EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 March 2017
EMA/15975/2016
Good Clinical Practice Inspectors Working Group (GCP IWG)

Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials

Adopted by GCP Inspectors Working Group (GCP IWG)	30 January 2017
Start of public consultation	12 April 2017
End of consultation (deadline for comments)	11 July 2017
Date of coming into effect	<DD Month YYYY>

Comments should be provided using this template. The completed comments form should be sent to gcp@ema.europa.eu

Keywords	***Trial Master File, TMF, eTMF, essential documents, GCP inspection, archiving, scanning, retention, destruction***

Important note:
A revised version of the reflection paper on TMF, considering comments collected during the public consultation (01 February – 30 April 2013), have been incorporated into this guideline, which has been prepared as part of the work related to the implementation of the new Clinical Trial Regulation (EU) 536/2014.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials

Table of contents

Glossary

AE:	adverse event
AQL:	acceptable quality limit
ATIMP:	advanced therapy investigational medicinal product
CRO:	contract research organisation
CV:	curriculum vitae
EU:	European Union
e-CRF:	electronic case report form
e-TMF:	electronic trial master file
GCP:	good clinical practice
GMP:	good manufacturing practice
IMP:	investigational medicinal product
IRT:	interactive response technologies
ISF:	investigator site file
IWG:	inspectors working group
MA:	marketing authorisation
QC:	quality control
QP:	qualified person
SMF:	site master file
SOP:	standard operating procedure
TMF:	trial master file

1. Executive summary

This guideline has been prepared to assist sponsors and investigators to comply with the requirements of the Clinical Trials Regulation (EU) No 536/2014 (referred to as the "Regulation") on clinical trials on medicinal products, concerning the trial master file (TMF). According to recital 52 of the Regulation "*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"*. Articles 57 and 58 of the Regulation make this mandatory. The same applies to the legal representatives and CROs or any other third party to the extent of their assumed trial related duties and functions. This guideline aims to collate and explain the requirements for the TMF as covered in the Regulation and ICH-GCP E6 to assist organisations in maintaining a TMF that facilitates trial management, GCP compliance and inspection. The document also addresses archiving of the TMF, clarifying retention times, in particular expectations in case of digitization and consecutive destruction of paper documentation.

2. Introduction

A TMF is the collection of essential documents that facilitates the conduct and management of the clinical trial and allows that the integrity of the trial data and the compliance of the trial with GCP can be evaluated. The Regulation does not differentiate between paper and electronic TMFs therefore all basic requirements are the same for both formats. The need for a TMF is set down in Article 57 of the Regulation. The TMF is used by sponsors and investigators for the management of the trial and by auditors, monitors and inspectors to assess whether the sponsor and the investigator(s) have complied with the Regulation, the principles and guidelines of GCP and with other applicable regulatory requirements. Article 57 states "*the clinical trial master file shall at all times contain the essential documents relating to that clinical trial.*" The requirement "*at all times*" means that the TMF should be updated, and completed in a timely manner. Article 58 of the Regulation also requires that "*any alteration of the content of the trial master file shall be traceable"*. The TMF should provide for document identification, version history, search, and retrieval, also, as stated in Articles 57 (and 58) "*it shall be readily available, and directly accessible upon request, to the (competent authorities of the) Member States*". The same requirements for access to the TMF should be in place for the monitors, auditors and ethics committees.

Article 47 of the Regulation requires sponsors and investigators to take appropriate account of ICH GCP E6 and to conduct the trial in accordance with GCP principles, two of which are:

- all clinical trial information should be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of the trial subjects remains protected[1];
- systems with procedures that assure the quality of every aspect of the trial should be implemented[2].

According to Article 57 of the Regulation, the essential documents are "*those pertaining to the trial which allow verification of the conduct of the trial and the quality of the data generated*"; therefore documents resultant from following the systems and procedures that assure the quality of every aspect of the trial are considered essential documents.

As referred to in Article 57 of Regulation "*The clinical trial master file shall at all times contain the essential documents relating to that clinical trial*", and this is to demonstrate that the systems with procedures have been implemented and complied with. Procedures should be in place to assure that the

[1] CPMP/ICH/135/95 2.10-2.11
[2] CPMP/ICH/135/95 2.13

TMF is complete, legible and accurate. The TMF should be sufficient to adequately reconstruct the activities undertaken in conducting the trial, along with decisions and their justifications, made concerning the trial. Consideration should be given to ensuring that the TMF is a set of documentation and/or computer systems that together confirm the validity of the trial conduct and the integrity of data collected without the need for additional explanation from the associated sponsor or site staff.

As trials can be large and complex involving many departments and partners (contract research organisations, vendors, etc.) the management of the TMF can become difficult. Organisations may currently be using an e-TMF to deal with this problem. However, this has also introduced new challenges and issues which together have led to organisations being unable to provide the TMF in an appropriate way for management and audit/inspection purposes as required[3].

This guideline provides detailed standards on how to implement and maintain a TMF which complies with the regulatory requirements.

3. TMF structure and contents

3.1. Sponsor and investigator TMF

The TMF is usually composed of a sponsor TMF, held by the sponsor organisation, and an investigator TMF held by the investigator(s). The investigator TMF is often referred to as the Investigator Site File (ISF) or Site Master File (SMF). The entire TMF for the trial, both of the sponsor and of the investigator(s)/institution(s), should be established at the beginning of the trial. In organising the TMFs, it is essential to segregate some documents that are generated or held by the sponsor only, from those that are generated or held by the investigator only, and vice versa. The investigator/institution is responsible for and should therefore have control of all essential documents and records generated by the investigator/institution before, during and after the trial (at all times). Where the investigator is employed by an institution which is the trial sponsor, the sponsor may delegate the task for maintaining the sponsor TMF to the investigator. In this circumstance, it is possible to combine the sponsor and investigator TMF for that site, which avoids the duplication of documentation. The same applies when the investigator and the sponsor are the same person. The documentation in the investigator TMF will contain some source documents, for example, subject screening and identity logs and consent forms which should remain under the sole control of the investigator due to data privacy regulations.

The investigator TMF may be electronic, with the system either provided by the sponsor, a vendor or by the health care institution. A situation where all the investigator site records are sent to the external sponsor for uploading onto an e-TMF system, which the investigator then accesses via a portal, would potentially breach data privacy requirements and give sole custody to the sponsor for source documents. Therefore, such a construct is considered unacceptable. Remote access, i.e. access to investigator documentation at the investigator site from a different location by sponsor personnel, to personal data of trial subjects in the investigator TMF, is unacceptable. Where a portal is used to provide documents to the investigator, if this is not part of the investigator TMF there needs to be a mechanism to ensure such documentation is filed in the official investigator TMF. Also, there should be an audit trail to demonstrate investigator access to documents in the portal at the appropriate time.

3.2. TMF structure

The sponsor and the investigator should identify and make a record of the location(s) of all of the potential documentation that is considered to form the TMF, even if several locations, departments, country organisations and systems are involved, so that it is effectively organised. Some documents

[3] Clinical Trials Regulation (EU) No 536/2014, Recital 52

may be pertinent to more than one clinical trial; for example product development level documents such as the investigator brochure or documents that are stored in a centralised system, such as central training records, SOPs and delegation logs, documentation demonstrating the validation of computer systems that are not trial-specific. Some records from GMP activities should also be defined as part of the TMF where these relate to the assembly and packaging of the IMP and confirm, where applicable, compliance with the randomisation schedule and blinding of the trial. Provision should be made for all these documents to be identified and retained as part of the TMF even if stored separately from the main TMF itself. There should be a suitable indexing, clear sign-posting to other locations, and a clear electronic file naming system in place for the TMF. This is recommended to be implemented across the sponsor organisation. The documentation should be filed in each appropriate section of the TMF in date sequential order as this facilitates provision of a clear audit trail. The index should be provided to inspectors and auditors to assist in locating documents in the TMF.

3.3. TMF contents

3.3.1. Essential documents

With reference to Article 57 of the Regulation the essential documents are the ones audited by the sponsor's independent audit function and inspected by the competent authorities of Member States as part of the process to confirm the validity of the trial conduct and management and the quality and integrity of the data collected. Essential documents should be complete, legible, accurate, unambiguous and signed and dated as appropriate. The TMF 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[4]. The documentation listed in ICH-GCP E6 section 8 defines the documents that are considered essential (where 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 as it is not an exhaustive list to reconstruct the conduct of the trial. The essential documents for the trial may be supplemented or may be reduced where justified (in advance of the trial initiation), based on the importance and relevance of the specific documents to the trial.

It is acceptable to combine some of the documents, provided the individual elements are readily identifiable. Article 57 of the Regulation states that the trial master file 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 for such trials, some documentation specified in the ICH-GCP E6 guideline may not be necessary due to the implementation of a risk proportionate approach (approach and examples can be seen in the relevant document[5]). 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 TMF. Any documentation which has been created during the trial, for example from complying with formal quality system procedures and that helps reconstruct and evaluate the trial conduct should be filed in the TMF, irrespective of whether it is explicitly listed in these guidelines or not. Duplication of any documentation in the TMF should be avoided.

Examples of documents that are essential, but not listed in section 8 of ICH GCP E6 include:

- any forms, checklists and reports etc. generated from following quality system procedures,
- QP certification of the IMP,
- assay method validation report for analysis of IMP or metabolite(s) in clinical samples,

[4] Clinical Trials Regulation (EU) No 536/2014 Article 57
[5] Document on risk proportionate approach in clinical trials

- ATIMP traceability records,
- documentation to demonstrate validation of trial-specific builds of computer systems (e.g. e-CRF and IRT).

3.3.2. Superseded documents

Superseded versions of documents necessary to reconstruct the trial should be retained in the sponsor TMF. Superseded versions should be present in the investigator TMF in a manner to allow reconstruction without the need to access the sponsor TMF, with evidence of receipt, review, approval (where necessary) and implementation by the investigator. Retention of a tracked changes version or change log that includes all changes to superseded versions may facilitate a reduction in the size of investigator TMF.

3.3.3. Correspondence

Relevant correspondence that is necessary for reconstruction of key trial conduct activities and decisions or that contains other significant information should be retained. This includes for instance correspondence with ethics committees, data safety management boards and regulatory authorities, correspondence to confirm sponsor approval of processes, documents, and decisions, and the communication regarding issues that arise in the trial conduct and how they are dealt with. Electronic correspondence (emails) may be retained electronically. The standards for electronic archiving in section 5.2.2 should be complied with. It must be ensured that both sent and received correspondence is filed in the TMF. Correspondence (paper and/or electronic records) are recommended to be effectively organised and filed in chronological order in an appropriate section in the TMF, i.e. not all in one section, but placed in the section relevant to what the correspondence concerns. Email correspondence should also be readily available and therefore it is unlikely that personal retention of emails, rather than a centralised repository, will facilitate this. Submission of emails to the TMF should be timely and emails should retain their provenance. Care should be taken regarding email 'chains' and attachments to ensure that relevant strands of conversations and their associated documents are maintained, but avoid duplication. If using a central repository to store emails then ongoing review should take place to ensure all information in email is available.

3.3.4. Contemporariness of TMF

As Article 57 states that the *"TMF shall at all times contain the essential documents relating to that clinical trial"*; it is important, therefore, to keep the TMF up to date, with documents placed in the TMF in a timely manner as this greatly assists the successful management of a trial by the investigator and sponsor (or party to whom the sponsor has delegated its duties). In trials that have more complex TMF arrangements with multiple parties involved, the timelines for submission and filing of documents to the TMF in procedural documents or TMF plans should be defined.

A final close-out of a trial can only be done when the investigator and sponsor have reviewed investigator/institution and sponsor TMFs respectively, and confirmed that all necessary documents are filed.

4. Organisation, security and control of TMF

4.1. Organisation of TMF

4.1.1. Contract research organisation and other sub-contractors

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, so access to the sponsor TMF (e.g. remote access to an e-TMF) or at least to relevant documents from it will be necessary in order to discharge their responsibilities effectively. In conducting contracted duties and functions, the CRO will be generating documentation that will need to reside in the TMF. Where there is co-sponsorship of a trial, there should be arrangements put in place for the TMF based upon the responsibilities that each co-sponsor holds. The contract or other document or procedure agreed between all parties should outline the arrangements for the TMF in some detail:

- which party holds the TMF (or which parts of the TMF each party holds when this is divided);
- the process for filing documentation in the TMF;
- the access arrangements for the involved parties;
- the structure and indexing of the TMF;
- where an e-TMF is being used, the details of the system;
- lists of applicable procedures to be followed and training requirements;
- documents that both parties should retain;
- agreed formats for electronic data (e.g. databases, images, laboratory data);
- arrangements for managing correspondence;
- how the TMF would be made available if either party were to be inspected;
- arrangements for when the trial is completed (the CRO may archive the TMF [or parts thereof] on behalf of the sponsor);
- arrangements for oversight of the quality control/quality assurance of the TMF by the sponsor and how this would be documented (e.g. audit reports, QC reports);
- retention times;
- procedures in case of an involved party closing down its business due to any reason.

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

4.2. Security and control of TMF

The entire TMF should be managed securely prior to and during formal archive to prevent accidental or premature loss, alteration or destruction of documents. Those who access the TMF in order to add or remove documentation should be controlled at all times (see 7.1). Also Article 58 of the Regulation clearly states that "*any alteration to the content of the TMF shall be traceable*". If archiving needs any transfer of data or documents (paper or electronic) it should be ensured that they are not lost or altered which should be ensured through validation.

The sponsor and investigator should have a system to identify all trials being conducted and the archive arrangements for the TMF for completed trials, particularly if the sponsor and/or investigator perform many trials and an external archive facility is being used. The system should track TMF documentation to and from the archive facility (particularly important where contract archives are being used).

The sponsor TMF may contain some information which could unblind personnel which need to remain blinded during the trial conduct and should therefore be appropriately controlled.

4.2.1. Storage areas for TMFs

The storage area for the TMF records should be appropriate to maintain the documents such 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 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 areas to be considered when assessing a suitable storage facility are recommended to at least include:

- Security – who can access the storage facility and documents?
- Location - what risks are there, for example from water, fire or other environmental impacts such as – excessive temperature, humidity, sunlight, contamination (dust, fumes, smoke etc.), pests (rodents, insects etc.)?
- Size – has it got the appropriate shelving to accommodate the expected documentation and ease of access?

It is essential that sponsors also make a documented assessment of the storage conditions at the investigator site for storage of the investigator TMF and that the investigator provides this information. The sponsor should be notified if the agreed arrangements are changed.

4.2.2. Electronic TMFs

Electronic TMFs should enable appropriate security and reliability to be in place, ensuring that there is no loss, alteration or corruption of data and documents occurs. The e-TMF is usually a document management system containing all the necessary controls listed below:

- user accounts (created and deleted within a formal approval process);
- secure passwords for users;
- a system in place locking/protecting individual documents or the entire e-TMF (e.g. at time of archiving) to prevent changes to documents;
- regular back up to a separate location;
- an audit trail in place to identify date/time/user details for creation, uploading, approval and deletion of and changes to a document;
- role based permissions for activities being undertaken and for files/documents with restricted access (e.g. randomisation codes, unblinded AE-data).

The e-TMF should be validated in accordance with published standards to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process. The procedures should describe system installation including functionality testing, system maintenance, system security measures, change control, data backup, recovery, contingency planning, decommissioning and, if

applicable, transition to a new system. All members of staff involved in the conduct of the trial and using the system should receive appropriate training.

Where different TMF systems are linked to facilitate the trial conduct, for example the CRO e-TMF system uploads documents into the sponsor e-TMF system, the process for transferring documents should be robust and should be validated to prevent failure of transferring parts or the entire content of the original TMF without loss, i.e. there should be a demonstrable 1:1 mapping between the content of the two systems. Where other systems hold trial documents and data, which are to remain in these systems for long term retention, the appropriate standards mentioned above need to be taken into account. Any electronic system that holds trial data and metadata (e.g. audit trails) required for reconstruction should be archived so they can be retrieved as usable datasets.

The metadata applied to documents should be formally defined to ensure consistency across all documents. This should also include the document date and where appropriate time, based on time zone, so that the files can be displayed in sequential order as well as the date of uploading. Version control should be applied to electronic documents in the system and if the document is printed to paper the same version control should be apparent on the printed version.

There should be a back-up of the e-TMF with the back-up stored in a separate location and/or media. Any migration of data and documents to new media or a new format should be validated to ensure long-term readability and there should be periodic test retrieval or restores to confirm the on-going availability of the data.

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 records are stored on electronic, magnetic, optical or other no-indelible media. In such cases suitable controls should be implemented to ensure that these records cannot be altered without appropriate authorisation and the creation of an audit trail. Digitised documents in the e-TMF should be a certified copy of the original.

5.1. Validation of the digitisation process

The use of e-TMFs and electronic archiving generally requires the digitisation of paper records to generate electronic copies of the documents. When original paper TMF documents are transferred to an electronic format, the process of transfer should be validated in order to ensure that the information will not be lost or altered. A certified copy is 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 a copy having the exact content and meaning of the original. Validation should comprise the following process steps:

- approval for digitisation;
- transportation of the records to the location of digitisation;
- preparation and digitisation of the records;
- indexing and assignment of metadata;
- import of the digitised records into the e-TMF system;
- quality control;
- destruction of the records;

- access to the e-TMF system;
- changes to documents and metadata;
- migration of digitally hosted/archived records;
- deletion of digitally hosted/archived records.

The organisation should maintain records to demonstrate that the digitisation is effectively validated.

As part of the validation a formal process should be in place for regular QC checks of digitised and indexed documents in the e-TMF. This would usually be undertaken on a sampling basis, including escalation procedures where errors occur beyond a pre-defined Acceptance Quality Limit (AQL). The sponsor is responsible for deciding the AQL. The AQL may vary for different sets of documentation on a risk based approach.

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

- accuracy of the metadata attributed to the document;
- quality of the image (suitable resolution, readability, legibility, reproduction of colour - where the colour has meaning, the quality of wet ink signature or annotations and handwriting in general etc.);
- whether it is the correct document (as expected);
- that the document has the correct number of pages;
- that a page or document is newly added to the digital archive or is marked as a corrected version of an already-existing page or document;
- the e-TMF audit trail associated with the document;
- chain of records transfer documentation;
- approval process (where applicable);

Post-scan adjustments to the image to increase legibility are acceptable, provided the limits of what may be undertaken is clearly specified in a formal procedure. It is not acceptable to utilise the scanning process to remove or add material to the image, for example to remove or add the header of a fax machine, or undertake physical ‘cut and paste’ or ‘correction fluid’ activities on the original paper record.

When a vendor is used for the management of the e-TMF and/or for the digitisation of TMF documents, as with any vendor or subcontractor being used for clinical trials, appropriate pre-qualification checks should be undertaken prior to placing the contract. It should be verified upfront whether the vendor has implemented adequate quality management measures. This includes for instance that records on the chain of custody are maintained (e.g. use of a TMF record transmittal form).

5.2. Destruction of original paper after digitisation

Sponsors should ensure that essential documents are not destroyed before the end of the required retention; however, transfer of certified copies to an e-TMF repository (either during the trial or for archiving) could enable earlier destruction of the original paper. This is dependent upon the sponsor’s e-TMFs meeting regulatory requirements such that inspectors would not need to request any original paper records.

Taking into account the implications for providing legally recognised evidence and after consultation with its liability insurer, the sponsor, as well as the investigator, should decide whether documents legally requiring a signature (e.g. written informed consent of trial participants, contracts) should be sorted out

and retained in the original form instead of being destroyed. Destruction of such paper original documents by the sponsor or investigator would be of particular higher risk to destroy than the following examples:

- A document may only have existed and been used in an electronic format (e.g. a spread sheet used for QC of edit check programs) and it is stored electronically. It has been printed on to paper just for filing.
- Documents that do not have wet ink signatures, thus the electronic version is a certified copy of the paper version that has been in the TMF (provided there are no additional annotations made, handwritten or otherwise, for example receipt stamps, fax machine header etc.).

6. Archiving and retention of TMF

Articles 58 (and 57) of the Regulation states 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 competent authorities (of the Member States)".*

The TMF should be archived appropriately to allow for supervision after the clinical trial has ended.

Access to archived data should be suitably restricted either by user access levels to the archive area of a server or by controls to access the storage area where the 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 future access to records and data is maintained. This could include maintaining the system (hardware and software) to access the data in its original 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 via written procedures.

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

6.1. Archiving of the sponsor TMF

With respect to the sponsor TMF, Article 58 of the Regulation states that "*the sponsor shall appoint individuals (archivists) 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[6]. The archivists should have a clear legal link to the sponsor, in that they are employed or contracted by the sponsor. The CRO should also follow this requirement. Withdrawal of 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, and to track and retrieve documents on loan from the archive.

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 CRO may wish to retain certified copies of the documentation from following its own internal procedures after the originals were handed over to the sponsor for archiving and the contract between the sponsor and CRO should address this. The storage of the sponsor's documentation may be

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

transferred to a sub-contractor (e.g. a commercial archive), but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor.

6.2. Archiving of the investigator TMFs

The investigator 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 record retention. The ultimate responsibility for the documents to be retained by the investigator/institution resides with the investigator/institution. The sponsor should obtain the investigator's/institution's agreement to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed. The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement. If the investigator becomes unable to be responsible for their essential documents (e.g. relocation, retirement etc.) the sponsor should be notified in writing of this change and informed as to whom the responsibility has been transferred. It is recommended that at investigator sites/institutions a person is appointed with archiving responsibilities, in particular where there are many investigator TMFs being managed.

The documents to be retained by the investigator may be stored in commercial archives. This may also be an option (in some Member States) for source data, when the hospital/institution is unable to retain patients' trial records, relating to clinical trials, for a sufficient length of time.

Storage of personal data is subject to applicable elements of Directive 95/46/EC and of the General Data Protection Regulation (GDPR), Regulation (EU) 2016/679, once applicable.

If the sponsor arranges the external archiving of the investigator TMF on behalf of the investigator, who should retain control of their part of the TMF, consideration should be given to data protection and confidentiality with respect to unauthorised access, so:

- the archived arrangements should be formally agreed and documented between the sponsor and investigator or health care institution;
- a formal procedure should be in place such that the documents are only released from the external archive with the approval of the investigator or institution. Permission from the investigator or institution should also be required to permit access to the contents of investigator site archived materials at the archive facility;
- the records should go directly between the investigator site and the archive facility independent of the sponsor, thereby ensuring that the sponsor does not have uncontrolled access to the investigator TMF.

6.3. Long term storage of the TMF

The long-term-storage of the TMF may be transferred by the sponsor to a sub-contractor (e.g. a commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor and the investigator for their part of the TMF. Therefore, they should undertake an assessment of the suitability of the facility prior to use and continue assessment once the organisation has been contracted. There should be a formal contract in place between the sponsor/investigator organisation and the archive company. Where the contracted facility is a company with several document storage locations, it is recommended that the sponsor/investigator ensures they are informed about the actual storage location of their TMF and notified if this changes. The contract is recommended to include provisions for the situation of the subcontractor or sponsor going out of business.

6.4. Retention times of TMF

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 guideline on transitory period for the application of Regulation (EU) No 536/2014.

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 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."*

For trials conducted under Directive 2001/20 EC the retention time is at least 5 years after completion (Directive 2005/28/EC).

For all trials where 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 must 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 EC (when there are no pending or contemplated marketing applications in the EC) 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*."

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

Trial subject's medical files should be retained in accordance with national legislation. 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 6).

In addition to these retention times for the trial documentation, records relating to the full traceability of the ATIMP have longer retention periods[7,8]. 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 records.

It is important that where an organisation has centralised records that may be relevant to a number of trials (for example staff training records or maintenance and calibration records for equipment used in the trial at a Phase 1 unit/hospital clinical research unit), that these are also considered in the arrangements for archiving and retention of specific trial records.

The above mentioned retention requirements for the documentation and medical records held by the investigator should be formalised, for example, in the contract between the sponsor, the investigator

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

and the institution. It is the responsibility of the sponsor to inform the hospital, institution or practice as to when trial documents no longer need to be retained and the sponsor should have systems in place to be able to do this. The sponsor should notify investigators in writing when their trial records can be destroyed.

6.5. 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".* Such a situation may occur, for example, when the marketing authorisation is transferred to another organisation. It is recommended to check the contents of the TMF before transfer to ensure all the originally archived records remain present. Any change in the location of the stored documentation should be recorded in order to allow tracking.

Investigators can retire; hospitals and CROs (e.g. Phase 1 units) can close or be acquired by other organisations such that the responsibility for the TMF is transferred. The contracts between the sponsor and the investigator or CRO should cover such eventualities and should oblige the investigator 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 retention time and that patient-related source documents have not been in the sole custody of the sponsor at any time (refer to section 4.1).

7. Provision of trial master file for inspection

7.1. Inspection readiness of TMF

Article 57 states "*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 the clinical trial and the quality of the data generated".* Sponsors and investigators are expected to keep the TMF up to date and ensure that it is complete at the end of the trial. About the TMF Articles 57 (and 58) of the Regulation also state that *"it shall be readily available and directly accessible, upon request, to (the competent authorities of) the Member States*.". The sponsor is recommended to undertake routine quality assurance activities of the TMF processes to ensure this.

Prior to the inspection, the inspector will usually discuss with the sponsor and investigator(s) the logistics of making the TMF available to the inspectors. A paper TMF (or e-TMF stored on media archived elsewhere) or certified copies relevant to the inspection site should be available for the inspection upon reasonable notice, whereas, access to e-TMFs (live and archived on servers) would be expected by inspectors to be essentially immediate (time only required to set up inspector access to the trials requested by the inspectors).

With reference to Article 57 of the Regulation, direct access to the TMF is expected. The inspectors should have read only access, without any restriction (e.g. to final documents), to the entire TMF[9] for inspection during preparation and conduct of the trial, which means that they can review the same TMF as used by the staff conducting the trial. Direct access includes all the systems that comprise the TMF as defined by the sponsor, however, due to the technical nature of some of these systems, for example those containing data rather than documents, these may require the direct access to be assisted by a representative of the sponsor familiar with the system. Organisations should be aware that GCP inspectors may have rights to seize original trial documentation if circumstances arise that require it. GCP inspectors can always request copies or print outs and can retain some or all of these. The GCP

[9] Clinical Trials Regulation (EU) No 536/2014 Article 57 [1]

inspectors' expectation is that an e-TMF should adequately replicate the paper based system that it is replacing and provide for suitable document identification, search, prompt retrieval and marking for future reference/copying. The e-TMF should allow review in an efficient manner, analogous to that possible with paper TMFs. Such a review should not take longer to be undertaken than for a paper TMF and should allow efficient, straightforward navigation and opening of documents permitting searching and browsing (analogous to leafing through a paper file). This would include:

- a folder structure to allow easy identification of TMF sections;
- a folder/file naming convention that readily identifies what each file/document is, so inspectors/auditors do not have to open numerous documents to locate those they need;
- the ability to open more than one document at a time to allow comparison (so size of screens or double screens important);
- the ability to provide access to the same type of document across all studies/sponsors/product etc. (i.e. if inspector needs to review documents for all/some selected studies/sites);
- the system is recommended to have an efficient speed of access and ideally not require the use of a nomenclature document or require time spent opening non self-evident named files to determine their content.

It is acknowledged that inspectors may need to familiarise themselves with an e-TMF. Any training should be an option for the inspector to choose and is anticipated to be very brief (taking no more than an hour).

The e-TMF will need the use of suitable equipment, to be provided by the organisation, for the inspector to view the documents. This equipment is recommended to facilitate the presentation of the documents at actual size.

8. References

- Clinical Trials Regulation (EU) No 536/2014
- CPMP/ICH/135/95 note for Guidance for Good Clinical Practice
- Detailed guidelines on good clinical practice specific to advanced therapy medicinal products 03/12/2009 ENTR/F/2/SF/dn D(2009) 35810
- Directive 2004/23/EC on quality and safety for human tissue cells
- Directive 2006/86/EC on traceability requirements for human tissue and cells