



PHLEXGLOBAL WHITE PAPER



The TMF Experts[®]

Points to Consider When Developing a TMF (Trial Master File) Strategy

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Executive Summary

Many organizations are currently outsourcing clinical trial activities to one or more contract research organizations (CROs). This strategy enables companies to leverage specialized expertise and take advantage of flexible resourcing throughout the conduct of a clinical trial. Outsourcing minimizes the costs of recruiting experts, building a team and maintaining an infrastructure. However, it can also add complexity as the organization looks to meet its compliance obligations regarding clinical trial documentation.

The documentation referred to in Article 15(5) of Directive 2001/20/EC as the **trial master file** shall consist of **essential documents**, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated.¹ This essential study specific documentation is also known as the TMF. As organizations try to minimize their reliance on paper files, the electronic TMF (eTMF) has emerged. A current industry initiative to standardize the organization of this content is known as the TMF Reference Model. This model is helping standardization efforts across paper and electronic systems.

As companies implement outsourcing strategies, CROs and sponsor organizations look for a common foundation on which to build their TMF capabilities. The following paper outlines some of the challenges organizations face when outsourcing clinical trial activities to multiple contract research organizations and a strategy to facilitate partnering and management of trial information between sponsors and CROs.

¹ [European Directive 2005/28/EC]

Sponsor and CRO Partnerships

Outsourcing has become a cost effective resourcing strategy across the clinical trial lifecycle. Many life sciences companies and their CRO partners must consider the complexities of using multiple CROs across clinical trials. Though this approach enables companies to choose partners based on regional capabilities, therapeutic expertise, or other study specific criteria, it presents challenges when addressing the study documentation compliance requirements. The implications of process, logistical and reporting issues make this a strategic as well as an operational decision. The resulting complexity can increase the risk of non-compliance whilst also using up any time and money that was initially saved by implementing an outsourcing strategy. And these time and money costs will be recurring with each new study that is initiated.

A typical sponsor organization outsources clinical trial activities to numerous CROs. Using a CRO eTMF system puts a significant burden on sponsor teams to learn multiple systems and processes. Learning multiple systems from different CROs can become a management nightmare. In addition to the training burden, maintenance of user accounts and validation have to be addressed for each system. The impact of working in multiple systems has a ripple effect throughout the organization and impacts Clinical, Regulatory, Quality Assurance and Data Management teams.



The risk of non-compliance is significant when you are asking clinical professionals to become proficient in multiple new systems and the supporting processes. Additional systems and processes add new variables and increase the likelihood of error. Non-compliance can often be attributed to well-meaning, skilled professionals who are forced to internalize too many different systems, processes and all of the nuances that must be mastered in order to be proficient.

The disjointed process of working with multiple systems also creates barriers to information assets. It essentially puts an additional burden on trained clinical teams to be able to access the information on behalf of other sponsor team members. This introduces yet another inefficiency into the process.

The Bigger Picture

Using many eTMFs from multiple CROs also impacts the sponsor's ability to gain insight into the trial master file content and process. One of the advantages of an eTMF is the ability to perform metadata analysis across trials and compounds in order to identify trends, training issues, etc. When a sponsor chooses to use multiple CRO eTMFs, they lose this ability to aggregate and analyze data across their portfolio. The loss of transparency also takes away any opportunity to evaluate process metrics and thus thwarts process improvements. This diminishes the value of the partnership for both the CRO and the sponsor.

When looking at the bigger picture, it is important to recognize who will be accessing the TMF content and why it is being managed in the first place. A well-organized TMF will support a thorough inspection or audit. From the CRO perspective, it is important to have insight into the TMF on an ongoing basis, throughout the conduct of the trial in order to manage operations and ensure compliance at each site while the study is still active. This enables the CRO to uphold the compliance expectations of sponsors and regulatory health authorities. From the sponsor perspective, it is also important to be able to respond promptly to any audit request.

If the sponsor is using different systems with different structures, they will most likely need additional time to identify and retrieve documents.

Any Quality Assurance professionals who may be hosting the audit would have to be proficient in all of the systems and structures. Stumbling through an unfamiliar system may give the perception that the sponsor is not managing TMF content well. This may trigger additional questions or create additional concerns.

From the auditor's perspective, it is important to facilitate controlled access to content in a smooth and seamless fashion. This is probably not realistic when moving between multiple systems. In the best case, if an auditor has to juggle between multiple systems and structures in order to review TMF documentation, he or she will be frustrated. In the worst case, the auditor won't be able to navigate the complexity and his/her frustration will lead to more in depth question or an expanded scope for their line of questioning. The auditor's job is to verify quality and compliance. A sponsor's job is to facilitate the auditor's job and ensure the success of the audit by having a well-organized and compliant TMF system and process. In this manner, sponsors can make sure that they are not only inspection-ready but also inspection-friendly.

This scenario presents the difficult challenge of collecting data and documents from multiple sources, and managing and organizing them in a manner that supports operational, compliance and the overall partnership objectives of CROs and sponsors. It highlights the need for a standardized approach to TMF management that supports disparate structures and terminologies and normalizes the control of this information over time.

TMF Process Challenges

Many CROs and sponsors do not specialize in TMF/eTMF systems and processes. Because of time, source and content variables, the resources and time required to create and maintain a compliant TMF are often underestimated.

Clinical documents enter the trial master file lifecycle where content is acquired (scanned), processed (quality checking and trouble shooting), stored (with metadata) and made accessible (via permission-based authority).

The ongoing support for this process requires an understanding of compliance requirements, knowledge of clinical documentation and application of quality processes that ensure accuracy and detail. It also requires automating technology that facilitates standardization of content and metadata as well as controlled access. Most sponsor organizations don't have the resources to support this process. Most CROs have clinical expertise but many don't have access to enabling technologies that support the core principles of content management.

TMF Functionality Challenges

Optimizing a trial master file requires focus on the challenges and an ongoing commitment to addressing those challenges with expertise, technology and quality processes. Those CROs who do have eTMF systems often struggle to support varying client approaches to TMF management. Many cannot support the implementation of sponsor-specific TMF structures because their systems are based on internal standards that are "hard-coded". This means that sponsors are forced to use the CRO documented structure which then may require mapping into the sponsor structure when the TMF is delivered at the end of the trial. The ongoing struggle to standardize internally and externally creates a great deal of redundancy, rework and adds to the cost of maintaining a compliant TMF.

CRO eTMF systems need to provide review and commenting functionality and external access for the sponsor to ensure TMF oversight. If external access is not possible, the TMF process becomes a "black box" with little visibility into status, compliance levels, trends, etc.

The Phlexglobal Approach

Phlexglobal is uniquely positioned to facilitate sponsor and CRO partnerships in clinical trial activities by providing a comprehensive solution that addresses the people, process and technology challenges of building and maintaining a compliant TMF/eTMF.

TMFs are our specialization. We are not a document management software vendor looking for an application in the clinical space. We are not a “body shop” throwing untrained resources at the problem. We are the TMF Experts. We are leveraging technology to optimize TMF processes while using our clinical expertise to ensure compliance. Our software and service solution joins sponsors and CROs so that both have visibility into the TMF process. We provide the resources to acquire, process, store and manage TMF content in an organized and compliant manner and we leverage technology to make that content available to stakeholders throughout the process. We focus on the TMF management so sponsors and CROs can conduct clinical trials and get new therapies to market.

Our technology enabled global TMF services provide a foundation for trial documentation that places sponsors and CROs on common ground, with controlled, common views of study data and documents.

We have contributed to and implemented industry standards across our TMF solutions. We partner with CROs and sponsors who understand the value of building and maintaining quality documentation throughout the clinical trial. We understand the risk of non-compliance and specialize in assisting sponsors and CROs to develop and maintain trial master files around the globe.



PhlexEview, our purpose-built eTMF technology, provides a controlled environment that supports TMF management activities. It offers permission-based access throughout the TMF process that can be configured to the artifact level. It enables powerful management reporting across studies, products and therapeutic areas, etc. Our flexible solution supports configurable TMF structures, thus minimizing traditional time consuming remapping exercises.

PhlexEview is the authoritative TMF source for numerous global organizations, their strategic partners and supporting CROs. It connects clinical trial content to the stakeholders who use it throughout the R&D process. It unites CROs and sponsors with an unprecedented level of transparency into the TMF process. PhlexEview allows CROs and sponsors to focus on core competencies while realizing efficiencies throughout the TMF process. In addition, the PhlexEarchive module provides support for storing, maintaining and retrieving TMF documents in an electronic archive. The PhlexEarchive module extends document control and connects the TMF lifecycle to the electronic archiving process in a seamless manner.

Phlexglobal leads the industry with flexible TMF solutions that increase productivity, decrease risk of non-compliance and enable CROs and sponsors to collaborate more effectively.

Traditional TMF Challenges	Phlexglobal Approach
Duplicate systems & structures increase training and support requirements	One system & structure reduces training and support investment and offers recurring value
Multi-system approach increases opportunities for error	One system and process reduces risk of errors
Loss of metadata analysis across multiple CRO systems	Support for metadata analysis across trials & products to identify trends, training issues, etc.
Difficult to support rapid response to audit questions	One system and structure supports CRO, sponsor and auditor in audit activities
Functionality sometimes means sponsors don't have access to TMF	Sponsor interaction incorporated into system and process. Permission based access delivers content to appropriate team members across partnering organizations
No trained resources for TMF management	TMF Experts support entire TMF lifecycle
Isolated process that offers no visibility	Flexible model that connects CROs to Sponsors throughout the TMF process

To learn more about Phlexglobal and PhlexEview, please visit our website at www.phlexglobal.com.