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An overview of the importance of the Trial Master File (TMF) and the required contents in clinical trials as stipulated in the ICH GCP guidelines

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Abstract

Aim: The Trial master File (TMF) is a method used worldwide to collect and file documents related to clinical trials. The aim of this study was to review the ICH GCP guidelines related to the TMF and to provide an overview of the requirements of the TMF.

Method: A review of the ICH CGP guidelines related to the TMF and additional resources.

Topics reviewed: Six main topics was identified and discussed to provide an overview: What is a Trial Master File (TMF), the importance and benefits of the TMF, TMF and essential documents as outlined in the ICH GCP E6 guidelines from section 8.1 to 8.4, electronic TMF (eTMF), additional documents filed in the TMF

Conclusion: The TMF set-up and maintenance during a clinical trial is essential to ensure all the required documents are filed and to ensure all the relevant documents are available and audit ready at all times.

Keywords: *Trial Master File, TMF, GCP, essential documents, investigator, sponsor*

Introduction

The validity and integrity of a clinical trial is essential to obtain approval from the ethics committee and regulatory bodies to conduct clinical trials in compliance with International Conference of Harmonization (ICH) Good Clinical Practice (GCP) guidelines. The Trial Master File (TMF) is a compilation of these essential documents obtained during initiation, conduction and close out of clinical trials. These documents stored in the TMF are important to prove the validity of the clinical trial, indicate the quality of the data obtained and provides prove of ICH GCP compliance for all the personnel involved in the clinical trial. The ICH CGP guidelines provides as list of all the essential documents needed to be filed in the TMF and their purpose in the clinical trial.

A procedure or plan should be in place to make sure the documents in the TMF is comprehensive and correct and should be able to provide all the necessary information to reconstruct the clinical trial from beginning to end precisely.

Method

The TMF plays an important role in clinical trials and consists of a collection of essential documents obtained during the conduct of the trial. For this investigation, the ICH E6 guidelines on the TMF are reviewed with the support of additional resources to identify the role of the TMF in a clinical trial and various concepts related to the TMF.

Literature overview

What is a trial master file (TMF)

Documents collected before, during and after a clinical trial provides prove that the study was conducted, the data collected is correct and valid and that the investigator and sponsor conducted the trial according to ICH GCP guidelines. These documents are collected at the site and by the sponsor and are collectively known as the TMF. The TMF consists of various essential documents as required by the different regulatory authorities. The TMF is started before the start of a clinical trial,

maintained through the conduct of the trial and after the trial to ensure all the required documents are collected until close out of the trial.[1, 2]

The importance and benefits of the TMF

Documents required for the TMF is important for several reasons related to the overall validity and integrity of the study. The collection and filing of essential document in the TMF is not only needed for new product approval but can be beneficial as well. [1, 2, 3]

Importance:

a) Evaluation of the validity and quality of the data collected
b) Required as prove the trial was conducted in accordance with the ICH CGP guidelines and other specified regulatory requirements
c) Evidence that both the investigator and sponsor was GCP compliant during the conduct of the study
d) Provides crucial information regarding the specific clinical trial to auditor's during an audit
e) The trial can only be completed upon collection of the last document and after it has been reviewed by the monitor to confirm all the required documents are present

Benefits:

a) The clinical trial can be reconstructed through the documents collected
b) The TMF provides an central access point to all the important documents for all the personnel involved in the conduct of the trial
c) The TMF is set-up in a chronological order ensuring easy access to the documents to auditor's and trial personnel
d) Timely collection of these documents contributes to the successful management of a clinical trial

TMF and essential documents as outlined in the ICH GCP E6 guidelines from section 8.1 to 8.4

As per the ICH GCP E6 guidelines section 8.1 essential document are defined as[1]:

Essential Documents are those documents that individually and documents that individually and collectively permit evaluation of the collectively permit evaluation of the conduct of a trial and the quality of the conduct of a trial and the quality of the data produced. These documents serve data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with investigator, sponsor, and monitor with the standard of GCP and with all the standard of GCP and with all applicable regulatory requirements.

As per the ICH GCP E6 guidelines from section 8.1 to 8.4 a list has been compiled outlining the minimum essential documents that has to be collected during the conduct of a clinical trial. Specific documents are collected at different stages of the trial as specified in the ICH GCP E6 guidelines section 8.2 to 8.4[1]:

1. Before the start of clinical phase of the trial
2. During the execution of the trial
3. After termination or completion of the trial

The TMF is set-up right at the beginning of the trial at both the sponsor's office and the investigator's/institution's site. The documents as indicated in Appendix 1 should be audit ready and available for an audit and inspections by the regulatory authorities at any given time. [1]

Electronic TMF (eTMF)

Due to the increased complexity of studies, especially oncology studies, and the difficulty managing paper TMF's for different departments, most organisations have moved over to eTMFs.[2]

The eTMF consists of various folders to account for all the different documents retained in a trial. The eTMF includes the essential documents, documents specific to the different departments including Laboratory, Biostatistics, Medical Monitor, Clinical Trial Supplies, IRB/EC, Data

Management, agreements and contracts and several more documents to ensure all the required documents for the different department are present. Unblinded areas are also set-up to ensure there is no premature unblinding and the integrity of the data stays intact. [2]

Different section may also be set-up in the TMF to ensure central or core documents are filed in one section and all site related section is filed in their respective sections as a method of access control to ensure confidentiality is not breached, especially during the conduct of an audit. [2]

The files and documents in the TMF should be filed in a chronological order as predefined in a type of folder structure or predefined directories and it is advised to keep this unified across studies instead of creating new folder structures or predefined directories for each trial. This will allow for flexible and general folders and naming conventions throughout and sections in the TMF that will not be used for a specific trial can be removed or indicated as not applicable. [2]

The use of an eTMF in clinical trials has various advantages such as detailed audit trials that have proven to be very useful in audits and inspections and changes to the documents can be tracked in the audit trial to ensure compliance with the applicable documents and regulations. [2]

Additional documents filed in the TMF

Apart from the essential documents, it is also necessary to ensure other study related documents are filed. [2]

All previous versions of documents should also be kept in the TMF to ensure in order to be able to keep track of changes made in the documents during the conduct of the study. These documents include protocols, informed consent forms, electronic case report forms, and investigator's brochure. [2]

Important correspondence should also be retained. Important decisions between the sponsor and site, sponsor and CRO, site/sponsor and regulatory authorities and any other communication that contains critical trial related information should be filed in the TMF. These documents range from letters to electronic emails. [2]

Quality control and access control of the TMF

Additionally to the essential and other required documents that should be filed in the TMF, a system should also be in place to ensure controlled access to the TMF and quality control should be performed to ensure the filed documents are legible and valid.

Access control requires provision and revoking of access through password protected user accounts as needed, restrictions on the type of access depending on the individual role of the user and an audit trial indication all the required information to accurately track uploads and changes to documents in the TMF. [2]

Additionally each document should undergo a quality control process to ensure the documents are legible, accurate and valid. These quality controls are predefined by the sponsor, site and CRO and every document owner should be compliant through the conduct of the study. Quality controls or quality checks include ensuring documents are filed in the same format, all required signatures are present, scanned documents are legible and not information has been removed or cut off in the process and all page numbers are present. Quality control is not just limited to the identification of issues and deficiencies, but also required corrective and preventative actions to eliminate and reduce future risk for the same quality issues. [3, 4]

Conclusion

There are many important aspects to consider with regards to the TMF and this process many be complicated and time consuming depending on the complexity of the study. The TMF should always be audit ready, in a chronological order, complete and accurate and portray conduct of a study as a whole to ensure the study is valid and to confirm the integrity of the data.

Although the TMF has improve tremendously over the past years and moved over to and electronic system allowing better control and audit trials, there is still room for improvement. As studies evolve to be more specific, complex and target specific, the TMF should also be developed to accommodate

for these changes to ensure all required documents are collected in the TMF and access to the TMF is restricted and controlled at all times. Future development of the TMF should focus on better access control, more user friendly systems, built in quality control checks and allow for easier identification of missing or incomplete documents.

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