Beyond Storage:

How CROs and Sponsors Work Together to Manage the Complexities of eTMF Oversight

Agatha

DZS Clinical Services

A WCG Subsidiary

USA | Europe | Asia

Introduction

The Trial Master File (TMF) serves as the repository of all the essential documents that support a clinical trial. The TMF acts as a record of the trial, documenting how the trial was conducted and providing evidence that the sites have all the necessary qualifications and training to conduct the trial.

But the role of the TMF is increasingly going beyond acting as a storage container for files. Trial documents must be carefully managed through collection, review, and inspection processes. As a result, the TMF has become the central hub for many trial processes, including the coordination and collaboration of trial stakeholders.

This paper discusses how clinical trial sponsors and contract research organizations (CROs) can work together, using an electronic TMF as a hub for collaboration and coordination to increase quality and improve efficiency.

Note from Ken Lownie,

Head of North American Operations, Agatha

Agatha is a life sciences applications company. We provide applications for clinical operations and quality processes for biotech, pharma, and med device companies.

We have been working with DZS for years. They are leaders in delivering clinical research services to life sciences companies and have helped identify new requirements and opportunities that drive innovation in our applications.

We share a vision that the new generation of software for clinical operations and quality goes beyond storing and tracking information. This latest generation of applications is not only faster to deploy and easier to use; they drive the interactions and processes that define “best practices” for executing clinical trials.

DZS Clinical Services
A WDB.G Subsidiary
USA | Europe | Asia

Note from Greg Ambra,

CEO, DZS Clinical Services

DZS Clinical Services provides full-service capabilities focused on supporting small to mid-size Pharma/Biotech/Device companies. Integrating seamlessly into operations wherever needed, our core services include clinical development, data analytics, post-marketing studies, and pharmacovigilance.

Our expertise in implementing e-clinical technology solutions streamlines processes and creates cost-efficiencies. We support our client projects with high-quality deliverables, strong communication, data transparency, and risk assessment capabilities. Based in the US, with global presence as a subsidiary of WDB Holdings having locations in Finland, Baltics, India, and Japan, our position is to be your direct line to maximized efficiencies.

The Role of the Trial Master File

Many small to mid-sized sponsor companies outsource the management of the TMF to a Contract Research Organization (CRO) because they don't have the staff, experience, or expertise to do it themselves. The CRO also stores its own internal documentation related to the trial, demonstrating that everything was completed according to the CRO's procedures and quality management system.

According to ICH-GCP requirements, the TMF is required for all trials. The guidelines state that the TMF and related Investigator Site File (ISF) for each site should be established at the beginning of the trial, at both the sponsor's location and the investigator/institution site. It also states that the trial can only be closed when the monitor has reviewed all files and confirmed that the necessary documents are in place.

Working together, the CRO and sponsor collaborate to ensure the TMF is comprehensive, accurate and quality checked (QC).

"The sponsor and investigator/institution should maintain a record of the location(s) of their respective essential documents, including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval." -Source

The FDA Shift to Remote Inspection of the TMF

The role of the TMF as a central place for coordinating trial activities was accelerated during the pandemic.

COVID forced significant changes in the clinical trial world, including the need to do more remote inspection and monitoring since travel was dramatically curtailed. Like CROs and Sponsors shifting to a remote site monitoring model, the FDA sees the benefits of remote TMF inspection in terms of travel costs, time savings, and more.

As a result, the FDA is starting to lean more towards remote inspections of trials, focusing primarily on the trial documentation with less interviewing and questioning of personnel.

The TMF should fully document what was done during a trial. The FDA expects it to tell the clinical trial's story and support that it was done according to standard operating procedures, regulations, and guidelines. This shift to remote inspection significantly impacts the need to ensure the TMF is set up and managed correctly. The organization of the documentation becomes even more critical to make it easy to provide information as the inspectors request it quickly.

"Any or all of the documents addressed in this guideline [ICH E6 GCP Guideline] may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies)."

- ICH E6 Good Clinical Practice (GCP) Guideline

"Establishing a TMF is a requirement under GCP and a critical tool for quality assurance and data integrity. The TMF permits the study to be independently created and is the central repository and means to collect and QC the Essential Documents collected before, during, and at the study termination. Utilizing a flexible, compliant, and easy to use system helps ensure the safety of trial participants and that regulators have access to reliable information related to the trial."

– Greg Ambra, CEO

Keep in mind that this shift does not mean the FDA will never want to interview personnel or interact with the CRO or sponsor. It simply reserves that right to specific situations or events.

How CROs and Sponsors Work Together to Manage the TMF

The sponsor owns responsibility for the TMF and decides how it wants the TMF managed. Thus, when CROs and sponsors collaborate in managing the TMF, the roles are well defined.

It's important to understand that "managing the TMF" often means different things to different groups. Therefore, it's critical to ensure that both the sponsor and the CRO are clear on what managing the TMF means and how it will work.

One of the first responsibilities of a CRO is to clarify upfront how the sponsor wants to manage the TMF. The scope of the services provided by the CRO regarding the TMF can include some, most, or all of the TMF management tasks.

For example, the sponsor can delegate responsibility for any of the following tasks to the CRO:

- Set up the TMF structure
- Manage access to the TMF
- Upload documents into the TMF
- Perform QC on the TMF documents
- Monitor the completeness of the TMF

The sponsor may also decide to perform one or more of these tasks themselves, essentially sharing responsibility for the TMF. For example, a sponsor may want to use their own Clinical Research Associates (CRAs) in a specific region to perform site management and collect documents, but then have the CRO manage the main regions. Who does what activity often depends on who is working with the sites and collecting the documents required in the TMF.

The sponsor may also decide to perform one or more of these tasks themselves, essentially sharing responsibility for the TMF. For example, a sponsor may want to use their own Clinical Research Associates (CRAs) in a specific region to perform site management and collect documents, but then have the CRO manage the main regions. Who does what activity often depends on who is working with the sites and collecting the documents required in the TMF.

Another example of sharing responsibility for the TMF is where the sponsor uploads all documents into the system. The CRO would then perform the QC of those documents and, often, the TMF overall to ensure that everything required is there. The reverse can also happen, where the CRO uploads the documents and the sponsor performs the QC process.

CRO and sponsor responsibilities can vary greatly, and these responsibilities and associated processes must be well defined. The TMF acts as a coordinating hub of these processes.

Managing the TMF vs. Holding the TMF

There is a difference between holding the TMF and managing it. Holding the TMF refers to where the TMF is stored. Managing the TMF relates to the tools used and who is doing the tasks. For example, the sponsor may hold the TMF on its private network, but the CRO manages its updates. Or, the CRO may hold and manage the TMF at its central office. When the TMF is managed via an electronic TMF (eTMF) application, holding it refers to where the eTMF is located and who controls its access.

The Importance of the Quality Check Process:

Every document in the TMF goes through the quality check (QC) process. So even when using an eTMF, there is still potential for things to be missing or incomplete.

Consider the following scenario: A site scans a document and sends it to the CRA. The CRA then sends that document to a central email or to the CRA on the project to upload it into the TMF system. In this example, the document passes through a few hands, and there is potential for something to be missing. For example, the person scanning the document may have accidentally misscanned the document, leaving out a key page (like the signature page). Without a QC check, you wouldn't know that this critical signature was missing.

Not every document needs to be signed or dated, but it's still essential to ensure that every document is complete and accounted for.

An electronic TMF application - an eTMF - is hugely beneficial because it delivers:

- **Improved Quality.**
  The TMF can be checked at any time for completeness with the ability to see "what's missing." With explicit "QC" capability to facilitate and attract quality checks on TMF documents, eTMF solutions help ensure that all TMF content is accurate.
- **Inspection Readiness.**
  An eTMF is, by its nature, always "up to date." Documents are available for inspection as they are created, versions are tracked, and signatures are collected to reduce the risk of audit findings.
- **Better Oversight.**
  Sponsors and CROs can collaborate within the eTMF itself, and study monitors can execute monitoring tasks directly within the eTMF to ensure effective oversight.
- **More Efficient Process Execution.**
  Review and approval workflows, notifications, and due dates for document processes are built into the system, and studies are executed faster, without unnecessary delays, while incorporating best practices.

eTMF Technology Enforces Process Coordination and Collaboration

You can manage the TMF through a paper process or using file shares or basic document storage apps like Dropbox, but it's not easy, and it's not the best approach when you are sharing management of the TMF between the CRO and the sponsor (or with sites that may be located across the globe).

The best way to support the coordination and collaboration of the TMF is to use an eTMF (electronic trial master file) solution.

The sponsor may also decide to perform one or more of these tasks themselves, essentially sharing responsibility for the TMF. For example, a sponsor may want to use their own Clinical Research Associates (CRAs) in a specific region to perform site management and collect documents, but then have the CRO manage the main regions. Who does what activity often depends on who is working with the sites and collecting the documents required in the TMF.

An eTMF application is better than a paper-based system. With a paper system, you need a central physical repository to store all your documents. Then, someone has to track these documents and feed that information to CRAs as they monitor sites, so they know what they need to collect from the sites. It's a labor-intensive process that does not provide a clear audit trail.

When multiple people from different regions need access to the TMF to upload, review, approve, and QC documents, an eTMF is a much better solution.

For example:

- CRAs in different regions can access the eTMF to quickly see what documents are present for their sites, whether they go on-site or work remotely.
- The team lead can run reports and view the status of all documentation.
- CRAs can easily see what documents they need to QC.
- Document reviewers receive notifications when documents are ready to review and quickly review and approve (or reject) the document.

Remote Site Monitoring

One additional advantage of a modern eTMF application is the support for remote site monitoring. With an eTMF, sites can submit documents into an electronic investigator site file (eISF) application, where the CRO can review them and quickly transition them directly to the TMF.

The CRA can access the eISF application securely and review protected health information, informed consent documents, and other site binder information to ensure the site is documenting its processes according to regulatory requirements.

Key Requirements of a Modern eTMF Solution

There are many things you should look for in a modern eTMF application. While we won't go into every feature, let's look at some key features to consider:

- **Intuitive and User Friendly:** For an application to provide efficiency in any process, its users must find it intuitive and easy to use. Clunky interfaces, multiple steps to complete a task, and cumbersome navigation contribute to an application CRAs will not want to use.
- **21 CFR Part 11 Compliant:** Clinical operations adhere to many regulations. The 21 CFR Part 11 regulation is critical to comply with when managing clinical trial documentation. This regulation establishes the criteria for managing electronic records and electronic signatures.
- **A Complete Audit Trail that is easy to follow:** Documents go through a workflow process as they are created, reviewed, approved, and finalized. The eTMF must provide an audit trail of everything that happens to a document and by whom.
- **A Tagging System:** Clinical trials create a great deal of documentation, and a tagging system provides a way to organize that information. The eTMF should offer the ability to define metadata according to your requirements.
- **Search By Metadata and Document Names:** Finding specific documents quickly during an audit or as part of your daily management activities is critical. Your eTMF should enable you to search against both document names and metadata.
- **Quality Check Process:** Every document in a clinical trial goes through a quality check process to ensure it is complete and accurate (e.g., all pages in a document are present, the document is signed or needs to be signed, is dated, and so on). The best eTMF applications provide a mechanism to manage this QC process within the application and report on its status.
- **Access and Permission Management:** Multiple users with different roles and responsibilities, often across companies and geographic areas, need access to the eTMF application. Therefore, the application must provide the ability to add multiple users and assign specific permissions to restrict what they can do in the application to only the things they are allowed to do.
- **Reporting and Data Export Capabilities:** Reports for individual trials or views across all trials help management understand the status of trial documents and readiness for inspection. The eTMF should also provide the ability to export the data for use in spreadsheets or to import it into other trial management systems.

Building a Hybrid (Shared) Responsibility Model for eTMF

If you are trying to figure out the best way to share responsibility for the TMF, consider these five steps to get you on the right track:

Create a Roles & Responsibilities Document or Checklist

The first thing you need to do is define the roles and responsibilities of your team.

Identify the Team

Here are the most common team roles involved with managing the TMF:

- **Functional Line Representative:** A functional line representative is similar to a service area representative or business unit/department member. This person is assigned specific TMF responsibilities according to their functional role.
- **Project Manager:** The project manager oversees the setup and management of the TMF, ensuring everything is in place in a timely manner.
- **Monitor:** The monitor(s) oversees the progress of a trial, ensuring the correct documents are recorded and reported on according to the protocol, standard operating procedures, GCP guidelines, and regulatory requirements.
- **TMF Owner:** What role does the sponsor (the TMF owner) play in managing the TMF?

In addition to these roles, you may identify additional team members that need to be involved TMF management.

Assigning Tasks (Responsibilities)

Once you identify your team, you need to assign tasks to each one. Some of these tasks include:

- Oversight of the TMF
- Write and maintain the TMF plan
- File TMF plan
- User access management
- Binder creation
- Shipping original documents
- Destruction of paper copies
- Filing documents in the TMF
- Paper Reconciliation
- Ongoing checks by CRO
- Data Integrity Check (QA/QC)
- Ongoing checks by the sponsor
- Readiness review
- Issue resolution
- Progress reports
- Archiving
- Trend analysis and action plan
- TMF transfer

See example table on the next page

Example Task Table

Task	Functional Line Representatives	Project Manager	Monitor	TMF Owner	Other 1
Oversight of TMF					
Write & maintain TMF plan					
File TMF plan					
Creation of binders management					
Shipping of originals					
Task					

Document an eTMF Plan

It's critical to understand how you will utilize an eTMF application to help you manage the TMF. To do that, you can add a section to the Trial Management Plan related to TMF management, or you can create a separate TMF plan document.

In your TMF Plan, outline the following items:

- **TMF Oversight & Access Arrangements** – Who will oversee the TMF, and how will team members access it.
- **TMF Content** – What documents go into the TMF, and how they are organized
- **Quality Assuranc**e – What is the QA process, and how are issues resolved?
- **Record and TMF Disposition** – What is the process to record documents in the TMF – both sponsor and investigator TMF?
- **Applicable SOPs** - What are the SOPs applicable to the trial?
- **TMF Training** – Who needs to be trained on the TMF, and how/where will the training take place.
- **Conducting TMF Reviews** – Who will conduct regular TMF reviews, and what does the process look like?
- **Transfers of TMF** – What is the process to transfer documents from sites to the TMF and the TMF contents to the sponsor during and at the close of the trial?

Set Up the eTMF System

Once you have your TMF plan defined, it's time to set up the eTMF application that will support TMF management. Every eTMF vendor will have a different process to help you get up and running, but here is Agatha's approach as they work with a customer to implement Agatha Clinical (eTMF):

1. Provision of the Agatha Clinical TMF environment

2. Set up initial users in Agatha with correct role and access

3. Determine TMF Structure

- **a.** Review standard TMF Reference Model content and identify any additions or deletions for the customer's needs
- **b.** Create a standard template for the customers TMF model

4. Create Study Workspace

- **a.** Configure the workspace for customer-specific processes such as user roles and access and workflow processes

5. Update User Acceptance Tests to reflect configurations

6. Execute UAT and Sign Validation Documents

7. Train Users

8. Implement in Production

Many sponsors use the DIA reference model as the structure for the TMF. However, some want to use specific file structures that don't follow the DIA reference model out-of-the-box. The project manager and trial lead work with the client to understand precisely how to set up the TMF, and then the system administrator creates that setup and adds sites into the system.

Set Up eISF for Sites to Manage their Documentation

Sites need their own place to store and manage documentation. Traditionally, they have managed this documentation in a paper binder, but there is software available that provides an electronic version – the electronic investigator site file (eISF).

With an eISF, TMF administrators create separate, secure areas for each site to manage their documentation. Both site personnel and the monitor have access to the eISF to manage and review site documents.

The eTMF and the eISF should be integrated to allow for a seamless flow of final documents from eISF to the eTMF.

Ensure Data Integrity / Quality Management Throughout the Trial

Managing user access to the eTMF and eISF throughout the trial is crucial for the quality management of the systems. Therefore, this aspect of the eTMF and eISF needs to be well documented and managed throughout the trial to ensure appropriate access rights are provided in a timely manner and remove access rights when needed. In addition, the flow of communication for notification to the system administrator of staffing changes should be well documented in the eTMF Plan.

Quality control (QC) review of individual documents in the eTMF/eISF and the review of the eTMF as a whole should be performed at intervals designated in the eTMF Plan. Responsibility for these tasks should be documented, and appropriate personnel should be trained on their specific role(s).

Conclusion

Working together, the sponsor and CRO can successfully manage the trial master file to ensure the study is inspection-ready at any time and documents are easy to find during monitoring or audit processes.

The key is clarity on roles and responsibilities and the use of an electronic TMF application that incorporates the storage of study documents and the processes that enable collaboration and coordination for the entire life of the study.

If you'd like to learn more about how CROs work with sponsors to manage the TMF or see how an eTMF application improves the efficiency of TMF management, reach out to DZS Clinical Services or Agatha.

About DZS Clinical Services

DZS Clinical Services is a Contract Resource Organization (CRO) established in 1984. It provides a full suite of clinical development, data, analytical, and pharmacovigilance services. Focused on improving trial performance and overall efficiency, DZS works with pharmaceutical, biotechnology, and medical device companies globally.

In 2018 DZS became a subsidiary of WDB Holdings Limited, located in Tokyo, Japan. It has offices in Finland and the Baltic region as well as India, Japan, and the US.

Phone: (732) 764-6970 **Email** | **Website** | **LinkedIn** | **Twitter** | **Facebook**

About Agatha

Agatha, Inc. is a leading strategic software solutions provider to the healthcare and life sciences industry. With offices in the US, Europe, and Japan, Agatha is dedicated to helping the world's hospitals, biotechnology, pharmaceutical, contract research organizations, and medical device firms optimize the management of their quality, regulatory and clinical documentation and processes.

Phone: : +1 646-891-5299 **Email** | **Website** | **LinkedIn** | **Twitter**