White Paper

eTMF as a Factory:

Key eTMF Elements and Practices for High Volume, High Quality Processing

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OVERVIEW

For many companies, eTMF is a high volume process. Big Pharma (and the CROs that support them) may be managing dozens, or even hundreds, of studies simultaneously.

These studies range from small Phase 1 studies of short duration to so-called "megatrials". A cursory look at the studies in clinicaltrials.gov reveals studies that would result in very large Trial Master Files:

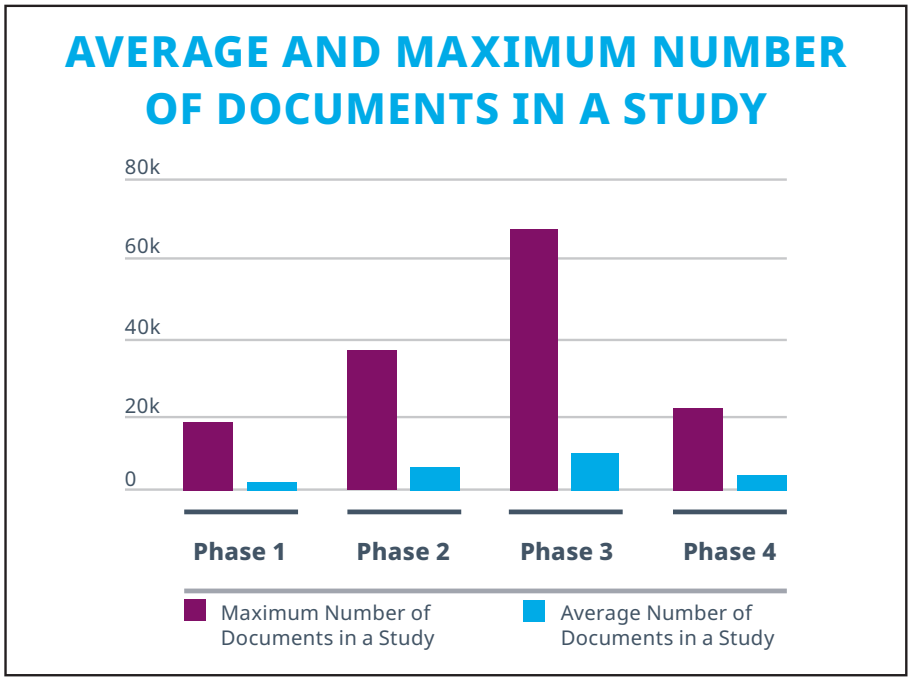
> Daiichi Sankyo's phase 3 study "Global Study to Assess the Safety and Effectiveness of Edoxaban (DU-176b) vs Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (EngageAFTIMI48)" lists 1002 sites in 46 countries.

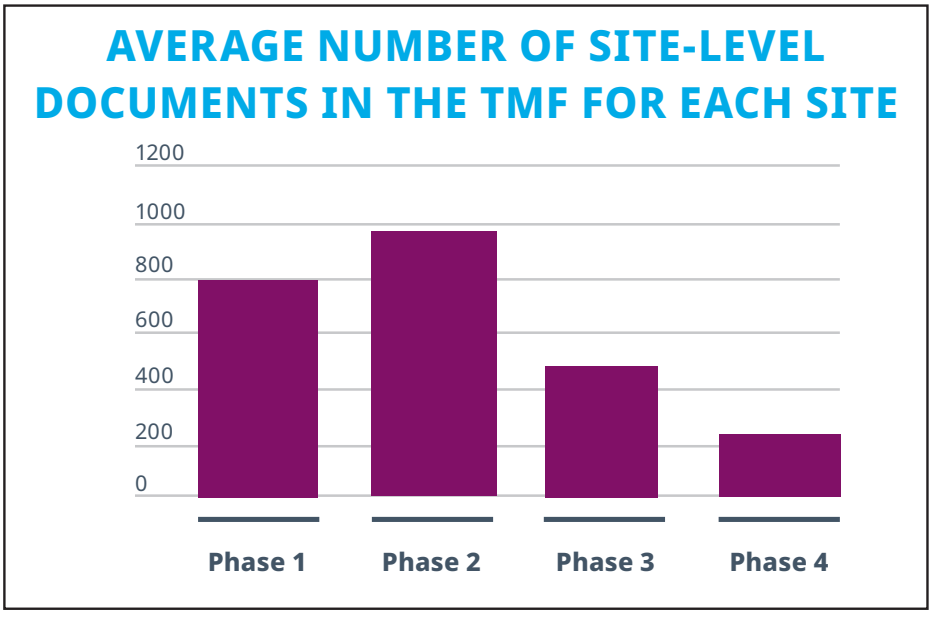
> Novartis' phase 3 study "Cardiovascular Risk Reduction Study (Reduction in Recurrent Major CV Disease Events) (CANTOS)" lists 1557 sites in 40 countries.

While most Tier 1 pharma has experience in dealing with large trials, they often fail to achieve the efficiency and quality they would expect in their TMF-related processes.

Even smaller companies experience high volume when running large Phase 3 studies. For example, the Exelixis "Study of Cabozantinib (XL184) Versus Prednisone in Men With Metastatic Castration-resistant Prostate Cancer Previously Treated With Docetaxel and Abiraterone or MDV3100 (COMET-1)" is being conducted in 12 countries at 264 sites. A study of this size might conservatively be expected to generate 5000 to 10,000 TMF documents, exclusive of subject-level documents such as Case Report Forms.

IQVIA's own research across our client base shows the average and maximum number of documents seen in our eTMFs. (figure 1). Furthermore, when subject-level documents are included, almost a thousand documents per site may be present in an eTMF (see figure 2).





To complicate matters, an organization with previous experience, processes and technology scaled for smaller trials will experience challenges when they do have to support large trials.

Ideally, an eTMF would operate like a well-oiled factory by using highly efficient, repeatable processes to achieve a defined level of quality using the minimum level of time and resources possible. This white paper examines some of the factors that would support making "The eTMF Factory" a reality.

STAGES IN MOVING THROUGH THE ETMF FACTORY

ACQUIRING AND UPLOADING DOCUMENTS

eTMF documents originate from a large number of sources. These may include other document management systems such as a Regulatory Electronic Document Management System (EDMS) or SOP system, a safety system, or a Clinical Trials Management System. Of course, a great many documents originate at study sites, IRBs/IECs and vendors. Although some of these documents may be received as electronic originals, a great many may be paper documents that need to be scanned.

Since scanning documents adds additional workflow steps to the process of acquiring TMF content, documents should be obtained as electronic originals wherever possible. Eliminating paper not only eliminates the need for scanning, but also removes the need for processes around transferring and archiving paper documents. Some steps in eliminating the need for paper include:

Providing electronic signature capability. Most organizations would not consider an electronic document requiring a signature to be an acceptable substitute for paper unless the signature is present – whether as a scanned wet-ink signature or an electronic signature. We often hear that an electronic original must be scanned because the only way to apply a signature is to print, sign and scan.

Better yet – eliminate the need for signature altogether. Most TMF documents do not have any regulatory requirement for signatures. [1] If your policies call for signatures in places the authorities do not require them, it's time to re-examine your policies. Authorities such as MHRA recognize this, stating "Signatures on documents are recommended only where it adds value; many documents require wet-ink signatures as a result of internal written procedures, without clarity on what the signature is actually for." [2]

Educating all parties on providing electronic originals wherever possible. A site may have to print a paper copy for their own archive, but can still deliver an identical electronic copy for the sponsor's archive.

When documents are available electronically, they can be uploaded to the eTMF singly or in batches. To support the "factory" approach, a contributor must be able to quickly identify and index documents. Key factors in achieving speed and accuracy include:

The ability to see content and metadata side by side. If a contributor has to launch content into a separate window manually to see a document, he or she may fail to do so, resulting in misidentified documents and incorrect metadata. Even if the contributor faithfully opens every document, the additional processing time adds up quickly when processing hundreds of documents a day.

Auto population of metadata to the maximum extent possible. Much of a document's metadata is already known if the document is uploaded to a waiting placeholder created when the study was planned. If no placeholder is available, basic information – such as product, study, country and site – should still be pre-populated. Auto-naming of documents based on type and metadata is essential. Manual assignment of document names for hundreds of documents a day is a major waste of time – and a source of inconsistency. At a recent conference, we were told a cautionary tale about a legacy system where users had found at least 10 different ways to spell the word "protocol" – with the associated documents then almost impossible to find in a search.

Easily accessed indexing instructions for specific document types. Most eTMFs allow documents to be assigned to between 400 and 800 distinct document types. No one is going to remember exactly how to categorize and index all of these document types, and having to open and search work instructions is time-consuming. Providing one-click access to indexing instructions and related information is a major accelerator.

A path to resolve questions. Just think about the last time you cleaned out your desk. What took the most time? Not putting the pencils back in the pencil jar or even filing the bills. What took the most time were the items you didn't know what to do with. You ponder them, put them aside, and hope clarity will emerge over time. If a TMF contributor has a mechanism to ask for assistance when the path forward is unclear, the process will move forward much more quickly and documents will not persist in the draft status indefinitely.

Scanning of some records is inevitable. When documents must be scanned, best results are generally achieved by using a central scanning function as they will have the equipment and training needed to ensure high quality images. Often, scanning cover sheets are used to identify documents that are presented for scanning. This allows the scan center to focus on their core competency – imaging – and avoids having to educate scanning personnel on identifying and indexing TMF documents. It also avoids the legacy approach of writing custom software for scanning systems to allow metadata to be entered as part of the scanning process. A well-designed scanning process using cover sheets to identify documents will allow those documents to be directly released into the eTMF for a final quality check.

PROCESSING DOCUMENTS

Most organizations require quality control checks on documents introduced into the eTMF to ensure a predefined level of quality is met. Some organizations may require 100% QC and others may allow sampling. Whatever approach is taken, QC is a significant workflow process in an eTMF.

Our client experience has shown that experienced QC personnel process hundreds of documents a day. Even a minute or two of delay in processing each document has a large impact on efficiency.

Important considerations in optimizing QC include:

Handle QC through a group inbox. Expecting a contributor to know who to direct each document to for QC – and taking the time to choose that user – is both unrealistic and inefficient. QC tasks should go to a group function. QC associates should be able to filter a group inbox to identify the tasks they should work on based on their priorities, which change too often for them to be identified as system rules. Direction may change on a daily or weekly basis depending on upcoming inspections, drug shipments, studies or sites with large amounts of documents that have become overdue, and more. An eTMF should provide the flexibility to handle those changing priorities.

Provide QC instructions for each specific document type in a convenient manner. In a similar manner to the instructions provided to the contributor, one-click instructions should be available to the QC associate to clarify what should be checked for each type of document. For example, there are often a large number of checks needed to ensure the correctness of a 1572, often involving cross-checking information in other documents.

Ensure documents display quickly. QC operations are often done in locations that are remote to the eTMF server. If each document takes many seconds – or even minutes – to load, productivity is impaired. Ensure network bandwidth and other infrastructure support operations at all your locations, and that when a user completes a task the next task is automatically loaded.

WORKING WITH DOCUMENTS

Once documents have completed QC and are generally available in eTMF, it must be easy for users to locate them in just a few clicks. The industry is moving away from traditional folder models for document storage as they are not intuitive and are often "click intensive." Instead, consumer style faceted searches and one-box quick searches – such as seen on Amazon and eBay – allow users to find what they are looking for much more quickly than what one of Wingspan's clients refers to as the "hunt and peck" approach.

ACQUIRING AND UPLOADING DOCUMENTS

One of the most important factors in improving performance and increasing quality is the ability to measure and evaluate your processes. In a well-run physical factory, the time to pass through each manufacturing stage is measured, and the rework or rejection experienced due to specific causes is known. This allows bottlenecks to be identified and addressed, and sources of variability and defects to be investigated and resolved. Likewise, an eTMF should provide insight into the time needed to complete each step in the process, as well as visibility into the causes of quality problems addressed through re-work.

Users should be able to "drill down" into metrics and reports to gain the necessary insights. For example, timeliness or quality may need to be examined on a per country, per site, per scan center, or per CRO basis to identify problem areas. These metrics also need to be compared across multiple time periods to determine if performance is improving or degrading. Without meaningful metrics, any attempt to achieve process improvement will be based on anecdotal evidence and is likely to achieve a poor return on investment.

SUMMARY

In the factory world, efficiency and quality have been driven for many years by examining processes to reduce the number of steps involved and avoid errors. Performance and quality metrics are also proven to contribute to success in the manufacturing environment.

Many of these approaches have a direct parallel in the eTMF world. Key factors to consider in implementing similar programs include:

- **Eliminating or streamlining steps wherever possible**
- **Ensuring that users have all the tools needed to perform the task at hand readily available**
- **Using metrics and reports to monitor and improve processes and quality**

Although these measures are important in any eTMF system, they become crucial for sponsors or CROs working with large studies or large numbers of studies, where small problem areas or delays rapidly lead to major inefficiencies.

REFERENCES

1. Signature Requirements for the eTMF, 2013, Kathie Clark.

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

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