Clinical trial master file migration: A preordained step for a centralized electronic trial master file

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Abstract
The need to speed up clinical trial processes in a cost-effective manner, increased importance of data integrity, and ensuring timely compliance to regulatory requirement updates regarding the Trial Master File (TMF), has made the pharmaceutical industry delineate the requirement to maintain a centralized TMF with quality control. With the exponential increase in the number of sponsors using centralized electronic TMF (eTMF), the shift of trend positively impacts the need for data migration requirements in the TMF space. With an objective to serve the readers handling migration projects, this review article discusses the data migration requirements in clinical operations and eTMF in clinical trials, possible techniques to consider avoiding anticipated roadblocks, and a few other key points. The article also focuses on steps to be taken post migration to ensure meeting the quality of the migrated data in terms of regulatory compliance.

Keywords: Data migration, Drug Information Association Reference Model, International Conference on Harmonization Good Clinical Practices, Medicines and Healthcare Products Regulatory Agency, Quality, risk-based approach, Trial Master File

INTRODUCTION

The clinical research industry fuels the development of path-breaking drugs, biologics, and devices. The clinical trials conducted are time-consuming, are expensive affairs, and generate large volumes of documents from the initiation of trials, Until close-out. The various types of clinical trial documents generated are collectively known as the Trial Master File (TMF), which forms the basis of the regulatory review process and approval.

Clinical trials and Trial Master File
Clinical trials are conducted to evaluate the safety, efficacy, and risk versus benefit of the new molecules. These trials and related activities need to be conducted in accordance with the guidelines of the International Conference on Harmonization of Good Clinical Practices (ICH-GCPs), applicable regulatory guidelines, study protocols, and standard operating procedures (SOPs). Conformity to these standards/guidelines helps ensure that the generated data are of good quality and are acceptable. As documentation is the key to a trial, extensive documents and data are generated in the course of the trial.

There are several published evidences that indicate the importance of a TMF. As mentioned by the European Medicines Agency, “A TMF is the collection of...
essential documents that is used by sponsors, CROs and investigators/institutions for the management of the trial and by monitors, auditors and inspectors to review and verify whether the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the principles and standards of GCP.\[1,2\] These essential documents contribute to the evaluation of the conduct of the trial, ensure rights and safety of the patients, and verify the authenticity and quality of data generated.\[3\] The clinical trial regulation (EU No. 536/2014) further sets requirements for a TMF. As per Article 52, in order to demonstrate compliance with protocol and regulatory requirements, a TMF should be kept with the sponsor.\[4\] In addition, GCP Directives 2005/28/EC Chapter 4, Article 16, state that a TMF shall provide the basis for an audit by the sponsor’s independent auditor and for inspection by a competent authority.\[4\] Finally, as per the retention policy, the clinical TMF should be archived appropriately to allow supervision (control/surveillance) post completion of a clinical trial.\[4\]

Thus, a TMF, the backbone to assess the conduct of a trial, has certain “set expectations” about its collection and upkeep and hence, the regulatory authorities are stringent about the maintenance of TMFs.

As per the Medicines and Healthcare products Regulatory Agency (MHRA) inspection outcome analysis in 2014, 33% of site inspections were delayed due to incomplete or unavailable TMFs.\[5,6\] In addition, as per a study conducted by CentreWatch, delays in clinical trials due to multiple factors cause potential loss as high as $8 million per day.\[7\] Thus, incomplete or/and inaccessible errors in the TMF will not only lead to regulatory noncompliance, but may also lead to huge financial losses to the sponsor company.

All the above presented factors highlight the importance of abiding by the regulatory requirements and maintenance of TMF as a key contributor to the successful inspection of a clinical trial, the “impact time” that a drug takes to reach the market, and potential financial gains to the sponsor.

**Origins of an electronic Trial Master File**

For majority of clinical trials before the year 2014, a TMF primarily comprised of paper documents captured in file cabinets. The management of such paper-based TMFs demanded extensive maintenance and had higher chances of error/oversight/risk, thus increasing the likelihood of noncompliance.

In 2014, the MHRA updated the definition of a critical GCP inspection finding.\[8,9\] which then included “Where provision of the Trial Master File (TMF) does not comply with regulation, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the regulations.” With the increasing need to comply with regulatory requirements, ensure speedy clinical trials, reduce cost to maintain the TMF, provide a real-time audit ready TMF at all instances, better utilize resources in the trial, and improve ease of conduct of the trial, the implementation of a centralized system was the need of the hour for a sponsor. The Annual Veeva Unified Clinical Operations Survey outcome was in alignment to the moving trend, where the percentage rate of adoption of electronic TMF (eTMF) had augmented from 13% in 2014 to 31% in 2017 and to 65% in 2018.\[10,11\]

Sponsors with a vision of adoption of a centralized system in line with the above trend will thus need to establish a robust established data migration strategy.

**Data migration**

Let us now discuss in brief the need and importance of data migration.

Migration is defined as the process of translating/ transferring data/documents from one validated system to another. As per the CFR21 Part 11, data migration should ensure that accurate and complete copies of the records are maintained when they are moved to a new system.\[12,13\]

**Need for data migration**

A pharmaceutical company can undertake TMF migration under the following situations:

1. Paper TMF to eTMF migration
2. TMF movement from legacy electronic systems to a centralized eTMF system within the sponsor
3. eTMF maintained by contracted research organizations (CROs) and returned to the sponsor during or after trial completion
4. Procurement and divestment of molecules resulting in the migration of TMFs between sponsors or CROs as per the business strategies.

**Known challenges of data migration**

In the context of migration of data and documents across all industry domains, many pharmaceutical as well as nonpharmaceutical companies have encountered several problems during the execution of new systems/configuration, etc.

A Data Migration Research Study in 2017 by Dylan Jones highlighted that 31% of the projects were unsuccessful in migration. Overall, 54% of the closed projects could not
be completed as per the plan, 64% overran the forecasted budget, and approximately 50% needed more efficient management and oversight. In addition, it was noted that the rate of success is subject to change based on the volume of data per project, number of legacy systems involved, and the approach to migration.

With the extended need of pharmaceutical companies to execute a TMF migration of the ongoing trial TMF, there is an imperative need for a planned strategy for successful migration.

**Points to be considered during migration**

The successful completion of a migration project depends majorly on robust planning, regular monitoring, and active risk management. The key to a successful migration is a well-defined work plan that lays down the ground requirements for migration.

**Migration scoping**

The plan should first include the “Migration Scoping” requirement that involves identifying the assets and the legacy studies that actually need migration to the centralized TMF system. Pharmaceutical companies can evaluate the studies on the basis of pivotal submission that supports the evidence of trial for the blockbuster molecules. In addition, in the associated sister studies, trials that have a high potential for inspection or rollover can be on the list. For other legacy nonpivotal studies, pharmaceutical companies can restrict the creation of the TMF Table of Content which can find its place in the eTMF as a one-stop shop for the study and retrieval of TMF location, when required. The finalization of the list should include the relevant business units and stakeholders for an effective execution.

**Quality review of the Trial Master File**

Post identification of the in-scope TMF, the next step is to “review the quality of the TMF” that will undergo migration. The TMF generated for legacy studies should be compliant with the sponsor electronic content management systems during generation of the documents. Requirements of scanning, quality control (QC) checks prior to the generation of certified copies, clear audit trail for document modification, etc., should be in line with the systems and sponsor and regulatory standards during the time of generation of document. Any noncompliance identified in the quality can be addressed via clarifications, deviations, and retrospective documentation as per the impact on compliance with regulatory standards. The current SOPs for collection and management of the TMF and system rules governing the new eTMF system should be evaluated for its acceptance and filling of the legacy TMF.

A risk-based approach can be undertaken for maintaining the quality, which has been discussed in the article further.

**Migration ground check**

At the ground level of the assessment, each study team that is impacted by the migration project should ensure that the below aspects are available before the study TMF initiates migration efforts.

- Plan/Define checklist that should list the points needed to be completed or adhered to during the premigration, migration initiation, execution, and completion phases. The checklist should be designed to provide a maximum error-free migration output
- As the specification and requirement at the study level will differ per study TMF, the teams should define the Responsibility-Accountability-Consulted-Informed matrix ensuring that each activity at a study level is assigned with appropriate accountabilities
- A well-defined study governance and communication plan with scheduled follow-up meetings is needed to have a close oversight on the migration steps per study. The forum should include the key study personnel, migration oversight committee, and the end migration user to discuss, resolve, and extrapolate any migration issues encountered in the overall project.

**Governance and monitoring-cruise phase**

Once the plan is executed, a “robust monitoring and governance mechanism” for the project should be in place to verify the progress at key milestones. As TMF migration involves multiple systems, different stakeholders, huge volumes of TMF documents, and multiple users, the chances of errors during the migration process are high. In-stream checks will help detecting the issue, preventing it from creeping in further and ensuring that the migration project is not impacted.

**Assess the quality and completeness of the migration**

With the completion of migration efforts, it is very critical to perform a review of the migrated TMF. (Data) Migration survey shows that 72% of data migration projects exhibit quality issues post migration activity. The key focus area during the review should be the completeness and correctness of the TMF.

As per the GCP Inspectorate-GCP inspection metrics report 2014–2015 and 2016–2017, 18.2% critical findings to sponsors were noted for issues in record keeping/essential documents including, but not limited to, missing/inconsistent documents filling in the eTMF. In addition to this, as per the MHRA GCP electronic archiving guideline 6.8, “Where data have to be migrated to a
new media or in a new format, then the transfer should be validated and fully documented, so that it can be subjected to audit, to ensure and demonstrate that there has been no loss, change or corruption to the data or metadata and that authenticity is maintained.”

Thus, sponsors need to perform quality review of the TMF during migration to be able to identify any alarming issues that could impact the TMF compliance and quality. In addition, migration needs to be assessed by a well-defined data QC plan post completion.

The QC plan can be defined on the basis of the following three principles:

1. Perform a spot check on certain zones of the migrated documents depending on the robust migration process and associated stakeholders
2. Perform a check on a statistically significant sample size for set parameters
3. Establish a risk-based approach for quality review with high-quality outcome and low-risk strategy.

The spot check or random sampling technique, if used, needs to be further evaluated and developed to ensure that the quality review outcome is significant and is in line with the purpose of the entire review cycle. Furthermore, the plan should establish that the TMF is ready for inspections post the above quality review techniques.

A more statistically significant approach – risk-based approach – needs the quality requirement and acceptance limit for any TMF document missing/misfiled to be ascertained. This approach can be illustrated by analyzing essential documents required for a clinical TMF. The ICH GCP E6 (R2) Section 8 enlists the minimum but not complete list of essential documents. A more comprehensive list was put together via the “TMF Reference Model initiative,” a subgroup of the Document and Records Management Community of the Drug Information Association (DIA) called the “DIA TMF Reference Model (TMF RM)” currently versioned v3.0. This TMF RM provides standardized taxonomy and metadata and outlines a reference definition of TMF content using standard nomenclature aiding derivation and maintenance of the TMF.

Analysis of the list of essential documents derived from the TMF RM in terms of missing/misfiled/quality issues in the document against its impact on the data for determining the safety of the patient, adherence to protocol, and integrity of the data collected will provide a robust review of the migrated TMF and help determine the quality of the project.

Irrespective of the principle used to review the migration outcome, the below bare-minimum checks should be included in the review process:

Correctness and consistency of metadata and filling of artifacts in the Trial Master File
One of the core requirements of the eTMF is to provide an easily accessible, identifiable, independent TMF during an inspection to allow the inspectors to review the study conducted without any delay. Use of inconsistent filling location or metadata for same document types, or incorrect location or metadata for different document types, obscures the ease of identifying the documents during an inspection or during retrieval of a TMF during submission. Incorrect/ inconsistent filling may result in the document not being found for timely review and thus developing/generating a critical finding on the TMF quality.

Archival of critical E-mails across functions in the Trial Master File
One of the key methods of communication, “E-mail” is a document used to record critical decision-making and trial conduct. At few milestones in a clinical trial, E-mails are the only evidence to show timely communication and for the awareness of critical information in a trial. To make certain that the TMF is complete and can demonstrate the conduct of a trial, the TMF should be examined for availability of the complete E-mail chains, where applicable.

Adherence to Attributable, Legible, Contemporaneous, Original, Accurate, and Complete principle
The Attributable, Legible, Contemporaneous, Original, Accurate, and Complete principles defined by the ICH GCP R2 (4.9.0) are the golden standards. The TMF documents should be weighed against each principle value and the nearest adherence to them should be established. A study TMF built on these standards affirms the quality of the trial and fulfills regulatory data integrity requirements. The legacy documents generated over a period of years should be evaluated to best fit the requirements.

Duplicate artifacts in electronic Trial Master File system
One of the critical issues highlighted in the MHRA inspection during the year 2016–2017 was duplication of artifacts in the eTMF system. This can majorly be due to legacy system migration for trials as the documents are possibly present in multiple copies across legacy noncentralized systems. Another contributing factor could be the use of inconsistent metadata (e.g., date, version) for the same document type, thus allowing multiple copies to
be uploaded at the same location without an intimation of duplication. This can be avoided by ensuring controlled migration with a precheck to make sure that the legacy systems hold one copy prior to migration.

**Presence of a premigration Trial Master File audit trail to verify the authenticity of the Trial Master File**

In order to comply with the TMF authenticity, the TMF audit trail report should be filed from the legacy systems to verify the timely generation of documents and actions taken during a clinical trial.

**CONCLUSION**

An amalgamation of awareness of the need for TMF migration in line with the regulatory requirements, importance of extensive project planning with in-stream monitoring, and quality reviews of the migration can facilitate near-to success migration of TMF to centralized TMF.

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**Conflicts of interest**

There are no conflicts of interest.

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