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Electronic Trail Master File (eTMF)

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ABSTRACT

The Electronic Trial Master File (eTMF) is a content management system that digitally captures, manages, shares, and stores critical documents and clinical trial content used in the pharmaceutical industry. A Trial Master File (TMF) is a structured collection of clinical trial documents used to demonstrate compliance with regulatory requirements. Before the introduction of eTMF, TMFs consisted primarily of paper documents collected in filing cabinets. The eTMF is essential for the timely conduct of clinical trials, reduces the cost of maintaining TMFs, and provides audit-ready TMFs in real-time, allowing for more efficient utilization of trial resources. The eTMF adoption has grown steadily over the years, and it is essential to establish a solid and established data migration strategy to ensure compliance with regulatory requirements.

Keywords: Electronic Trial Master File (eTMF), Clinical Trial, Trial Master File (TMF)

INTRODUCTION

Electronic Trial Master File (eTMF) is an application that uses server software and technology to guide and assist in the creation, collection, storage, tracking and filing of essential clinical study documents. A Trial Master File (TMF) is a structured collection of clinical trial documents used to demonstrate compliance in order to assess the quality of data collection. The TMF contains study-level, country-level, and site-level files that were collected at different times during the study (eg, closest to the start of the study).A related feature set, the Electronic Investigator Site Master File (eISF) portal, can be used with your eTMF to facilitate file exchange between the sponsor/CRO and the site. The clinical research industry drives the development of breakthrough drugs, biologics and devices. Conducting a clinical trial is a time-consuming and expensive affair, and generates extensive documentation from start to finish of the trial. The different types of clinical trial documentation generated are collectively known as the Trial Master File (TMF), which forms the basis of the regulatory review and approval process. [1]

History and Background:

In order to comply with government regulatory requirements for biopharmaceutical clinical trials, each organization involved in a regulated clinical trial must maintain and store certain "essential records" related to the clinical trial to ensure compliance. Depending on the regulatory jurisdiction, this information is typically stored in a Trial Master File or TMF. Historically, TMFs consisted primarily of paper documents, images, and media captured centrally in physical filing cabinets. Government agencies involved in the regulation of clinical trials, such as the United States The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have technical programs in place. In the United States, the FDA has regulations, CFR 21 Part 11, that supports the use of electronic records, digital media, and digital signatures in clinical trials. In Europe, the European Medicines Agency has published policies supporting the use of digital signatures in clinical trials. In clinical trials and healthcare, companies with manual, paper-based systems are looking to transition to automated electronic enterprise content management (ECM) systems to ensure higher levels of regulatory compliance and reduce business risk. With the FDA's Part 11 policy supporting the use of electronic records and digital signatures instead of paper, US organizations participating in US clinical trials can switch from paper-based TMFs to electronic TMFs (eTMFs) while complying with FDA regulatory policies.[3]

What is the electronic trial master file (eTMF)?

An electronic master file, or eTMF, is a test master file in electronic or digital format. It is a method for capturing, managing, sharing and digitally storing critical documents and clinical trial content. To better understand, let's first describe what a Trial Master File or TMF is. Each organization involved in a regulated clinical trial, typically a pharmaceutical or Biotechnology Company must comply with government regulatory requirements for those clinical trials. One of the key criteria for meeting regulatory compliance is the retention and storage of certain essential documents related to this clinical trial. Essentially, a trial master file is a set of basic documents and content that shows how a clinical trial is conducted, managed, and compliant with regulatory requirements. These basic documents can be used to assess the conduct and quality of clinical trials. "Test Master File contains files essential for a clinical trial that may be overseen by a regulatory agency. To comply with government regulatory requirements applicable to a clinical trial, each organization participating in a clinical trial must maintain and store certain files, images associated with the clinical trial and its content. Depending on the regulatory jurisdiction, this information may be stored in a Trial Master File or TMF. Electronic Master File or eTMF is a test master file in electronic or digital format. It is a method of digitally capturing, managing, sharing and storing critical documents and clinical trial content. "The Electronic Trial Master File (eTMF) is the trial master file in electronic format (digital content). It is a content management system used in the pharmaceutical industry that provides a formal means organize and store documents, images, and other digital content of clinical drug trials that may be subject to compliance with government regulatory agencies. The term eTMF covers the strategies, methods and tools used throughout the lifecycle of clinical trial regulatory content. "[2]

Sources of Electronic Trial Master Files:

For most clinical trials prior to 2014, the TMF consisted primarily of paper documents collected in filing cabinets. Managing these paper-based TMFs is maintenance-intensive and has

greater potential for error/omission/risk, increasing the likelihood of non-compliance.In 2014, the MHRA updated the definition of key PCB inspection findings to include "if the provisions of the Trial Master File (TMF) do not comply with regulations, because the TMF is not easily available or accessible, or that the TMF is, thereby impeding or preventing inspectors from carrying out their compliance verification functions." With the growing need to meet regulatory requirements, ensure timely clinical trials, reduce the cost of maintaining TMFs, and in any case to provide audit-ready TMFs in real time, to better utilize trial resources, as well as improve the ease of running trials, sponsors implementers urgently need a centralized system. Veeva's annual Unified Clinical Operations survey results are in line with the trend, with electronic TMF (eTMF) adoption growing from 13% in 2014 to 31% in 2017 and 65% in 2018. Therefore, sponsors looking to adopt a centralized system that aligns with the trends outlined above should establish a solid and established data migration strategy. [1]

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Required Components of the eTMF:

System As far as the FDA is concerned; the required components, controls and policies of the eTMF used in clinical trials in the United States comply with the requirements of US FDA CFR 21 Part 11. As of August 2003, the FDA has issued additional guidance for industry outlining the components, controls, policies, and validation required for electronic systems and electronic signatures. According to the FDA, systems used to store electronic records or documents are generally subject to the following controls and requirements:

- Limit system access to authorized persons
- Use operating system controls

- Use operating system controls authority controls
- Use device controls

Who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks

- Establish and enforce written policies that hold individuals accountable for actions that occur under their electronic signatures.
- System documentation.
- Controls for open systems are consistent with controls for closed systems described above (§ 11.30) Requirements related to electronic signatures (eg. §§ 11.50, 11.70, 11.100, 11.200 to 11.300).
- Audit trail of records (timestamp of records)
- Export of records to portable formats such as PDF or XML.
- System validation
- Documentation and record system to store essential clinical trial documents, no Government organizations define how eTMF content should be classified, or the metadata standards that can be used for content indexing, or the electronic formats that should be used to store templates or exchange eTMF data. Due to the lack of standards to represent eTMF content, the interoperability of eTMF information and the exchange of content between systems and applications is inefficient.[4]

Essential documents:

The list given is ICH GCP compliant and represents the essential documents required before the start of the clinical phase of the trial:

- IB/SmPC or other specific and current information on the IMP.
- Consent form informed.
- Funding statement.
- Insurance statement.
- Between parties to trial contracts signed between [ex. Sponsoring investigators and pharmaceutical or medtech companies].
- IEC.
- Notice and compilation of any written information provided to study participants, such as recruitment forms or publicity materials.
- Clearance/approval/notification of protocol by health authorities in accordance with applicable regulatory requirements.
- Documentation concerning the qualifications (CVs, etc.) of the sponsoring researchers/co-researchers and other relevant probationary staff.[5]

Global Electronic Trial Master File (eTMF) Market Dynamics

• Rising usage of eTMF:

As information technology becomes more widely used in the healthcare industry, the usage of ETMF also increases. There are several advantages to using eTMF, including the fact that it only needs to be installed once and can be reused multiple times. Additionally, eTMF applications can easily handle the load of large amounts of data as clinical trials progress and expand. Clinical trials have increased significantly in several countries as the burden of COVID-19 has increased. For example, according to official clinical trials, the clinical trial data load is expected to double due to COVID-19. This means that a large amount of data will be generated during the trial, which should accelerate demand for eTMF in this area. [6]

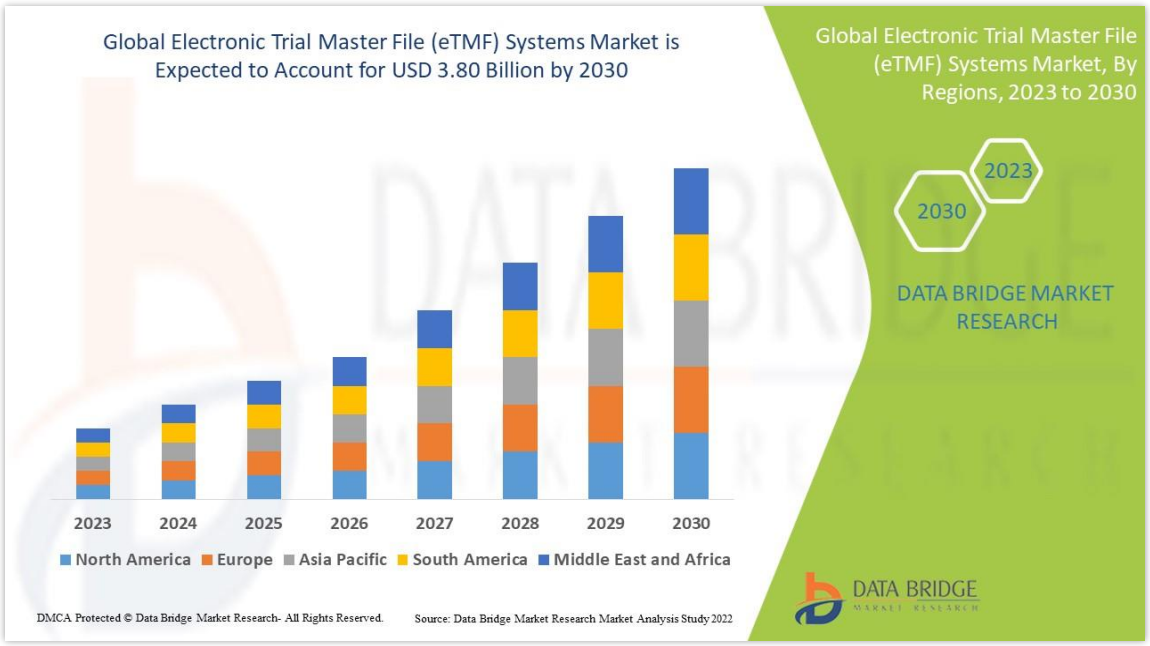

Fig-Global Electronic Trial Master File (eTMF) Market Dynamics [6]

Benefits of the eTMF:

- System many groups involved in biopharmaceutical clinical trials are looking to move from paper-based document management systems in filing cabinets to online electronic document management systems where documents are stored online in electronic archives. By implementing a comprehensive eTMF system to automatically capture and manage TMF documents and records, organizations can reduce unnecessary risk and increase efficiency in clinical trials that often come with manual paper-handling processes. There are many reasons why a business might want to implement an effective eTMF management application:
- Growing regulations: State, federal, and industry regulations are constantly growing and changing.

  Risk.
- Management: Significant risks and penalties for non-compliance, including fines and fees charged to customers. The system implies confidence that you have met the agency's compliance requirements.

- Increased durability of documentation - Automated systems have been shown to produce fewer inaccuracies than manual paper-handling processes; ability to use automated quality control mechanisms;
- Improve team profitability and increase clinical trials: anytime, anywhere, via any device is faster than manual paper handling. Sharing electronic files with clinical trial stakeholders: such as investigators, institutions, and clinical research centers can help resolve issues faster and accelerate clinical trial milestones Personnel processing and administrative costs.
- Save time: exchange, view documents anytime, anywhere access to documents from any device allows business operations to go faster than manual paper-based procedures.
- Reduced auditing and reporting costs – Automated reporting and recovery from ECM-based systems can significantly reduce auditing and reporting tasks and improve product quality through a simplified audit and management.
- Reduce costs by increasing filing efficiency and reducing cumbersome paperwork.
- Faster document search and retrieval.
- Helps minimize trial start and end times.
- Documents/reports can be ready for audit sooner if paper systems and compliance are improved. Allows easy access, approval, sharing andϖ management of clinical documents from a web-based application anytime, anywhere.
- Reduce common errors in manual paper documentation. [7]

Business process change is inevitable:

The implementation of eTMF offers the opportunity to move from a passive TMF management process used in paper or archived eTMF to an eTMF fully integrated with business processes and other electronic clinical systems. These may include: clinical trial management systems (CTMS), electronic data capture (EDC), electronic signature tools, standard operating procedures (SOPs), secure databases, initiation, electronic health records and other electronic systems used in the conduct of clinical research

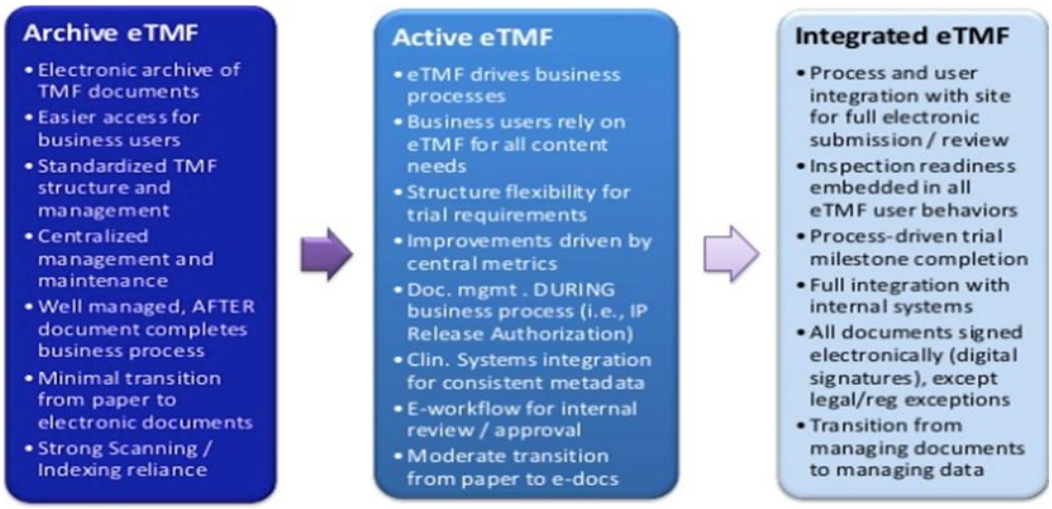

Fig-Business process change is inevitable

In a truly integrated eTMF, all documents, real-time Key Performance Indicators (KPIs) and metrics are generated and managed within the system using automated workflows. Research centers, contract research organizations, and sponsors have easy access to operational and subject-level data that represents the true state of research. For example, increased system integration can trigger the generation of document placeholders in eTMF (e.g. inspection visit reports and follow-up letters), as well as related specific workflows (e.g. Review and approval of follow-up visit report) in accordance with the study management plan and SOPs.

Effective implement action of the eTMF therefore requires companies to have the skills to develop and implement a robust and detailed communication and change management plan (socialize change). The TMF Champion or TMF Process Owner, typically with a background in IT and/or TMF Operations, performs a thorough assessment of the scope of business process changes (current state versus desired state) and impact on the internal organization (roles and responsibilities), SOPs, eTraining) and partners (CRO, sites).

This TMF innovator builds organizational ownership through senior (top-down) sponsorship, establishes a steering committee and a transformative network of subject matter experts who act as the "eTMF voice" in their functional groups and contribute to the development of new business processes and system implementation (bottom up).

To mitigate the risks associated with a complete transition from paper to eTMF, sponsors may need to acquire change management skills and experience with external business practices. These include clinical operations consultants, TMF migration and implementation specialists, and eTMF business and strategy teams in large CROs (Chontas, 2016). These are valuable sources of additional information as eTMF adoption grows, peer networks, industry benchmarks, and published audit results. [8]

CONCLUSION:

Electronic Trial Master Files (eTMF) are digital systems that manage clinical trial documents. These systems were developed to assist in the creation, collection, storage, tracking, and filing of essential clinical study documents, and are used to demonstrate compliance and assess the quality of data collection. eTMFs are a method for capturing, managing, sharing, and digitally storing critical documents and clinical trial content. These documents form the basis of the regulatory review and approval process. Before eTMFs were developed, most clinical trials relied on paper-based Trial Master Files (TMFs), which were collected in filing cabinets. Paper-based TMFs require a lot of maintenance and have greater potential for error/omission/risk, increasing the likelihood of non-compliance. In 2014, the MHRA updated the definition of key PCB inspection findings to include "if the provisions of the TMF do not comply with regulations, because the TMF is not easily available or accessible, or that the TMF is, thereby impeding or preventing inspectors from carrying out their compliance verification functions." With the growing need to meet regulatory requirements, ensure timely clinical trials, reduce the cost of maintaining TMFs, and provide audit-ready TMFs in real time, sponsors implemented eTMF systems. The adoption of eTMFs has grown from 13% in 2014 to 31% in 2017 and 65% in 2018. Government agencies involved in the regulation of clinical trials, such as the FDA and EMA, have technical programs in place that support the use of electronic records, digital media, and digital

signatures in clinical trials. The adoption of eTMFs has enabled sponsors to establish a solid and established data migration strategy, leading to improved ease of running trials, better utilization of trial resources, and reduced costs of maintaining TMFs. eTMFs must have specific components and controls to meet FDA requirements, including document management, system security, and audit trails. As clinical trials continue to drive the development of breakthrough drugs, biologics, and devices, eTMFs will remain a critical tool for managing clinical trial documents.

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