Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

eTMF – A Regulators Perspective

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Agenda

- EU Legislation and Guidance News/Updates relating to TMF
- Structure and Content of e/TMF
- Inspecting eTMFs
- GCP Findings for eTMFs
- Critical Grading update by MHRA

Access to the eTMF

Is it possible for inspectors to access, directly, with reasonable notice, the eTMF that is used by your employees?

a) Yes
b) No

Reference Documents

EU Clinical Trials Directive 2001/20/EC (relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)

EU GCP Directive: 2005/28/EC (laying down the principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisations of the manufacturing or importation of such products) into UK law.

REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Also **Delegated and Implementing Acts**

Reference Documents

Recommendation on the content of the trial master file and archiving July 2006, Volume 10, Chapter V

EMA/INS/GCP/636736/2012: Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials

EMA GCP INSPECTORS Questions and Answers

EU GCP Inspectors Working Group - Subgroup

NEW GUIDANCE
March 2016

Important note:
It has been decided that the revised version of the TMF document, based on the comments collected during the public consultation, will be incorporated into a guidance on TMF as part of the work related to the implementation of the new Clinical Trial Regulation (EU) 536/2014. **A public consultation on the new guidance will follow in due course**.

CPMP/ICH/135/95: “Note for Guidance on Good Clinical Practice” (ICH E6)

NEW ADDENDA

ICH E6 GCP Addenda

- All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification. **This principle applies to all records (paper or electronic) referenced in this guideline.**

- The sponsor and investigator/institution **should maintain a record of the location(s) of their respective essential documents.** The **storage system (irrespective of the media used) should provide for document identification, search and retrieval**.

- Depending on the activities being carried out, **individual trials may require additional documents not specifically mentioned in the essential document list. The sponsor and/or investigator/institution should include these as part of the trial master file.**

- When **a copy is used to replace an original document, the copy should fulfil the requirements for certified copies**. **Certified Copy -** A paper or electronic copy of the original record that has been verified (e.g. by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

- The **investigator/institution should have control of all essential documents and records generated by the investigator/institution** before, during and after the trial.

- The sponsor should ensure oversight of any trial-related duties and functions carried out on its behalf.

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Addendum_Step2.pdf

Why is a Trial Master File Needed?

Now….

The verification of compliance with the standards of good clinical practice requires data, information and documents to be inspected, which means the competent authority conducting an official review of documents and records. **[Directive 2001/20 EC]**

In the future…

'Inspection' means the act by a competent authority of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the clinical trial site, at the sponsor's and/or contract research organisation's facilities, or at other establishments which the competent authority sees fit to inspect. **[Regulation (EU) No 536/2014 (52)]**

Why is a Trial Master File Needed?

Now…

The **trial master file shall provide the basis** for the audit by the sponsor's independent auditor and **for the inspection** by the competent authority.

[**GCP Directive 2005/38/EC: Chapter 4 Article 16]**

In the future…

In order to be able **to demonstrate compliance with the protocol and with this Regulation**, **a clinical trial master file, containing relevant documentation to allow effective supervision** (monitoring by the sponsor and **inspection by Member States), should be kept by the sponsor and by the investigator**.

[Regulation (EU) No 536/2014 (52)]

The **sponsor and the investigator shall keep a clinical trial master file**…. **It shall be readily available, and directly accessible upon request, to the Member States.** The clinical trial master file kept by the investigator and that kept by the sponsor may have a different content if this is justified by the different nature of the responsibilities of the investigator and the sponsor.

[Regulation (EU) No 536/2014 Article 57]

Inspectors have a right of direct access to the TMF.

Regulatory requirements are the same (and have always been the same) for paper and electronic TMF

The Content of the TMF

Now…

…the **trial master file shall consist of essential documents**, which **enable both the conduct of a clinical trial and the quality of the data produced to be evaluated**. Those **documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice [GCP Directive 2005/38/EC: Chapter 4 Article 16]**

In the future…

….The **clinical trial master file shall at all times contain the essential documents relating to that clinical trial** which **allow verification of the conduct of a clinical trial and the quality of the data generated….**

[Regulation (EU) No 536/2014 Article 57]

The sponsor of a clinical trial and the investigator shall ensure that the clinical trial is conducted in accordance with the protocol and with the principles of good clinical practice.

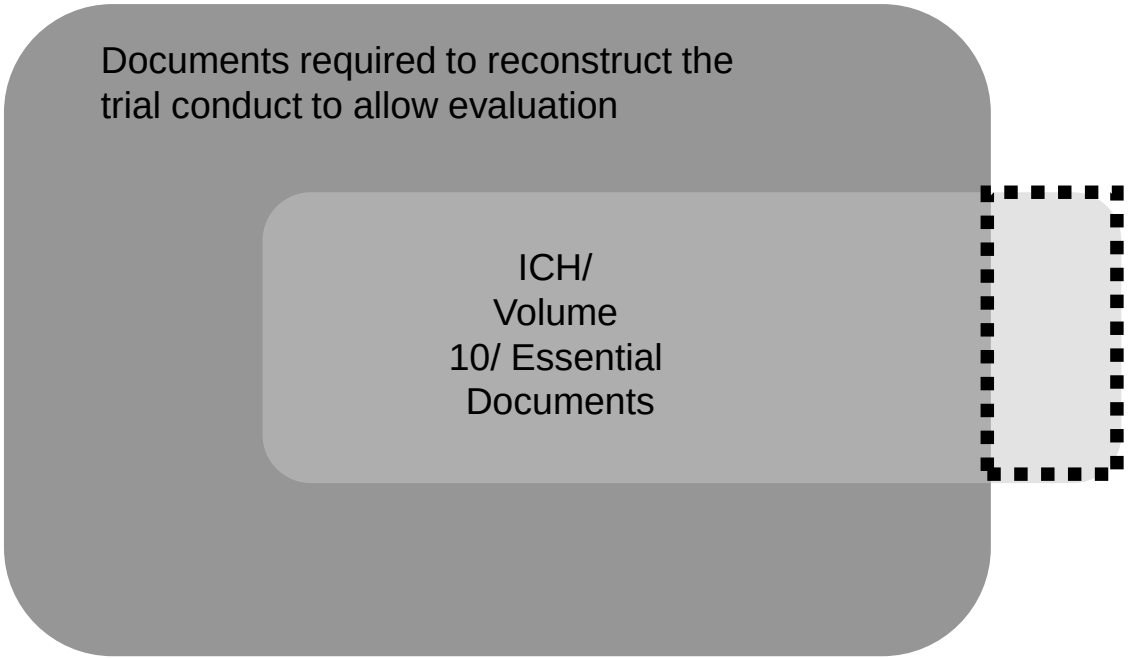
[Regulation (EU) No 536/2014 Article 47]

Essential Documents

Which one of these would you NOT regard as an essential document?

a) Set of standard operating procedures used for the trial
b) Code break envelopes
c) An email from an investigator asking to clarify an eligibility criterion
d) Annotated draft protocol following review by team member
e) Project team meeting minutes
f) Spreadsheet showing QC of statistical programming
g) Completed test scripts for testing the build of an eCRF or IWRS
h) Job descriptions of sponsor's staff involved in the trial
i) All of the above are essential documents

Essential Documents



▪▪▪▪▪▪▪▪▪▪▪▪ Documents not applicable or not required for the trial

ICH - International Conference for Harmonisation

Essential Documents for a trial cannot be completely identified from a published guidance checklist.

Maintenance of the TMF

EU Guidance (TMF_1, GCP_2) covers filing in a timely manner, indexing, use of electronic media etc.

Essentially, during the trial and afterwards, the TMF should be up to date or complete, well structured, date ordered, indexed and documents in it should be complete, signed and dated (where applicable) and legible.

1. Recommendation on the content of the trial master file and archiving July 2006
2. CPMP/ICH/135/95: “Note for Guidance on Good Clinical Practice” (ICH E6)

Maintenance of the TMF

Is your TMF?

a) All paper
b) One electronic system that contains all the trial essential documents
c) Several electronic systems that between them contain all the trial essential documents
d) A mixture of paper and at least one electronic system that between them contain all the trial essential documents
e) Don’t know

Maintenance of the Trial Master File

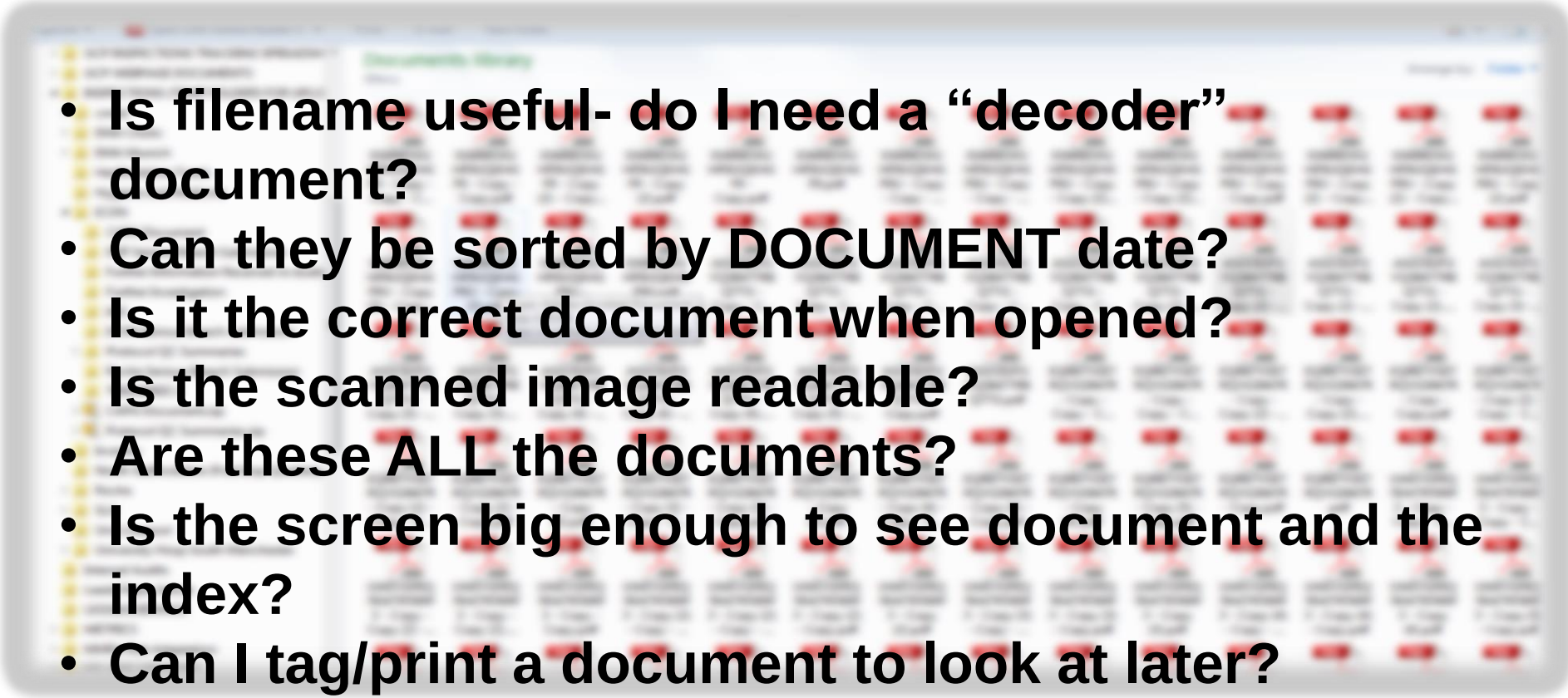
Does your organisation have formal processes to define and maintain the TMF?

a) Yes
b) No

Maintenance of the Trial Master File

Electronic Trial Master File

Electronic Trial Master File



- Is filename useful- do I need a “decoder” document?
- Can they be sorted by DOCUMENT date?
- Is it the correct document when opened?
- Is the scanned image readable?
- Are these ALL the documents?
- Is the screen big enough to see document and the index?
- Can I tag/print a document to look at later?

Provision of the e/TMF for inspection

For inspections of clinical trials, inspectors may require you to provide for inspection:

- Sponsor TMF relating to investigator sites (site Level), files with country-relevant documentation (country level and trial level)
- Specific sections of the TMF or all of it (dependent upon the scope of the inspection)
- For contracted out trials (where TMF is managed by the CRO), the sponsor's "oversight files" may be required instead of/in addition to the CRO's TMF dependent upon inspection scope and trial status

Provision of TMF for Inspection

What are the issues you face in providing the TMF (paper or electronic) to the inspectors?

Provision of TMF for inspection

Direct Access is an inspector's right, however, issues with "Hybrid TMF":

- Paper/ eTMF;
- 'Formal' eTMF plus one or more electronic systems.

- Direct Access to primary eTMF system or Paper Files is expected (often organisation's perception of what the TMF is).

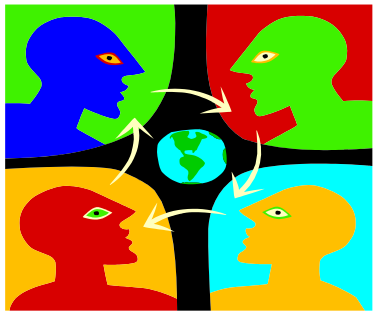
  Access to a certified copy (sponsor would have to demonstrate that this is an accurate and reliable copy) may be acceptable to the inspector.

- Direct Access to **other systems** that contain TMF documents (often the organisation is unaware that these are part of the TMF) is expected.

  Access via a system user, access to a certified copy (sponsor would have to demonstrate that this is an accurate and reliable copy), or by specific document request may be acceptable to the inspector.

Provision of e/TMF for inspection

- The organisation should discuss the provision of the eTMF (or specific sections) with the Lead Inspector when the inspection is being planned:
  - Organisation should know what the e/TMF is and where all of its documents are located
  - Should have formal processes to define, manage and control the e/TMF
  - Should decide how the e/TMF will be provided to the inspector in accordance with the regulatory requirements
- Failure to meet the requirements agreed during the planning is **NOT** acceptable



Globalisation of Trial Functions

Activities outside of UK, but involving UK Patient data (e.g. Data Management, Pharmacovigilance).

Rights to see documentation, but scope of inspection may determine what is acceptable to the inspector:

- Actual TMF documents (direct access)
- Certified Copy of TMF documents
- Access to particular documents via document requests

TMF Review by Inspectors

YOUR EXPERIENCE OF INSPECTION –

- Inspectors browse through it all from start to finish in correct order?
- Inspectors browse particular sections of interest from start to finish?
- Inspectors have a list of documents they want to see and find them in the TMF?
- Inspectors request documents from TMF with a document request form?
- Inspectors ask someone to show them a document in the TMF?
- Inspectors mark up documents for later discussion?
- Inspectors use your SOPs to identify your quality records then find them in the TMF?
- Inspectors ask for documentation that you don't have in your TMF?

ALL OF THEM!

Inspection of eTMF

- The TMF provided should be in the form as used by clinical operations staff/QA (especially if inspecting a live trial).
- Inspectors (auditors) should have direct “read only” access for an eTMF and without reliance on a “eTMF super-user”.
- eTMF systems should :
  - have an effective speed of access to view documents.
  - be user friendly so inspectors do not need extensive training to use it (this could happen prior to inspection).
- GCP Inspectors do not have to sign any document (aside from site/facility access badges/sign in) at an inspection.
- GCP Inspectors are not required to follow organisation’s SOPs/Policies relating to accessing the TMF.

Inspection of eTMF

- An e-TMF should allow review in an efficient manner, analogous to that possible with paper TMFs i.e. review should not take longer.
- Ability to mark documents for later reference is valuable within an eTMF (“yellow sticky” equivalent).
- Access to the original paper records may be required.
- Review of validation processes/documentation and QC of an eTMF etc. should be expected.

Moving to eTMF

- Review all systems, processes and functional areas to assess location of all essential documents and data to ensure appropriate structural design for your organisation

- Ensure auditing/inspection needs are built into eTMF functional requirements

- Piloting the system and initial paper filing to new structural inventories has been useful to organisations

- Risk based approach to migration of trials into the new eTMF system
  - New trials, Ongoing trials, Used in Submissions etc.

Inspection of e/TMF

The provision of the TMF is your way to demonstrate compliance. Failure to provide the TMF in an appropriate way for MHRA domestic inspections will result in critical findings and potential further inspection days. For EMA inspections, if inspectors cannot assess compliance, this may mean the application for a MA is rejected.

Inspection outcome

UK amended Critical finding definition:

Where provision of the Trial Master File (TMF) does not comply with Regulation 31A 1-3, as the TMF is not readily available or accessible, or the TMF is incomplete to such an extent that it cannot form the basis of inspection and therefore impedes or obstructs inspectors carrying out their duties in verifying compliance with the Regulations

Common Inspection Findings

- Inadequate access to TMF, including:
  - Organisation unable to provide full TMF (paper or electronic) for inspection;
  - Paper/ Electronic hybrid impeded inspection (no clear index);
  - TMF separated by functional groups dispersed over no. of systems without direct access;
  - No inspector access to e.g. IMP, Data Management files located outside of the e‘TMF’

Inspection findings continued..

- ‘Artificial TMF’ provided;
- System users unable to locate documents;
- QC checks insufficiently performed or documented;
- Incorrect documents uploaded to eTMF;
- Poor file labelling;
- No process for archiving of electronic files;
- Inadequate equipment provided to inspectors for eTMF review.

Summary

- Organisation's responsibility to meet regulatory requirements for provision of the e/TMF, failure to do so is likely to result in:
  - Major/Critical findings
  - Termination of inspection and revisit
  - Additional days fees
- Whilst we appreciate there is a change from paper to electronic systems in clinical trials, compliance with regulatory requirements is still necessary at all times
- Inspectors aim to clarify and agree with organisation prior to the inspection, how and what will be required for the TMF inspection, however, during the inspection it may be necessary to change this dependent upon what is found.
- The commissioning of new eTMF systems by an organisation should include regulatory requirements as part of the specification of the functional/user requirements.