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Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)

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1. Executive summary

Trial master file (TMF) plays a key role in the successful management of a trial by the investigator/institutions and sponsors. The essential documents and data records stored in the TMF enable the operational staff as well as monitors, auditors and inspectors to evaluate compliance with the protocol, the trial's safe conduct and the quality of the data obtained. This guideline is intended to assist the sponsors and investigators/institutions in complying with the requirements of the current legislation (Directive 2001/20/EC and Directive 2005/28/EC), as well as ICH E6 Good Clinical Practice (GCP) Guideline ('ICH GCP guideline'), regarding the structure, content, management and archiving of the clinical trial master file (TMF). The guidance also applies to the legal representatives and contract research organisation (CROs), which according to the ICH GCP guideline includes any third party such as vendors and service providers to the extent of their assumed sponsor trial-related duties and functions. The ICH GCP guideline provides information in relation to essential documents to be collected during the conduct of a clinical trial. The risk-based approach to quality management also has an impact on the content of the TMF. To ensure continued guidance once the Clinical Trials Regulation (EU) No. 536/2014 ('Regulation') comes into application, this guidance already prospectively considers the specific requirements of the Regulation with respect to the TMF.

2. Introduction

A TMF is the collection of essential documents that is used by sponsors, CROs and investigators/institutions for the management of the trial and by monitors, auditors and inspectors to review and verify whether the sponsor and the investigators/institutions have conducted the trial in line with the applicable regulatory requirements and the principles and standards of GCP. The legislation does not differentiate between paper and electronic TMFs (eTMFs). Therefore, all basic requirements are the same for both formats or when used in combination as a hybrid TMF. Article 57 of the Clinical Trial Regulation states "*The clinical trial master file shall at all times contain the essential documents relating to that clinical trial"*. Article 20 of Directive 2005/28/EC and Article 58 of the Regulation also require that after archiving "*Any alteration to the content of the trial master file shall be traceable."* The TMF should provide for document identification, version history, search and retrieval[1]; also, as stated in both Directive 2005/28/EC (Article 17) and the Regulation (Articles 57 and 58) it shall be archived in a way that ensures that it is readily available and directly accessible upon request, to the competent authorities of the Member States.

Article 47 of the Regulation states that sponsors and investigator/institution shall take appropriate account of the ICH GCP guideline and shall conduct the trial in accordance with GCP principles, two of which are:

- "*All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification*"[2];
- "*Systems with procedures that assure the quality of every aspect of the trial should be implemented. Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.*"[3].

Documents and records containing information and data resultant from following the systems and procedures that assure the quality of every aspect of the trial and that, as per Article 16 of Directive

[1] CPMP/ICH/135/95 8.1
[2] CPMP/ICH/135/95 2.10
[3] CPMP/ICH/135/95 2.13

2005/28/EC and Article 57 of the Regulation, enable verification of the conduct of the trial and the quality of the data generated are considered to be essential documents and should be retained.

The sponsor's and any CRO's quality management system should have procedures (e.g. standard operating procedures (SOPs)) in place to manage all aspects of the TMF to assure that the TMF is complete, legible and accurate. The investigator/institution should also ensure the TMF is managed to achieve the same outcome. The TMF documentation should be sufficient to adequately reconstruct the activities undertaken in conducting the trial, along with decisions and justifications made concerning the trial.

Documents and records in the TMF should collectively permit confirmation of compliance with the protocol and GCP and the integrity of data collected without the need for additional explanation from the sponsor, CRO or investigator/institution staff.

This document provides guidance for implementing and maintaining a TMF that complies with the regulatory requirements.

3. Trial master file structure and contents

3.1. Sponsor and investigator trial master file

The TMF is usually composed of a sponsor TMF, held by the sponsor organisation, and an investigator TMF held by the investigator/institution. The investigator TMF is often referred to as the investigator site file (ISF). The TMF for the trial, both of the sponsor and of the investigator/institution, should be established at the beginning of the trial. There should only be one TMF for a clinical trial, comprising the sponsor and investigator parts. In organising the TMF, it is essential to segregate some documents that are generated and/or held by the sponsor only, from those that are generated and/or held by the investigator/institution only (e.g. subject identification code list filed in the investigator TMF only and master randomisation list filed in the sponsor TMF only). The investigator/institution is responsible for all essential documents generated by the investigator/institution and should therefore have control of them at all times[4]. In cases in which the investigator is employed by an institution that is the trial sponsor, the sponsor may delegate the task for maintaining all or part of the sponsor TMF to the investigator. In this circumstance, it is possible to combine the delegated part of the sponsor TMF and investigator TMF for that investigator/institution, which avoids the duplication of documentation; however, the responsibility for the sponsor TMF remains with the sponsor. The same applies when the investigator and the sponsor are the same person. When there is co-sponsorship of a trial, there should be arrangements in place for the maintenance of the TMF based upon the responsibilities that each co-sponsor holds. Role-based permissions should be established for activities being undertaken, such as restricted access to files/documents (e.g. randomisation codes and unblinded adverse event data).

3.2. Contract research organisations

The sponsor may choose to outsource duties and functions of the sponsor to a CRO. The sponsor remains responsible for the trial and will need to maintain oversight. Therefore, access to the CRO-maintained part of the sponsor TMF (e.g. by remote access to an eTMF) or at least regular access to relevant documents from it will be necessary to fulfil these responsibilities effectively. In conducting contracted duties and functions, the CRO will be generating documentation that should reside in the TMF. The clinical trial contract/agreement and other documents and procedures agreed between all parties should outline the arrangements for the TMF in some detail, such as:

[4] CPMP/ICH/135/95/ 8.1

- which party holds the TMF (or which party holds which parts of the TMF when this is divided);
- the structure and indexing of the TMF;
- the access arrangements for the involved parties;
- when an eTMF is being used, the details of the system and change control management;
- lists of applicable procedures to be followed and training requirements;
- type of documents that each party should retain;
- arrangements for managing correspondence;
- how the TMF would be made available to the competent authorities;
- arrangements for when the trial is completed (the CRO may archive the TMF [or parts thereof] on behalf of the sponsor); if there is a contractual arrangement for the CRO to transfer all essential documents they have generated to the sponsor for archiving, the arrangement should ensure the sponsor retains the full set of documents and makes it readily available and accessible for inspections (including inspections related to the CRO's duties and functions);
- arrangements for oversight of the TMF performed by the sponsor and how this would be achieved (e.g. audit reports and/or monitoring);
- retention times;
- arrangements regarding the archiving of and access to data/documents held in centralised systems (such as central training documents and central e-mail repository);
- procedures in case of an involved party closing down its business for any reason.

If multiple CROs are involved, the sponsor should clearly define expectations regarding the creation, management, exchange or remote access and retention of documentation amongst CROs. Specific requirements may be put in place when CRO interaction is required.

The sponsor should provide CROs access to sponsor essential documents of the TMF that are required by the CRO to execute their delegated duties and functions.

When a CRO is used for the management of the eTMF and/or for the digitisation/transfer of TMF documents, appropriate pre-qualification checks should be undertaken prior to contracting the CRO. It should be verified during the clinical trial that the CRO's quality management measures are complied with.

3.3. Third parties-contracted by investigator/institution

The investigator/institution may choose to delegate duties and functions related to the conduct of the trial to a third party (e.g. site management organisation or external archive). In such circumstances, the third party may generate/hold essential documents relating to the contracted duties. The applicable principles in section 3.2 should be considered.

3.4. Trial master file structure

When starting a clinical trial, the sponsor and the investigator/institution should identify and maintain a record of the location(s) of all the potential documentation that is considered to form the TMF, even if several locations, departments, country organisations and systems are involved. There should be a primary TMF system for holding essential documents, which could be entirely electronic, entirely on paper or a hybrid of both. Other systems including central systems may exist that hold essential

documents (e.g. a central e-mail repository, SOP-management system, central training records, delegation logs, software validation records and records concerning more than one trial, e.g. investigator's brochures (IB)) relevant to the trial and should therefore be part of the TMF. The number of these other systems should be minimised with the priority focussed on placing documents in the primary TMF system. Documents applicable to multiple trials do not need to be duplicated in several TMFs.

There should be a suitable overall index or table of contents to enable the location of essential documents in the TMF to be traced. Whether the TMF is paper or electronic, it is recommended that this is implemented and standardised across the investigator/institution, sponsor organisation or CRO, if applicable. The documentation should be filed in each appropriate section of the TMF in chronological order. Consideration should be given to defining the dates used for document filing; for example, the date of receipt, the date of filing into the (e)TMF, the date of approval or the date of expiration.

3.5. Trial master file contents

3.5.1. Essential documents

"Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced".[5] Essential documents help assist the investigator/institution and sponsor in the successful management of the trial and demonstrate adherence to the standards of GCP and all other applicable regulatory requirements.

The TMF kept by the investigator/institution and the one kept by the sponsor have a different content, due to the different nature of the responsibilities of the investigator/institution and the sponsor[6], and as defined in the ICH GCP guideline.

Article 57 of the Regulation states that the TMF essential documents' content shall take into account *"all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial".* Therefore, some documentation specified in the ICH GCP guideline may not be necessary due to the implementation of a risk proportionate approach[7]. The justification for reducing documentation should be documented in the TMF. The documentation listed in the ICH GCP guideline section 8 defines the documents that are considered essential (as appropriate to the trial) and which documents should be filed in the investigator/institution or sponsor TMF, or both; however, this list should not be used as a definitive checklist for TMF content. It is not an exhaustive list. Depending on the activities being carried out, many trials require additional documents not specifically mentioned, therefore the sponsor and/or investigator/institution should include any documentation that facilitates reconstructing and evaluating the trial conduct, as part of the TMF. Unnecessary duplication of documentation in the TMF should be avoided.

Examples of documents that are considered essential when generated for a specific trial, but not listed in section 8 of the ICH GCP guideline include:

- completed forms, checklists and reports etc. related to the trial, generated from following quality system procedures of the sponsor, investigator or any third-party performing trial activities on their behalf;
- qualified person certification of the IMP;
- assay method validation report for analysis of IMP or metabolite(s) in clinical samples;

[5] CPMP/ICH/135/95/ 8.1
[6] Clinical Trials Regulation (EU) No 536/2014, Article 57
[7] Risk proportionate approaches in clinical trials, EudraLex Vol. 10, Chapter V

- advanced therapy investigational medicinal product (ATIMP) traceability documents;
- documentation to demonstrate validation of trial-specific builds of computer systems (e.g. electronic case report form (eCRF) and interactive response technologies (IRT) and electronic patient-reported outcomes);
- data management documentation, e.g. data management plan, data validation plan and data-review meeting minutes;
- statistics documentation, e.g. SAS program validation, statistical analysis plan and sample size estimations;
- delegation log as part of the investigator/institution TMF.

Documents demonstrating software validation may be retained by a CRO when the activity has been contracted by the sponsor, but the sponsor should ensure continued access to these documents in the contractual arrangements with the CRO for the required archiving period. Documents relating to the trial-specific software configuration are part of the TMF and it should be determined whether these are maintained/archived by the sponsor or CRO providing this service. Some documents from good manufacturing practice activities should also be defined as part of the TMF, for example, when these relate to the assembly and packaging of the investigational medicinal product (IMP) and confirm, as applicable, compliance with the randomisation schedule and blinding of the trial.

3.5.2. Superseded documents

During a document's development (e.g. clinical trial protocol development and release), the sponsor's/CRO's procedures may require input and review by various functions. The documentation to demonstrate that the process was followed should be retained.

Superseded versions of final documents are necessary to reconstruct the trial and should therefore be retained in the TMF. Superseded versions of sponsor-produced documents (e.g. trial protocol, IB and eCRF) should be present in the investigator/institution TMF in a manner to enable reconstruction without the need to access the sponsor TMF, with evidence of date of receipt, review and/or approval (when necessary) and date of implementation by the investigator/institution.

3.5.3. Correspondence

Relevant correspondence that is necessary for reconstruction of key trial conduct activities and decisions should be retained. This includes correspondence with ethics committees, data safety monitoring committee and regulatory authorities (confirming sponsor approval of processes, documents and decisions and the communication regarding issues that arise in the trial conduct and how they are dealt with). Similarly, electronic correspondence (e-mails and associated attachments between CROs, sponsor departments, investigator/institution) should be readily available and may be retained electronically. It should be ensured that both sent and received correspondence is filed in the TMF. One or more separate central repository may be used (e.g. for e-mail), as long as they are clearly defined as being part of the TMF (see section 3.2). Care should be taken regarding e-mail 'chains' and attachments to ensure that relevant strands of conversations and their associated documents are maintained. For archiving of correspondence see section 6.3.

3.5.4. Contemporariness of trial master file

The requirement "at all times" within Article 57 of the Regulation means that the TMF should have all documentation added in a timely manner during the trial, as this greatly assists the successful

management of a trial by the investigator/institution, the sponsor and CROs to whom the sponsor has delegated its duties. The timelines for submission and filing of all documents to the TMF in procedural documents or TMF plans should be defined. This is particularly important for more complex TMF arrangements with multiple parties involved.

4. Security and control of trial master file

4.1. Access to trial master file

The TMF should be managed securely at all times to ensure completeness and to prevent accidental or premature loss, unauthorised alteration or destruction of documents. Access to the TMF should be based on a role and permission description that is defined by the sponsor and/or investigator/institution.

The sponsor TMF and investigator/institution TMF may contain some information that could unblind personnel who need to remain blinded during the trial conduct. This should be appropriately controlled, e.g. storage of the documentation in another system or repository and/or by a role and permission description that is defined by the sponsor and/or investigator/institution.

4.1.1. Storage areas for trial master file

At all times the storage area for the TMF documents (such as paper or electronic media archives and server rooms) should be appropriate to maintain the documents in a manner that they remain complete and legible throughout the trial conduct and the required period of retention and can be made available to the competent authorities of the Member States, upon request. Adequate and suitable space should be provided for the storage of all essential documents from completed studies. The facilities should be secure, with appropriate environmental controls and adequate protection from physical damage. The factors to be considered when assessing a suitable storage facility, should take into consideration certain factors such as security, location (e.g. environmental risk factors) and size.

Sponsors should make a documented assessment of the conditions at the investigator site/institution for storage of the investigator/institution TMF during the clinical trial and for archiving. The sponsor should be notified, if the agreed arrangements are changed (e.g. sub-contracting of storage).

4.1.2. Sponsor/CRO electronic trial master file

Electronic TMFs should enable appropriate security and reliability, ensuring that no loss, alteration or corruption of data and documents occur. The primary eTMF is a system for managing documents that should contain the controls listed below:

- user accounts;
- secure passwords for users;
- a system in place locking/protecting individual documents or the entire eTMF (e.g. at time of archiving) to prevent changes to documents;
- regular backup;
- periodic test retrieval or restores to confirm the on-going availability and integrity of the data;

- an audit trail in place to identify date/time/user details for creation and/or uploading deletion of and changes to a document (explanation of the deletion or modification, if necessary);[8,9]
- role-based permissions for activities being undertaken, such as restricted access to files/documents (e.g. randomisation codes and unblinded adverse event data);
- the suitability of the system for archiving purposes should be appropriate;

The above principles also should apply to any electronic systems defined as part of the TMF (e.g. SOP-management system, e-mail central repository).

The eTMF systems should be validated to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process.[10]

All staff members involved in the conduct of the trial and using the system should receive appropriate training.

When different TMF systems are linked to facilitate the trial conduct, e.g. when the CRO eTMF system uploads documents into the sponsor eTMF system (possibly by an intermediate system), the process for transferring documents should be robust and should be validated to prevent any loss. Any electronic system that holds trial data and metadata (e.g. audit trails) required for reconstruction should be archived so that the contained trial data and metadata can be retrieved as usable datasets.

Metadata are structured data that describe the context, content, and structure of a file. They facilitate management, identification, accessibility and retrieval of files. Metadata may include information such as creator or author, time and date of creation, archiving date, location in the eTMF, file title or keywords, version, file type, file size, and other file properties.

Metadata applied to documents should be formally defined to ensure consistency across all documents. This should include the predefined document date (e.g. date of creation) and when appropriate, time, based on standard time zone, so that the files can be displayed in chronological order. For documents subject to version control, the use of file names should not replace version details being visible on displays and printouts.

Any migration of data and documents to new media or a new format should be verified to ensure long-term readability and to maintain integrity.

The appropriateness of the storage system should be evaluated based on the file format used, e.g. whether the eTMF-document-management system is appropriate for the storage of dynamic data files (e.g. Excel files and SAS datasets), where needed and does not require such files to be rendered as a PDF. Within the eTMF-document-management system, PDF files generated from dynamic data files in other systems (e.g. IMP shipping reports generated from IRT datasets and monitoring visit reports generated from the clinical-trial-management system (CTMS) datasets) might be uploaded to the primary TMF system; if so, the original dynamic file should be retained in the original system.

4.1.3. Investigator electronic trial master file

The investigator/institution TMF (hereinafter referred to as Investigator TMF) may be electronic, paper or hybrid format. When an investigator/ institution eTMF is used the following requirements should be taken into consideration:

[8] Directive 2005/28/EC, Article 20
[9] Clinical Trials Regulation (EU) No 536/2014, Article 58
[10] CPMP/ICH/135/95 5.5.3

- A complete investigator TMF should be available before, during and after the trial, and accessible under the control of the investigator/institution, independent from the sponsor.
- The documentation in the investigator TMF includes some source documents containing personal data that enable the data subjects to be directly identified (i.e. direct identifiers of trial subjects); for example, subject identification code list, subject-related source documents and signed consent forms, which should remain under the sole control of the investigator/institution due to data privacy requirements. In general, information (data/documents) shared with the sponsor/CRO or uploaded into a database or filing system that is managed by the sponsor/CRO, should only contain data of trial subjects, which has been pseudonymised. The documents containing direct identifiers of trial subjects, such as the subject medical files, the identification code list and informed consent forms, should be maintained separately by and under the control of the investigator/institution.
- The uploading of any investigator/institution-generated essential documents onto a sponsor/CRO-maintained eTMF system bears the risk that the investigator has no control of and no continuous access to its documents. If an eTMF is to be used for such documents, the contractual arrangements for the system and the hosting of the data should identify the investigator/institution, as owner of/responsible party for these documents.
- The investigator/institution is responsible for the suitability of the investigator TMF. Regardless of what arrangements are put in place for an eTMF, these should ensure that this responsibility can be fulfilled and that the investigator/institution maintains continuous access to and control of the files and their documents. When a third party eTMF is used, there should be assurance that the investigator/institution can fulfil their responsibility.
- Many documents within the investigator TMF are those provided by the sponsor (e.g. protocol, IB, procedural manuals, etc.). Access to these documents in a part of the sponsor eTMF could be undertaken by investigator's/institution's access to a web portal, or by the sponsor uploading these in the investigator/institution eTMF directly. In this situation there should be procedures and controls in place that demonstrate at all times when versions of documents were made available to the investigator/institution and when these documents were accessed (e.g. through an audit trail) and implemented by the investigator/institution.
- All agreements should include provisions for the situation that any of the parties mentioned above are going out of business and how the integrity and accessibility of the complete investigator TMF will be maintained throughout the required archiving period.
- 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.

4.2. Quality of trial master file

Article 57 of the Regulation states "*The clinical trial master file shall at all times contain the essential documents*". The sponsor and/or investigator/institution should implement risk-based quality checks (QC) or review processes to ensure the TMF is being maintained up-to-date and that all essential documents are appropriately filed in the TMF. Areas to consider during QC and review include the following:

- all essential documents generated available in the TMF;
- documents filed in the appropriate locations;
- documents added to the TMF in a timely manner;

- documents correctly indexed;
- documents only accessible according to the assigned roles and permissions;
- review of the audit trail (for eTMF).

In addition to TMF-level QC above, there should be an adequate risk-based document-level QC, as described in section 5.1 for certified copies.

The sponsor should also undertake routine QA measures, e.g. system audits of TMF-management processes.

In addition, the sponsor should ensure the TMF is readily available and directly accessible to the competent authority, e.g. for inspection purposes.

5. Scanning or transfers to other media

According to Article 58 "*the media used to archive the content of the clinical TMF shall be such that the content remains complete and legible*" throughout the retention period. Particular attention should be paid when documents are stored on electronic, magnetic, optical or other non-indelible media. In such cases suitable controls should be implemented to ensure that these documents are complete and cannot be altered without appropriate authorisation and the creation of an audit trail.

The ICH GCP guideline requires that copies (irrespective of the media used) in the eTMF that irreversibly replace originals should be certified copies of the original.

5.1. Certified copies

A certified copy is a paper or electronic copy of the original document 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 the same information, including data that describe the context, content and structure, as the original. The ICH GCP guideline requires that copies (irrespective of the media used) in the eTMF that irreversibly replace originals should be certified copies of the original. Any transfer or conversion (e.g. digitisation or printing), which does not fulfil the criteria for a certified copy, is not suitable to replace an original file.

A process should be in place for risk-based QC checks of certified copies, before destruction of the originals.

It is recommended that the QC checks include the following quality features:

- congruency of the information contained between original and certified copy;
- accuracy of the metadata attributed to the document (when applicable);
- accuracy of file name; including that it is marked as an updated version of an already existing document;
- quality of the image (suitable resolution to allow readability as per the original, legibility and reproduction of colour — when the colour gives meaning and legibility of wet-ink signatures or annotations and handwriting in general etc. (when applicable));
- the eTMF audit trail associated with the document (when applicable);
- approval of the certification process (when applicable);

5.2. Other copies

Some copies of documents in the TMF do not replace the original and therefore do not require certification (e.g. original wet-ink signed contracts held at the legal departments of the sponsor and the investigator/institutions and copies in the sponsor and investigator/institution TMF; original delegation log in investigator/institution TMF and copy in sponsor TMF). The creation of such copies for a TMF should be defined in a written procedure. The procedure should ensure that the copy is of sufficient quality for the intended purpose.

5.3. Scanning or transfer to other media

Printing, copying, transferring or digitisation (e.g. scanning paper document to PDF) should account for the nature of the file in question:

- Static files (e.g. PDF scan) containing information or data that are fixed/frozen and allow no interaction to change the content. Paper document digitised as pdf, e.g. scanned ethics approval letter.
- Dynamic files (e.g. Excel-spreadsheet with automatic calculation) include automatic processing and/or enable an interactive relationship with the user to change content (e.g. eCRF). A certified electronic copy may be retained in different electronic file formats to the original record, but the equivalent dynamic nature (including metadata) of the original record should be retained.
- When static files are created from dynamic files for storage in the primary TMF system, the original dynamic file should be retained in the original system.
- A conversion from a dynamic file into another dynamic file format can serve as a certified copy.
- The eTMF system should not be limited to static files only, if dynamic files need to be included.

Digitisation or transfer adjustments to an image are acceptable only in the context of increasing legibility and should not be used to remove or add material to the image (e.g removing or adding the header of a fax machine, or undertaking physical ‘cut and paste’ or ‘correction fluid’ activities on the original document).

5.4. Validation of the digitisation and transfer process

The use of eTMFs and electronic archiving may require the digitisation of paper documents or the transfer of electronic documents to generate electronic copies of the documents. The process of digitisation or transfer should be validated to ensure that no information is lost or altered.

5.5. Destruction of original documents after digitisation and transfer

Sponsors and investigators/institutions should ensure that essential documents are not destroyed before the end of the required retention; however, creation of certified copies, meeting the requirements outlined in section 5.1 to an eTMF repository (either during the trial or for archiving) could enable earlier destruction of the originals.

Examples of documents that have a low risk from destruction:

- A paper copy of an electronic original can be destroyed, as long as the original remains in the TMF (e.g. a printout of a monitoring visit report placed in a TMF).
- Paper documents that do not have legally required wet-ink signatures; the digitised version can serve as a certified copy of the paper version of the original in the TMF.

6. Archiving and retention of trial master file

Articles 58 and 57 of the Regulation, both state that *"the content of the clinical TMF shall be archived in a way that ensures that it is readily available" "and directly accessible, upon request, to the Member States."* Article 58 of the Regulation and Article 20 of Directive 2005/28/EC, also state that *"any alteration to the content of the clinical trial master file shall be traceable".*

The TMF including the audit trail (for eTMF) should be archived appropriately to enable supervision after the clinical trial has ended. The dynamic character of the audit trail should be preserved, when applicable. Archiving should be undertaken after the investigator/institution and sponsor have reviewed that their filed TMF documentation is complete.

Access to archived data/documents should be suitably restricted either by user access levels to the archive area of a server and/or by access controls to the storage location where the (electronic or paper) media are retained. Additionally, the electronic documents or data that have been archived should be protected from unauthorised changes to maintain authenticity.

It is important that access to documents and data is maintained for the entire archiving period. This could include maintaining the system (hardware and software) to access the data in its original archived format, or the use of a new system to emulate the old software or migration of the data into a new format to ensure continual access with new software. This issue should be addressed by the organisation by written procedures.

Media used to store the data may potentially deteriorate or become obsolete, thus transfer to an alternative media would need to be considered. The media should be stored under appropriate conditions. Any transfer or migration needs to be validated to ensure that migrated data have the same information as the original, including metadata. The transfer of data to new media as technology advances would need to be considered by the organisation.

An external archive providing retention of paper documents or electronic media or electronic storage (e.g. cloud data centre) may be used for archiving of the TMF. When an external archive is used by the sponsor or investigator/institution, they should undertake an assessment of the suitability of the facility prior to use and continue quality assurance measures once the organisation has been contracted. There should be a formal agreement in place between the sponsor/investigator/institution and the external archive. In cases the external archive has several storage locations, the sponsor and/or investigator/institution should ensure they are informed about the actual storage location of their TMF and notified if this changes. The agreement is recommended to include provisions for the situation of the sponsor or external archive going out of business.

6.1. Archiving of sponsor trial master file

With respect to the sponsor TMF, Article 58 of the Regulation states that *"the sponsor shall appoint individuals within its organisation to be responsible for archives. Access to archives shall be restricted to those individuals"*. The appointment and appropriate training of these individuals should be documented[11]. These individuals should be employed within the organisation of the sponsor or the organisation contracted by the sponsor. Withdrawal of and/or access to essential documents from archives should be under the control of the named individuals responsible for archiving. An archive index/log should be maintained by the sponsor/CROs to record all TMFs that have been entered into the archive. For paper-based archived TMFs, an index/log should be used to track when the TMF is retrieved, accessed and returned. For electronically archived TMFs, tracking can alternatively be ensured

[11] Clinical Trials Regulation (EU) No 536/2014, Article 49

by the audit trail. The individual responsible for the archived documents should ensure that any documents removed from the TMF are reconciled without unauthorised alterations on return. For an archived eTMF in a suitably restricted area the individual responsible should grant read-only access to those wishing to access the content of the eTMF with an audit trail to record this activity.

In the case that a sponsor has subcontracted a CRO for certain duties, the sponsor is responsible for ensuring the archiving of the documentation generated by the CRO from following its internal procedures. The contract between the sponsor and CRO should specify whether the CRO wants to retain original documents of their part of the TMF or certified copies thereof, after the certified copies or the original documents respectively were handed over to the sponsor for archiving, in order to retain evidence of compliance with their (CRO) internal procedures. The sponsor's TMF may be transferred to a CRO for archiving (e.g. an external archive), but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor.

6.2. Archiving of investigator/institution trial master file

The investigator/institution should make the sponsor aware of the storage arrangements for their essential documents and conversely the sponsor should inform the investigator/institution in writing of the need for document archiving. The ultimate responsibility for the documents to be retained by the investigator/institution resides with the investigator/institution. If the investigator/institution becomes unable to be responsible for their essential documents (e.g. relocation, retirement, closure of institution, etc.) the sponsor's agreement with the investigator/institution should stipulate that the sponsor is notified (preferably upfront) in writing of this change and informed to whom the responsibility will be/has been transferred. The new individual/institution responsible should be independent of the sponsor and should be free of any conflict of interest.

The documents to be retained by the investigator/institution including source data may be stored in external archives, but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the investigator/institution. The investigator/institution should maintain a list of all trials being conducted and the archiving arrangements for the respective TMFs.

Storage of personal data is subject to applicable elements of the general data protection regulation, Regulation (EU) 2016/679.

If the sponsor arranges the external archiving of the investigator TMF on behalf of the investigator/institution, (who should retain control of their part of the TMF), consideration should be given to personal data protection and confidentiality from an unauthorised access, so:

- the archiving arrangements including location of the (electronic) archive should be formally agreed and documented between the sponsor and investigator/institution;
- a formal procedure should be in place such that the documents are only released from the external archive or (remotely) accessed with the approval of the investigator/institution;
- the documents should be physically or electronically transferred directly between the investigator site/institution and the archive facility independent of the sponsor, thereby ensuring that the sponsor/CRO does not have access to the investigator TMF.

6.3. Retention times of trial master file

The sponsor should determine which requirements apply to the respective clinical trial in relation to the start and end dates and whether the trial is used, or intended to be used, to support a marketing authorisation, as the retention requirements are dependent on these factors, as follows.

For trials conducted under Directive 2001/20/EC the retention time is at least five years after completion (Directive 2005/28/EC).

For all trials in which the clinical trial data are used to support a marketing authorisation (including Paediatric Use Marketing Authorisations under Regulation 1901/2006), Directive 2003/63/EC (amending Directive 2001/83/EC) states that essential documents should be retained for at least 15 years after completion or discontinuation of the trial or at least two years after the granting of the last marketing authorisation in the European Union (when there are no pending or contemplated marketing applications in the EU) or for at least two years after formal discontinuation of clinical development of the investigational product, whatever is the longest.

Directive 2003/63/EC (amending Directive 2001/83/EC) also states that "*the sponsor or other owner of the data shall retain some of the documentation pertaining to the trial for as long as the product is authorised. This documentation shall include the protocol (…), standard operating procedures, all written opinions on the protocol and procedures, the investigator's brochure, case report forms on each trial subject, final report and audit certificate(s), if available*. *The final report shall also be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised*."

The Regulation provides in Article 98 for transitional provisions for trials authorised on the basis of Directive 2001/20/EC. For guidance on these provisions see the 'Clinical Trial Regulation Questions and Answers' (EudraLex Vol. 10) on transitory period for the application of the Regulation.

For trials not transferred to the Regulation and conducted under Directive 2001/20/EC that have an end of trial notification submitted according to Article 10 in the transition period, the archiving requirements of the Directive 2001/20/EC will apply.

As per Article 58 of the Regulation "*unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical TMF for at least 25 years after the end of the clinical trial. However, the medical files of subjects shall be archived in accordance with national law."*

Retention times, as laid down in Article 58 of the Regulation, Directive 2005/28/EC and Directive 2003/63/EC for sponsors' documents also apply to the documents retained by CROs or other agents of the sponsor under agreement with the sponsor.

Digitisation of the subject's medical files is acceptable provided the process is validated such that the institution can demonstrate that these are certified copies of the originals, which are kept in a format that ensures that the data can be retrieved in the future (see section 5).

In addition to these retention times for the trial documentation, documents relating to the full traceability of the ATIMP have longer retention periods[12,13]. These are 30 years after the expiry date of the product or longer if required by the clinical trial authorisation. This will include the relevant documentation contained in the sponsor and investigator TMF as well as the trial subjects' medical files.

It is important that when an organisation has centralised documents that may be relevant to a number of trials (e.g. software validation, SOPs, staff training records or maintenance and calibration records for equipment used in the trial at a Phase 1 unit/hospital clinical research unit), the retention time of these is also considered in relation to the defined retention period for the specific trial documents.

Retention requirements for the documentation and medical files held by the investigator/institution should be formalised, for example, in an agreement between the sponsor, the investigator and the

[12] Directive 2004/23/EC, Article 8
[13] Directive 2006/86/EC, Article 9

institution. It is the responsibility of the sponsor to inform the investigator/institution in writing, as to when trial documents no longer need to be retained.

6.4. Archiving, retention and change of ownership/responsibility

As stated in Article 58 of the Regulation *"any transfer of ownership of the content of the clinical trial master file shall be documented. The new owner shall assume the responsibilities set out in this Article".* It is recommended to check the contents of the TMF before transfer to ensure all the originally archived documents remain present. Any change in the location of the stored documentation should be recorded to enable tracking.

When the responsibility for the TMF is transferred, the agreements between the sponsor and the investigator/institution or CRO should cover such eventualities and should require the investigator/institution or CRO to notify the sponsor in such circumstances. The sponsor should take appropriate actions in such circumstances to ensure that the TMF remains available for inspection for the required archiving time and that patient-related source documents have not been in the sole custody of the sponsor at any time (refer to section 3.1).

7. References

- CPMP/ICH/135/95 Guideline for good clinical practice E6 (R2)
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products 03/12/2009 ENTR/F/2/SF/dn D(2009) 35810
- Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Directive 2001/83/EC on the Community code relating to medicinal products for human use
- Directive 2003/63/EC amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use
- Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells
- Directive 2005/28/EC on laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- Directive 2006/86/EC on traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells
- EudraLex Vol. 10, Chapter V, Risk proportionate approaches in clinical trials (found under set of documents applicable to clinical trials that will be authorised under Regulation EU No 536/2014, once it becomes applicable)
- Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004
- Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)
- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use, and repelling Directive 2001/20/EC