# MHRA's GCP Findings: It's About Oversight

Author: Michael Smyth, Division President and Corporate VP,
Life Sciences Solutions at TransPerfect

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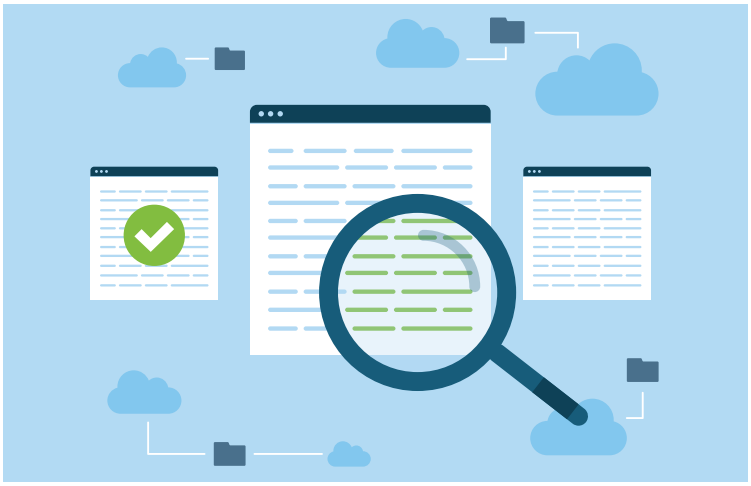
A well-managed eTMF saves time, money, and reduces risk. As a life sciences company, reducing clinical trial costs while accelerating processes and eliminating inspection findings is music to the ears! All of these benefits are at the fingertips of life sciences organizations, but they are elusive without the proper processes and oversight. Due to perceived operational costs, smaller companies can be hesitant to adopt an eTMF, or to surround their chosen eTMF platform with the processes and oversight necessary to truly see the full return on investment where significant "soft costs" disappear.

Part of putting the necessary eTMF processes and oversight in place and reducing the pain of inspection findings is understanding what regulators are thinking when they inspect your eTMF. The MHRA's GCP Inspections Metrics Report for April 2016–March 2017 provides a window into companies that learned their lessons the hard way. The report covers overall findings, but in this paper we will hone in on the critical findings around the TMF and recording/keeping of essential documents.

There is nothing to suggest that the companies whose findings show up in this report are specifically underperforming organizations. In fact, it is probably safe to assume they are all pretty well-oiled machines filled with consummate professionals. However, people, and the companies that employ them, have their limitations. These assumptions—combined with the findings in the report—should serve as a wake-up call. Companies cannot "technology" their way out of proper eTMF management. Each finding is an obstacle to getting a therapy approved. The associated expenses cascade and the upfront expenses that seemed burdensome before the study commenced become diminutive by comparison.

Now, let's review the findings and lessons learned from the report. We hope these insights help to appreciate the criticality of the TMF in the oversight of a development program.



## SPONSORS WITH PAPER TMF FROM FINDINGS

- *"...the TMF did not contain all the essential documents required to enable the reconstruction of trial events and demonstrate compliance with the regulations and the organization's own quality system. Several essential documents were retained within different electronic systems which were not defined to be part of the TMF and to which inspectors were not provided direct access (even with a guide user)."*
- *"...the TMF maintenance had been contracted out to a third-party contractor; there was limited information available in the organization's own files to demonstrate effective oversight of clinical trial activities to fulfill its obligations as a sponsor."*

## LESSONS LEARNED:

1. **Use a Single System:** Ideally, sponsors adopt a single system to maintain their TMF. If a sponsor is going to use multiple systems, both paper and electronic, define the systems and the hierarchy of where documentation will be maintained.
2. **Give Regulators Easy Access:** Assume the regulatory authorities are going to need access to all systems (disparate or centralized) to see TMF documentation. It is the sponsor's obligation and burden of proof to show the required documentation. Regulatory authorities should need limited training in order to navigate the electronic systems. While obviously not as instinctive as the user access experience on Amazon, Google, or Facebook that do not require any training, regulators expect the systems to provide an intuitive review process.
3. **Use Available Subject-Matter Experts:** Choose vendors who will challenge and educate you on how to maintain inspection readiness and regulatory compliance. Not because your team is not knowledgeable, but because SMEs have the experience guiding these processes at scale across many companies and studies. You are paying for their perspective—take advantage of it!

## SPONSOR RECORD KEEPING/ ESSENTIAL DOCUMENTS FROM FINDINGS

- *"...the Trial Master File (TMF) had a number of issues with finding and accessing documents in the eTMF, as evidenced below."*
- *"...inspector requested documents that could not be located in the eTMF. Despite assistance of the study team and the eTMF experts, not all these documents could be found over the 4-day inspection, and those that were took two days to locate."*

- *"...many documents missing from the eTMF, for example signature sheets, correspondence, emails, and previous versions of documents."*
- *"...eTMF was incomplete and unreliable with incomplete emails, duplicated documents, blank/incomplete documents, the same name for many different documents, same document under different names in different locations, and missing documents."*
- *"...eTMF management SOP required that there be monthly QC of all eTMFs at a study level, but this did not occur."*
- *"...audit trails for all 5 eTMFs reviewed during the inspection showed there was a large number of documents uploaded following the inspection notice prior to the inspection showing the eTMFs were not being updated regularly and therefore were not being kept in an inspection ready state."*

# LESSONS LEARNED:

1. **Address QC in Your SOPs and eTMF Plans:** First and foremost, follow your SOPs. Second, have a TMF plan, and third, **make sure all staff knows it and sticks to it.** The discovery that monthly QC of the eTMF was missed either means:

   **A)** An SOP was perhaps too specific of the general process and it should have been more broadly defined, or

   **B)** The QC frequency needed to be defined within the study-specific TMF plan.

   Hopefully, the sponsor has since adjusted its SOPs/plan templates to reflect better documentation processes and is training staff to comply.

2. **Strive for Real-Time Inspection Readiness:** Since the eTMF summits started six years ago, practically each one has featured sponsors presenting studies where real-time inspection readiness is not maintained. Many have presented the situation shown in the findings, where notice of an inspection causes a flurry of activity from team members to get all documents into the eTMF. While some assert that the eTMF provides *too much information* to regulators (such as when documents were uploaded), we would argue that this is *exactly the point*.

   The eTMF allows for real-time updates, whereas the old method—when all updates were made through passing paper—took a lot longer. 20 years ago, TMFs were treated more passively, but now we've realized the value of having one true real-time source accessible to all team members.

   The ability to maintain real-time inspection readiness translates to such gains in risk reduction—and returns on time and effort—that criticizing certain data as too much information is a very arbitrary concern by comparison.

3. **Capture Study Correspondence in Real Time:** The bane of every company's existence is getting correspondence into the eTMF. It is not a surprise that correspondence came up missing in these findings. Most companies maintain their correspondence outside of the eTMF, in places like shared Outlook folders or external cloud-based drives. This external storage means they have to get this information into the eTMF at the end of the study in PST or other unreadable formats. It also should not be a surprise that regulators don't like this at all. To make this more complicated, correspondence is often stored in those external locations without review for relevance to the study. You want to show correspondence on topics like subject waivers and protocol deviations, but you also see an irrelevant correspondence about the closest hotel for a CRA visiting a site. It is possible to get correspondence into the eTMF on a real-time basis **in a readable format,** and companies that do so will dramatically reduce the opportunity for related findings.



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info@trialinteractive.com

4. **Automatically Address Duplicate and Naming Issues:** Use a system that automatically checks for and deduplicates documents during the QC process. Pick an eTMF that provides auto-naming for relevant documents to avoid the situation listed above, where there are instances of the same document saved under different names.

5. **Make Locating Documents Easy:** Regulatory authorities and other study personnel need to be able to get what they need immediately. Days-long delays trying to locate the correct documentation does not benefit anyone involved in the process. Make it easy for regulatory authorities to find required documents by using a system that offers robust search (with save and share capability) and easy-to-use filtering.

# CRO RECORD KEEPING/ ESSENTIAL DOCUMENTS FROM FINDINGS

- *"The Trial Master File (TMF) presented for inspection did not meet the requirements of the legislation for it being the basis of the inspection, readily available, directly accessible and complete, to the extent that the TMF impeded inspectors from assessing GCP and legislative compliance. The inspection was extended as it required the Inspectors to return after four months to enable review of clinical trial compliance. In the interim period, the CRO were required to undertake significant work to ensure the three selected TMFs were complete for inspection. It took them full four months to ensure the completeness of the three selected TMFs. Over 3,000 documents had been created/uploaded into one of the trial TMFs and over 5,000 documents had been uploaded in to another of the selected TMFs. Although this ensured that the selected TMFs could be inspected during the extended part of the inspection the following issues were required to be assessed across trials and a robust CAPA plan was implemented:*
  - *It was not clearly defined in agreements with the trial Sponsors the scope of the Trial Master File (TMF) that was required to be held by the CRO i.e. the whole TMF or parts of the TMF in relation to the activities delegated to the CRO.*
  - *The TMFs selected for inspection were found to be significantly incomplete, to such an extent that the trial conduct could not be reconstructed, and the inspection had to be extended. This was found to be a systematic issue, with the eTMF being considered and used as a final document repository rather than a contemporaneous system used to manage the trial.*
  - *The eTMF lacked essential functionality.*
  - *The TMFs had not been maintained to a sufficient standard and therefore issues were found with the accuracy and reliability of the TMFs. For example, documents being named incorrectly, misfiling, duplication, etc."*

# LESSONS LEARNED:

1. **Check Your CRO's TMF Practices:** When selecting a CRO, sponsors need to do their due diligence on their CRO's TMF and eTMF practices. It is a critical piece in clinical trial management oversight. The CRO evaluated here did not have a handle on its TMF process, which led to a CAPA.

2. **Use a Time-Tested eTMF:** *"The eTMF lacked essential functionality."* What this likely means is the CRO tried to use a homegrown eTMF, a document sharing system, or a vendor system that was not adequate. While we do not know the specifics, there could be many possibilities—

such as the system violating 21 CFR Part 11, missing computer system validation requirements, or missing documentation. Lack of an audit trail would be essential functionality in order for the MHRA to verify activity in eTMF. Such lack of functionality would not occur with a properly vetted and time-tested e-clinical platform.

3. **Define Oversight Responsibilities in the TMF Plan:** In the findings above, there was no clear definition in the agreement and/or TMF Plan that made it known to the regulatory authorities how the TMF documentation was overseen between the sponsor and the CRO. Oversight should be well defined with any CRO or third-party provider so it's clear who is handling what documentation during the course of the study should that change, such as in the event of a company acquisition.

4. **Auto-Naming and Auto-Routing is Important:** Naming error appears again. This is likely due to the eTMF system not having a robust functionality to auto-name and auto-route documentation to the correct location and a lack of duplicate document detection.

5. **The Costs of Findings Outweigh Costs of Prevention:** With GCP compliance unverifiable in this finding, the product—if it was approvable—was likely delayed. Regulators had to return after four months to reevaluate. This finding must have been costly. The TMF reconciliation process with the CRO alone, considering other staff and vendors that may have been brought in to fix the TMF, would be responsible for considerable unnecessary expenses. That does not include the cost of each additional day product approval was delayed until the TMF could be verified. If we use the conservative $1M a day for each delay in product approval, this likely cost the sponsor well over $120M! Ouch!

# SPONSOR DATA MANAGEMENT

## ELECTRONIC PATIENT REPORTED OUTCOME (ePRO) DEVICES AND COMPUTER SYSTEM VALIDATION (CSV) ISSUES

## FROM FINDINGS

- *"...eDiary devices used by subjects did not have an audit trail to verify when entries were being made and by whom. While the data provided to the investigators contained a form "save time" this was not reflective of when data was actually entered and there was no way to verify who entered the data as username and login were not captured in the audit trail."*
- *"The portal used to manage DCFs did not have an audit trail, so if changes were made to a request after it was submitted by the investigator these could not be identified."*
- *"A critical finding was given to a niche service provider for Computer System Validation (CSV) due to lack of validation documentation of a key eCRF software release. There was insufficient documentation to be able to reconstruct the design, build, test, and release the version, and so it was therefore not possible to confirm that the software release was in a validated state currently and prior to its release. At the time of the inspection, the following key documentation was not available: final version of the user specification, final version of the design specification, the traceability matrix, complete set of populated test scripts, and re-test scripts to show all functionality had been tested and passed."*

# LESSONS LEARNED:

1. **Verify Your Vendor's Audit Trail:** While the above findings are not related to TMF or eTMF, they highlight a basic neglect by the sponsor in qualifying the vendor who provides the ePRO devices and software. It is important to verify the presence of an

audit trail. 21 CFR Part 11 was not adhered to in the development of the systems mentioned above, which should be a basic tenet of e-clinical software development and computer system validation.

2. **Be Sure Your Vendor is Experienced:** When choosing an e-clinical vendor, make sure they have significant experience navigating the regulatory landscape, and can back it up with documented SOPs, procedures, and a solid SDLC for their software and validation of that software.

# CONCLUSION

Process and technology innovation are critical to help life sciences companies bring products to market. Global regulations will and should continue to evolve to ensure standards are followed and products are safe and effective.

The findings in the MHRA report show that companies, for various reasons, are taking on unnecessary risk and cost in not adopting process and technology innovation that would keep them in compliance with and easily verifiable eTMF. Teams have different access to GCP experience. Often external expertise is necessary to educate on best practices and best solutions for running a cost- and risk-controlled program. In the end, the costs of regulatory findings vastly exceed the costs of getting it right from the start. Asking questions and challenging each other, our industry colleagues, and regulators is only going to raise the global standards, which is great for patients and the companies that develop truly life-changing products. We can all agree that avoiding findings that delay product approvals is a top priority, and most—if not all—findings in the report are avoidable if TMF management is approached correctly from the beginning.

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info@trialinteractive.com