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**Review Article**

# ELECTRONIC TRIAL MASTER FILE (eTMF) - AN INDISPENSABLE TOOL THAT COLLECTS AND FILES ESSENTIAL DOCUMENTS OF A CLINICAL TRIAL: A REVIEW

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**ABSTRACT**

Every organization involved in clinical trials in the BioPharma industry maintains a trial master file comprised of thousands of pages of regulatory documents required for each clinical trial. Managing thousands of clinical documents, tasks and processes using a paper-based or hybrid trial master file system can be overwhelming and can introduce errors and oversights that put your clinical trial at risk for noncompliance. An Electronic Trial Master File provides an industry best practice approach to document management which allows you to gain the insight you need to efficiently manage clinical trials and accelerate time to market. In order to move toward an all Electronic Trial Master File, organizations typically use an Enterprise Content Management system in their efforts to manage clinical trial regulatory documents. The Electronic Trial Master File is recommended to ideally be a document management system containing all the necessary controls. Adoption of electronic document management processes is becoming essential to business productivity, cost savings and shortened BioPharma product development timelines.

**Keywords:** Electronic Trial Master File, Adoption, BioPharma industry and product development.

**Abbreviations:** NCI: National Cancer Institute; NIH:National Institutes of Health; ECM:Enterprise Content Management system; eTMF: Electronic Trial Master File; TMF:Trial Master File; XML: Extensible Markup Language; HTTP:Hypertext Transfer Protocol; CDISC:Clinical Data Interchange Standards Consortium; HL7:Health Level-7; FDA:Food and Drug Administration ; ICH-ICH:International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use- harmonized tripartite guideline. Guideline for good clinical practice; CFR: Code of Federal Regulations; OCR: Optical character recognition; EU: European Union; SOP: Standard operating procedure; CMIS: Content Management Interoperability Services specification; OASIS: Organization for the Advancement of Structured Information Standards; NCBO: National Center for Biomedical Ontology; NCIT: National Cancer Institute's Thesaurus ontology.

## INTRODUCTION

Every organization involved in clinical trials in the BioPharma industry maintains a trial master file or 'TMF' comprised of thousands of pages of regulatory documents required for each clinical trial. It mainly contains essential documents and artifacts associated with a clinical trial which are subject to compliance with ICH GCP, FDA 21 CFR Part 11 and other regulatory requirements.

For the majority of clinical trials, clinical trial regulatory documents are primarily paper documents captured centrally in physical file cabinets. These paper-based TMFs are a centralized set of central documents that typically are used to support and comply with applicable regulatory requirements and Good Clinical Practices. Traditionally the required documents, document names, document classification

scheme and document content requirements vary from sponsor to sponsor, creating a high degree of variability and inconsistency in the TMF. Many sponsors establish internal TMF standards, however, for many sponsors and clinical trial stakeholders, no classification scheme or 'content model' for the content or documents in a TMF existed.

The TMF must not only contain adequate and accurate data, but it must also be organized in a manner suitable for evaluation by inspectors, and sharing with clinical study team members both internally and externally.

Managing thousands of clinical documents, tasks and processes using a paper-based or hybrid TMF system can be overwhelming and can introduce errors and oversights that put your clinical trial at risk for noncompliance.

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

- Difficulty in meeting regulatory requirements
- Time required to starting up trials
- High cost of managing TMF content
- Difficulties in Providing access to global team members to access documents
- Poor communication and collaboration with trial personnel
- Insufficient internal resources
- Inability to maintain audit ready TMFs
- Inefficient processes for global team members to contribute
- Lack of visibility into the status of clinical trial documentation
- Time required to locate and manage documents

An eTMF provides an industry best practice approach to document management which allows you to gain the insight you need to efficiently manage clinical trials and accelerate time to market.

**eTMF SYSTEM BENEFITS**

Many organizations involved in BioPharma clinical trials want to move from paper-based document management systems contained in file cabinets to online electronic document management systems where documents are stored online in electronic archives. By implementing a comprehensive, eTMF system that automates the capture and management of TMF documents and records, organizations can prevent unnecessary risk and can often realize clinical trial cost savings over manual paper handling processes.

There are many reasons that businesses may wish to put an effective eTMF management application in place:

- Growth in Regulations: State, Federal and industry regulations continue to grow and evolve
- Risk Management: Significant risks and penalties for non-compliance, including fines, and customer lawsuits. systems provide confidence that you have met agency regulatory compliance requirements
- Enhanced document quality - automated systems have been proven to make fewer errors than manual paper handling processes; ability to implement automated quality control processes
- Improves team productivity and Accelerates Clinical Trials: sharing, viewing documents anytime, anywhere from any device is faster than manual paper retrieval. Electronic document sharing with clinical trial stakeholders: e.g., Investigators, agencies, and clinical research centers can help resolve issues faster and accelerate clinical trial milestones
- Cost Savings: Save document mail and overnight courier costs; save document physical storage costs; save administrative staff document handling and management costs
- Time Savings: - sharing, viewing documents Anytime, anywhere from any device access to documents helps move business operations forward faster than manual, paper-based processes
- Reduced auditing and reporting costs - automated reporting and retrieval of ECM based systems can significantly reduce auditing and reporting labor and enhanced product quality through easier audits and management.

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

In order to move toward an all electronic TMF or eTMF system, organizations typically use an Enterprise Content Management system (ECM) in their efforts to manage clinical trial regulatory documents. The ECM based eTMF provides automated methods and workflows to collect, classify, index, archive and report on documents and content. Digital

 

signatures may be used to minimize paper-based signature capture, minimize handling processes and to significantly cut mail and overnight delivery expenses. A the base of any ECM system is a schema or classification system, document tagging terms or 'metadata,' as well as a database, also known as a repository, which retains the eTMF electronic documents for search, reporting and other management tasks.

While the paper-based TMF reference model for paper is a great starting point for managing paper based TMFs, it lacks several core foundational components that would make it suitable for use as a schema for an eTMF:

An effective eTMF system model builds on the following foundational components:

1. Machine readable classification scheme - The ability of a computer to read the classification scheme and to use it to create the online electronic TMF repository enables consistency, productivity and interoperability.
2. Published, standards-based terms available in machine readable format.
3. Automated digital signature capture option to minimize paper handling.
4. Automated document audit trail and workflow history.
5. Based on web standards - Most ECM systems support XML, HTTP or other web standards to exchange, view and manage eTMF content.

In order to gain the benefits offered by electronic automation of paper-based processes in clinical trial regulatory document management, it's important to consider the underlying foundational schema or 'content model' that will be used to implement an ECM for eTMF's. While the paper-based TMF Reference model is useful as a starting point to create an eTMF content model, the paper TMF Reference model lacks many of the core foundational components highlighted above. This makes the TMF Reference model unsuitable for use as a content model in eTMF deployment. The paper-based TMF Reference model has no provision for digital signatures, no specification for how files should be tagged with metadata or how TMF repositories and archives can be exchanged or made searchable on an internet/intranet. The paper-centric TMF Reference model is human readable but not machine readable, making it impossible to import into an ECM system. If the model paper-centric TMF Reference model could be converted to a machine readable format, it would still not provide the foundational components necessary to support electronic paper handling workflows, search and interoperability.

## CORE COMPONENTS OF AN eTMF SYSTEM

The core components of an eTMF system are based on a combination of1) Standards- based core metadata and a published TMF taxonomy – ideally based on NCI/NIH, CDISC, HL7 term databases; 2) A flexible taxonomy or hierarchical model including document classifications, document types, document descriptions, and metadata; 3) A standards-based electronic content management system that allows customization of the eTMF taxonomy for addition of new document types and metadata, 4) A fully customizable search facility that allows intelligent, precise search across one or more eTMF archives, 5) Interoperability that allows anyone to open, view, or edit an eTMF archive without the need to purchase the application that created the archive.

## CORE eTMF SYSTEM REQUIREMENTS

**Acquisition:** Document acquisition primarily involves accepting and processing documents or content. In an eTMF, documents are acquired electronically and stored electronically. Documents may be acquired from the web or email or via automated business processes. To eliminate paper from a clinical trial study, electronic signing using digital signatures from authenticated users is often used. Digital signatures are accepted in place of wet signatures in most countries worldwide including the USA and the EU, thereby averting the need to scan a document. Where paper is still used for wet-signed documents or other non-digital content items, conversion from paper documents to electronic document images is done via scanners or multifunction printers. Optical character recognition (OCR) software is sometimes used, whether integrated into the hardware or as stand-alone software, in order to convert digital images into machine readable and searchable text. Optical mark recognition (OMR) software is sometimes used to extract values of check-boxes or bubbles. Capture may also involve accepting electronic documents and other computer-based files.

 

**Classification:** Routing of the document to the proper eTMF classification for indexing. Classification is used mainly as a preparation for indexing.

**Indexing:** Indexing is the process of adding unique document identifiers so that documents can be rapidly retrieved from the system. Document indexes are comprised of metadata which is retrieved from a pre-defined index classification topology. Often some level of indexing can be automated by utilizing a database to lookup metadata attributes. When automated workflows, digital signing and all digital processes are used, often indexing and classification can be automated, saving labor and processing time.

**Storage:** Store electronic documents. Storage of the documents often includes management of those same documents; where they are stored, for how long, migration of the documents from one storage media to another (hierarchical storage management) and eventual document destruction.

**Compliance:** Compliance rules capture document collection requirements, policies and procedures. For example, an FDA 1572 document must be collected for each investigator in a clinical trial. Compliance rules ensure that the right documents are collected in the eTMF according to pre-set rules. Often the eTMF compliance rules are expressed as part of an SOP or standard operating procedure. A compliance officer or regulatory document officer may be responsible for developing and implementing required compliance policies and procedures. eTMF applications 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 adherence to FDA rules related to security and electronic signing.

**Document Quality:** If a document is to be distributed electronically in a regulatory environment, then the document should be quality checked through a pre-defined quality control process. Acceptance sampling using standards-based processes such as ASTM-E105 to sample incoming document batches is one such method of document quality control to help ensure document integrity and quality for large batches of documents.

**Auditability:** Auditability of the eTMF is twofold: 1) Audit trail of system access, login and user activity should be auditable for all system resource usage (21 part CFR); document workflow history including date, event (e.g., approved, submitted, created, modified), source of event and person involved; 2) Document compliance audits: Internal document compliance audits play a key role in document compliance and quality. Auditors should have online access to the eTMF documents and reports to review the eTMF archive with the goal of identifying potential violations of policies and procedures. Policies and procedures should specifically document the scope, frequency, and procedures of audits. Audits should be both routine and event-based.

**Reporting:** A set of standard preconfigured document management reports should be offered by the eTMF. Often a user can subscribe to the eTMF to receive these reports via email. As an example, a report listing documents captured by document type, documents captured by site, documents captured by investigator or other person, documents captured by category. Also missing documents by site, by document type, and by person are useful to provide proactive notice that a document has not yet been collected or is missing.

**Search and Retrieval:** Retrieve the electronic documents from the storage. Although the notion of retrieving a particular document is simple, retrieval in the electronic context can be quite complex and powerful. Simple retrieval of individual documents can be supported by allowing the user to specify the unique document identifier, and having the system use the basic index (or a non-indexed query on its data store) to retrieve the document. More flexible retrieval allows the user to specify partial search terms involving the document identifier, document type, and/or parts of the expected metadata. This would typically return a list of documents which match the user's search terms. Some systems provide the capability to specify aBoolean expression containing multiple keywords or example phrases expected to exist within the documents' contents. The retrieval for this kind of query may be supported by previously built indexes, or may perform more time-consuming searches through the documents' contents to return a list of the potentially relevant documents.

**Integration:** Many document management systems offer content integration and exchange capabilities. Open standards allow some level of integration with other

 

software and systems. Most recently, major enterprise document management vendors collaborated on a new specification to enable easier integration and web-based exchange of enterprise documents and records. The Content Management Interoperability Services specification (CMIS) is a format for improving interoperability between Enterprise Content Management systems.OASIS approved CMIS as an OASIS Specification on May 1, 2010. While CMIS can be used as a transport for communicating document information between systems, it fails to specify any format for an archive's metadata, document type names or other core schema. The eTMF ontology will resolve this, allowing eTMF archives to be easily exchanged, imported or exported via the CMIS standard.

**Metadata:** Metadata attributes or 'tags' are typically assigned to each document type/content type. These tags are used to capture data values for each document for classification, search and reporting. The metadata and the metadata values are then stored with either the document in the eTMF archive, or with the actual document embedded as metadata tags. Examples of standards-based metadata are document archive metadata such as 'Date' or 'Creator' from Dublin Core metadata, or 'Site ID' to identify a study site, from NCI thesaurus.Metadata values are the data that is stored with the metadata attribute. The document management system may also extract metadata from the document automatically or prompt the user to add metadata. Some systems also use optical character recognition on scanned images, or perform text extraction on electronic documents. The resulting extracted text can be used to assist users in locating documents by identifying probable keywords or providing for full text search capability, or can be used on its own. Extracted text can also be stored as a component of metadata, stored with the image, or separately as a source for searching document collections.

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

**eTMF Content Model:** An eTMF content model is a published, flexible, machine readable hierarchy of classifications, metadata terms, and relationships that acts like an electronic filing organization plan. The eTMF content model allows seamless automated creation of eTMF repositories and archives. Based on published vocabularies, terms and classifications, the eTMF content model supports automated content classification, digital signatures, audit trails, automated workflows and web-based information exchange. ETMF content models should be sharable and network discoverable. To facilitate web based clinical trial content interoperability, semantic technologies are often used to share information ontologies. eTMF content models can be expressed as web sharable ontologies, allowing organizations to share information electronically through the internet. The first eTMF content model ontology was developed by CareLex and published at the National Center for Biomedical Ontology's site, NCBO BioPortal. The CareLex eTMF Content model ontology utilizes and links to the National Cancer Institute's Thesaurus ontology, NCIT.

Although the FDA and other regulatory agencies have defined the requirements for electronic document and record systems that store clinical trial essential documents, no government agency has defined how eTMF content should be classified, or the standards for metadata that may used in content indexing, or the electronic format(s) that should be used to model, store or exchange eTMF data.

**eTMF SOLUTIONS IN MARKET**

CareLex, Forte Research, Fujitsu, HL7, Mayo Clinic, NextDocs, Oracle, Paragon Solutions, Phlexglobal, Safe-BioPharma, SterlingBio, and SureClinical.

**CONTROLS AND SECURITY, TRAINING AND VALIDATION OF eTMF**

The eTMF is recommended to ideally be a document management system containing all the necessary controls listed below to be completely acceptable. The storage of documents within folders in a computer systems' operating

 

environment without the minimum controls below is unlikely to be considered acceptable.

The eTMF system should enable appropriate security to be in place which is recommended to include, as a minimum:

- User accounts could be created and deleted within a formal approval process and in a timely manner;
- 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 back up

Additionally, the eTMF would ideally have the following attributes:

**a)** Where there is approval of documents via a workflow system, there should be use of digital signatures;
**b)** Role based permissions for activities being undertaken;
**c)** Audit trail in place to identify date/time/user details for creation, uploading, approval and changes to a document.

The eTMF should be validated to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process and for change control. All members of staff involved in the conduct of the trial and using the system must receive appropriate training and this should be documented. User manuals and helpdesk are recommended be in place as part of the validated system as appropriate.

**eTMF VENDORS**

When a vendor is used for eTMF management, as with any vendor or subcontractor being used for clinical trials, appropriate pre-qualification checks should be undertaken prior to placing the contract, Where TMF documents are moved from the sponsor to the vendor for scanning, a formal procedure should be in place to ensure chain of custody records are maintained (e.g. use of a TMF record transmittal form)

**ELECTRONIC ARCHIVING**

The use of electronic systems for such activities as data management, statistical analysis, reporting, trial management systems and eTMFs means that electronic documentation and data are likely to need to be retained. The data may be on a server or on transportable media, e.g. media drives/pens drives, Compact Discs, tapes etc. The following is recommended to be considered with respect to electronically archived data:

- It could be subject to back up (with the backup media stored in a separate location);
- Storing the data in differing formats on different types of media (or even on the same media from different manufacturers;
- access to archived data should be suitably restricted;
- The electronic documents or data that have been archived must be protected from unauthorized changes to maintain authenticity.
- future access to records and data should be maintained (processes to overcome media, software and hardware becoming obsolete)
- periodic test retrieval or restores to confirm that ongoing availability of the data is being maintained; where data is required to be migrated to new media or a new format, then the transfer/migration of data to a new media/format should be validated (no loss, changes or corruption to the data or meta data and that authenticity is maintained).

**INSPECTION/AUDIT OF eTMF AND THE PROBLEMS FOUND**

Inspectors/Auditors are not averse to reviewing an eTMF during a GCP inspection/Audit. The legislation does not differentiate between paper and eTMFs therefore all the requirements are the same; however, the use of an eTMF at an inspection/audit presents additional challenges to both the inspector/Auditor and the organisation.

Inspectors/Auditors expectation is that the eTMF should adequately replicate the paper based system that it is replacing, in terms of the usability and time taken. The organisation is recommended to consider that the requirements for inspectors will also be reflective of the requirements of any auditors and the system is recommended to be designed and developed or purchased with this in mind.

Inspectors/Auditors will require direct access to the eTMF system as used by the organisation. The access is recommended to be a read only access without any restriction to any part of the eTMF. There may be additional electronic systems that have eTMF documents (identified in

the eTMF as part of the eTMF structure); access to such systems is also required by the inspector/Auditor.

The eTMF will need the use of suitable equipment for the inspector /Auditor to view the documents. This equipment is recommended to facilitate the presentation of the documents at actual size, which in most cases would be A4 paper, and the size is recommended not to be reduced due to other areas on the screen, for example, directory/index structure, toolbars etc.

The system is recommended to have an efficient speed of access and ideally not require the use of a nomenclature document or require time spent opening non self-evident named files to determine their content. The system and equipment would ideally be akin to flipping the pages of a book and it would be useful if there is a system tool available to print or mark documents for subsequent retrieval and examination as well as the ability to compare documents side by side. Finally, if documents from the eTMF are required to be copied and retained by the inspector/Auditor, the organisation is recommended to be able to facilitate this. A search tool in the eTMF is also recommended. Following are the Problems found with eTMFs during inspection/Audit.

- Organisation was unable to provide a full eTMF for inspection/Audit purposes on request of the auditors/ inspectors. In some cases resulting in additional inspection/auditing days required.
- Staff that was put forward as "system users" for eTMF was also unable to locate documents requested by the inspector/Auditor.
- Failure to fully document and perform effective Quality Control checks on documents uploaded into eTMF – the result being that the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were missing pages, incorrect documents, poor quality scans.
- Incorrect documents located in the eTMF - for example from other trials.
- There was poor, often repetitive, sometimes incorrect labelling of files, resulting in excessive time wasted opening and closing pdf documents in the eTMF when attempting to locate documents.
- There was no accurate record with the details of documents sent to contractor for uploading into eTMF.

## CONCLUSION

Adoption of electronic document management processes is becoming essential to business productivity, cost savings and shortened BioPharma product development timelines. The key to implementation of interoperable eTMF systems is use of a standards -based content model; standards based vocabulary, and web standards-based technologies.

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