorities, including significant TMF updates with Revision 2 to ICH E6 (E6R2) and the 2018 European Medicines Agency TMF Guideline.

And yet despite the increase in eTMF utilization, Health Authority attention and sponsor awareness, TMF Quality continues to be an issue for many organizations. Issues in TMF Quality are driven by many factors, including the complexity of today's trial protocols, frequent change in outsourcing models, and the use of new eClinical systems, to name a few. In this white paper, we will discuss how it is possible to attain TMF Quality sufficient to withstand health authority inspection by thoughtful and deliberate management of four key TMF cornerstones, which include:

- Trial-specific TMF Index
- Detailed TMF Plan
- Execution of TMF Quality Actions
- TMF Human Factor



TMF Quality Cornerstone 1: Trial-Specific TMF Index

The operative word in TMF Reference Model is model; it is the starting point for a robust and inspection-proof TMF record baseline, but not a one-stop solution for TMF Quality. Every organization needs to assess and adapt the Model to their operating practices and SOPs. The TMF Reference Model was created and is maintained through committee output from the perspective of scores of life science company volunteers, and has inherent compromises and approximations. The TMF Reference Model contains some records that are applicable only to specific trial types, and some records that are grouped that may need more specificity for your organization to enable TMF Quality.

In determining which TMF Reference Model records fit the organization, all functions with a trial role need to be consulted. Typical functions include Clinical Operations, Regulatory Affairs, Data Management, Biostatistics, Investigational Product Management, Vendor Management, and Quality Assurance.

The resultant record list establishes the baseline TMF Master List or TMF Index which is generally published as a component of the organization's TMF SOP, and should be configured as such in eTMF systems.

For each trial, the TMF Master List baseline is then used as a starting point to create the trial-specific TMF Index. One best practice is to designate a TMF Manager expert in the TMF Master List who works with the trial lead and team members to determine what records are applicable to their specific trial, thus supporting the production of an accurate and actionable TMF Index. Unless this critical step is accomplished at the start and adjusted as applicable throughout the course of the trial, it is not possible to check TMF Quality. The trial-specific TMF Index can also identify the responsible roles, storage location(s), anticipated collection period, and any notes helpful for managing a particular record type. The trial-specific TMF Index is a cornerstone of TMF Quality, and leveraged as guideposts for both TMF processing and for future inspections. At Advanced Clinical the TMF Index is actively managed through the life of the trial and is formalized as a component of each trial's TMF Plan.

All members of the trial team should collaborate on the creation of the trial's TMF Plan, which serves as the source of TMF insights for future inspections and drives the TMF Quality actions.

TMF Quality Cornerstone 2: TMF Plan

All members of the trial team should collaborate on the creation of the trial's TMF Plan, which serves as the source of TMF insights for future inspections and drives the TMF Quality actions. The TMF Plan should detail both the sponsor and all of the trial's vendor(s) TMF management practices during trial conduct, as well as any record transfer activity at trial closure. In outsourced trials, it's especially important to think through and codify each party's responsibility for TMF record management, TMF quality management, and TMF oversight. As stated in the EMA TMF Guideline: **"If multiple CROs are involved, the sponsor should clearly define expectations regarding the creation, management, exchange or remote access and retention of documentation amongst CROs."** It's incumbent on all trial sponsors to ensure full outsourcing clarity in every trial-specific TMF Plan.

The TMF Plan does not need to repeat process steps already detailed in any applicable TMF SOPs. Rather, the TMF Plan should be considered the source of TMF Quality commitments for each specific trial. Advanced Clinical's TMF Managers meet with clinical leads and applicable team members to ensure all the components of the TMF Plan are right-sized for the specific trial, and continue to iterate versions of the TMF Plan throughout the trial's lifecycle. TMF Plan review should be conducted at a minimum annually, with a final review accomplished at the end of the trial.

TMF Quality Cornerstone 3: TMF Quality Actions

An additional critical activity is for the trial team to carefully consider the various layers of TMF Quality activities. While they can be defined by different names depending on the organization, there are several distinct components of TMF Quality that need to be assessed.

- **TMF Quality Checks (TMF QC):** TMF Quality Control (QC) is the action of confirming that an individual record meets the ALCOAC standard. Each record filed in the TMF must be **A**ccurate, **L**egible, **C**ontemporaneous, **O**riginal, **A**ttributable, and **C**omplete. At Advanced Clinical our document managers perform rigorous TMF QC on each record as it is processed in our eTMF system.

  While some organizations still perform 100% QC of each TMF record, others have taken a risk-based approach. Risk-based approaches vary and can include checking a percentage of critical record types, or spot-checking accuracy during a time period, or for a subset of sites. When taking a risk-based approach, it is important to identify the approach, the permittable quality thresholds and the plan for corrective actions in the TMF Plan.

- **TMF Completeness Reviews:** TMF Completeness review is the action of confirming that all records required to tell the trial story have been filed as dictated in the TMF Plan. The purpose of a TMF Completeness review is to identify any content missing within a certain time period. Unless a trial is of very short duration, these reviews need to be done on a periodic basis. Many eTMF systems have helpful triggers for TMF completeness. At Advanced Clinical we compare eTMF system reports to the trial-specific TMF Index to assess completeness, and leverage eTMF functions to request records that are missing or expired. In addition to accounting for expected records, the team needs to consider the TMF records that were not anticipated. Given the complex and dynamic nature of trials and trial team membership, best-practice is to review TMF completeness of the trial's story as a team exercise periodically during the trial's conduct, focusing on document completeness for unplanned and unforeseen events. For this activity, trial story boards, the issues / actions list, and risk management trackers are all very helpful tools.

- **TMF Quality Reviews:** TMF Quality Review is the action of confirming that the TMF components are in agreement and will collectively demonstrate sufficient detail for a health authority inspection. TMF Quality Reviews include many comparisons, such as Informed Consent Form template version dates to Ethics Committee approval dates, verification of training records to staff lists, confirmation of monitoring reports to visit logs, etc. TMF Quality Reviews may also include TMF Oversight activities, where a sponsor confirms the quality of TMF management actions performed by a vendor. Some organizations combine the actions for TMF Completeness and TMF Quality reviews; others perform them separately since they can be significantly different assessments of TMF health.

- **eTMF System Quality:** Many modern eTMF systems offer excellent reporting and dashboard tools that can deliver real-time data for TMF quality assessments. On a periodic basis, the organization should also confirm the system's ability to withstand inspection. System SOPs and validation documentation must meet the applicable health authority regulations, e.g. U.S. 21CRF Part 11. Periodic mock or dry run inspections are also a critical indication of eTMF system health, especially considering increasing reliance on remote health authority inspections. Mock inspections allow test procedures, and accommodate for inspector's access expectations. As noted in the U.K.'s Medicines & Healthcare products Regulatory Agency (MHRA) post on Good Clinical Practice (GCP) Inspections: **"Review your TMFs and work out what electronic system access is going to be required for the inspection to ensure the Inspectors have complete and direct access."**

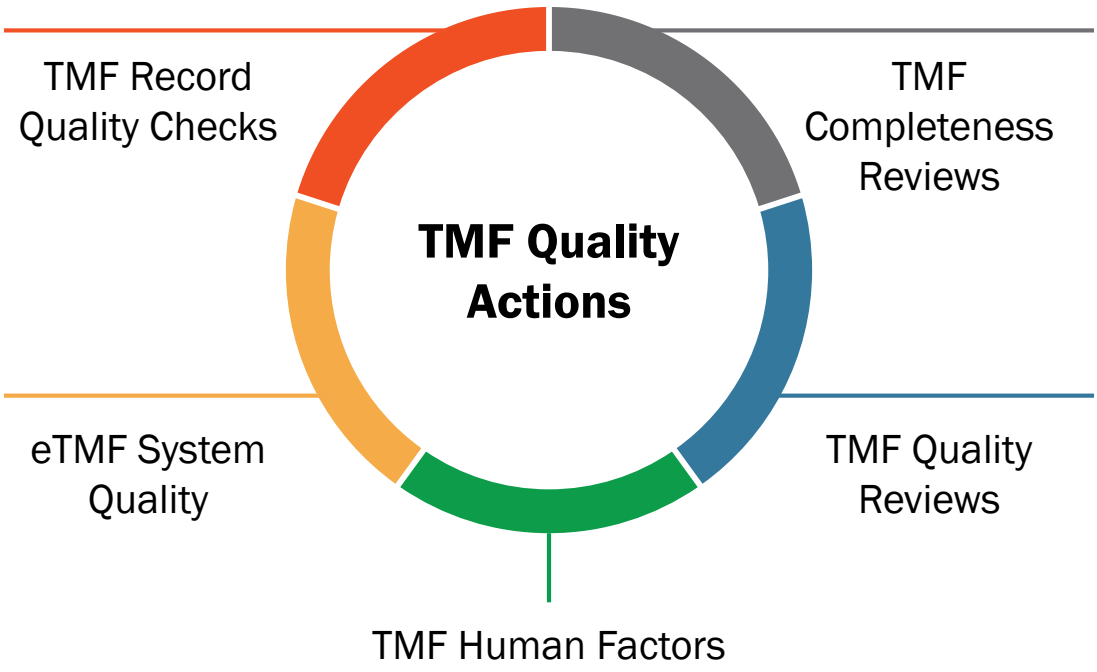
TMF Quality Cornerstone 4: The Human Factor

eTMF systems are only as good as the quality records and data they contain, and those records and data are entered by humans. The most sophisticated eTMF systems are excellent tools, but can only demonstrate the quality actions of the end-user community. Since the TMF ultimately documents the story of an **experiment**, it is not possible for an eTMF to automatically alert for every piece of missing content or every inconsistency within the records. The human factor is still the critical success factor in TMF quality and will remain so for the foreseeable future. At Advanced Clinical, we know the human factor is critical, and actively meet with clients to discuss trial TMF quality issues, actions and results. We also know it is equally important to closely monitor our internal metrics to ensure our TMF processes meet our quality TMF standards.

The TMF Quality imperative needs to percolate throughout the entire organization. Senior management must mandate, govern, and support TMF Quality rigor. Trial team members must commit to and be held accountable for filing ALCOAC records and completing their TMF quality commitments as per the TMF Plan. End users need sufficient TMF training, support, resources and encouragement to successfully complete their TMF responsibilities.

At the end of the day, the most critical human factor in TMF Quality is the health authority inspector whose perspective is: **If it's not recorded, it didn't happen.**

> **At Advanced Clinical, we know the human factor is critical, and actively meet with clients to discuss trial TMF quality issues, actions and results.**



Conclusion

TMF Quality, Why This Matters as Keys to Inspection Readiness
Attaining TMF Quality sufficient to withstand health authority inspection boils down to ensuring the trial story is fully and autonomously documented. The crucial TMF Quality components each require thoughtful and deliberate management. By carefully laying the groundwork, taking action on critical TMF Quality activities, and attending to the human success factors, organizations can be confident in achieving TMF inspection success:

- Right-size an accurate and complete trial-specific TMF Index
- Mandate internal and external quality behaviors in the trial's TMF Plan
- Confirm TMF Quality through reviews of TMF QC, completeness, quality and systems
- Remember that humans are the critical success factor for TMF quality

JP Miceli

Director, Document Management

As the Director of Document Management for Advanced Clinical, JP Miceli is responsible for CRO and FSS TMF activities. JP oversees all TMF staff, project management, business development and budgeting, TMF migrations, implementations and system deployment, and acts as the eTMF system administrator and owner. JP's background includes more than twenty years of industry experience at sponsor and CRO organizations, with a primary focus on GxP records management and clinical documentation. JP has been a member of the TMF Reference Model group since 2010 and is currently an active member of the TMF Reference Model Change Control Board, with his main attention centered on oversight of the Reference Model Zone Teams.