Safeguarding public health

GCP Inspection of Trial Master Files

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Why do we need a Trial Master File?

- Adopt detailed guidelines on the documentation relating to the clinical trial that constitutes the master file **[Directive 2001/20 EC]**
- 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]**
- GCP PRINCIPLES:
  - All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, inter-preted and verified **[Directive 2005/28 EC]**
  - The necessary procedures to secure the quality of every aspect of the trial shall be complied with **[Directive 2005/28 EC]**

Organisation, Structure and Content of Trial Master Files

- Sponsor, Investigator and made complex by CRO use:
  - Clarity on documentation held by CROS and contracts:
    a) the transfer of sponsor activities being delegated and assumed by the CRO
    b) how the TMF will be managed (who, where, what, when) in relation to the delegated duties and tasks.
    c) What will CRO retain? Will CRO records be retained by sponsor?
- Essential documents: ALL those documents showing the trial was in compliance with the principles and guidelines of GCP and reconstructs fully the trial events:
  - Generated from following organisations procedures
  - Not restricted to Volume 10/ICH GCP section 8 or DIA model
  - Risk adaptations in trial management – impact on TMF records

Organisation, Structure and Content of Trial Master Files

- The TMF management and structure should be established at the start of the trial and the TMF organised to facilitate inspection and management of the trial:
  - SOP recommended to identify all components etc of TMF
  - Clearly structured to account for documentation levels and the trial complexity (Global, Country, Investigator, CRO etc.)
  - Easy location of documents - clear and appropriate indexing system for the sections/documents.
  - Avoid duplication of documents.
  - Correspondence should be relevant and organised.
  - Contemporaneous
  - Documentations should be complete, legible, accurate, and unambiguous and signed/dated as appropriate.

- Keep the TMF for at least 5 years [longer for trials supporting marketing authorisations– some documents for lifetime of product]
- Named individual responsible

Availability of Trial Master Files

- For the inspection the sponsor should provide:
  - The full Trial Master File not just "clinical operations documentation" (unless only particular areas specified by the inspection)
  - For global trials, the relevant parts of the TMF for the site inspected should be available.
  - Need to ensure that access is readily available (and can be retrieved if archived) upon request of the competent authorities.
- The TMF provided should be in the form as used by the sponsor (especially if inspecting a live trial)
- Direct Access should be provided to all sections of the TMF (including multiple electronic systems, if applicable).

eTMFs

- Transfer of documents from paper into the eTMF subject to QC (validated) process.
- Transfers should be certified for accuracy, completeness and legibility.
- Transfer should not conceal any physical change to the document (e.g. cut & paste to remove or add items, use of correction fluid etc.)
- Ability to demonstrate documents are authentic, complete and legible copies of the original documents.
- Controls to ensure records cannot be altered without appropriate authorisation and the creation of an audit trail for records stored electronically (or on other non-indelible media).
- Controls should be in place on access/use the eTMF system (security).
- Must be able to access electronic media in future to ensure accessible and legible when in long term archive (e.g. ability to access software/hardware dependency, test restores etc.)
- Destruction of original paper records – risk based approach

Practical Considerations for Inspecting eTMFs

Inspectors NOT adverse to using eTMFs, however, for eTMFs and other electronic systems that include TMF documentation, there are practical considerations:

- Direct access to the live eTMF (no super user)
- User friendly (including no excessive training)
- Availability of appropriate equipment
- Adequate speed for viewing documents
- Ability to mark documents for later reference
- Ability to compare documents
- Structure / indexing should allow easy identification of sections and documents
- Adequate document quality
- Access to the original paper records if required
- Ability to review the validation processes/documentation and QC of eTMF etc.

Advantages of eTMFs

- eTMFs can have advantages and potential benefits:
  - Availability of documentation globally addressing issues with access for all concerned parties (CROs etc.)
  - Reduces duplication, so only one version needs to exist
  - Reduces fragmentation of the TMF
  - Ability to provide access to the same type of document across all studies/sponsors/product etc.
  - Search features
  - Environmental benefits (reduces need for paper, document transit and travel for audit/inspection/trial management etc.)

IN FUTURE:
  - *Direct access to the e-TMF through secure internet links leading to "Virtual GCP Inspections" of TMF by inspectors based at their offices.*

Summary MHRA GCP Inspection Findings Relating to TMF & eTMF (1)

- Organisation was unable to provide a full TMF (paper and electronic) for inspection purposes on request of the MHRA GCP inspectors. In some cases resulting in additional inspection days required
- All the documentation was not contained in the TMF and eTMF. (e.g. was restricted to the contents of ICH E6 Section 8 documents)
- TMF documentation held outside the UK and documents relevant to UK trial sites was not able to be accessed by the inspectors.
- Failure to record the location of documents that should be in the TMF.
- Lack of clarity on what constituted the TMF for the trial.
- The paper TMF structure (poor indexing etc.) did not facilitate review to evaluate the conduct of the trial.
- The sponsor provided an "artificial TMF", thus failed to provide adequate direct access.
- Staff that were put forward as "system users" for eTMF were unable to locate documents requested by the inspector.

Summary MHRA GCP Inspection Findings Relating to TMF & eTMF (2)

- Failure to fully document and perform effective QC checks on documents uploaded into eTMF.
- Incorrect documents located in the TMF and eTMF.
- There was poor, often repetitive, sometimes incorrect labelling of files, resulting in excessive time wasted opening and closing documents in the eTMF when attempting to locate documents.
- There was no accurate record with the details of documents sent to contractor for uploading into eTMF.
- There was a failure to document activities to allow reconstruction of the trial conduct.
- The organisation did not provide adequate equipment for the inspector to review the eTMF.
- GCP inspectors regularly give findings for documentation within the TMF not being version controlled, fully completed and signed & Dated (where document requires it).

References

- 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)
- EU Directive: 2003/63/EC (amending Directive 2001/83/EC of the European parliament and of the council of the community code relating to medicinal products for human use)
- Recommendation on the content of the trial master file and archiving July 2006, Volume 10, Chapter V
  http://ec.europa.eu/health/documents/eudralex/vol-10/
- CPMP/ICH/135/95: "Note for Guidance on Good Clinical Practice" (ICH E6)
  http://www. ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html
- EMA GCP INSPECTORS Questions and Answers
  http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000072.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800268ad
- DIA TMF Model
  http://www.diahome.org/en/HomePage/EDM+Corner.htm

Any Questions?