Electronic Trial Master File: Gaining Efficiency for Oversight and Control

PEER REVIEWED

Maintaining an electronic trial master file (eTMF) is far more than storing study documents on the sponsor's file server. EMA's reflection paper on trial master files provides guidance in identifying requirements and expectations. They can only be met by mastering important challenges, but an eTMF introduces a new level of efficiency in TMF handling.

Background

The essence of maintaining a trial master file (TMF) is to allow reconstruction of trial conduct. This requires us to map all trial activities into documents, each representing a piece of a jigsaw. These documents are created by global teams with a variety of systems, usually at different locations. It is, therefore, not surprising at all to hear auditors and inspectors complaining about incomplete TMFs, missing audit trails, and bad structure, as well as lack of data integrity and sponsor oversight.

Evolving towards using electronic TMFs (eTMFs) seems like the appropriate solution to all these issues and challenges. They enable big pharma and large CROs to provide multinational teams with instant access from all over the world. Smaller companies realise the gain in efficiency an eTMF would offer, enabling them to conduct TMF-related processes with limited resources.

But when looking at the aforementioned complaints, one will quickly realise that the underlying issues are not related to the storage medium but to the corresponding processes. Instead, implementing electronic TMFs introduces additional challenges, e.g. security issues, missing user-friendliness, file formats etc.

EMA's Reflection on TMF

EMA's reflection paper on TMFs is a guidance document by the GCP Inspectors Working Group that was released in 2013. It outlines organisational aspects, controls, contents and inspection considerations. It is important to note that it applies to paper TMFs as well as to electronic TMFs. It is the first European guidance on maintaining an electronic TMF, removing some uncertainty among sponsors, CROs and eTMF vendors. Furthermore, its inspection perspective can be useful when trying to combine technical and regulatory requirements.

Three key challenges are addressed repeatedly within this guidance:

1. The TMF's accessibility and authenticity throughout the retention period
2. The inspector's confidence in TMF completeness and accuracy
3. The sponsor's responsibility towards the TMF

With regard to eTMFs, the reflection paper refers to the legislation, which does not differentiate between paper TMF and electronic TMF. It mentions the additional challenges; but it also states that "inspectors are not averse to reviewing an eTMF" and that remote visits may assist in planning inspections. Both statements reflect the inspector's acceptance of eTMFs as well as the way inspections benefit from eTMFs.

Technical Considerations

From a technical point of view, a TMF would look like files being stored into folders of a computer system. Such TMF-like file collections can be found within many organisations, usually being the result of the paper TMF's access limitations or of insufficiently understanding TMF requirements. The reflection paper states that such file collections are "unlikely to be considered acceptable".

EMA's reflection provides minimum security recommendations that have to be met. According to widely accepted standards and regulations (e.g. 21CFR11), additional requirements should also be met. These include:

- formal processes for user account management
- strong passwords for users as well as role-based permissions on a per-need basis
- regular system backup, preferably to an off-site location
- encrypted data transfer
- automatically maintained audit trail including timestamp, user and modification that can be accessed easily (Figure 1)
- disaster recovery and business continuity planning
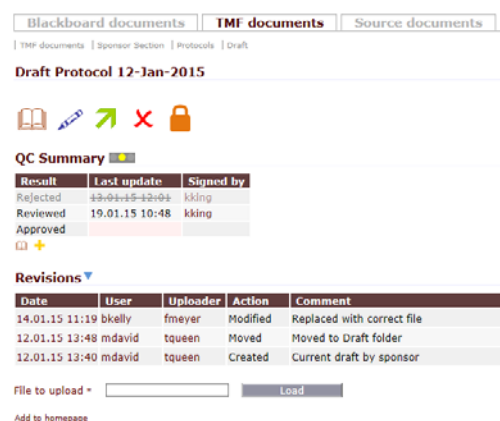- locking of documents or folders to prevent further changes (Figure 1)

Figure 1 Details of a document in QCTMS TMF showing folder path, QC results, audit trail and various editing options including document locking. 'Add to homepage' marks a document for subsequent retrieval.

The reflection paper suggests the functionality of a document management system. Such systems will usually offer file uploading, role-based permissions, audit trailing, document locking, as well as additional metadata to be stored. Of course, using such systems also requires corresponding procedures to be in place, e.g. for validation, training, management or change control.

Mastering TMF Complexity

The reflection paper identifies the TMF user's inability to locate requested documents as being one of the common problems found during GCP inspections. Such problems usually indicate an inappropriate TMF structure, insufficient training, or a lack of system usability. This is in contrast to a key feature of an electronic TMF: the capability to easily search a vast amount of heterogeneous documents.

EMA recommends standardised TMF structures within one organisation, suitable indexing, self-evident filenames, dedicated tools for searching, and the ability to mark documents for subsequent retrieval.

In routine use we have seen that these recommendations are fully valid. TMF structure and filenames need to be subject to frequent control, which partially can be conducted automatically (e.g. specific patterns for filenames) in order to identify potential deviations.

Investigator TMF (ISF)

When talking about TMFs, we usually focus on the sponsor TMF. But the TMF also comprises the investigator TMF, also called investigator site file. Most of the investigator site files contain six binders which need to be stored during and after the clinical study for several years at the study site. Assuming that a moderately active study site runs five studies per year, the investigator needs to archive 300 binders of the different site files after 10 years' active involvement in clinical studies. Beside the ineffective system of maintaining paper files at site, the clinical monitors spend several hours preparing the investigator site file and about 10% of the onsite monitoring time to control the binders and keep them up to date.

15-20 years ago we saw organisations realising that an electronic CRF would offer important advantages over paper CRFs, e.g. improved data quality, better oversight, and cost-savings. We currently see a quite similar turn from paper ISFs to electronic ISFs, with a slowly but steadily growing demand from sponsors of different sizes. This offers a great chance to really have a complete TMF that is location-independent and that can therefore be accessed remotely. Even a hybrid approach, keeping a paper-based binder for documents not to be handed out to the sponsor (e.g. identification logs) would offer important advantages. Nevertheless, such hybrid approaches need to be documented well to ensure that inspectors will find a consistent TMF instead of a fragmented one.

Scanning Procedures

One of the key challenges when using an eTMF is ensuring that all paper documents are accurately scanned into electronic documents. Scanning results strongly depend on parameters like resolution, colours, and file format. Therefore EMA's reflection recommends validated scanning procedures as well as effective scanning quality control. A typical scanning procedure defines responsibilities, devices to be used, device settings, further processing steps (e.g. image enhancement or OCR for later full text search) as well as QC responsibilities and activities. Such quality control should comprise accuracy of metadata, image quality, correctness, audit trail completeness, and approval (if applicable).

In routine use, scanning procedures also involve whether the original paper record can be replaced by the corresponding electronic record. Currently, there is only limited advice on this, despite being an important topic in many other fields, too. Because of this uncertainty we recommend a hybrid approach retaining essential documents as paper records, while replacing all other documents by their electronic equivalent.

Attention should also be paid whenever documents are scanned in different places (e.g. clinical sites), because a centralised QC would involve paper records to be sent for comparison.

Efficient Oversight and Control

EMA's reflection frequently highlights the sponsor's responsibility with regard to oversight and control. When using paper TMFs, gaining oversight and ensuring control can be difficult, because it requires physical access and deals with large amounts of documents. The reflection paper requires regular checks of documents on a sampling basis. Such subsets of documents are checked according to validated procedures, with defined acceptable error rates and escalation procedures. A risk-based approach is encouraged. With regard to the TMF, such risks could be missing or inaccurate documents. An electronic TMF offers an important advantage, because its document database can be queried in many ways, e.g. to identify incomplete sections, missed timelines, or wrong file formats. Automated checks increase efficiency of control, because the effort can be focused on pre-selected patterns indicating deviations. Two examples illustrate the use of automated checks (Figure 4):

1. Within an electronic TMF, the number of documents in each folder or section can easily be retrieved. Depending on trial progress, specific TMF sections are expected to contain documents (e.g. after EC approval). If they do not contain any document, this might indicate that documents are either missing or being filed incorrectly. Within an electronic TMF, such empty sections can be retrieved easily.
2. Each document change can be found in the document's audit trail. If no documents have been

changed within a certain period of time this might indicate that the TMF's contemporariness cannot be ensured.

TMF Status

	Site	Documents		Last update	
G	General TMF	406		14.01.2015	
S	Site TMF	9		23.05.2015	

Table

▼ Table   Pdf

Figure 2 Top level summary of TMF status indicating deviations in currentness and completeness.

With common reporting and alerting tools, sponsors are able to establish automated processes, which incorporate documented alerting levels and notification schemes. Applying such automated techniques also documents the sponsor's effort to conduct replicable checks, which in turn should increase the inspector's confidence in accuracy and completeness.

Sponsor oversight also benefits from the aforementioned reporting techniques. For example, the number of documents per section can be used to track the CRO's effort in maintaining the TMF.

Of course, these automated tools are useful to efficiently pre-select documents and sections to be checked. They do not supersede a document quality control process. An eTMF system should therefore support automated reporting as well as documentation of quality control (Figure 2).

QC Summary

Result	Last update	Signed by
Rejected	13.01.15 12:01	kking
Reviewed	19.01.15 10:48	kking
Approved		

Figure 3 Summary of QC results for a document. The document has been rejected first; a new version has been reviewed, but not approved yet.

Ensuring Inspection-readiness
It is the sponsor's responsibility to ensure TMF contemporariness, which includes completeness and accuracy. In routine use, the most common problem is documents not being filed in time. Of course, this applies to paper TMFs as well as to electronic TMFs. Based on many years of audit experience, we can say that it is likely to be impossible to keep a paper TMF inspection-ready within multinational studies. It would cost too much manpower, as well as too much money and time, to merge the documents of different locations in such a

timely manner to fulfil this requirement.

When using electronic TMFs, inspection-readiness can be supported by applying two simple measures:

1. Automatically checking the eTMF for file changes can assist in identifying situations where documents are not uploaded in time.
2. Providing users with visual feedback (e.g. highlighting with red text colour) for documents that are not filed yet.

Both measures require timelines for submission and for filing to be defined; preferably a TMF filing SOP contains timelines as well as steps for control (Figure 3).

Besides TMF contemporariness, the reflection paper highlights the inspector's expectation towards system access: Access has to be provided within reasonable time, which applies to all sections, even if these are archived or if they are stored off-site (e.g. investigator TMF). Gaining instant and/or remote access is one of an eTMF's key benefits. Therefore, inspectors expect to receive immediate access to the entire TMF.

Archiving an eTMF
TMF contents need to be retained for up to 30 years. For paper TMFs, such retention periods usually involve high storage costs. For electronic TMFs this raises two important challenges:

1. Compatibility issues: Contents can only be accessed if software tools are available to read the corresponding file format.
2. Storage media lifespan: Common digital storage media (e.g. CDs, DVDs) tend to fail after 10-20 years; or the storage technology becomes obsolete.

Dealing with these challenges is a common problem in all areas where electronic records require long-term storage. EMA's reflection paper also addresses these challenges but lacks specific recommendations with regard to file formats, software tools etc.

File formats for long-time storage are usually chosen to be non-compressed and/or human-readable (for improved robustness), non-proprietary (to avoid dependency from certain vendors), and standardised. Usually PDF/A is chosen for documents, TIFF or PNG for images. Common office file formats like doc/docx (Microsoft Word® documents) or xls/xlsx (Microsoft Excel® spreadsheets) are proprietary, therefore not promising to be readable in 30 years. For e-mail correspondence, the reflection paper suggests the use of so-called PST files. The authors of this article do not share this recommendation, because PST files are proprietary and can easily be corrupted. A standardised export to PDF/A preserving relevant metadata (e.g. e-mail address and timestamp) should be considered.
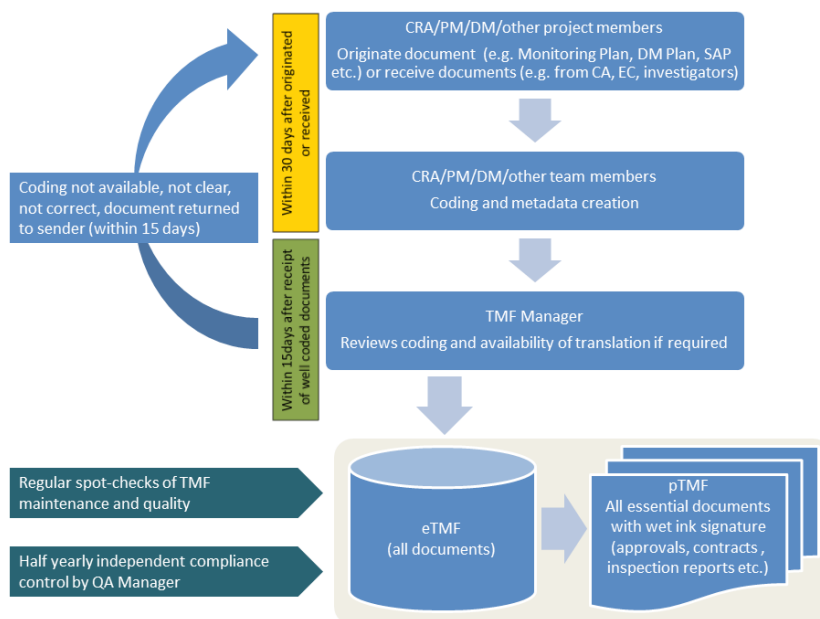
Figure 4 Example of an eTMF management process using a hybrid approach

Meeting these requirements is inevitable for an eTMF system, but these are quite common and well covered by previous standards and regulations.

Transforming paper records to electronic records for long-time storage remains a key challenge, where we will still find much uncertainty. Currently, hybrid approaches as well as additional control effort should be a reasonable answer to this uncertainty. In any case, profound technical knowledge is needed to choose appropriate formats and technologies.

In defiance of these uncertainties and challenges, an electronic TMF offers a level of accessibility and oversight we cannot expect from a paper TMF. The obvious gain in efficiency by automated TMF reporting tools makes an electronic TMF a valuable option for large, medium and small organisations. It will enable the trial team to focus on what really affects TMF completeness and accuracy.

Compatibility issues also arise from the underlying base technologies, e.g. database systems. With database systems becoming unusable, important TMF metadata will also be lost. Therefore, archiving of databases to appropriate formats like XML has to be considered.

The storage media lifespan can be overcome by migrating TMF contents to another storage medium. This involves checking for authenticity, in order to provide evidence that the migration strategy does not alter any TMF contents.

Conclusion

EMA's reflection paper provides the key requirements as well as the underlying concepts and expectations. It clearly expresses the inspectors' expectation to obtain confidence in TMF completeness and accuracy. It highlights the well-known sponsor responsibility. And it addresses various questions regarding accessibility throughout retention periods of up to 30 years. Paper TMFs have been used for many years and they do not involve any compatibility issues. But in times of digital business processes (e.g. e-mail correspondence), one might wonder if a paper copy of these accurately and reliably reflects the process.

Every sponsor being responsible for a paper TMF will agree that meeting the reflection paper's requirements will require an effort most sponsors cannot expend. An electronic TMF offers evident benefits: It can be accessed remotely from global teams, and it reduces storage and transportation requirements drastically. Of course, this transformation reminds us of the change from paper CRFs to electronic CRFs. Sponsors, CROs and system vendors already active in the e-CRF field will be aware of the specific validation and security requirements.

Andreas Grund (MSc, PhD) has worked since 1997 in the clinical research area. He worked in different positions in the areas of clinical monitoring, quality assurance, project management and training. In 2004 the CRO "GCP-Service International" was founded by Andreas Grund in Bremen (Germany). He developed a critical view for inefficient processes in clinical studies, which is why he invented in 2009 an online-based quality risk management tool (QCTMS). Since 2013 he has been president of the Association of International CROs (AICROS).
Email: agrund@gcp-service.com

Jörg Mielebacher (PhD) has studied medical informatics and has worked in this field for more than 15 years. He is an experienced IT consultant and software specialist, with a specific focus on automated analysis of processes in clinical research. He is founder and CEO of PCQ Pilots in Bremen (Germany), a vendor of various software solutions for clinical research, including e-CRF, e-TMF, risk management, randomisation, and training.
Email: joerg.mielebacher@pcq-pilots.com