Pharma iQ

a division of IQPC

Top Challenges with Late Stage Trial Master Files

Trial Master Files & Inspection Readiness

Top Challenges with Late Stage TMF

The transition from a paper to an electronic Trial Master File (TMF) system is a significant task. In many cases, some pharma and biotech firms (sponsors) may find that they are in the late stages of digitising their TMF system resulting in some documents being left as hard copies. Ahead of the 2017 Trial Master File conference we examine the top challenges that are attached to operating trials with a late stage TMF.

1 Maintaining a TMF in its entirety

Some professionals wrongly view the TMF as merely a filing method to archive documentation, when in reality the TMF acts as a storyteller. It is designed to tell the story of how the study is being structured and how certain stages are reached to an auditor / investigator.

Rather than viewing e-TMF as an archive tool, using it to generate the document from first draft to finalisation, the workflow is vastly simplified. With paper TMFs, feedback is collected by email and then documents are printed and stored appropriately. eTMFs allow for comments and other activities to be consolidated through one platform.

A sponsor could be handed a critical finding if an inspector identifies inconsistencies between a study's specifications, company policies and the ICH GCP regulatory guidelines. For example, if a firm decided to almost deviate from an SOP or an internal working document, an inspector could assume they were deviating from company processes.

A critical finding could result in a financial penalty, or worse, the termination of a study. Therefore, it's important that consistencies are maintained throughout every individuals work relating to a TMF. The task of preserving the TMF's quality needs to be enforced as the responsibility of every study team member.

2 Change management

Change management is one of the dominant challenges when implementing a late stage TMF. Some professionals are slow to adapt to using the electronic tools and processes to manage documents even when the benefits are made clear. It's important to ensure that the team is willing to adapt to the new processes required for the eTMF, and this willingness may not occur naturally. Training is going to be a likely necessity for a handful of people within

Top Challenges with Late Stage TMF

the business.

For sponsors or CROs working with a TMF that is mostly electronic, Michael Zorer, Head of Clinical Operations at AOP Orphan Pharmaceuticals recommends defining the system to be used for the entire trial from the outset. This system could encompass naming conventions and ensuring documents are consistently uploaded. It can prove painful to try to implement these concepts half way through a trial.

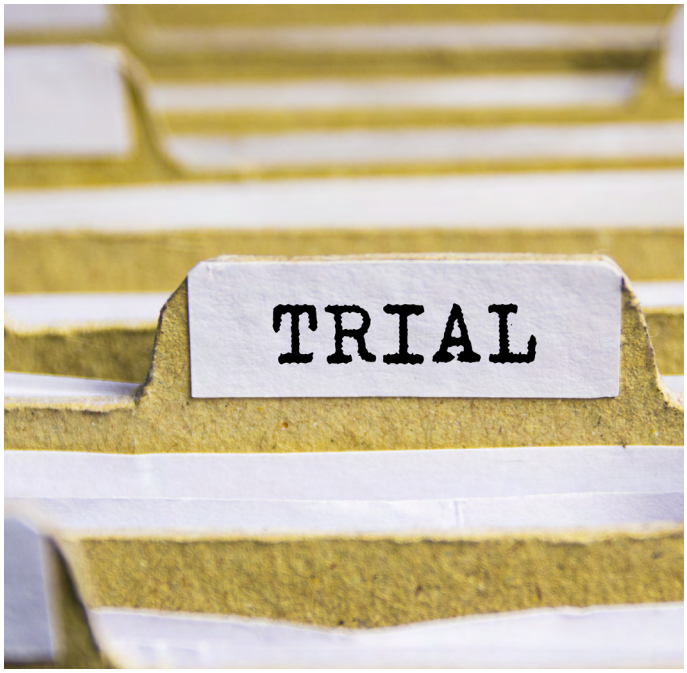
3 Cost

One of the downfalls to the implementation of an eTMF is the expense required. In comparison to a paper TMF, it costs considerably more to implement an eTMF study, especially with a debut eTMF study. There are various updated directives focusing tightly on eTMF, like the ICH GCP addendum. As part of the implementation process consultants may be required to review and realign internal processes to ensure everything is compliant and effective, which will require funding.

4 Collaboration

When working with a CRO that doesn't have access to a sponsor's systems there may be documents that are printed and signed by the sponsor on paper e.g., contracts. So, to maintain visibility, it's important that those documents are digitised and posted into the eTMF as per the sponsor's validated process.

It's often lost in translation that a sponsor



is solely responsible for a TMF even when the CRO's TMF is being used. When a CRO is contracted for a study, the CRO maintains the study, but they are not responsible for the maintenance, upkeep and the overall inspection readiness of the TMF.

Therefore, sponsors need to ensure they have adequate access to their CRO's trial documents, while using a system that preserves the data's security. This oversight will confirm to sponsors whether their CRO is keeping the TMF up to date and filing documents in the correct locations at the necessary times. Although, sponsors may not be familiar with the templates used by the CRO which can create some difficulties. Reporting systems with KPIs for the CROs are useful so the sponsor can be sure that the TMF is in good shape.

Multi-national trials are likely to have multiple collaboration partners who may have their own procedures or their own systems. This software conflict can prove to become fairly complex when multiple parties are needed

Top Challenges with Late Stage TMF

to work on one system and avoid having duplicate documents or parallel TMFs.

5 Inspection readiness

In April 2017, the European Medicines Agency (EMA) published draft regulatory guidelines around TMF conduct. These can be accessed **here.**

The new draft guidance says that as well as being kept up to date, the TMF should be:

- Completed by the end of the trial
- It should be readily accessible on the demand of member states
- QA processes should be conducted with every day business
- It should be archived for 25 years after the clinical trial.
- Inspectors have the jurisdiction to demand the original documentation if needed.

The pharma firms tend to be constructed with various systems, be them data-capture systems, budget systems, randomisation systems.

The functionality of these systems can sometimes conflict with the logistics of having one centralised TMF system.

With this in mind, it is important to clearly explain to inspectors how the TMF is set up so sponsors can proactively manage expectations. So sponsors may have 90% of their file in the main eTMF system and the remaining 10% is managed outside the system. It is important to ensure that those external systems are fully explained to inspectors while specifying the type of documents so auditors can have full visibility.

6 Following a validated process

When a TMF is mostly electronic it is important that a strong validated process is followed when scanning in the paper documents. By deploying the needed quality checks, sponsor firms can be sure that electronic versions of hard copies are legitimate. Hard copies or documents can be kept for archiving so in the case of an inspection auditors can see that both the original and scanned copies are the same. When it comes to paper documents from relevant sites, sponsors will need to ensure that their validated process is still followed.

In regards to the logistics of the validated system, its important to consider whether this constitutes using a machine that is deemed as validated or trusting people to follow the process required by the validated system.

7 Quality metrics

Whether it is paper or electronic, it's vital that a TMF has apt monitoring measures

Top Challenges with Late Stage TMF

from a project point of view and a company compliance perspective. A large challenge is presented by the size of a TMF – which contains thousands of documents. Metrics should monitor aspects such as whether the TMF is complete and clear at all times. This means that the expected documents, based on the stages of the trial, are present in the system at the required times in their final form. However it can be a fairly complex project to verify the real quality of a TMF in terms of completeness.

Examples of simple metrics:
• Time of upload
• Correct scanning quality
•Readability
• Number of pages

As there are thousands of documents being managed in a TMF, the file's individual stakeholders need to take responsibility for the quality of the file in how it is written and compiled. Niche quality metrics need to be embedded into different departments that come into contact with the TMF.

8 Duplicates

From a system building perspective, there can be challenges with having multiple versions of the same document. With some eTMF systems, once the print version is added into the system the KPI will register as green, however the system can lack flexibility to track any subsequent versions of that document.

Michael asks the question of when a print document is digitised is it a mandatory requirement to keep the paper version or can it be discarded to avoid having the parallel hard copy? AOP Orphan Pharmaceuticals has stored some of the hard copy parallels of files within their contracted CRO's eTMF.

9 Integration – centralised system

Sponsor companies tend to operate with multiple legacy systems that generate TMF documents and then one centralised system is used to manage the majority of the TMF documents. In this scenario, sponsor companies can choose one of two strategies:

- Continue to use the legacy systems in their existing infrastructure and once documents are finalised in those systems they are copied into the main TMF system. This is not ideal in regards to workload as this will require people to double file and monitor that the two systems are fully aligned. Other challenges with this are that traceability can be lost between the two systems as well as the trail of how the documents were managed in their initial systems.

- Alternatively, the sponsor could choose to retain the documents in the existing systems. Challenges will arise, however, in the case of an inspection because those systems need to be accessible for the TMF document to be directly available for the inspectors – as per regulation. Sometimes this will require an inspector access

Top Challenges with Late Stage TMF

profile to be set-up in the systems. From an inspector's perspective this is not ideal they prefer the number of systems to be limited.

For more insight on the subject of TMF management and to discuss these challenges with Michael, attend the 2017 Trial Master Files Conference.

Take Action And Attend:

Trial Master Files & Inspection Readiness

25-28 September 2017 | Amsterdam

New for 2017

- Be 100% prepared for your next inspection with our **full-day Inspection Readiness Training Course**
- Discover how to use collected clinical trial data, and **new eTMF technologies,** to increase profits and improve efficiencies with a Strategic Discussion on Business Benefits
- Discover the best change management practices for transformational projects with **Case Studies on Migration of EDMS** and eTMF Tools and eTMF Transitions
- Perfect your outsourcing strategies with expert presentations from sponsors and CROs on **TMF Outsourcing to CROs** – Practical Oversight and Lessons Learned
- Analyse the best practices for linking documents and data created in other repositories with your TMF to ensure completeness with a Panel Discussion on **TMF Integration & Sustainability**

Call: +44 (0)207 036 1300

Visit: www. trialmasterfile.iqpc.co.uk

Email: enquire@IQPC.co.uk

Download Agenda