

# Taking Charge of the Clinical Trial Master File

## Six simple but effective steps to set the TMF in the right direction

The clinical trial master file (TMF) is a bit of a misnomer, in that it is not really one file. It is “the collection of essential documents which allows the conduct of a clinical trial to be reconstructed and evaluated”. It is the story of how the trial was conducted and key decisions were made during its process. Considering that clinical trials can take years, involve hundreds or thousands of patients over many sites in multiple countries, are supported by a variety of external vendors, involve several different functions, and can run to many hundreds of thousands of “records”, it is clear that maintaining a TMF is a complex endeavour. Most companies struggle with it, and no one escapes an inspection by the health authority (be it the FDA, the MHRA or any of the others) without TMF-related inspection findings.

Many companies treat the TMF as a necessary evil – something that needs to be maintained but doesn’t add any value. This is an understandable mistake. However, in today’s world, pharmaceutical companies claim they are all about data, and the TMF represents a vast data set that deserves to be properly maintained and managed. Companies that do this will find that the value they can generate from high-quality data sets – some large companies run hundreds of clinical trials per year – will far outweigh the cost and headache of keeping on top of their TMFs.

Of course, this will not happen by itself. The keyword is “control”, and companies will need to recognise that they are not in control of their TMFs before taking the steps necessary to make the TMF an asset.

### Your TMF Does Not Have to Put You at Risk of Critical Health Authority Inspection Findings

From our analysis of clinical trial master file Health Authority (HA) inspection results, we have found common TMF-related indications associated with poor inspection outcomes. If these indications are present, you will be at high risk of critical findings from HA

inspections. The indicators can be easily identified and, with the right focus, effectively managed. They are:

#### Missing Records of Essential Documents

These are expressed in many organisations as 1) relevant trial documents not in the TMF or other predefined and validated systems, 2) required correspondence or emails not filed, and 3) difficulty locating the documents in the TMF. Missing documentation makes it challenging to evaluate the integrity of the trial data or compliance with regulations. Our analysis indicates that “missing TMF records” is one of the most commonly observed critical findings from HA inspections.

#### A Poorly Defined TMF

A TMF structure which does not clearly and fully identify the documents to be filed in a central TMF system, versus those in ancillary systems, leads to significant challenges in confirming where the TMF records are held during GCP audits or inspections. In some cases, when the TMF is robustly defined, the structure of the electronic filing folders might not be aligned with the TMF index, and this leads to a misaligned and consequently out-of-control TMF.

#### Records Filed in the Wrong Location

Even with a clearly defined TMF index, lack of understanding of the required documents or how they are to be filed in the TMF is another commonly observed indicator. This mostly people-related issue can be expressed as 1) product-level documents filed in study-level folders, 2) documents filed inconsistently or named incorrectly, and 3) documents duplicated and filed in multiple systems. With the advanced technology solutions in the market today, wrongly filed documents can easily be identified.

#### Untimely Filing of Essential TMF Documents

The common use of the TMF as a late-stage document repository, rather

than an “active contemporaneous system”, often leads to a rush to file large quantities of TMF records just after HA inspection notification. Untimely submissions, which HA inspectors can easily identify from data audit trails, lead to out-of-date TMFs and non-compliance with clearly defined contemporaneous requirements – which is another frequent reason for critical HA inspection findings.

#### Poor-Quality Oversight of the TMF

Poor oversight of the internal or third-party vendor TMF is another common reason for an out-of-control TMF. This is often expressed as poorly defined quality-control processes, lack of adherence to the TMF review process or frequency as defined by the standard operating procedures, vague scope of the sponsor’s versus the contracting vendor’s TMF quality responsibilities, system functionality limitations, or inability to collect and utilise quality metrics to enable preventative action planning. Commercial clinical trial sponsors often use multiple third-party vendors in trial management, and the inability to align TMF documents across these organisations and take control of quality oversight remains a stumbling block.

These commonly observed issues are particularly exacerbated during mergers and acquisitions, as the various parties involved apply a different understanding of the TMF and the associated standards, processes, systems and naming conventions.

#### Taking Charge of Your TMF

We have identified six simple but effective steps that can be used to take charge of the TMF and avoid hefty penalties for poor TMF management. These are:

##### 1. Define

At an enterprise level, the clinical trial organisation needs to define and agree on a common understanding and use of the TMF – as either a document repository or a knowledge management system. If

the TMF is to be used as a document repository, the expectation needs to be clearly set that it is the storage location for contemporaneous filing of all TMF documents. Engagement with the filed document/data will not be required for knowledge capture – just for storage and archiving purposes. Increasingly, companies are setting the purpose of their TMFs as active knowledge management systems that are used not only for storage and archiving, but also for knowledge and insight mining in managing trials. Deciding which of the two approaches will be used is crucial, as switching between both options leads to confusion.

## 2. Identify

At a study or product level, it is critical to define the required TMF record types based on the regulatory requirements that are relevant to reconstructing the conduct of the trial. The Drug Information Association's (DIA's) TMF Reference Model, which is widely accepted by the life science industry and regulatory experts, provides comprehensive information about essential TMF record types (artifacts). Although most record types (79 per cent of the 249 named artifacts) in the model are "core" and must be submitted in the TMF if produced during a trial, a significant amount are "recommended", and submission is not compulsory. Defining and justifying the "core" and "recommended" document types to file in the TMF (before initiating a study) enables an efficient start to TMF record management.

## 3. Reveal

TMFs are complex and require timely information from multiple stakeholders. Key to the successful set-up, maintenance and close-out of a TMF is the disclosure of the operational details required to collect the right information at the right time. This involves disclosing the roles (not just



functions) that will be responsible for contributing the predefined record and data types, expected frequency of filing the documents, document contributor quality checks to ensure correctness and completeness, systems to be used and associated system access, issue escalation pathways, etc. Having this information agreed, and preferably signed off, before a trial starts provides the clarity that is often missing in TMF management. The DIA's TMF plan provides a robust template for organising the TMF.

## 4. Evaluate

A TMF is not a static system, and as such, the set-up defined at the start of the trial is bound to change throughout the life of the trial as study information, roles and systems change. It is simply not effective just to have one version of the TMF plan with pointers to ancillary systems throughout the life cycle of the trial; the plan needs to be contemporaneous with the TMF to maintain control. Updates to pointers should be put through the change-control process for an efficient and systematic approach to managing changes.

## 5. Check

Study teams understand and appreciate the importance of data integrity; the FDA guideline of "Attributable, Legible, Contemporaneous, Original and Accurate" (ALCOA) data is widely understood. However, given the high volume of TMF records generated during a trial, it is impossible to check every document. Quality checks are easier if carried out frequently – preferably every three to six months. A risk-based approach could also be applied to having to do 100 per cent review of every record.

## 6. Train

Maintaining a compliant TMF requires routine training, refreshers, and reminders, as TMF obligations are not always at the top of study teams' agendas. Given the recent success in company-wide understanding of adverse-event reporting – which is well established in most companies today compared to 15 years ago – the TMF could follow a similar path to achieve the same level of success; i.e., the importance of a compliant TMF culture will need to be promoted company-wide, with regular, detailed

training for roles involved. Companies that educate associates regularly, with senior management endorsement of the importance of the TMF, are much more likely to establish TMF mastery.

## Turning the TMF into an Asset

Ensuring compliance, avoiding inspection findings, and staying away from the last-minute dash, as well as the required heroics to be ready for inspections, are all very good reasons for a company to get control and stay on top of its TMF. With that in mind, there is a much bigger prize at stake. Biopharmaceutical companies are realising more and more that they are, in fact, data-driven organisations. It is a bit of a headscratcher that a trial master file, which is effectively the complete record of a clinical trial, is not seen as a valuable data set. Combine that with the fact that there is one for every clinical trial, and one gets a sense of the scope and richness of these data sets – all the more so when there is a significant number of them.



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