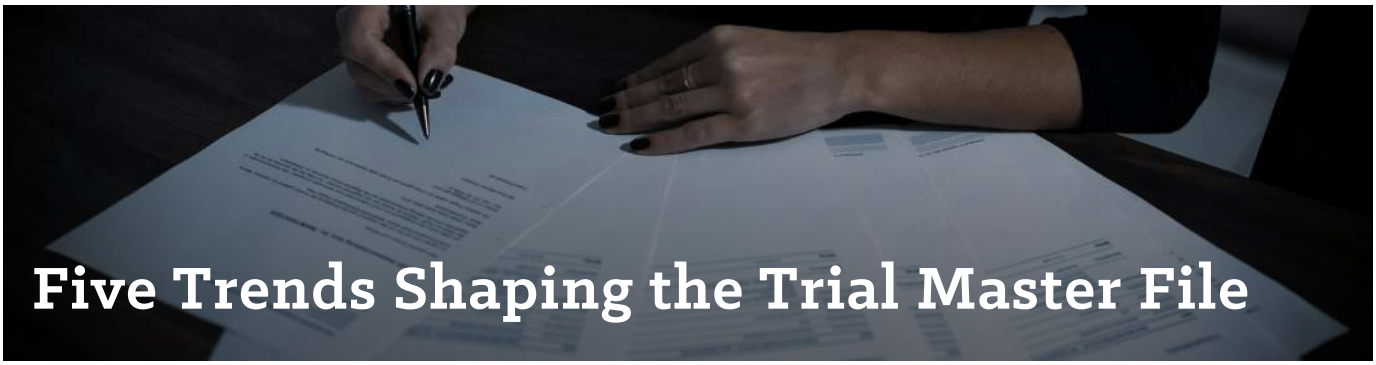

Five Trends Shaping the Trial Master File

The trial master file is integral to demonstrating that a clinical trial has been conducted in accordance with good clinical practice (GCP). The sponsor must therefore ensure their TMF is complete, timely, and accurate at all stages of a trial and across the document lifecycle.

Managing the TMF, however, has often been a challenge for organizations due to resource shortages and document owners not having enough experience with the TMF. Increasingly, artificial intelligence is playing an integral role in improving management and oversight of the TMF, which will have hugely beneficial implications for industry.

Indeed, AI is already shaking up TMF inspection readiness and TMF health in many different ways. As adoption of AI grows and as the sophistication of AI models expands, several key trends will gain traction as companies seek to ensure they meet compliance requirements with the TMF.

Trend One: TMF Health is Becoming a Greater Priority

Regulatory agencies are becoming more interested in the both the TMF itself and the processes around it, and industry is starting to see more guidelines around how their documents and data are stored.[1] They are not only looking at what is in the TMF but also how it gets there, how it's managed on an ongoing basis, and its oversight.

In the past, inspectors focused mostly on ensuring the documentation was in the TMF. However, that led to organizations acting reactively, getting their documentation uploaded and doing a huge push on quality control only when they found out they were having an inspection. That undoubtedly became more and more apparent to the regulators during their inspections and audits, and increasingly they are emphasizing the importance of having the TMF in a good state at all times.

As a result, inspections now look more at the processes and workflows, requiring companies to demonstrate that they are uploading their documents in a timely fashion and that they are keeping track of what needs to be in the TMF.[2]

AI can help to get companies inspection ready, speed up the preparation process and improve their TMF health, particularly if they are resource constrained.

Trend two: Digital disruption, including AI, is shaking up the TMF

Having AI solutions focused on the TMF is new to the industry, but there are growing options for using automation and AI to solve different problems. One example is document classification. Using AI to help classify your documents saves time for everyone involved in the TMF and helps those document owners that are less familiar with the filing structure.

From a TMF health perspective, therefore, AI will help to reduce misfiles, which is key when inspectors conduct an audit of the TMF, because misfiles will raise the risk of inspection findings. In fact, our internally generated data shows that between 9% and 12% of quality issues are due to documents being filed in the wrong place.

Another area where AI can come to the fore is with ongoing periodic review to ensure documents are organised and complete. While this is not something that is in use in production environments yet, many of the existing AI capabilities will be able to be utilized to enable this. With metadata extraction being combined with identifying document relationships, an AI solution will be able to proactively check the completeness of the TMF and identify gaps. AI also can shake up risk-based QC by doing the additional check on documents that are easier to classify, reducing the need to do that QC manually.

Trend Three: AI Lets Smaller Organizations Ensure they have a Healthy, Inspection-ready TMF

Smaller and mid-size companies that we work with typically struggle to determine which documents to QC, because they don't have the human resources to manage all the TMF documents. The option open to those companies has, until more recently, simply been to focus their limited resources on catching the biggest problems, knowing that other problems will slip through the cracks.

But when you have documents that will not have any oversight, it does raise concerns. For example, the document owners who filed them might not be very familiar with the TMF and might have misfiled those documents. If that occurs, the company may face an inspection finding.

AI can help to prevent some of these issues from occurring by providing document owners with proper classification suggestions when they are uploading their documents, and therefore this is one area they won't have to QC later on.

Next, having automated QC checking for non-key documents means that at least those documents will get some oversight, given there just aren't the human resources for those companies to review everything. Automation or AI can look for quality issues such as missing pages and carry out classification and other metadata checks.

If you can automate some processes, it will contribute to improving your TMF health without having to increase your staffing levels.

Trend Four: AI Places a Different Emphasis on Personnel Roles with the TMF

Having AI manage many of the less strategic processes could potentially revolutionize the role of the TMF expert. For example, rather than focusing their time on conducting quality control on

documents, they could potentially use the time to engage with their clinical research organizations and improve the CRO process.

Another area where the TMF team could redirect their time and effort is in improving site engagement, understanding what worked, what didn't, what sites they would want to work with again and which principal investigators they would want to work with again.

Having AI manage mundane tasks would allow TMF experts to leverage their skills in different areas, expand their roles and potentially enjoy a positive career path within the TMF team, rather than spending all their time conducting document quality control.

While the issue of staff cuts is contentious and creates concerns about AI taking over jobs, there is no indication that AI would take over strategic roles. However, it does offer companies an opportunity to either cut some costs on less strategic roles or at least not to have to invest in more staffing to manage QC activities.

As an example, we've relatively recently introduced AI to enable our services team to better support clients. That has resulted in some job cuts, but, more specifically, it has allowed the services team to focus on more strategic support.

Ultimately, AI can help to make TMF teams more efficient while continuing to ensure the quality of the TMF. For those smaller companies that have had to balance where to focus their QC, AI helps to improve the overall quality and allows the team to focus on more strategic activities that will improve the TMF health.

Trend Five: AI will Become Your TMF Early-warning System

One important aspect of the TMF is what is referred to as periodic QC or completeness quality checking. This process is something that all TMF teams should be doing and it's something regulatory agencies look at. By way of example, in its guidance on good clinical practice for clinical trials the UK's Medicines and Healthcare products Regulatory Agency (MHRA) notes: "The complete TMF is the basis for inspection and all the documents in it must be made available to the inspectors."[3]

The problem is that you have documents coming from different sources. Often those documents either indicate that there's another document necessary or it indicates that there's data that needs to be added into the system as a result of content of that document.

This might be site documents such as the site delegation log or very often the Form FDA 1572, which includes the list of investigatorsiv. Often that 1572 will look fine when it's put into the TMF. However, what is often overlooked is ensuring all information about investigators in the trial was captured, including their CV, their professional license, a financial disclosure form, and training documentation. Part of the periodic completeness QC involves going through that document to ensure that information on each investigator listed in the document is captured in the TMF.

This is very manual, labor-intensive work since it requires having people look through all those documents. When you're talking about big studies, or companies that are running lots of studies, typically these completeness checks are only carried out on each site once a year. That means if there is an issue, it will be some time before that problem is noticed.

Having AI review these documents to check what is missing would offer companies a real-time early-warning system that information about an investigator was missing from the TMF, or, by way of another example, that documents from a protocol amendment are missing.

Eventually having AI conduct these types of checks and provide the TMF team with a to-do list to complete the TMF would allow companies to do away with periodic quality control checks.

While AI is not yet able to manage these more sophisticated QC checks, it is where the technology is heading and ultimately will give companies far better oversight of their TMF.

An Essential TMF companion

AI is becoming an important tool for good TMF health. As AI algorithms become more accurate and sophisticated, there is greater potential for AI to take over many of the mundane tasks that currently require TMF teams to manage, allowing those teams to focus on strategic activities and at the same time making sure the TMF is complete and inspection ready.

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