Review Article

Trial Master File and Clinical Document Management Importance

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ABSTRACT

Organizations engaged with clinical trials in the Biopharma sector maintain trial master file containing thousands of pages of regulatory documentation needed by each clinical trial. Handling thousands of clinical documents, tasks and processes using a paper-based or modified master file system can be daunting and can lead to inaccuracies and oversights that put your clinical trial at risk for non-compliance. Clinical trial sponsors face significant obstacles in the assembly of TMF, especially when dealing with broad, multinational, multicentre surveys; with all newly introduced archiving technologies, it is becoming progressively difficult to ensure that TMF is complete. It is expressed specifically in the number of inspection findings reported and issued by the EMA. Wirth in life sciences sector, fulfilling the standards of regulatory authorities through their supervision of the planning, operation, documentation and monitoring of clinical trials is also intended to include the required confidence that the privileges, health and well-being of trial subjects are secured and that the outcomes of the trials are credible. The Trial Master File (TMF) is the foundation of what is being reviewed by inspectors to show conformity by sponsors, trial monitors and investigators with the Good Clinical Practice (GCP) standards as well as with other relevant regulatory criteria. Based on the concepts of quality risk management in clinical trials, we have defined the quality standards for the various document categories in the TMF as well as the tolerance limits for missing documentation. This article provides information on what sort of documentation and processes are most relevant for the achievement of high-quality TMF.

Keywords: eTMF, ECM, ICH GCP, audit, Metadata, Repository, data integrity, OASIS.

INTRODUCTION

While the TMF has traditionally consisted of paper documents and other "essential documents" (e.g. images and media) stored centrally in physical file cabinets, the strong desire to reduce costs and speed up the approval process of clinical trials has shifted to the electronic handling and storage of these documents. Electronic TMF (eTMF) solutions have been available. The White Paper seeks to help clinical operations teams better recognize the causes for this loss and provide a view about what 'real eTMF' demands in today's dynamic, global clinical trial environment.

What is Trial Master File?

Validity and integrity of the clinical trial is mandatory in order to obtain authorization from the Ethics Committee and regulatory authorities for the conduct of clinical trials in accordance with the guidelines of the International Conference of Harmonization (ICH) Good Clinical Practice (GCP). A TMF is a collection of documentation that makes it possible to evaluate the conduct of the clinical trial, the credibility of the trial data and the compliance of the trial with the GCP. It is also essential to make it possible for the trial to be ameliorated by the sponsor, since it allows appropriate individuals access to the necessary documentation of the trial.

From 1996 to the present, the clinical trial system has changed significantly, requiring additional documentation in the TMF[1]. The documentation embedded in the TMF should be appropriate to accurately reconstruct the activities of the trial, together with the key decisions taken in relation to the trial. Consideration should be given to the fact that the TMF is a stand-alone set of documentation that does so.

In today's regulatory environment, the files must always be "audit ready." Regulatory authorities may inform the sponsor and request that they be provided with a specific document for inspection. The timely filing and organization of these documents is therefore of the paramount importance. A coherent system must be used in such a way that documents can be stationed and made available for use by the study team as well as for regulatory inspection in a reasonable time frame.

EMA inspectors have frequently identified problems with TMF, including that sponsors often fail to provide a comprehensive TMF. In its "Reflection Paper on GCP Compliance," the EMA stated that TMFs should be complete and accurate[1].

Where trial management operations are hired to third parties, the sponsor shall introduce procedures to ensure adequate supervision of all assigned functions. This can be accomplished by:

(a) Evaluating that the individuals and organizations assigned to the functions of trial management are

appropriately qualified and capable of performing those functions.

(b) Ensure that all parties are aware of their roles and responsibilities (for example, by clearly defining them in contracts and agreements).

(c) Maintain lines of interaction to ensure that the obligations of all candidates are met (for example, by receiving progress reports).

(d) All documentation on the clinical trial should be recorded, processed and stored in a form that enables fair reporting, interpretation and validation[2].

(e) Systems with measures to ensure the reliability of each aspect of the trial should be implemented. Aspects of the trial which are essential for ensuring the safety of the human subject and the dependability of the results of the trial should be the concentrate of such systems[3].

(f) Any alteration of the particulars of trail master file shall be identifiable[4].

It is worth noting at this point that a TMF can be either a hard copy repository or, more often than not, an electronic equivalent. Similar attention is needed when organizing the file architecture, but additionally, appropriate reassurance and audit trail amenities can help in document tracking (when documents are filed, updated and/or retrieved). A further point is to ensure that data and documents are kept in such a way as to ensure their integrity and legibility over the duration of the study and the archival period.

WHAT IS eTMF?

Due to the increased intricacy of studies, in particular oncology studies, and the difficulty of managing TMF paper for different departments, most organizations have moved to eTMFs[5].

The Electronic Trial Master File offers an industry-recommended practice approach for data management that enables you to accomplish the perspective you need to handle clinical trials profitably and accelerate time to the industry. In order to shift towards an all-electronic Trial Master File, organizations commonly use the Enterprise Content Management System to process clinical trial regulatory files. The Electronic Trial Master File should preferably be a document management system containing all the necessary controls. The adoption of electronic document management processes is becoming crucial to business productivity, cost savings and the reduced development of Biopharma products.

The eTMF comprises vital documents, documents specific to the multiple departments, including Laboratory, Biostatistics, Medical Monitor, Clinical Trial Supplies, IRB / EC, Data Management, Agreements and Contracts, and several other documents to ensure that all required documents for the different departments are available. Unblinded areas are also set up to ensure that there is no premature blindness and that the integrity of the data remains intact.

A different section may also be set up in the TMF to ensure that central or core documents are filed in one section and that all site-related sections are filed in their corresponding sections as a means of access control to ensure that confidentiality is not infringed, in particular during the conduct of an audit.

Files and documents in the TMF should be filed in chronological order as predefined in the type of folder structure or predefined directories, and should be kept cohesive across studies instead of creating new folder structures or predefined directories for each trial. This will allow versatile and general folders and naming conventions throughout and sections of the TMF that will not be used for a specific test to be removed or stated as not applicable.

The use of eTMF in clinical trials has several tangible benefits, such as precise audit studies that have proved to be very advantageous in audits and inspections, and changes to the documents can be monitored in the audit study to ensure consistency with the applicable documents and regulations[5].

There are protocols detailing the minimum content required by the TMF, but the file itself is usually the obligation of the study sponsor. Over the last few years, the electronic Trial Master File (eTMF) has received substantial attention for the interoperability of TMF into the digital content platform. This column compares the differences between the paper TMF and the validated eTMF.

SUCCESS IN MOVING FROM PAPER-BASED TMF ARCHIVES TO ELECTRONIC TMF ARCHIVES

In order to move towards an all-electronic TMF or eTMF system, organizations typically use the Enterprise Content Management System (ECM) to manage clinical trial regulatory documents. ECM-based eTMF provides computerized methods and workflows for document and content collection, classification, indexing, archiving and reporting. Digital signatures can be used to mitigate paper-based signature capture, minimize handling processes and significantly reduce mail and overnight delivery costs. The basis of any ECM system is the schema or classification system, the terms of the document marking or 'metadata,' as well as the database, also known as the repository, which retains eTMF electronic documents for search, reporting and other management tasks.

While the paper-based TMF reference model for paper is a great resource for managing paper-based TMFs, it possesses a number of basic elements that would make it feasible for paper-based eTMFs. No two eTMF systems are the same.

An appropriate eTMF system model is based on the following core components:

1. Machine-readable classification strategy-The ability of a computer to read the classification scheme and use it to create an online electronic TMF database allows consistency, productivity and interoperability.

2. Published, standard-based terms readily accessible in machine-readable format.

3. Automated digital signature capture capability to minimize paper handling.

4. Automated document audit trail and history of the workflow.

5. Web Standards-Most ECM systems support XML, HTTP or other web norms for exchanging, viewing and assessing eTMF content.

In order to gain the benefits offered by electronic automation of paper-based processes in the management of clinical trial regulatory documents, it is important to consider the underlying basic schema or 'content model' that will be used to implement the ECM for eTMF. While the paper-based TMF Reference Model is beneficial as a reference point for creating an eTMF content model, the paper TMF Reference Model lacks many of the fundamental elements depicted above. This makes the TMF Reference Model unsuitable for use as a content model in eTMF deployments. The paper-based TMF Reference model has no provision for digital signatures, no configuration as to how files should be categorized with metadata, or how TMF repositories and archives can be exchanged or searched on the internet / intranet. The paper-centric TMF Reference model is human-readable but really not machine-readable, making it nearly impossible to import to the ECM system. If the paper-centric TMF Reference model could be transformed to a machine-readable format, it would still not include the basic components needed to support electronic paper handling, search and interoperability.

Paper is an expensive, time-consuming and disorganized material to be purchased and used. Preparing files, binders and racks to house TMF material is unreliable and clearly more expensive for businesses to manage than for electronic files. Carrying paper documents — either by standard mail or courier — can also be a waste of money, taking into account shipping charges and enhanced staff time required to manage the majority of the documentation.

Warehousing can also be a challenge. Paper TMFs produce a significant number of documents and therefore require a huge quantity of office space for accommodation. Other considerations that add to the total cost of storage are recommended practice measures such as limiting access to documents and preventing and protecting fire / water damage. In addition, some national laws have document retention periods extended to 25 years after the end of the clinical trial, increasing the price of keeping TMF paper and often culminating in off-site storage fees. On the other hand, the eTMF provides efficiency in these same areas. Most eTMF systems provide cloud-based storage space.

Remote accessibility is another advantage of eTMF system. Sponsors, remote staff and other organizational staff can access and review files from off-site locations. For example, clinical research associates have the ability to review files at an investigation site directly against eTMF without incurring additional costs. Files can be retrieved 24/7 and some eTMF systems can be congruent with a smartphone. In the end, the eTMF system reduces the cost margin regardless of the complexity that affects the cost of paper TMFs, such as the trial phase, the number of sites and the total patient.

With regard to geography, North America holds the highest possible share of the global eTMF market and is likely to take up over the corresponding period. The interesting evaluation of cloud technology in various sectors, which include healthcare, is the key factor accountable for North America's supremacy in the global eTMF market. North America generates the largest amount of cloud traffic each year, i.e. 1891 EB (Exabyte) due to ease of use and low cloud infrastructure costs.

However, Asia Pacific is also estimated to contribute to the development of the global eTMF market. This growth is ascribed to developments in the pharmaceutical industry. India and China are two major regions that are making efforts to establish the pharmaceutical industry. In India, for instance, high-quality medicines are available at a low cost that has fueled development in the pharmaceutical industry. As a result of these considerations, the Asia-Pacific region is expected to maintain a substantial share of the global eTMF market in the coming years.

TRIAL MASTER FILE STRUCTURE AND CONTENTS

1) Sponsor and investigator trial master file

The TMF is generally comprised of the sponsor TMF, carried by the sponsoring organization, and the investigator TMF, carried by the investigator / organisation. Investigator TMF is frequently referred to as the Investigator Site File (ISF). The TMF for the trial, both of the sponsor and of the investigator / institution, should be established at the start of the trial. Only one TMF should be available for the clinical trial, consisting of the sponsor and the investigator parts. In arranging the TMF, it is crucial to segregate certain files that are produced and/or held by the sponsor only from those obtained and/or held by the investigator / organisation only (e.g. subject identification code list filed only in the TMF investigator and master randomisation list issued only in the TMF sponsor).

The investigator / institution is liable for all the essential documents produced by the investigator / institution and must therefore have control of them at all times[6]. In cases where the investigator is employed by an institution that is the sponsor of the trial, the sponsor may outsource the task of maintaining all or part of the TMF sponsor to the investigator. In this circumstance, it is possible to combine

the delegated part of the TMF sponsor and the TMF investigator for that investigator / institution, which avoids duplication of documentation; however, the responsibility of the TMF sponsor remains with the sponsor.

The same pertains if the investigator and the sponsor are the same person. When a trial is co-sponsored, arrangements should be in place to maintain the TMF on the basis of the responsibilities that each cosponsor holds. Role-based permissions should be established for activities underway, such as restricted access to files / documents (e.g. randomisation codes and unblinded adverse event data).

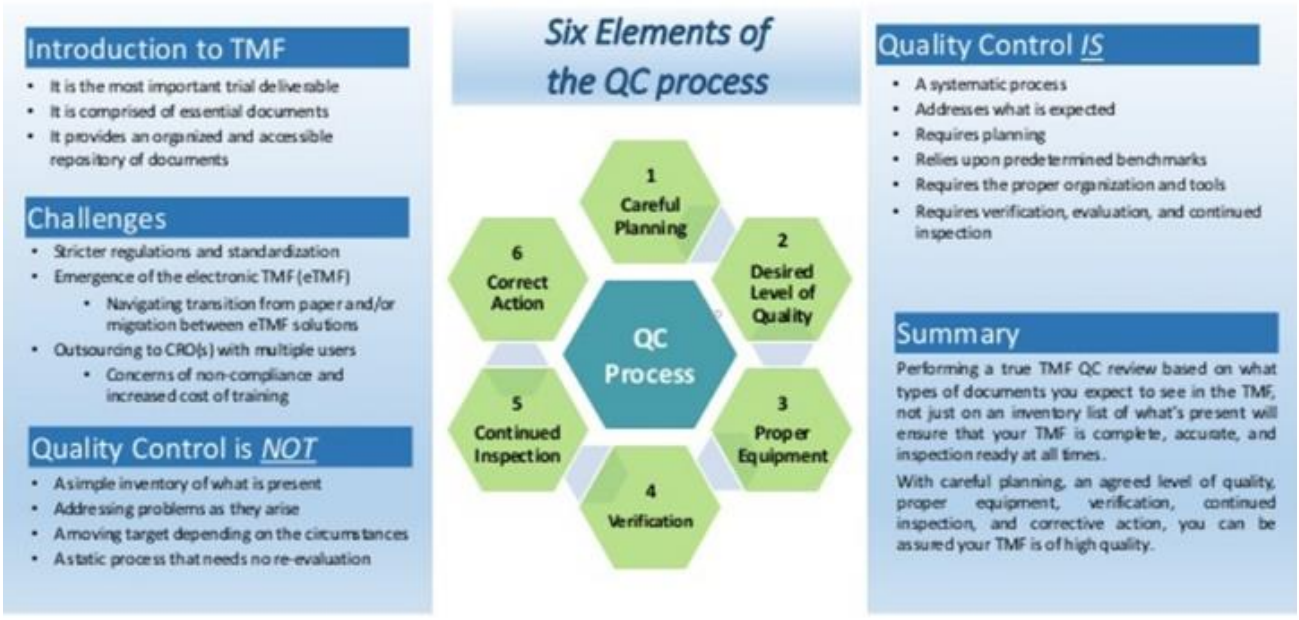
2) Trial master file structure

When starting a clinical trial, the sponsor and the investigator / institution should identify and preserve a record of the location(s) of all potential documentation considered to be TMF, even if there are several sites, departments, nation organizations and systems engaged. A primary TMF system for carrying essential documents, which could be entirely digital, entirely on paper or hybrid, must be in place. Other systems, which include central systems, may exist that hold 6 essential documents (e.g. Central e-mail database, SOP-management system, primary training records, delegation logs, software verification logs and data relating to further than one trial, e.g. investigator brochures (IB)) appropriate to the trial and should therefore be part of the TMF. The number of these other systems should be reduced, with necessity being given to the placement of documents in the primary TMF system. Documents relevant to multiple trials do not need to be duplicated in multiple TMFs.

An appropriate overall index or table of contents should be provided to allow the location of the integral documents in the TMF to be attributed. Whether the TMF is paper or electronic, it is recommended that it be enforced and standardized across the investigator / institution, sponsoring organization or CRO, where applicable. Documentation should be filed in chronological order in each appropriate section of the TMF. Consideration should be given to defining the dates used for filing documents, such as the date of receipt, the date of filing in (e)TMF, the date of approval or the date of expiry.

Must the TMF be kept up to date or is it acceptable to organize the TMF at the end of the study?

Regulatory authorities expect the TMF to be preserved in a constant state of readiness for examination. This requires records to be filed within the TMF in a reasonable time. Each organization should describe the timeliness of its procedural documents or the TMF plan. Managing up-to-date TMF helps to provide supervision of the clinical trial. If the sponsor waits until the end of the trail to ensure that the TMF is complete, it is much more challenging and sometimes impossible to acquire complete records. When using eTMF, timeliness becomes very transparent because the records are time and date stamped when they are introduced to the TMF.



APPROACH FOR DEVELOPING QUALITY AND TOLERANCE LIMITS FOR TMF

The influence on "Safety, rights and wellbeing of patients" along with "data integrity" was used as the basis for the risk assessments. This is in compliance with the EMA's view that these are the ultimate principles in GCP and that they should guide the assessments of quality in clinical trials[7].

As a first move, a risk assessment was carried out for all 148 desired forms of core documents included in the DIA TMF Reference Model Version 2 (2012)[8] and provided as a data publication at Dryad[9].

The team members assessed the effect of the lacking process on patient privacy and the safety and integrity of the clinical data using a 10-point scale.The impact was rated as "critical" (between 8 and 10) if the missing process had a

direct impact on the patient's rights and safety or integrity of the trial data. "Major" (score between 5 and 7) has been used if it could have an impact on the patient's rights and safety or integrity of the test data. A score around 2 and 4 was selected for a "minor" effect that would have no anticipated impact on patient rights and safety or integrity of trial data. Finally, a score of 1 was applied if the missing process had no effect on the integrity of the patient's rights and safety or trial data, but only had an impact on the clinical trial documentation.

In the second step, a risk assessment was carried out to assess how much effort would be required to replace or replace the missing document in the TMF, assuming that the related process was performed for the clinical trial (i.e., that the document was produced during the trial but was not available in the TMF).

The level of effort required to track or replace the document was assessed for all core documents assessed in Step 1. If the original was available, the document type received a risk score of 1; if a copy could be entered in the TMF, the missing document received a score of 2. When the document was missing but the process could be shown to have taken place using other documents, a score of 3 to 6 was assigned to this validation effort.

eTMF SYSTEM REQUIREMENTS ACQUISITION

Document acquisition primarily involves the acceptance and processing of documents or contents. Documents are purchased electronically and stored electronically in the eTMF. Documents may be obtained from the web or through e-mail or through automated business processes. Electronic signing using digital signatures from authenticated users is often used to remove paper from a clinical trial study. Digital signatures are accepted instead of wet signatures in most countries worldwide, including the USA and the EU, thus avoiding the need to scan a document. Where paper is still used for wet-signed documents or other non-digital content items, the conversion from paper documents to electronic document images is done via scanners or multi-function printers. Optical Character Recognition (OCR) software is sometimes used, whether integrated into the hardware or as stand-alone software, to integrate digital images into machine-readable and searchable text. Optical Mark Recognition (OMR) software is frequently used to extract values from checkboxes or bubbles. Capture may also include the receipt of electronic documents and other machine-based documents. However, these file systems must have some basic functionalities to cater to the need of management of TMF. Some of them are as follows:

Classification: Forwarding the document to the proper classification of the eTMF for indexing. Classification is mainly used as an indexing preparation.

Indexing: Indexing is the process of adding unique document identifiers so that documents can be quickly retrieved from the system. Document indexes consist of metadata that is retrieved from a predefined topology index classification. Often some level of indexing can be automated by using the metadata attribute search database. When computerized workflows, digital signage and all electronic processes are used, indexing and classification can often be automated, saving working time and processing time.

Storage: Store your electronic documents. Document warehousing often includes the management of the same documents; where they are preserved, for how long, the migration of documents from one storage device to another (hierarchical storage management) and the possible demolition of documents.

Compliance: Compliance rules shall capture the specifications, policies and procedures for the collection of documents. For example, a document of the FDA 1572 must be collected for each investigator in a clinical trial. Compliance rules ensure that the correct documents are collected in the eTMF in accordance with the preset rules. The eTMF compliance rules are often conveyed as part of a SOP or standard operating procedure. The Compliance Officer or Regulatory Document Officer may be responsible for the development and implementation of the required enforcement policies and proceduresApplications for eTMF as used in clinical trials in the USA are subject to regulatory compliance under FDA 21 CFR Part 11 Regulations and should be independently validated and audited for compliance with FDA safety and electronic signature rules.

Document Quality: If a document is to be dispersed electronically in a regulatory environment, the quality of the document should be checked through a predefined quality control process. Acceptance of sampling using standard-based processes such as ASTM-E105 to sample incoming document batches is one such document quality control method that helps ensure document integrity and quality for large batches of documents.

Auditability:

Auditability of the eTMF is twofold:

1) System access audit trail, login and user activity should be auditable for all system commodity use (21-part CFR); document workflow history including date, event (e.g. approved, submitted, created, modified), event source and person involved;

2) Document compliance audits: administrative document compliance audits play a key role in document compliance and quality. Auditors should have internet access to eTMF documents and reports to review the eTMF archive with a view to identifying potential breaches of policies and practices. Policies and procedures should specifically document the breadth, intensity and procedures for audits. Audits should be regimen and event-based.

Reporting: The eTMF should offer a set of standard pre-configured document management reports. The user can often subscribe to the eTMF to obtain these reports by e-mail. For example, a report enumerating documents executed by document type, documents captured by site,

documents captured by investigator or other person, documents captured by category. Missing documents by site, by document type and by person are also useful for proactive notice that a document has not yet been collected or is missing.

Search and Retrieval: Retrieve electronic documents from the warehouse. Although the notion of retrieving a particular document is simple, it can be quite complex and powerful to retrieve it in an electronic context. Simple processing of individual documents can be supported by enabling the user to specify a unique document identifier and the system to use a basic index (or a non-indexed query in its data store) to retrieve the document. More flexible retrieval allows the user to indicate partial search terms that include the document identifier, document type, and/or parts of the expected metadata. This would normally return a list of documents that match the search terms of the user. Some systems include the ability to specify aBoolean expression containing different keywords or example phrases that are expected to exist within the contents of the documents. Retrieval of this type of query may be supported by pre-built indexes, or may perform more time-consuming searches through the contents of documents to return a list of potentially relevant documents.

Integration: Many data management systems provide content assimilation and exchange capabilities. Open standards enable for some degree of integration with software and systems. Most recently, major innovation document management vendors have worked together on a new specification to facilitate the integration and web-based exchange of enterprise documents and records. The Content Management Integration Services Specification (CMIS) is a format for improving the compatibility of Enterprise Content Management systems. OASIS approved CMIS as an OASIS specification on 1 May 2010. While CMIS can be used as a transport to communicate document information between systems, it does not determine any format for the metadata, document type name or other core framework of the archive. This will be resolved by eTMF ontology, allowing eTMF archives to be easily exchanged, imported or exported via the CMIS standard.

Metadata ascribes or 'tags' are typically allocated to each type of document / content type. These tags are used to capture data values for each document for categorization, search and reporting purposes. Metadata and metadata values are then stored either with the document in the eTMF archive or with the actual document integrated as metadata tags. Examples of standard metadata are document archive metadata such as 'Date' or 'Creator' from Dublin Core metadata, or 'Site ID' from NCI thesaurus to identify a study site. Metadata values are data stored with a metadata trait. The document management system may also immediately extract metadata from the document or prompt the user to add metadata. Some systems also use heuristic analysis for scanned images or perform text extraction on electronic documents. The resulting extracted text can be used to aid users in locating documents by identifying probable keywords or providing proper text search capability, or it can be used on its own. Text derived can also be stored as a metadata component, stored with an image, or separately as a document collection search source.

eTMF Archive Format: Published document database format that allows Biopharma content archives to be exchanged and stored in both physical formats (e.g. CD or DVD-ROM) and web-based formats. Documents in the archive used for eSubmissions must be in PDF format. PDF formatted documents cannot be easily modified, are secure and support the embedding of digital signatures. The PDF template is accepted by US and European agencies and is typically used as a document format in online eTMF repositories or offline archives. PDF documents and metadata record content can be stored in an online document repository or, as an option, in a separate file for offline access, such as an encoded document.

OASIS eTMF STANDARD TECHNICAL COMMITTEE

As more and more life science organizations move to automated electronic systems, this shortcoming of the TMF Reference Model is addressed by the OASIS Standard Technical Committee. This group coordinates the efforts of clinical trial sponsors, contract research organizations and suppliers to develop an ISO standard.

The OASIS initiative has as a stated objective to "…define machine readable formats for clinical trial master file content interoperability and data exchange to include:

(a) an eTMF content classification model consisting of a conventional vocabulary and content classification ontology;

(b) a set of eTMF content classification rules and procedures;

(c) an eTMF data model and an interoperability format for the exchange of electronic test master file information for the clinical trial realm, where eTMF content can be exchanged through either cloud or physical media.

While this action plan is gaining momentum and the first revised version has been published, it remains to be seen whether its model is entirely consistent with the TMF Reference Model, or whether the differences between these standards will add complexity to the TMF business, especially as new versions are released by each group.

CRITICAL INSPECTION FINDINGS

Some regulatory bodies have included TMF deficiencies in their list of crucial findings. The critical point is that, during inspections, inspectors often found unfinished TMFs or were unable to access the TMF. "Incomplete" does not mean that only one or two documents are lacking, but that the inspector finds the TMF unfinished to such an extent that it cannot form the basis for the inspection and, therefore, impedes or hinders the performance of its duties by verifying compliance with the regulations. For more

information on the definition of crucial findings, it may be useful to read "Updated definition of a critical GCP finding" from MHRA, one of the most important European regulatory agencies.

In overview, the MHRA found such deficiencies in 35% of its inspections of studies sponsored by commercial organizations, giving a clear assurance that this is a common challenge encountered by many in the life sciences sector. The MHRA points out that this is especially problematic with electronic TMFs.

More troubling, this statistic suggests that eTMFs are going to fail more often than old-fashioned, sheet-based TMFs. During a gathering between European GCP inspectors and industry representatives, the industry excused this with the designation of eTMF implementation, stating that eTMF has not yet been implemented, needs to be seen as a work in progress and that innovation is slowly maturing. The astonished inspectors were far from acknowledging this industry view and excuses, trying to point out that eTMFs had been around for quite a while.

The industry's explanations aside, this level of eTMF impairment suggests the root cause: technology matures (too) slowly. With so many life science companies offering difficulties complying with eTMFs, the vendors of these solutions have continued to fail.

Inspectors / auditors do not object to the review of the eTMF during the GCP inspection / audit. Accordingly, the legislation does not distinguish between paper and eTMFs all requirements are the same; however, the use of eTMF during the inspection / audit presents additional challenges for both the inspector / auditor and the organisation.

Inspectors / auditors expect the eTMF to recreate the paper-based system that it replaces in an appropriate manner, in terms of functionality and time taken. The organization is recommended to consider that the requirements for inspectors will also represent the criteria of any auditor, and it is suggested that the system be designed and implemented or purchased with this in mind.

Inspectors / auditors will require direct access to the eTMF system as used by the organization. Access is suggested to be read-only access to any part of the eTMF without any restriction. Additional electronic systems may have eTMF documents (identified by eTMF as part of the eTMF structure); connectivity to such systems is also required by the inspector / auditor.

In order to view the documents, the eTMF will need the use of appropriate equipment for the inspector/auditor. This equipment is recommended to facilitate the presentation of documents at the actual size, most of which would be A4 paper, and it is recommended that the size should not be limited due to other areas on the screen, such as database / index structure, toolbars, etc.

It is recommended that the system has a profitable speed of access and, ideally, does not necessitate the use of a nomenclature document or require time spent opening non-obviously named files to determine their contents. The system and equipment would preferably be similar to turning the pages of a book, and it would be useful if there were a system resource available for printing or marking documents for subsequent retrieval and examination, as well as the opportunity to compare documents side by side. Finally, if the documents of the eTMF are required to be copied and retained by the inspector / auditor, it is recommended that the organization be in a position to promote this. An eTMF search tool is also recommended.

• The organization was unable to provide the full eTMF for inspection / audit purposes at the recommendation of the auditors / inspectors. In some cases, additional inspection / audit days are necessary.

• Staff who were presented as "system users" for eTMF were unable to locate the documents requested by the inspector / auditor.

• Failure to fully document and perform effective quality control checks on documents uploaded to eTMF – as a result, the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were lacking pages, inaccurate documents, low quality scans.

• Incorrect documents located in the eTMF, e.g. from other trials.

• There was impoverished, often predictable, sometimes inaccurate labelling of files, resulting in undue time loss in opening and closing PDF documents in the eTMF when trying to track down documents.

• There was no accurate interpretation of the documents sent to the contractor to be uploaded to eTMF.

RISK ASSESSMENTS

The overall risk assessment combined the results of step 1 (the impact of a process that was not performed) with step 2 (the effort to replace or substitute a document). The overall risk assessment was calculated using the following formula:

Risk Priority Number (RPN) = (impact of missing process) ^{2} × effort to replace the document

- Since the significance of patient rights and safety was regarded to be much more essential than the effort needed to replace or remove a document, the rating for the influence of the missing process was laid out in the above formula. The consequent risk preferential number (RPN) was calculated on a risk-ranking matrix to measure the overall risk category.
- The FDA guidance defines threat as "a combination of the likelihood of damage occurring and the seriousness of the harm"[10]. The quality system is defined as" the sum of all aspects of a system that implements quality policy and ensures that quality objectives are met[10].
- Combined as one, they are represented as "a deliberate process for assessing, controlling,

communicating and reviewing risks to the quality of the drug product throughout the product lifecycle."

- These concepts, on their own, may seem over-reducing, puzzling, and frustrating to apply. Upon release of the new guidelines, many in the industry have held or attended 'R2 impact' meetings introducing this concept of risk-based systems.
- These conferences often started back with a brainstorming session to distinguish risks, most of which ended with a stakeholder pushback or a long list of accusations.
- Risk-based thought process, however, does not enable the updating of your documentation mechanisms or day-to-day experience, but instead the ability to perceive on existing systems and the willingness to make adjustments when new information is provided.
- As part of being able to comply with ICH E6(R1), your organization has already quality systems in place.

Documented procedures and validated methods that are being developed, implemented and kept up to date:

- Documentation system that maintains and allows the insertion of any information / documentation (quality records / essential documents) to demonstrate the actions taken, decisions taken and results achieved;
- Suitable training of sponsor staff as well as staff in subsidiaries, agreement research organizations (CROs), suppliers or other content providers and on trial sites;
- quality control, for example, on-site tracking of test sites and central analytical facilities and/or through centralized monitoring methods;
- Quality assurance, including internal and external audits conducted by independent auditors[11].
- The bullets above are the justification behind the development of SOPs, the creation of a document hierarchy (such as the TMF Reference Model), the requirements for documents and filing systems, the training of staff and the quality control (QC) of TMF documents. Risk-based quality management takes the quality system framework one step forward by recognising hazards on a regular basis.

THE IMPORTANCE AND BENEFITS OF TMF

Documents required for the TMF is important for several reasons related to the overall validity and integrity of the study. The collection and filing of essential document in the TMF are not only needed for new product approval but can be beneficial as well [12,13,14].

Importance:

(a) Validity and quality assessment of the data collected.

(b) Required as proof that the trial was performed in compliance with the ICH CGP Guidelines and other designated regulatory requirements.

(c) Evidence that both the investigator and the sponsor were GCP compatible during the conduct of the study.

(d) Provide critical information on the particular clinical trial to the auditor during the audit.

e) The trial can only be completed upon collection of the last document and after it has been reviewed by the monitor to confirm all the required documents are present

Benefits:

(a) The clinical trial may be recreated by means of the documents gathered.

(b) The TMF shall provide a central access point for all relevant documentation for all personnel involved in the handling of the trial.

(c) The TMF shall be determined in a chronological order to ensure easy access to documents for auditors and trial staff.

(d) The timely collection of these documents shall contribute to the successful completion of the trial.

eTMF system benefits

Many groups involved in BioPharma clinical trials want to move from paper-based document management systems in file cabinets to online electronic document management systems where documents are stored online in electronic archives. By enforcing a comprehensive eTMF system that automates the capture and management of TMF documents and records, organizations can reduce unnecessary risks and can often make efficiencies in clinical trials through manual paper managing processes. There are many reasons why companies may wish to implement an effective eTMF management application:

• Growth in Regulations: State, Federal and Industrial Regulations continue to grow and evolve.

• Risk management: substantial risks and penalties for non-compliance, which include penalties and customer charges. Systems involve trust that you have met the Agency's regulatory compliance requirements.

• Improved document durability – automated systems have been shown to make fewer inaccuracies than manual paper managing processes; ability to adopt automated quality control mechanisms;

• Enhances team profitability and increases clinical trials: sharing, displaying documents at anytime, anywhere from any device is faster than manual paper processing. Electronic document sharing with clinical trial stakeholders: e.g. investigators, agencies, and clinical research centers can help resolve issues more quickly and accelerate clinical trial milestones

• Cost savings: save on mail and overnight courier costs; save on physical storage costs; save on administrative staff handling and management costs.

• Time Savings: Exchanging, viewing documents Whenever, anywhere from any device, accessing documents helps to

move business operations quicker than manual, paper-based procedures.

• Reduced auditing and reporting costs-automated reporting and retrieval of ECM-based systems can significantly reduce auditing and reporting tasks and improve product quality through easier audits and management.

CONTROLS AND SECURITY, TRAINING AND VALIDATION OF eTMF

Ideally, eTMF is suggested to be a document management system comprising all the essential regulations listed below to be entirely acceptable. The warehousing of documents in folders in the operating atmosphere of computer systems without the minimum controls below is unlikely to be considered appropriate.

The eTMF system should make it possible to have appropriate security in place which it is recommended to include as a minimum:

• User accounts could be developed and deleted in a formal approval process and in a timely manner;

• Secure user passwords;

• System in place to lock / protect individual documents or the entire eTMF (e.g. during archiving) to prevent document changes;

• Regular backup;

Additionally, the eTMF would ideally have the following attributes:

(a) Where approval of documents is made through a workflow system, digital signatures should be used;

(b) Role-based permissions for activities to be undertaken;

(c) an audit trail in place to identify date / time / user details for the creation, upload, approval and modification of the document.

The eTMF should be validated in order to demonstrate that the functionality is appropriate for the intent, with structured procedures in place to handle this mechanism and to control change. All staff members engaging in the behaviour of the trial and using the system must obtain adequate training and this must be documented. User manuals and helpdesk are recommended to be in place as part of the quantified system as adequate. Security and control of trial master file.

Access to trial master file

The TMF should be managed securely at all times to make sure fullness and to avoid accidental or premature loss, unauthorized alteration or destruction of documents. Access to the TMF should be based on a role and permission description characterized by the sponsor and/or the investigator / institution. The TMF sponsor and the TMF investigator / institution may contain some information that might unblind personnel who need to remain blind during the trial. This should be properly controlled, e.g. by storing documentation in another system or repository and/or by a role and permission description as defined by the sponsor and/or investigator / institution.

Storage areas for trial master file

At all times, the warehouse for TMF documents (such as paper or electronic media archives and server rooms) should be acceptable to maintain the documents in such a way that they remain complete and legible throughout the trial and the period of preservation required and can be made accessible to the competent authorities of the Member States upon request[18]. Adequate and appropriate space should be obtained for the storage of all the essential documents of the completed studies. Infrastructures should be secure, with appropriate environmental controls and optimal protection against physical damage. Factors to be considered when estimating an appropriate storage facility should take into account certain factors such as safety, location (e.g. environmental risk factors) and size. Sponsors should make a documented assessment of the conditions at the investigator site / institution for the TMF investigator / institution during the clinical trial and archiving. The sponsor should be notified if the agreed provisions are changed (e.g. storage subcontracting).

Sponsor/CRO electronic trial master file

Electronic TMFs should enable appropriate security and reliability, ensuring that no loss, alteration or corruption of data and documents occur[19]. The primary eTMF is a system for managing documents that should contain the controls listed below:

• user accounts;

• secure passwords for users;

• a system in place locking/protecting individual documents or the entire eTMF (e.g. at time of archiving) to prevent changes to documents;

• regular backup;

• periodic test retrieval or restores to confirm the on-going availability and integrity of the data[15].

• an audit trail in place to identify date/time/user details for creation and/or uploading deletion of and changes to a document (explanation of the deletion or modification, if necessary)[16,17].

• role-based permissions for activities being undertaken, such as restricted access to files/documents (e.g. randomisation codes and unblinded adverse event data);

• the suitability of the system for archiving purposes should be appropriate;

The above principles also should apply to any electronic systems defined as part of the TMF (e.g. SOP management system, e-mail central repository).

The eTMF systems should be validated to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process[17].

All staff members involved in the conduct of the trial and using the system should receive appropriate training.

When separate TMF systems are connected to facilitate the actions of the trial, e.g. when the CRO eTMF system uploads documents to the sponsor eTMF system (possibly through an optimal system), the document transfer process should be robust and validated to prevent any losses. Any electronic system that holds test data and metadata (e.g. audit trails) required for reconstruction should be archived in such a way that the included test data and metadata can be retrieved as usable datasets.

Metadata is structured data that describes the context, content and structure of a file. They promote file management, identification, convenience and retrieval. Metadata may include information such as creator or author, time and date of creation, date of archiving, eTMF location, file title or keywords, version, file type, file size, and other file properties.

Metadata applied to documents should be officially defined in order to ensure coherence across all documents. This should include the predefined date of the document (e.g. the date of creation) and, where appropriate, time based on the standard time zone, so that the files can be displayed in chronological order. For documents that are subject to version regulate, the use of file names should not replace version details that are visible on displays and printouts.

Any migration of data and documents to new media or a new format should be verified to ensure long-term readability and to maintain integrity.

The suitability of the storage system should be assessed on the basis of the file format used, e.g. whether the eTMF-document-management system is suitable for storing dynamic allocation files (e.g. Excel files and SAS datasets) where necessary and does not require such files to be rendered as PDF files. Within the eTMF document management system, PDF files produced from dynamic data files in other systems (e.g. IMP shipping reports generated from IRT datasets and monitoring visit reports generated from the Clinical Trial Management System (CTMS) datasets) may be uploaded to the primary TMF system; if so, the original dynamic file should be retained in the original system.

CHALLENGES

Following are the major challenges companies face in managing essential documents and trial master files:

• Difficulty in meeting regulatory standards.

• Time required to start trials.

• High cost of managing TMF content.

• Difficulties in providing access to the documents for global team members.

• Poor communication and collaboration with trial staff.

• Insufficient internal resources.

• Inability to maintain audit-ready TMFs.

• Inefficient procedures for global team members to make a significant contribution.

• Lack of visibility on the designation of clinical trial documentation.

• Time required to locate and handle documents.

An eTMF provides an industry best practice strategy to document management that allows you to achieve the insight you need to control clinical trials efficiently and facilitate time to the market.

GUIDANCE ON TRIAL MANAGEMENT

The following provide further information and guidance on trial management:

The Overview of Trial Management Systems Workstream Document provides an overview of the activities associated with the management of the trial as well as the requirement for supervision and documentation of those activities.

The Tracking Procedures Workstream Document provides further data on the types of monitoring that the sponsor may perform (e.g. on-site monitoring or central statistical monitoring) and documents all elements of the monitoring process. Additional examples of risk adaptation are also provided in the preceding Joint Project Workstream Documents:

- Monitoring Trial Scenarios illustrating the monitoring strategy applied to five very different trials.
- Trial Monitoring Option Checklist is a tool used in conjunction with other resources to help define and develop strategies for each trial.
- The MHRA GCP Guide outlines the expectations for the management and monitoring of the trials and provides a detailed description of all key processes and many examples of risk adaptation.
- The Trial Managers Network (TMN) is a source of practical support and guidance for the trial management process and has published comprehensive guidance: A Guide to Efficient Trial Management.
- The MRC HTMR Network hosts a series of webinars on the conduct of the trial, including the Monitoring of Efficient Testing: the role of central statistical monitoring.
- The Incorporated Standards of Reporting Trials (CONSORT) reporting guidelines suggest that a precise record of patients considered for RCT participation be preserved.
- The SEAR (Screened, Eligible, Approached, Randomized) framework provides a deliberate way to

record the flow of potential participants through the recruitment process to support better recruitment practices in clinical trials.

- Guidance on enhancing the impact of qualitative research on RCT feasibility studies has been developed to help researchers consider the full range of contributions that qualitative research can make in relation to their particular study.
- The use of qualitative methods to inform Delphi surveys on the core outcome of the identified development identifies some of the issues that COS developers need to consider.
- Designing and applying progress criteria for internal pilot studies.

DISCUSSION

The TMF should document the trial processes in an appropriate manner, ensuring that patients' rights are respected, that their safety is assured and that the trial data are reliable. Not all documents in the TMF are of similar value when documenting these conditions. The absence of some documents (and their associated processes) may have a vital impact on these outcomes, while others may have almost no influence at all. Therefore, when considering how to ensure adequate TMF quality, it is important to assess the importance of the individual documents rather than simply to consider the aggregate number of documents filed. Tolerance limits for missing documents cannot therefore be specified in a consistent manner and should be assessed on the basis of the impact on patient rights and safety and integrity of the trial[20]. Our strategy determines the importance of the missing document and, in addition (if the trial process has been carried out but the document is missing), indicates the amount of effort needed to replace it. We have produced a list of document types of very high and high importance, which should be centered on ensuring an adequate high-quality TMF while, on the other hand, identifying lower risk areas that require less importance and attention during quality control steps, without harming the integrity of the entire document. This list could be of major assistance to anyone working with TMFs, e.g. helping to ensure sufficient and constant maintenance of TMF or prioritizing inspection preparation efforts in the event of short timelines and limited resources[21].

The team also assessed other deficiencies (e.g. poor scanning quality) identified in the QC checks. Respective quality expectations, tolerance limits and the corresponding QC procedures are not included here, but will be published in a separate article as they require extensive treatment.

CONCLUSION

There are many important factors to take into account with respect to TMF, and this process will be complicated and time consuming depending on the complexity of the study. The TMF must always be ready to audit, in chronological order, finish and precise, and carry out a study as a whole to make sure that the study is legitimate and to verify the credibility of the data. Although the TMF has improved enormously over the last few years and has moved to an electronic system that allows for better control and auditing, there is still room for improvement. As the studies evolve to be more precise, complex and specific to the target, the TMF should also be developed to accommodate these changes in order to ensure that all required documents are collected in the TMF and that access to the TMF is restricted and controlled at all times. The future development of the TMF should focus on better access control, more user-friendly systems, built-in quality control controls and easier identification of missing or incomplete documents.

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