White Paper

eTMF AND THE eCLINICAL UNIVERSE:

How electronic trial master files work with other eClinical Systems to help you meet regulatory requirements

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INTRODUCTION

The electronic Trial Master File (eTMF) is an increasingly important eClinical technology used to manage the set of essential documents required for every clinical trial.

The eTMF is a specialized form of an Electronic Document Management System (EDMS) optimized to manage the processes around creating or uploading clinical trial documents and completing the workflow processes needed to finalize, secure and archive them. While small Phase 1 trials may only have a few documents, large Phase 3 or Phase 4 trials require tens of thousands of documents. As a result, better systems and increased automation offer the opportunity for meaningful cost and time savings. The eTMF contains a wide variety of documents that the regulatory authorities have determined are necessary to allow the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with GCP to be evaluated – often augmented by additional documents required by the sponsor. Each trial has its own specific set of required documents based on the trial details such as the nature of the investigational product, the countries in which the trial is being conducted, or the phase of the study. Completeness and accuracy of the TMF is a significant regulatory requirement, and regulatory agencies conduct audits of TMFs by direct examination of sponsors' eTMF systems.

THE eCLINICAL UNIVERSE

The eTMF exists within a universe of eClinical systems that manage trial aspects such as logistics, safety, data collection and analysis, legal, and many others. Often, these systems are the sources of data or documents needed for the Trial Master File. An efficient and compliant eTMF must work in harmony with a variety of eClinical systems in order to contain the required information. Table 1 provides an overview of the eClinical systems that may provide data and documents to eTMF, or in a few cases, require access to documents stored in eTMF. Furthermore, these documents must be available in a timely manner. In recent guidance, the EMA has stated "The TMF should to be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF "inspection ready" [1]. Furthermore, if documents required in the eTMF aren't available in a timely manner, the system study and site milestones may be delayed. For example, site initiation and regulatory green light depend on receiving final clinical trial agreements.

Table 1 eClinical Systems Interfacing with the eTMF

eClinical System	Information Potentially Exchanged with eTMF
Clinical Trials Management System (CTMS) Manages the planning, preparation, performance, and reporting of clinical trials, with emphasis on tracking deadlines and milestones.	The CTMS is generally the authoritative source of descriptive data pertaining to trials, such as their characteristics, study sites, investigators, milestones, etc. In addition, documents such as monitoring reports that are required in the Trial Master File may originate in a CTMS.
Contract Management System Manages the creation, review and approval of legal contracts.	Manages and archives legal documents such as confidentiality agreements, clinical trial agreements, and contracts with investigators, vendors, and partners.
Regulatory Electronic Document Management System (EDMS) Manages documents used in clinical trials authorizations and marketing authorizations made to regulatory authorities.	Organizes the study information submitted to regulatory authorities, such as protocols, study reports, and FDA 1572s. Some of this information originates in the eTMF and is pushed to the Regulatory EDMS, and some originates in the Regulatory EDMS but must be part of the Trial Master File.
Customer Relationship Management (CRM) System May be used to manage site and investigator information.	May be an authoritative source of information concerning investigators and sites. Also increasingly used to manage recruitment documents such as Site Feasibility Questionnaires.
Safety / Pharmacovigilance System Captures and reports on adverse events.	System of record for adverse event reporting and generation of safety documents such as Line Listings and Summary Tabulation Reports as well as various other safety reports.
Interactive voice / web response systems (IVRS/IWRS) Performs randomization, emergency code-break, and drug / medication supply management.	Generates various reports concerning randomization and clinical supply distribution and reconciliation that are part of the Trial Master File.
Electronic Data Capture (EDC) Capture, report on, and interrogate clinical data collected at study sites	Contains electronically collected case report forms. [Rarely, but occasionally, stored directly in eTMF.]
Electronic Patient Reported Outcome (ePRO) Collects information directly from trial subjects.	Contains electronically collected patient diaries. [Rarely, but occasionally, stored directly in eTMF.]
Learning Management System (LMS) Administers, documents, tracks, reports on and delivers education courses or training programs	Contains GCP and study-specific training materials and records.

DEFINING THE INTEGRATIONS

When documents exist in other eClinical systems, especially when those are the systems of record (official repositories) for the documents, it's not a given that copies must be retained in the eTMF. The UK Medicines and Healthcare products Regulatory Agency (MHRA) discusses this topic in the Good Clinical Practice "Grey Guide" [2]:

> The documentation does not all necessarily need to be in the same location, but it must be clear where it is held from TMF procedures or indexes as it must be readily available both during the trial and during the archiving retention period following the trial. For example, it may be appropriate for an organization to determine that serious adverse event (SAE) cases will all be retained in the pharmacovigilance department, including the suspected unexpected serious adverse reaction (SUSAR) receipt confirmation, rather than printing it off the pharmacovigilance database and filing in the TMF.

The EMA has provided more guidance on managing documents in multiple systems [1]:

> The sponsor should identify where all of the potential documentation that is part of the TMF is located, even if it is several systems, so that it is effectively organized (Recommendations on the content of the trial master file and archiving Section 2). This detail, may, dependent upon its complexity require formal documentation in a procedure (e.g. SOP). In large organizations, the TMF could include documents from across a variety of different departments and systems other than clinical operations, for example, Data Management, Statistics, Pharmacovigilance, Clinical Trial Supplies, Pharmacy, Legal, Regulatory Affairs etc., as well as those provided or held by CROs. Sometimes documents may need to be located in a separate location to the main TMF records, for example those that contain information that could unblind the study team.

This leaves the sponsor with three options:

1

Leave the document in its original location and do not replicate. This approach sounds attractive, but if the document is needed for TMF-centric work processes, it may not be readily available to people performing those processes. Regulatory audits are also a concern. The EMA states [1] that if there are "... additional electronic systems that have TMF documents (identified in the TMF as part of the TMF structure), access to such systems is also required by the inspector". Allowing direct access by an auditor to a myriad of systems may not be practical or desirable.

2

Copy the document into the eTMF. Whenever possible, this should be an automated process so that documents are replicated in a uniform and reliable manner. The process must account for documents subject to update or deletion as well.

3

Create a link to the document in the eTMF. This option supports basic good document management principles, but impediments may exist. For example, eTMF users may not have access to the other systems, those systems may not support linking to the content, or security in the other systems may not be designed to allow this type of access.

Another complicating factor is that eClinical technologies may not be used uniformly across all trials. For example, it's common that some of a sponsor's trials may use Electronic Data Capture while others use paper Case Report Forms. In these cases, more than one approach may need to be developed and documented.

eClinical Systems Include:

- *CTMS*
- *Contract Management System*
- *EDMS*
- *CRM System*
- *Safety/Pharmacovigilance System*
- *IVRS / IWRS*
- *EDC*
- *ePRO*
- *LMS*

SOLVING THE PROBLEM

The first step in establishing eTMF's place in the eClinical Universe is to determine which eTMF documents originate in other eClinical systems – and agree upon the system of record for each type of document. Usually, this will be the system where the document is created and approved, as this system will retain the audit trail entries and any electronic signature so that the document can be used in place of a paper record. However, if the originating system belongs to a partner or vendor, it may make more sense to consider the eTMF the system of record.

After that, the need for the document in the eTMF can be determined. If the decision is made not to replicate the document to eTMF, keep in mind that in accordance with the MHRA guidance [1], "it must be clear where it is held from TMF procedures or indexes".

If the document is to be replicated or linked, the next step is to define how that process will work. If only a few documents need to be obtained from a given system, an automated process is probably not justified. In this case, a standard procedure should be defined for when the documents are to be uploaded to eTMF (e.g., upon approval, at a milestone…), who is responsible, and what quality checks should be performed.

Automated processes may be justified for larger volumes of documents (based upon an estimated return on investment) or if there is concern that key documents might become out of date, resulting in compliance risks. In this case, the next decision point is how to implement the integration. Many eClinical systems have predefined integration points called web services or APIs. In some cases, these methods are clearly the best choice for document and data transfer. However, keep in mind the need to respond to changes over time. For example, if you develop an integration that is specific to your CTMS, you will need to re-validate that integration if that CTMS is upgraded (even if the eTMF did not change), and to completely replace it if you change to a different CTMS.

An alternative approach is to use an export and import process. With this approach, the originating system will (periodically or on demand) export documents to a specified location such as a fileshare or ftp site. A metadata file that provides information about the documents in a simple, standard format will be exported as well. Your eTMF should be able to accept the files and metadata and place the documents in the correct location in the eTMF. Documents can either be imported to a final status or undergo a QC process. With this approach, import from a variety of disparate systems should be possible without excessive dependence on the details of those systems.

FACTORS FOR SUCCESS

The completeness, timeliness and reliability of your eTMF system depends upon it receiving the correct documents as they become available, regardless of where they originate. To ensure that eTMF will operate accurately and efficiently within the eTMF universe:

Identify and document the authoritative source of each document

If required documents will not be available in the eTMF, ensure that their official locations are fully documented and available to those that need to work with them, including agency auditors

Plan any automated integrations based on return on investment and risk reduction analysis

Consider the impact of system integrations on the stability and validated status of the eTMF

Develop and document a procedure for ensuring that manual transfers of documents from other systems are completed in a timely and accurate manner, including determining how users responsible for transfer will know when new or updated documents become available

REFERENCES

1. "Reflection paper on GCP compliance in relation to trial 5 master files (paper and/or electronic) for management, 6 audit and inspection of clinical trials", European Medicines Agency, 1 Feb 2013.

2. "Good Clinical Practice Guide", Medicines and Healthcare products Regulatory Agency (MHRA), 2012

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