Phone: +1 833 366 6887
Email: contact-us@ennov.com
Website: http://ennov.com

MHRA TMF Finding Inspection Checklist

Introduction

On February 12, 2021, The UK Medicines & Healthcare Products Regulatory Agency (MHRA) published their annual **GCP INSPECTIONS METRICS REPORT.** This report covered the period from 1 April 2018 to 31 March 2019.

The report provides excellent insight into MHRA's compliance concerns. In this edition, there were a number of detailed findings related to the Trial Master File.

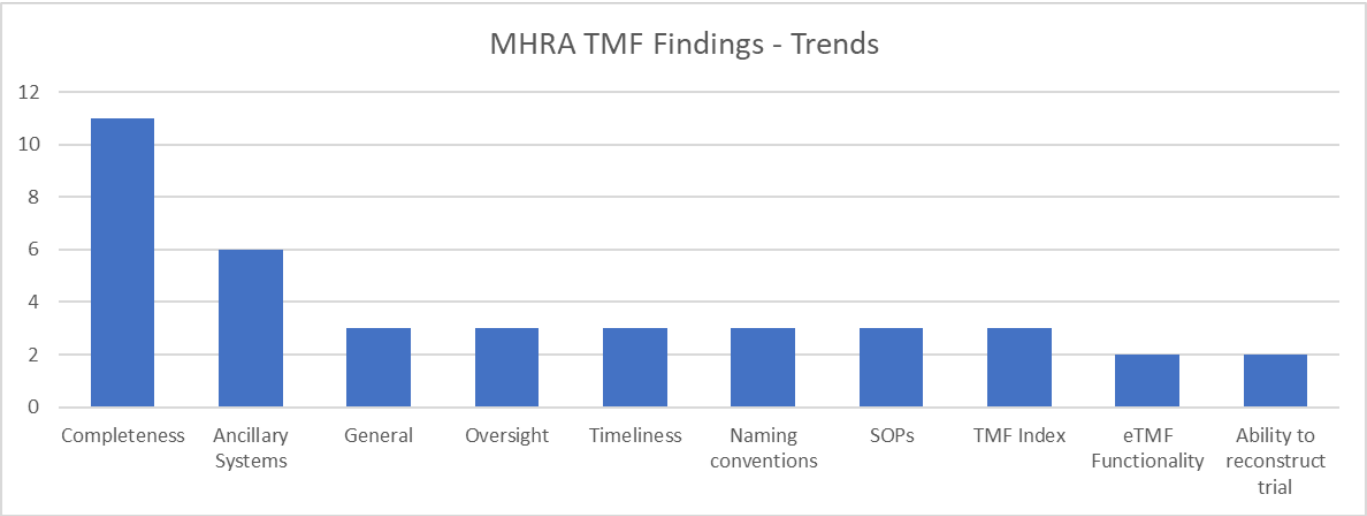
The report includes findings in three categories:

- Sponsor: 8 inspections, 4 with at least one critical finding, and 7 total critical findings. **2 of these were directly related to the Trial Master File**. For one sponsor, this was a major finding at the previous inspection of this organisation and was therefore escalated to a critical finding
- CRO: 11 inspections, 4 with at least one critical finding, and 6 total critical findings. **1 of these was directly related to the Trial Master File**.
- Non-Commercial Entity: 11 inspections, 2 with at least one critical finding, and 3 total critical findings. **1 of these was indirectly related to the Trial Master File**.

TMF-related observations were also common beyond critical findings. Although MHRA does not provide details, Record Keeping/Essential Documents was actually the most common area of findings, accounting for about 18% of all total findings for sponsor inspections.

Trends

The report contained a total of 33 individual observations related to eTMF. When the observations were categorized, a number of trends emerged, which are summarized below (showing only observations that occurred more than once).



Some important trends include:

- **TMF Completeness**. Numerous observations related to the completeness of the TMF. In some cases, completeness was lacking because the scope of the TMF did not include all essential documents, especially if not stored in the core eTMF. Other observations could be traced to failure to file required documents and lack of oversight in including completeness. TMF completeness issues are not new or suppressing, but show that some organizations are not taking action based on previous years' observations.
- **Ancillary Systems**. This area showed increased focus by MHRA. Observations included failure to define ancillary systems as containing TMF content, lack of control and oversight, and failure to define the system of record in TMF SOPs and indices. As a result, this area is tightly coupled. with completeness issues.
- **Naming Conventions**. Inspectors should be able to rely on consistent naming conventions to identify documents and understand their contents without having to open documents.

Recommended Review Actions

The table below catalogs each MHRA TMF-related observation and a set of review actions recommended to avoid such observations. Some of the actions are one-time actions, some are periodic, and some would be used pre-inspection. Because the MHRA had similar findings for multiple organizations, a given action may appear multiple times.

The TMF Reference Model has published several recourses that may be helpful in implementing review actions:

- Inspection Readiness RACI: RACI Toolkit to help prepare TMF for regulatory inspections (Approved 09-Nov-2016)
- Inspection Readiness Presentation: PowerPoint slides presented to group meeting January 9, 2017
- Inspection FAQs: Common inspection questions with answers, and regulatory resource list (Approved 15-Mar-2017)
- Date Conventions Guidance: Guidance notes to be used with Date Conventions columns (Approved 15-Feb-2017)

Finding	Categories	Recommended Review Actions
The TMFs presented to inspectors being incomplete or inaccurate, which resulted in an inability to reconstruct the trial or procedural conduct to enable the verification of GCP compliance.	Completeness, Accuracy, Ability to reconstruct trial	• Review how you define and monitor completeness • Review how document dates are assigned to TMF documents to assist in reconstructing the trial • Have a third party (internal or external) examine the TMF to determine if a trial can be reconstructed
Several documents being filed outside the core electronic TMF (eTMF). Whilst the TMF master list did state that these were filed across various locations, it did not index exact locations and direct access could not be provided to inspectors.	TMF Index, Ancillary Systems	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems, and indicates the system of record for all content • Review access procedures for ancillary systems, and whether your position is to allow direct access to inspectors hands-on or using an expert to guide access
A number of "Data" files were classified as non-essential and filed outside the eTMF, this included SAE data listings. Such data files, however, were essential for demonstrating key safety processes and sponsor oversight and thus should have been held in the eTMF.	Ancillary Systems	• Note: this appears to contradict previous MHRA guidance that live data files are best left in systems/locations allowing direct access and data manipulation. • Review your approach to indexing, storing and providing access to SAS datasets
Documents could not readily be located due to file naming conventions that had been applied.	Naming conventions	• Confirm that your naming conventions are clearly defined and applied • Review naming conventions to ensure that they allow viewers to understand the content of documents without having to open them • If possible, have your TMF software automatically apply defined naming conventions; do not allow users to change
There were several examples of documents/data not being uploaded in a timely manner. alongside evidence of the eTMF having been updated substantially just prior to the inspection.	Timeliness	• Ensure that a policy is in place for monitoring TMF timeliness • If possible, take advantage of eTMF reports and dashboards to automatically produce this information • Define what actions should be taken when TMF timeliness falls below defined thresholds
The Standard Operating Procedures (SOPs) that were supposed to detail the eTMF best practices for quality management did not define the TMF and how it should contain all trial essential documents. It also did not define all the different systems that make up the TMF.	SOPs	• Review your TMF SOP to ensure it is comprehensive • Ensure that the TMF SOP defines quality management practices • Ensure that the TMF SOP details all systems that contain TMF content
Essential documents were not defined in the SOP nor was there any clear policy and process to ensure the accurate completeness of the TMF contemporaneously.	SOPs, Timeliness, TMF Index, Completeness	• Ensure that the TMF SOP or a referenced document (TMF Index) includes your definition of essential documents and a list of essential documents • Ensure that the TMF SOP defines the process to ensure completeness and timeliness of the TMF

Finding	Categories	Recommended Review Actions
There were several functionality issues with the eTMF system. For example, the Library view relied on other software (Excel®) to sort and filter documents as per binder levels which was time consuming. The functionality within the system itself should aid inspection and document review, whereas this was a work around. In addition, there was no functionality to identify files not appearing in the binder view.	eTMF Functionality	• Have a third party (internal or external) exercise the navigation, sorting and filtering capabilities of the eTMF to ensure it is fit for purpose • Review your eTMF validation materials to ensure validation was adequate and performed against a User Requirements Specification • Test to confirm that any folder, binder or filter views of the TMF contain all expected documents
The TMF did not meet the requirements of Regulation 31A which resulted in inspectors having to request a large number of documents in order to conduct the inspection as well as an additional office-based inspection.	General	• Have a third party (internal or external) confirm that they can locate documents given a number of scenarios (for example, "locate all protocol deviations for Trial X" or locate all principal investigator CVs filed in 2020 for Trial x").
The TMFs reviewed were incomplete to such an extent that they could not form the basis of inspection and therefore impeded/obstructed inspectors carrying out their duties in verifying compliance within the Regulations.	Completeness	• Ensure that the TMF SOP defines the process to ensure completeness of the TMF • Ensure that a policy is in place for monitoring TMF completeness • Define what actions should be taken when TMF completeness falls below defined thresholds
There was a failure to define the TMF within the quality system and there were several issues identified with procedures covering the TMF that resulted in the TMFs provided to inspectors being incomplete.	SOPs, Completeness, General	• Ensure your TMF SOP clearly defines the scope and content of the TMF and the core and ancillary systems used to manage it • Ensure that your documented procedures and work instructions adequately cover TMF activities • Ensure all users are trained on SOPs and work instructions. Consider refresher training • Define a process for monitoring the effectiveness of procedures, work instructions and training
For some trials, ancillary systems that contained essential trial documents had not been defined to be part of the TMF and were not subject to the same controls as a TMF.	Ancillary Systems	• Ensure your TMF SOP clearly defines the scope and content of the TMF and the core and ancillary systems used to manage it • Review the compliance of ancillary systems with user requirements, GCP, 21 CFR Part 11 and Annex 11 • Review the validation status of ancillary systems
One trial had a paper TMF defined, yet all documents required to reconstruct trial activities and compliance with the quality system were not filed in this paper TMF but rather kept in alternative electronic systems/locations.	Completeness	• If you have a paper TMF as a system of record, review procedures for ensuring that all required content is filed • Discourage use of a "Shadow TMF". If you must use this construct to provide availability to remove users, clearly define how the paper TMF and electronic backup will be synchronized, and how you will ensure that synchronization is up-to-date and reliable.

Finding	Categories	Recommended Review Actions
The paper TMF was used as a document archive rather than a working TMF and trial team members did not have access to the paper TMF, but instead used an electronic "shadow TMF" during the trial. Upon review, it was found that there were a large number of documents in the "shadow TMF" which were not filed in the paper TMF.	Shadow TMF	• Discourage use of a "Shadow TMF". If you must use this construct to provide availability to remove users, clearly define how the paper TMF and electronic backup will be synchronized, and how you will ensure that synchronization is up-to-date and reliable.
There were a number of essential documents for a trial retained by vendors which were not defined in the TMF plan or TMF index.	Ancillary Systems	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems • If content is stored in vendor systems, clearly define how it will be transferred and archived at the end of a trial, and how it will be accessed during an inspection of an ongoing trial
The TMF index for a trial was at an artefact level and the quality system did not address an overview all the systems holding essential documents.	TMF Index	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems, and indicates the system of record for all content
There was a lack of effective oversight QC of an eTMF by the sponsor.	QC, Oversight	• Review your oversight framework: when are reviews conducted, by whom, what are the review criteria and how are reviews documented (including what activities occurred and any resulting findings) • Perform a comprehensive review of oversight findings across multiple reviews, looking for patterns and deficiencies • Review document QC practices (prior to finalizing documents) to ensure they are effective and make best use of limited resources.
Several issues were identified with the eTMF including examples of missing, misfiled, misnamed and duplicated documents.	Completeness, Naming Conventions, Duplicates	• Confirm that your naming conventions are clearly defined and applied • Review naming conventions to ensure that they allow viewers to understand the content of documents without having to open them • If possible, have your TMF software automatically apply defined naming conventions; do not allow users to change • Review how you identify duplicate documents. Is this done by your eTMF software? Does it identify literal duplicates (content exactly the same) or potential duplicates (documents not identical doing to being scanned multiple times, but identical metadata)? How are duplicates addressed?
The CRO's eTMF provided for review by the inspectors did not contain all the essential documents required to enable the reconstruction of trial events. Additionally, the eTMF failed to demonstrate compliance with the regulations and the CRO's quality system.	Completeness, Compliance Ability to reconstruct trial	• Review the compliance of systems with user requirements, GCP, 21 CFR Part 11 and Annex 11 • Have a third party (internal or external) examine the TMF to determine if a trial can be reconstructed

Finding	Categories	Recommended Review Actions
A number of essential documents were retained within different electronic systems which were not defined to be part of the TMF.	Ancillary Systems	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems
The eTMF provided did not meet the definition of a TMF as per regulation 31A (1-3) and could not form the basis for inspection.	General	• This would require a very comprehensive review of the eTMF
The TMF content was not defined in the QMS including all systems, locations and documents that comprised the TMF for the selected trials. As a result, there was a lack of control of documents across various sections of the TMF.	Ancillary Systems, TMF Index	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems
The eTMF system lacked essential functionality to enable inspection of the trials to such an extent that it impeded the review of process documentation (thereby increasing document requests) to be able to verify compliance with regulations.	eTMF Functionality	• Have a third party (internal or external) exercise the navigation, sorting and filtering capabilities of the eTMF to ensure it is fit for purpose • Review your eTMF validation materials to ensure validation was adequate and performed against a User Requirements Specification
There were inconsistencies with naming conventions of documents in the eTMF which made it difficult to identify particular documents/ groups of documents. Additionally, document descriptions were not reflective of the contents and thus documents had to be opened to identify what they were.	Naming conventions	• Confirm that your naming conventions are clearly defined and applied • Review naming conventions to ensure that they allow viewers to understand the content of documents without having to open them • If possible, have your TMF software automatically apply defined naming conventions; do not allow users to change
The TMF for a selected trial was incomplete to such an extent that key trial processes could not be reconstructed from the available documentation.	Completeness	• Review how you define and monitor completeness • Review how document dates are assigned to TMF documents to assist in reconstructing the trial • Have a third party (internal or external) examine the TMF to determine if a trial can be reconstructed
There were examples of documents not being added to the eTMF in a timely manner.	Timeliness	• Ensure that a policy is in place for monitoring TMF timeliness • If possible, take advantage of eTMF reports and dashboards to automatically produce this information • Define what actions should be taken when TMF timeliness falls below defined thresholds
The eTMF system audit trial was extremely limited and could not be used for the review of TMF completeness over time.	Audit Trail	• Review the eTMF audit trail against the requirements of 21 CFR Part 11 and Annex 11; define a remediation strategy if issues are identified

Finding	Categories	Recommended Review Actions
There was no clear audit programme in place or periodic review of the eTMF system audit trial to demonstrate oversight and quality assurance of completeness and accuracy of the TMF systems in place.	Oversight	• Ensure you have a procedure defined for review of the audit trail including how often reviewed or triggering events, who is responsible, and review criteria
The Master Randomisation List and Patient Randomisation List were present in the TMF and could be accessed by anyone that had access to the TMF including blinded trial team members.	Completeness, Unblinding	• If unblinded content is stored in the eTMF, ensure that the security model protects the blind • If unblinded content cannot be stored in the TMF until the blind is lifted, confirm that a secure alternate location is defined and a procedure exists for uploading unblinded content to the eTMF after the blind is lifted
There was no information or procedure within the TMF that described how allocation of patients would be managed to ensure that allocation was balanced or not required between different groups.	Completeness	• Review your TMF index to ensure it covers all TMF content, whether stored in the core eTMF or in ancillary (including vendor) systems, and indicates the system of record for all content
The Master Randomisation List within the TMF was not version controlled or marked in any way to indicate provenance and approval status.	Version Control	• Ensure that all content is identified by version (if versioned, status, and document date
No Interim analysis had been pre-defined in the previous version of the trial protocol and no statistical analysis Plan was available in the TMF to describe how the data would be analysed and reported.	Completeness	• Review your TMF index to ensure it covers all TMF content required by Health Authorities or needed to reconstruct the trial and ensure the safety of human subjects
There was insufficient documentation within the trials TMF and associated Research and Innovation files with the participation of the investigator site to ensure that the trial was conducted appropriately.	Oversight	• Review your TMF index to ensure it covers all TMF content required by Health Authorities or needed to reconstruct the trial and ensure the safety of human subjects