Optimise Your eTMF Strategy

An electronic trial master file (eTMF) sits at the centre of a complex structure of people, process and technology. Processes include many stakeholders ranging from internal departments (clinical operations, regulatory, data management) to external partners (CROs, committees, ethics boards and labs) to regulators. Activities are controlled by a quality management system and require evidence that defined processes were followed. Operating the eTMF requires significant resources, and needs grow each year as the number and size of an organisation's trials increase.

Given the critical role that the TMF plays in ensuring data integrity and the safety of human subjects, the serious impact of negative inspection findings, and the challenges with maintaining a cost-effective solution, an optimised eTMF strategy is an excellent investment. A successful strategy will encompass regulatory compliance, quality, and cost-effectiveness. That strategy can then be mapped to a set of tactics that enable the strategy to meet its objectives.

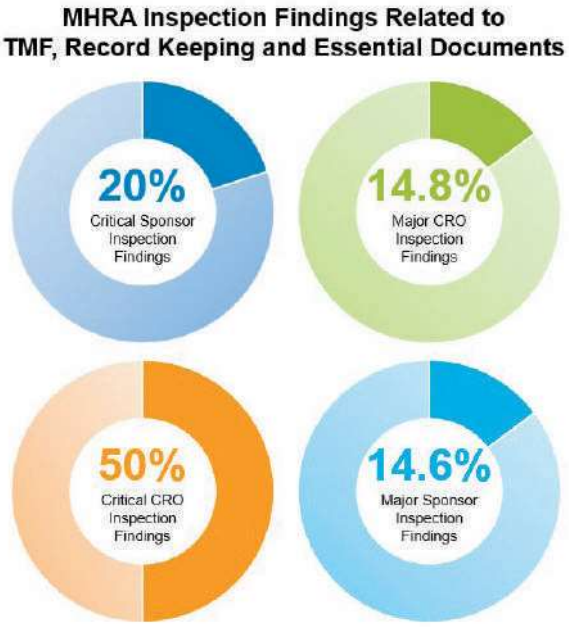
The need for an eTMF strategy is not limited to those organisations implementing eTMF for the first time. It should be part of an overall continuous process improvement philosophy even for mature organisations with extensive eTMF experience.

Regulatory Compliance – Designing with the End in Mind

Regulatory compliance can be defined as an organisation's adherence to laws, regulations, guidelines and specifications relevant to its business processes. Compliance is measured by the health authority inspector – the ultimate customer of the eTMF. TMF-related issues account for a significant portion of inspection findings.

Every decision made in an eTMF strategy should include a consideration of how it would be viewed by a TMF inspector. The following are examples only, meant to illustrate how a tactical decision can support or undermine the overall eTMF strategy.

- How are records organised and named? While it's more work to create accurate document names, MHRA inspection findings have been given based on "the same name for many different documents" and "documents being named incorrectly".[1] Inspectors need to locate documents quickly without having to open a series of documents that can't be differentiated without looking at the content.
- What records are in the primary eTMF, and what are stored elsewhere? How can those files be located? Health authorities state that there should be a primary TMF system for holding essential documents, and a suitable overall index or table of contents to enable the location of essential documents in the TMF to be traced.[2]



- Can you ensure that a scanned copy is a complete and accurate representation of a paper original? This is a prerequisite to destroying paper originals.

Table 1 shows how health authority requirements such as these can be traced into an eTMF strategy and then into tactics.

Health Authority Requirement	Strategy	Tactics
Inspections should be completed within the stated timeframes, without inspectors having to return because required documents could not be located.	Ensure that the eTMF can be easily navigated and searched, and that document names clearly and accurately represent the content.	Require document submitters to provide succinct but descriptive document names. Train them on both the importance of doing so and the best practices in document naming.
There should be a clear understanding of which records are located in the primary TMF and which are located elsewhere, and the ability to quickly retrieve all records, sometimes with guided access.	Determine the proper location of each record, considering the need to handle dynamic files such as Excel or SAS.	Develop a TMF index that describes where each record is held and how it is made available for inspection. Ensure that records are created in the assigned systems, and verify that they are created, finalised and accessible as part of eTMF completeness checks.
Paper originals should only be destroyed when required certified copies have been created.	Determine which copies need to be certified and define a certified copy process.	Develop, validate, train on and execute a certified copy process.

Table 1 Tracing health authority requirements into associated strategy and tactics

Studying published inspection findings, listening to conference presentations on agency inspections, and surveying the organisation's collective experience of inspections will help to determine what strategies and tactics are needed. The TMF Reference Model has created an inspection readiness RACI, presentation and FAQ list that incorporates the experience of a cross-section of industry.[3]

Quality – A Risk-based Approach

ICH Q9 defines quality as "the degree to which a set of inherent properties of a product, system or process fulfills requirements."[4] Therefore quality and regulatory compliance are not synonymous.

An effective eTMF strategy is built on quality by design (QbD). ICH Q8 defines QbD as "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". An important associated concept also defined by ICH is the critical quality attribute (CQA): "A property or characteristic that when controlled within a defined limit, range, or distribution ensures the desired product quality".[5]

Translating these concepts into the eTMF involves identifying the sources of eTMF risk and the CQAs that can be used to measure them. Usually, eTMFs are measured by their completeness, their contemporaneousness (timeliness of filing), and the quality of documents. Depending on how the TMF is used, other CQAs might be relevant; for example, whether monitoring visit reports are filed before the next visit, whether safety reports are promptly distributed to sites, or whether regulatory package documents are properly filed and finalised before drug shipment to sites.

eTMF strategy will identify CQAs specific to the organisation and the tactics that will allow them to be measured and monitor, resulting in corrective and preventative actions as needed. Both strategy and tactics will evolve over time as an organisation matures and gains experience in identifying sources of risk.

Cost-effectiveness – An Opportunity for Reward

Cost-effectiveness is the relationship between monetary inputs and the desired outcome. In the most recent survey by the TMF Reference Model, 30% of respondents felt their TMF was somewhat or very cost-efficient, with another 31% reporting a neutral perception.[6]

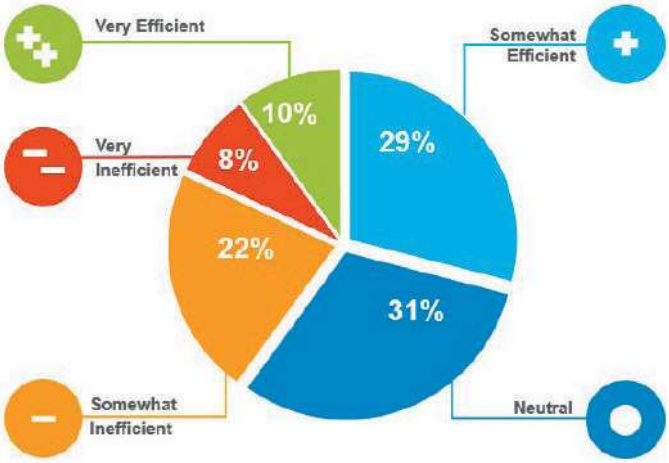
Although there is little published data concerning eTMF costs, it's safe to conclude that the majority of costs are attributable to labour rather than technology. The largest cost component at most organisations is related to eTMF quality control (whether done in-house or outsourced), with cost spikes occurring if any sort of eTMF remediation is needed.

Therefore, to increase cost-effectiveness, ask the questions:

- Are tasks being performed that are not necessary, as they do not strongly support compliance or quality?
- Are users performing tasks efficiently?
- Are users performing tasks that could be automated?

Identifying Non-value-added Activities

In examining tasks to determine if they actually contribute to compliance and quality, keep in mind what is being done to meet health authority guidance and regulations, and what is being done due to sponsor or CRO regulations. Internally required activities should be reviewed as part of the eTMF strategy to re-focus on what truly adds value.



- **Translations.** Are translations being done that are not required by regulations or by ethics boards? If they are not truly necessary, they are adding to the burden of both clinical operations and eTMF.

- **Handling of paper.** Sources of eTMF inefficiency in this area include scanning of documents that can be obtained as electronic originals, requiring wet ink signatures, and collecting paper originals that can be left with sites. Not only does scanning documents add time and increase the QC burden, but destroying original paper then requires a certification process.[2] Collecting wet ink signatures often does not add value, as this necessitates the circulation of paper for signature even though research shows that health authorities only require signatures for about five document types in TMF.[7]

- **100% QC.** EMA states "The sponsor… should implement risk-based quality checks (QC) or review processes."[2] MHRA GCP recommends "a formal process… for regular checks of documents in the eTMF, usually on a sampling basis, including escalation procedures where issues arise."[8] Thus there is ample evidence that health authorities will accept less than 100% QC provided there is a risk-based framework in place. Hecht *et al.* have published a methodology for a risk-based approach for quality assessments of TMFs.[9]

- **Repeated Activities.** Usually, document submitters are responsible for ensuring that their documents are "TMF ready". Depending on document details, they may need to check for scanning quality, completeness of forms, presence of required signatures, page numbering, etc. Consider whether it's worthwhile for QC associates to repeat these checks.

Promoting Task Efficiency

Several factors contribute to efficient execution of tasks. Of course, an eTMF with a well-designed user interface promotes efficiency, but is not necessarily sufficient. Some other factors that may promote efficiency include:

- Ensuring that a user has all the information needed to make quick and accurate decisions. For example, if the user has a question on document metadata for a specific type of document, how much time is needed to find the answer? If the user has to log into a portal, locate a document and search for the document type to find the information, efficiency is decreased.

- Removing low-value metadata. If users are spending significant time entering metadata, re-examine the value of that metadata.

- Minimising rework. Monitoring quality control failures and instituting preventative actions can drive down rework, making QC faster as well as avoiding the time needed to address issues.
- Organising work. A variety of studies have shown that repetition decreases the time to complete a task and increases accuracy. Organising tasks so that QC associates specialise in sets of document types will increase QC efficiency.

Often, an informal time and motion study focusing on document upload and QC will uncover many ideas for increasing efficiency. Submitters and QC associates no doubt will have ideas on how their work can be streamlined as well.

Implementing Task Automation

The volume of work needed to maintain a compliant, high-quality eTMF is daunting. Ultimately, automation, artificial intelligence and machine learning will replace much of the need for filing and quality checks currently done by humans. An eTMF strategy should address how automation will be increased in the near future, and how the organisation will prepare for more sophisticated solutions several years from now.

In the short term, options for increasing automation may be limited. An opportunity may exist for organisations using commercial eTMF software: taking advantage of software features that aren't currently being used.

Many companies implement a software solution without using all the available features. That is often a sound decision. Today's eTMF systems can support an extensive set of processes, but some of them need significant requirements definition, process redesign, change management or training. The best approach is to focus on getting the core processes implemented in an efficient and compliant way, then to consider implementing more advanced features such as site portals, study startup and IP Greenlight functionality, or site document reconciliation.

For organisations running a steady-state, healthy eTMF, it may be time to revisit features that weren't enabled in the original implementation or to explore new features the vendor has added. Forming a cross-functional working group to examine the possibilities is a small investment that can yield significant improvements in compliance, quality and cost.

Machine learning and AI offer great promise for automating document classification and metadata assignment, quality control, and translation. However, solutions that would be trusted by industry aren't available commercially today. It's reasonable to expect that will change in the next several years. So, a focus on preparing for automation is another sound investment.

For example:

- In order to prepare for auto-classification and metadata extraction, work to standardise and increase use of document templates that promote the ability to recognise a document and extract its metadata.
- Research how documents should be structured to enable machine translation.

Conclusion

The eTMF is a critical component of executing clinical trials whose safety and efficacy results will be accepted by health authorities. Developing and executing an eTMF strategy based on risks, goals and constraints specific to an organisation positions

the organisation for successful inspections, assists in controlling operating costs, and decreases the probability of expensive and time-consuming remediations due to unforeseen risk.

REFERENCES

1. Medicines & Healthcare products Regulatory Agency (MHRA) (11 May 2018). GCP INSPECTIONS METRICS REPORT METRICS PERIOD: 1st April 2016 to 31st March 2017. https://assets.publishing.service.govM.uk/government/uploads/system/uploads/attachment_data/file/706356/GCP_INSPECTIONS_METRICS_2016-2017__final_11-05-18_.pdf, visited on 29 July 2019.
2. European Medicines Agency (06 December 2018). Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf, visited on 29 July 2019.
3. Various resources on https://tmfrefmodel.com/resources, visited on 29 July 2019.
4. International Conference on Harmonisation (9 November 2005). ICH HARMONISED TRIPARTITE GUIDELINE QUALITY RISK MANAGEMENT Q9. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf, visited on 29 July 2019.
5. International Conference on Harmonisation (August 2009). ICH HARMONISED TRIPARTITE GUIDELINE PHARMACEUTICAL DEVELOPMENT Q8(R2). https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q8_R1/Step4/Q8_R2_Guideline.pdf, visited on 29 July 2019.
6. TMF Reference Model Survey (September 2015). https://tmfrefmodel.com/wp-content/uploads/2016/10/2015-tmf-survey-overview.pdf, visited on 29 July 2019.
7. Kathie Clark (November2014). Signature Practices and Technologies for TMF: An Industry Overview. https://www.wingspan.com/presentations/signature-practices-and-technologies-for-tmf/, visited 26-Jul-2019.
8. Medicines & Healthcare products Regulatory Agency (MHRA) (24 Sep 2012). Good Clinical Practices Guide.
9. Hecht, A., Busch-Heidger, B., Gertzen, H., Pfister, H., Ruhfus, B., Sanden, P. H., & Schmidt, G. B. (2015). Quality expectations and tolerance limits of trial master files (TMF) - Developing a risk-based approach for quality assessments of TMFs. German medical science : GMS e-journal, 13, Doc23. doi:10.3205/000227. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4677593/pdf/GMS-13-23.pdf, visited on 29 July 2019.

Chet Shemanski

Chet Shemanski a proven business and information technology professional with extensive experience serving the healthcare and global life sciences industries. He has specific expertise in software product commercialization including product management, product marketing, solution strategy and alliance management. Chet is a subject matter expert in eClinical and eRegulatory technologies, the author of industry journal articles and a speaker at industry conferences.