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TMF Questions & Answers
At ExL Events 7th TMF Summit, London, UK
October 2018

Published on 07-Nov-2018
Revised on 17-Dec-2018

<u>NOTE: THE COMMENTS MADE BY THE INSPECTOR ARE THE INSPECTORS OPINIONS AT THE TIME OF CONFERENCE TO ASSIST CONFERENCE DELEGATES AND SHOULD NOT BE INTERPRETED AS FORMAL GUIDANCE FROM MHRA OR EMA.</u>

Published on 07-Nov-2018
Revised on 17-Dec-2018

General

1. In your opinion, which eTMF system have you found to be the easiest or most user friendly to navigate?

Expectations were presented around what Inspectors like in terms of user friendliness in an eTMF, and comparing that to what they used to do be able to do in paper in the past: tag documents, sort in date order, see documents in folders in the system (binder view), structured index, able to print, able to compare documents. There are many systems and companies need to evaluate to fit their requirements so not going to recommend or endorse a system.

2. How should training for inspectors be approached and tracked across systems, across companies, etc. .?

Training should be as short as possible. Training and trying to access multiple systems takes too long, especially when access doesn't work. Training really needs to be minimized. Inspectors have used different systems; recommend that the eTMF vendors keep records of inspector training and then provide to the sponsors for subsequent inspections to prevent inspectors having to take the training again.

Audit trails

3. Can you state your requirements for eTMF audit trails? What is mandatory?

Think of audit trails from a data integrity focus – ask yourself two questions: do you have all data from all electronic systems and do you review the data on a risk based approach? Viewing the audit trails can give you information about compliance to GCP. May depend on the functionality of your eTMF. Could be workflow actions, who has accessed, when and what they looked at, did they delete anything (as the legislation states that any alteration shall be traceable [after archiving])? All of this could be looked at to determine timeliness of uploads. How do you confirm compliance e.g. for an eCRF does the system show that database lock actually happened on the day reported in the paperwork? Audit trail of eTMF is not as high priority of review vs. eCRF, ePRO, PV systems where subject data is collected.

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4. What do you look for in an audit trail?

Sometimes it's not an audit trail but an actual report is the best way to view this information from the eTMF (e.g. document finalization). Inspectors do not want a flat file, wants the data, with ability to produces graphs, etc.   Electronic systems give these benefits. Inspectors like the data and like to analyse the data themselves.

5. Would you expect people to be checking audit trails to ensure that things are working as they should?

Validation of the system will prove things are working as they should. Audit trail review for data integrity focus should be part of oversight.

6. Moving a TMF from one place to another, audit trail sent in Excel and immutable.   Is that ok?

Need to consider archiving for 25 years but analyzing a PDF format is problematic for review. Using an electronic system has benefit and having its audit trail come as dataset, a dynamic file type is advantageous. MHRA currently requests datasets in Excel®.

7. Where to keep the audit trails if you import them?

TMF is defined by a lot of different systems. So if you have a massive dataset you have to look at what is the best system to store in, you need to define that for yourself and just ensure that you are able to find them. Sponsors should receive the audit trail back with the eTMF from the vendor.

8. Audit trails and what data to get back. Working with IRT and EDC vendor. What do you expect those vendors to give to sponsors at the end of day?

 MHRA have looked at about 15 eVendors and majority had major findings for essential documents (contracts).   Some vendors do not think they have to comply with GCP (it is the sponsor's responsibility) and do not know that they have TMF content or what essential docs are. What you get back at end as deliverables are mostly top-level validation documents and likely not everything.   What is the long term access to where their software validation documents are maintained, including testing records. They expect sponsor to arrange to have long-term access to these records. Help desk tickets are also looked at when inspecting these vendors. Sponsors should request the ongoing help desk

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tickets or long term access to the help desk tickets. You need to define everything that the vendor has generated, and who will maintain/archive it.

9. UAT and test scripts created by vendor.

Sponsor should be testing requirements for the trial and executing UAT scripts – looking at failures and how they are fixed. Vendors should have an oversight approach to the sponsor's UAT.

In summary, Inspectors would like to see audit trails in an analyzable format of all systems being used, with good contractual records on how to access to essential documents: help desk tickets, UAT, validation etc.

Certified copies

10. When is a Certified Copy needed?

Certified copy requirements have evolved in the current guidance. A certified copy is not required if the original paper is kept. The current EMA guidance in draft clarifies that if an original document exists elsewhere e.g. in the ISF and a copy is needed in e.g. the Sponsor File, this copy does not need to be certified as the original still exists.

11. Can you destroy paper if a certified copy has been created?

A certified copy can replace an original paper which can then be destroyed. If the original has not been destroyed, the MHRA may ask why. If you certify copies and then don't destroy the originals, are you confident you have a certified copy because what is rationale for keeping the paper? Not necessarily a finding, but would need explanation on why you would still be keeping the paper originals. Inspectors may want to look at the paper.

12. If you certify copies and put in eTMF, but then find a page missing, and original was thrown away - is that a finding?

Possibly. Inspectors would look to see if this is indicative of bigger problem and what is impact. This may involve the sponsor undertaking an impact assessment. If issue(s) is known, it is best to share issues with eTMF up front and have a discussion about any CAPA rather than letting inspectors find it

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and spending time on finding it and gathering/documenting evidence. At some inspections the sponsor revealed their knowledge/CAPA relating to TMF issues late in the inspection.

13. What is a certified scan process?

Process should be validated, with a level of ongoing QC to confirm the process and those doing the process must be trained. There is no need to sign and date a certified copy if a validated process was followed. It is up to each organization to decide what the process will be.

Draft documents

14. Are drafts required in the TMF?

If drafts are the only way to demonstrate that the organization has followed an SOP process, then a draft may be required in the TMF. However, the ability to demonstrate that an SOP process is followed may be possible in a different way. This may be more important for the main trial documents. If a company has kept draft documents, the MHRA have the right to see these documents, even if the draft documents are not kept in the defined TMF.

15. If draft documents are not accessible and final documents are not present, would your concern be no access to the drafts or that the final documents are missing?

In terms of keeping draft documents, it has been proven to find issues, example of Statistical Plan and data reviewed being changed, so we could ask to see the drafts. If there are final documents that exist and not part of the defined TMF then that would likely to be a finding relating to an incomplete TMF.

16. Drafts and working copies are stored somewhere else. If we offered within eTMF should we offer through an audit trail?

If you have drafts and then don't offer them to be seen, then the MHRA may ask for them. Drafts should be viewable in the system if they are in it. Example seen where documents that had been issued to sites (therefore finalized) (e.g. CRF completion guidelines and other data management documents) were maintained in draft format until trial end in the eTMF and not visible to the inspector. Once access to read/view draft documents was granted, many issued documents were available in the TMF. If draft documents are retained by the sponsor (see Q14) then view of these could be seen via audit trail for HISTORY, but the current draft should be viewable in the TMF.

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Process

17. If a document has been signed and then needs to be corrected how would you expect it to be done?

eSignature would need to be invalidated if document changes. PDF of the corrected wet ink signed document using a validated process and upload into the eTMF.

18. Have a document that is filed electronically and signature page is wet ink, is that ok?

Yes. The wet ink Signature page scan filed alongside the document, i.e. can be seen as one complete document as the signature page references the main document.

TMF study index

19. Should the TMF Index be 'live' and constantly updated? Do you expect it to be up versioned for every change?

MHRA does not need to see detailed index initially as this is more of a tracking tool: just a topline index of where all of the documents are for the TMF and which systems are used. Tracking every document is more of a tracking tool and quite big and a live document. Define in quality management system the systems that comprise the TMF and the type of documents in them at top level. The tracking tool may be accessed to identify the location of specific documents.

It is acceptable to see documents in different systems. Recommend to maximize the documents in the primary TMF, but if you cannot keep a document there then you need to ensure the alternative system that the document is in meets all requirements for access as well as long term archiving.

Emails

20. Can emails be kept in Outlook® and not in eTMF? How can it be used? Outlook® is not validated.

Emails are important for reconstructing the story of a clinical trial. Emails are hard to review if saved as PDF and uploaded to eTMF, as sometimes the PDFs are not searchable.

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It is easier to review emails in the email software though there have been some software on discs that can allow searching. Outlook® is stated in this question. You could keep emails as PST files so that the emails can be reinstated into the email software. Outlook® is good for searching with key words. Correspondence is usually essential to reconstruct the trial story so you need to have processes to make emails available and preferably not in one large non-searchable file dump. In response to question about the features of Outlook that are helpful for building functionality in eTMF systems, searching for words in title or subject or text of emails themselves and able to quickly search are used by inspectors.

It is fine to have emails in the email software whilst the trial is ongoing, but the organization needs to consider long term storage after the trial is completed.

NOTE: This prompted lively discussion within the audience and the inability to preserve emails in a PST due to retention policies likely clearing out PST files periodically.

Miscellaneous

21.FDA, EMA, MHRA – are they all in alignment?

FDA not so aligned as it is the inspector's understanding that the USA legislation does not require TMF to be retained and that FDA inspectors currently do not the request the TMF. EMA and MHRA are aligned

FDA has shadowed MHRA inspectors and quite interested in what MHRA do and looking to develop joint inspections and do side by side inspections.

EMA Guidance – possibly available by end of 2018 (1st November stated at the conference was not met).

22.There is a guidance on eclinical systems being developed – will there be any system specifics around eTMF included ?

Current proposal is that that focus will be generic aspects for all types of e-systems in clinical trials, for example, electronic archiving, e-signatures, validation, certified copies etc… Then there will be

Published on 07-Nov-2018
Revised on 17-Dec-2018

sections on specific systems (IRT, ePRO, EDC). For the eTMF, this is likely to cross reference the separate TMF guidance.

23. MHRA blogs on inspection expectations.   Will anything be formalized?

Blogs used to communicate quickly and are popular and are there to potentially build future guidance.

24. How many systems are too many?

A reasonable number!   It depends.   Not 47 as was presented at one inspection. Recommend to place as many documents in the primary TMF system as possible and reduce the number of systems holding TMF documents. The protocol could be kept in a different system, as long as its location is defined.

25. Do you think there will come a time that people with paper will not be compliant.

No, nothing wrong with having a paper TMF. Should not feel compelled to move to eTMF especially for a single site study. Technology should not dictate changing the paper process.

Sponsor declaring it's an eTMF does not necessarily make it an eTMF. Needs to be a process and following the guidelines.

26. Do inspectors look for compliance to GDPR ?

MHRA does not inspect against the GDPR directly as this has separate UK authorities responsible.   If they see something that appears to be a breach of patient confidentiality, which may result in a GCP finding relating to the relevant GCP principle, then the inspectors can seek guidance from these authorities.

27. eISF and not allowing remote sponsor/CRO access?

Revision, per clarification from Andrew Fisher received on 11-Dec-2018:

Slides were based on the draft of the TMF guidance at that time. The Q&A question 27 answer is compatible and clarifies why remote access to such information would not be acceptable. The guidance since then has been subject to some revisions.   For remote access, the following is now stated:

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Revised on 17-Dec-2018

"Remote access by sponsor or CRO personnel to the investigator TMF should only be possible to the documents where personal data that enable the data subjects to be directly identified (i.e. direct identifiers of trial subjects) is not present or has been pseudonymised".