EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 June 2015
EMA/INS/GCP/636736/2012
Good Clinical Practice Inspectors Working Group (GCP IWG)

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

Draft

Draft Adopted by Good Clinical Practice Inspectors Working Group for release for consultation	12 December 2012
Start of public consultation	1 February 2013
End of consultation (deadline for comments)	30 April 2013

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5505
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Executive summary

This reflection paper has been prepared to bring together the requirements of EU[1] legislation and guidance relating to the TMF[2]. This is deemed necessary by the EU GCP IWG[3] Inspectors due to the numerous questions asked by organisations in relation to the TMF (in particular eTMFs[4]) and also to the repeated inspection findings concerning the TMF that have been made. The reflection paper aims to set out the requirements for the TMF as covered in directives and guidance and to give recommendations to assist organisations in maintaining a TMF that facilitates trial management, GCP compliance and inspection. The paper also addresses archiving of the TMF, clarifying retention times and gives some recommendations regarding destruction of paper documentation.

2. Introduction

A TMF is the collection of documentation that allows the conduct of the clinical trial, the integrity of the trial data and the compliance of the trial with GCP to be evaluated. The requirement for a TMF is set down in Directive 2001/20/EC[i] Article 15(5) and the TMF forms the basis for inspection (Directive 2005/28/EC[ii] Article 16). The TMF is used by auditors and inspectors to assess the compliance of the trial with legalisation and guidance and by sponsors, monitors and investigators for the management of the trial (Recommendations on the content of the trial master file and archiving [iii] Section 3 and Note for Guidance on Good Clinical Practice CPMP/ICH[5]/135/95[iv] Section 8.1).

Directive 2005/28/EC Article 16 also defines essential documents as those which enable both the conduct of the clinical trial and the quality of the data to be evaluated. It further states that these documents must show whether the investigator and sponsor have complied with the principles and guidelines of good clinical practice and with the applicable regulatory requirements. Further guidance on these documents is contained in Note for Guidance on Good Clinical Practice CPMP/ICH/135/95, EMA Inspectors Working Group Q&A[v] and in Recommendations on the content of the trial master file and archiving.

Two of the GCP principles within the Directive 2005/28/EC (and similar wording is within Note for Guidance on Good Clinical Practice CPMP/ICH/135/95) are:

- all clinical trial information shall 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. (Directive 2005/28/EC Article 5);
- the necessary procedures to secure the quality of every aspect of the trials shall be complied with (Directive 2005/28/EC Article 2 [4]).

The documentation resultant from conducting the trial and following the necessary procedures must be retained (Directive 2005/28/EC Article 17). Procedures should be in place (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 2.13) to assure that the TMF is complete and accurate. The TMF must be sufficient to adequately reconstruct the trial activities undertaken (Directive 2005/28/EC Article 16), along with key decisions made concerning the trial and thus should be prepared and maintained appropriately (Recommendations on the content of the trial master file and archiving, Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4, 5.5.7 & 8). Consideration should be

[1] European Union
[2] Trial Master File
[3] Good Clinical Practice Inspectors Working Group
[4] electronic Trial Master File
[5] International Conference on Harmonisation

given to the TMF being a stand-alone set of documentation that does not require additional explanation from the associated sponsor or site staff.

As trials can be large and complex involving many departments and contract research organisation, the management of the TMF can become difficult. Organisations are now using an electronic TMF (eTMF) to deal with this problem, but this has also introduced new challenges. Together these issues have led to organisations being unable to provide the TMF in an appropriate way for management and audit/inspection purposes as required (Directive 2005/28/EC Article 16).

3. Legal basis

This document is a reflection paper[vi] of the GCP Inspectors Working Group. The paper is intended to cover the use of TMF and eTMF in all clinical trials in the EU/EEA[6] (or in third countries in case the clinical trial reports are submitted as part of Marketing Authorisation Applications to EU/EEA regulatory authorities). The requirements have their basis in the Directive 2001/20/EC, Directive 2005/28/EC, Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 and Recommendations on the content of the trial master file and archiving and expectations and recommendations are based on interpretation of these requirements.

4. Organisation and control of trial master files

4.1. Sponsor and investigator files

The TMF is normally composed of a sponsor TMF, held by the sponsor organisation, and an investigator TMF held by the investigator(s) (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 8.2 and Recommendations on the content of the trial master file and archiving Section 3). The investigator TMF is often referred to as the investigator site file. These files together are regarded by GCP Inspectors as comprising the entire TMF for the trial and should be established at the beginning of the trial (Recommendations on the content of the trial master file and archiving Section 3 and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 8.1). In organising the TMFs, it is essential to segregate some documents that are generated or held by the sponsor from those of the investigator and vice versa (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 8.2, 8.3 and 8.4, Recommendations on the content of the trial master file and archiving Sections 3.1, 3.2 and 3.3), as some documentation held by the investigator should not be provided to the sponsor, for example those documents that would result in breach of subject confidentiality (Directive 2005/28/EC Article 5, Directive 2001/20/EC Article 3 [2] c and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 2.11), unless they are the same organisation, for example when the sponsor is a hospital/health institution and the investigator is an employee of the hospital/health institution.

4.2. Contract research organisation (CRO)

The sponsor may choose to contract duties and functions of the sponsor to a CRO[7], which increases the complexity of the TMF. The sponsor is still responsible for the trial and will need to maintain oversight (Directive 2005/28/EC Article 7 and Recommendations on the content of the trial master file and archiving Section 6), so access to the TMF (e.g. remote access to eTMF) may be necessary or the sponsor may decide that the CRO needs to provide specific documents to the sponsor. The role of the CRO in the trial should to be formally documented, usually in a written agreement between the sponsor and the CRO, outlining in detail the duties and functions transferred to the CRO (Note for

[6] European Economic Area
[7] Contract Research Organisation

Guidance on Good Clinical Practice CPMP/ICH/135/95 5.2.2). In conducting these allocated duties and functions, the CRO will be generating documentation that will need to reside in the TMF (Directive 2005/28/EC Article 16). In addition, the CRO may have been delegated the duty of managing the sponsor's TMF. The contract or other document or procedure is recommended to outline the arrangement for the TMF in some detail. This is recommended to address:

- which party holds the official 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 both parties;
- the structure and indexing of the TMF;
- where an eTMF is being used, the details of the system;
- lists of applicable procedures to be followed and training requirements;
- documents that both parties must retain;
- arrangements for managing correspondence;
- how the TMF would be made available if either party was 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[8] reports).

It is important the documentation generated by the CRO from following its internal procedures is retained and sponsors must consider this part of the TMF (Directive 2005/28/EC Article 2[4] and 16).

4.3. TMF structure

The sponsor should identify where all of the potential documentation that is part of the TMF is located, even if it is several systems, so that it is effectively organised (Recommendations on the content of the trial master file and archiving Section 2). This detail, may, dependent upon its complexity require formal documentation in a procedure (e.g. SOP[9]). In large organisations, the TMF could include documents from across a variety of different departments and systems other than clinical operations, for example, Data Management, Statistics, Pharmacovigilance, Clinical Trial Supplies, Pharmacy, Legal, Regulatory Affairs etc., as well as those provided or held by CROs. Sometimes documents may need to be located in a separate location to the main TMF records, for example those that contain information that could unblind the study team. This contrasts with a small single centre non-commercial trial, where the documentation is likely to be much less and could be limited to just the sponsor-investigator and pharmacy files.

Some documents 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, for example central training records, SOPs and delegation logs. Provision must be made for these to be identified and retained as part of the TMF for the required retention period (Directive 2005/28/EC Article 16), even if stored separately from the main TMF itself. If potential difficulties (e.g.

[8] Quality Control
[9] Standard Operating Procedure

cross reference in the TMF becomes out of date) are envisaged with this arrangement, the documents are recommended to be copied and placed in the trial TMF at the time of archiving.

There should be a suitable indexing system in place for the TMF to ensure that the documentation is appropriately sorted and filed, which facilitates audit, inspection and trial management (Recommendations on the content of the trial master file and archiving Section 2). This is recommended to be implemented across the sponsor organisation so that the TMF has the same structure irrespective of the location of the trial and the organisation. The sponsor is recommended to decide if a formal procedure is required to define standard indices or whether statements in the protocol together with a trial specific index in the TMF are sufficient. The use of a formal procedure and a standard indexing system (rather than creating "trial specific" indices repeatedly) in organisations sponsoring several trials may facilitate compliance. There could be some flexibility in the index to facilitate the TMF is fit for purpose for the actual study (for example, removal of sections that are clearly not applicable). The documentation is recommended to be filed in each section of the TMF in date sequential order as this facilitates provision of a clear audit trail. The index could be provided to inspectors and auditors to assist in locating documents in the TMF.

For investigator TMFs, the sponsor may, and usually does, provide assistance to the investigator site by providing a suitable file and structure for the file. There is no obligation on the investigator to use this (unless contracted to do so) and the investigator may use their own structure if they so wish.

4.4. TMF security and control

The sponsor's TMF is the repository of all the information that is necessary to reconstruct the trial and therefore its security and maintenance is important (Recommendations on the content of the trial master file and archiving Section 2). It is recommended that it is stored such that those who access the TMF in order to add or remove documentation are controlled whilst the trial is in progress. The risk of a lack of control would potentially be missing documentation at the end of the trial. Some organisations may archive the documentation on an ongoing basis to prevent loss, particularly where eTMFs are in use. The investigator's TMF should be stored securely to prevent accidental or premature destruction (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4 and Recommendations on the content of the trial master file and archiving Section 8) and it is recommended access is restricted such that only study staff (and monitors, auditors and inspectors) can gain access to the documentation.

5. Trial master file contents

5.1. Essential documents

The documentation listed in section 8 of ICH GCP and section 3 of the Volume 10 TMF guidance defines the minimum of documents that are considered essential (where appropriate to the trial); however, this list is not recommended to be used as a definitive checklist for TMF content. The essential documents listed in regulatory guidance can be regarded as a subset of the potential documentation that could be regarded as essential for reconstruction of the conduct of the trial. Any documentation which has been created during the trial and that helps reconstruct and evaluate the trial conduct must be filed in the TMF, irrespective of whether it is explicitly listed in these guidelines (Directive 2005/28/EC Articles 16 and 17). Sponsors, CROs and investigators are recommended to consider the value of a document in this regard when deciding to file it in the TMF.

5.2. Superseded documents

Superseded versions of documents must be retained within the TMF (Directive 2005/28/EC Articles 16 and 17), for example the Investigator's Brochure or the protocol as these are necessary to reconstruct activities in the earlier part of the trial. In the case of the Investigator TMF, it is acceptable to retain evidence that the document has been received/ implemented rather than retention of the superseded document itself, but the actual document must be available in the Sponsor TMF.

5.3. Correspondence

Relevant correspondence that is necessary for reconstruction of key trial conduct activities and decisions or that contains other significant information must be retained (Directive 2005/28/EC Articles 16 and 17, Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 8.3.11 and Recommendations on the content of the trial master file and archiving Section 3.2.11). Some CRO organisations for example, rely solely on email correspondence to confirm sponsor approval of processes, documents, and decisions. There is usually extensive important communication (e.g. regarding issues that arise in the trial conduct and how they are dealt with) between sponsors, CROs, investigator sites, ethics committees and competent authorities. Electronic correspondence (emails) may be retained electronically, provided the requirements for eTMF and electronic archiving are considered. Emails are recommended to be saved to ensure that the associated metadata is retained, for example as .pst files rather than pdf documents or being printed and signed. Correspondence (paper and emails) are recommended to be effectively organised and filed in chronological order in an appropriate section in the file. Duplication of any documentation in the TMF is recommended to be avoided, but this often occurs with email correspondence and with attachments. Sections including correspondence must be complete (Directive 2005/28/EC Articles 16, 17 and 20). During GCP inspections it is often seen that only copies of letters received rather than those both sent and received are filed (such as Research Ethics Committee correspondence), such that the TMF only contains half of the audit trail.

5.4. Documents from following quality system procedures

Any quality record produced from following a quality system procedure must be retained in the TMF to demonstrate compliance (Directive 2005/28/EC Articles 2[4], 16 and 17). Examples include evidence of QC checks, documentation on Regulatory Green Light, Database Lock Forms etc.

5.5. Contemporariness of TMF

The TMF should to be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF "inspection ready" (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Section 3). GCP inspectors would raise concerns if the TMF appeared out of date such that the ability to manage and oversee the trial conduct was questionable. In trials that have more complex TMF arrangements with multiple parties involved it may be useful to define the timescales for submission and filing of documents to the TMF in procedural documents or TMF plans.

6. Provision of trial master files for inspection

As per Article 16 of Directive 2005/28/EC, it is required that the TMF (or requested part[s] of it) for the trial is readily available and for the TMF to be produced at any reasonable time during the trial conduct and for at least 5 years after the trial completion (Directive 2005/28/EC Article 17) (longer for trials

supporting marketing authorisations (EU Directive 2003/63/EC[vii]) or as per national legislation). This is applicable to both sponsor and investigator TMF. The requirements and logistics of TMF provision will usually be confirmed with the sponsor/investigator prior to the inspection by the inspector. Sponsors and investigators are recommended to have considered how to make the TMF readily available to the inspectors, this includes making arrangements to review the TMF at a CRO site (where the TMF maintenance has been delegated by the sponsor). A paper TMF (or eTMF stored on media archived elsewhere) relevant to the inspection site must be able to be made readily available (Directive 2005/28/EC Article 17), for example within a few days. Access to eTMFs (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).

The inspectors must have direct access to the entire TMF (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Section 2), which means reviewing the TMF as used by the staff conducting the trial. A copy or artificial construction of it is unlikely to be accepted for trials currently in the live phase and puts an additional QC requirement on the sponsor. A copy may be acceptable for archived TMFs (see below). Direct access includes all the systems that comprise the TMF as defined by the sponsor. GCP inspectors may not wish to be supervised during the review of the TMF. GCP inspectors inspecting their own countries may have rights to seize trial documentation if circumstances arise that require it and organisation should be aware of this right.

Remote access to eTMF without the inspector visiting the site may assist in planning inspections and could, in future, potentially form part of the inspection dependent upon national legislation and inspection practices.

7. Electronic trial master files

7.1. eTMF content

The eTMF could contain digital documents in their original format, potentially with digital signatures, or records that have been converted from another format, such as paper documents that have been converted to digital images, which may contain wet-ink signatures. The metadata applied to documents is recommended be formally defined to ensure consistency across all documents. As part of a quality system for GCP (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.1.1) version control should be applied to electronic documents in the system and if the documented is printed to paper the same version control should be apparent on the printed version.

7.2. Controls and security, training and validation of eTMF

The eTMF is recommended to ideally be a document management system containing all the necessary controls listed below to be completely acceptable. The storage of documents within folders in a computer systems' operating environment without the minimum controls below is unlikely to be considered acceptable.

The eTMF system should enable appropriate security to be in place (Recommendations on the content of the trial master file and archiving Sections 5 and 6), which is recommended to include, as a minimum:

- user accounts could be created and deleted within a formal approval process and in a timely manner;
- 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 back up.

Additionally, the eTMF would ideally have the following attributes:

- where there is approval of documents via a workflow system, there should be use of digital signatures;
- role based permissions for activities being undertaken;
- audit trail in place to identify date/time/user details for creation, uploading, approval and changes to a document.

The eTMF should be validated to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process and for change control (Directive 2005/28/EC Article 5, Recommendations on the content of the trial master file and archiving Section 5 and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.3). The validation of the system should follow previously published standards[viii]. The documentation for this process must be retained (Directive 2005/28/EC Article 16 and 17). All members of staff involved in the conduct of the trial and using the system must receive appropriate training and this should be documented (Directive 2005/28/EC Article 2[2]). User manuals and helpdesk are recommended be in place as part of the validated system as appropriate. It may be appropriate for the eTMF to be introduced as "pilot" before implementation.

7.3. eTMF at the investigator site

The sponsor will require copies of some investigator TMF documents for the sponsor TMF and these could be provided electronically (e.g. scanned and uploaded to a web based portal) provided there are appropriate controls in place (see 7.2 and 7.4).

Whilst it has not yet been seen by GCP inspectors, there is the potential for the investigator TMF itself, held by the principal investigator, to also become electronic, with the system either provided by the sponsor, a vendor or by the health care institution. The documentation in the investigator site file will contain some source documents, for example, subject screening and identity logs, consent forms, drug accountability records etc., and the control of these must remain under the investigator (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4 and 8.3, Recommendations on the content of the trial master file and archiving Section 3.2). A situation where all the site records are sent to the external sponsor for uploading onto an eTMF system, which the investigator then accesses via a portal, would breach this requirement. The sponsor should consider the EMA GCP Inspectors Working Group Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials[ix] (Directive 2005/28/EC Article 4), as the considerations and recommendations will have applicability to source documents contained in eTMFs. Whatever system is used, long term access to the eTMF documentation by the investigator must be assured (Directive 2005/28/EC Article 17 and Directive 2003/63/EC).

7.4. Scanning or transfers to other media

The use of eTMFs and electronic archiving generally require the scanning of some paper records to generate electronic copies of the documents. The QC of the scanning, as part of the validation or subsequent sample QC activities could assess, for each document reviewed, one or more of the following:

- accuracy of the metadata attributed to the document (it is recommended that the sponsor has defined the required metadata in a formal procedure);
- quality of the image (readability, reproduction of colour, the quality of wet ink signature or annotations and handwriting in general etc.);
- whether it was the correct document (as expected);
- that the document had the correct number of pages;
- the eTMF audit trail associated with the document;
- chain of records transfer documentation;
- approval process (where applicable);
- scanned images should be at appropriate resolution so that when viewed at actual size on the screen (as per the original) the image is clear and legible.

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 the header a fax machine has added, or undertake physical 'cut and paste' or 'correction fluid' activities on the original paper record (Directive 2005/28/EC Article 20 and Recommendations on the content of the trial master file and archiving Section 5). Documents within an eTMF must remain complete and legible in all aspects (Directive 2005/28/EC Article 20 and Recommendations on the content of the trial master file and archiving Sections 5 and 6) which gives information about the way the document was prepared. This holds especially true for contracts and forms completed by hand. It would not be acceptable, therefore, to create an electronic version of a form that had been previously completed by hand and then file that instead of the original.

When original paper TMF documents are transferred to an electronic format (or other media) the system of transfer should be validated in order to ensure that the transfer of documents is without loss and to ensure that certifiable copies are made (Recommendations on the content of the trial master file and archiving Section 5). A certified copy can replace the original paper record (Recommendations on the content of the trial master file and archiving Section 5). All transfers should be certified for accuracy and completeness by someone with appropriate authority (e.g. trial manager), as part of the quality assurance system (Recommendations on the content of the trial master file and archiving Section 5). This does not necessarily mean that the individual reviews every document, but that they have adequately approved the validated system that is being used. If 100% checks are not performed proper justification is recommended to be provided, including validation files proving that the process provides reliable and unaltered copies. It should be ensured that the transferred documentation can not be modified or deleted (Recommendations on the content of the trial master file and archiving Section 5). This could be achieved by system design and/or through the use of a cryptographic key obtained from a trusted authority. The organisation should maintain records to demonstrate to GCP Inspectors that the transfer system is effectively validated (Directive 2005/28/EC Article 5, Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.3 and Recommendations on the content of the trial master file and archiving Section 5).

Where the transfer of documents is undertaken using a validated process, a formal process is recommended to be in place for regular checks of documents in the eTMF. This would usually be undertaken on a sampling basis, including escalation procedures where errors occur beyond a pre-defined acceptable error rate. The sponsor is responsible for deciding this value and it may vary, and the QC levels vary for different sets of documentation on a risk based approach.

7.5. eTMF vendors

When a vendor is used for eTMF management, as with any vendor or subcontractor being used for clinical trials, appropriate pre-qualification checks should be undertaken prior to placing the contract (Directive 2005/28/EC Article 7[1], Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.2.1 and Recommendations on the content of the trial master file and archiving Section 6). Where TMF documents are moved from the sponsor to the vendor for scanning, a formal procedure should be in place to ensure chain of custody records are maintained (e.g. use of a TMF record transmittal form) (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 2.13).

7.6. GCP Inspection of eTMF

GCP Inspectors are not averse to reviewing an eTMF during a GCP inspection. The legislation does not differentiate between paper and eTMFs therefore all the requirements are the same, however, the use of an eTMF at an inspection presents additional challenges to both the inspector and the organisation.

The GCP Inspectors expectation is that the eTMF should adequately replicate the paper based system that it is replacing, in terms of the usability and time taken. The organisation is recommended to consider that the requirements for inspectors will also be reflective of the requirements of any auditors and the system is recommended to be designed and developed or purchased with this in mind.

It is acknowledged that inspectors may need to familiarise themselves with an eTMF. Any training should be an option for the inspector to choose and is anticipated to be very brief (taking no more than an hour). GCP Inspectors will require direct access to the eTMF system as used by the organisation (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Sections 2 and 3). The access is recommended to be a read only access without any restriction to any part of the TMF. There may be additional electronic systems that have TMF documents (identified in the TMF as part of the TMF structure), access to such systems is also required by the inspector.

The eTMF will need the use of suitable equipment for the inspector to view the documents. This equipment is recommended to facilitate the presentation of the documents at actual size, which in most cases would be A4 paper, and the size is recommended not to be reduced due to other areas on the screen, for example, directory/index structure, toolbars etc. The organisation is responsible for providing suitable equipment to view the eTMF.

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. The system and equipment would ideally be akin to flipping the pages of a book and it would be useful if there is a system tool available to print or mark documents for subsequent retrieval and examination as well as the ability to compare documents side by side. Finally, if documents from the eTMF are required to be copied and retained by the inspector, the organisation is recommended to be able to facilitate this. A search tool in the eTMF is also recommended.

8. Retention and destruction of trial master file contents

8.1. Retention times

The sponsor and the investigator must ensure that the documents contained, or which have been contained, in the TMF are retained for at least 5 years after the conclusion of the trial (Directive 2005/28/EC Article 17) or in accordance with national regulations. Trials where the data are used to support a marketing authorisation have further requirements and must be retained for at least 15

years after completion or discontinuation of the trial or for 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 (Directive 2003/63/EC). Directive 2003/63/EC states the sponsor or other owner of the data must retain some of the documentation for as long as the product is authorised. Additionally, this documentation must include (as a minimum) the trial protocol (which must include the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, details of the investigational product, the reference medicinal product and/or the placebo used), any standard operating procedures used for conducting the trial, 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, staff training records. Finally, the final report must also be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorised.

Trial subject's medical files should be retained for at least 5 years (Directive 2005/28/EC Article 17) (and this is recommended to be in their original format) and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Scanning or microfiching of patient notes is acceptable provided the process is validated such that the institution can demonstrate that it is an authentic copy of the original and is kept in a format that means that the data can be retrieved in the future (see more detailed information above). It is recommended that the notes of patients that have been involved in clinical trials are clearly identified to prevent premature destruction.

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 (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.12 and Recommendations on the content of the trial master file and archiving Section 7). The retention requirements of the sponsor needed for the documentation and medical records held by the investigator should be formalised, for example, in the contract between the investigator/ institution and the sponsor (Recommendations on the content of the trial master file and archiving Section 7). The sponsor would be expected to have systems in place to alert the investigator when the records are no longer required to be retained (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.12 and Recommendations on the content of the trial master file and archiving Section 7). The sponsor should notify investigators in writing when their trial records can be destroyed and up until that point the investigator or institution should take measures to prevent accidental or premature destruction of these documents (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4). The ultimate responsibility for the documents to be retained by the investigator or institution resides with the investigator or institution (Recommendations on the content of the trial master file and archiving Section 6). 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 (Recommendations on the content of the trial master file and archiving Section 6).

In addition to these retention times for the trial documentation, records relating to the full traceability of the IMP for Advanced Therapies have longer retention periods. 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 files as well as the trial subjects' medical records. Further information can be found in the EU detailed guidance on GCP for advanced therapy medicinal products (2009)[x].

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, as they may be required to be produced if the trial is inspected (Directive 2005/28/EC Article 16 and 17).

The protocol or the formal procedures and any applicable contracts of the sponsor are recommended to contain details of the retention times for all the trial documentation as outlined above or the process used to determine how long particular documentation will be retained for and how this would be documented.

The requirements for the retention of sponsors' records also apply to the records retained by CROs or other agents of the sponsor, unless arrangements have been made to transfer the documents to the sponsor. The details of the retention time of documents held by CRO are recommended to be formalised in an agreement between the sponsor and the CRO.

Investigators can retire, hospitals can close and CROs (some of which are also investigator sites, e.g. commercial phase 1 units) can go out of business or be acquired by other organisations. The sponsor is recommended to ensure that agreements with the investigator cover such eventualities to ensure that the documentation remains available for inspection for the specified retention time. The investigator should notify the sponsor of such circumstances and it is the investigator's responsibility to organise retention of the documents and data of clinical trials conducted in this site, including medical files of patients that participated in these trials, so the sponsor should check this has occurred. Sponsors must ensure that provision is made to make the archived documents for trials conducted in the EU available to the EMA and member states throughout the retention period, including documentation held by CROs (Directive 2005/28/EC Articles 16 and 17).

8.2. Named individual responsible for archiving TMF

In respect of the sponsor TMF, the sponsor must appoint a named individual within the organisation to be responsible for archiving the documents which are, or have been, contained in the TMF and that access to these documents shall be restricted to those appointed individuals and auditors or inspectors (Directive 2005/28/EC Article 19). This could be undertaken by either having a specific archivist role or combining the archiving duties with another role, but either way there should be clear documentation to support the appointment and appropriate training provided (Directive 2005/28/EC Article 2[2]). The archivist is recommended to have a clear legal link to the sponsor, in that they are the sponsor themselves or employed or contracted by the sponsor. Where there is a change of ownership of data or documents connected with the clinical trial, for example, transfer of a marketing authorisation to another organisation then the sponsor must record the transfer and the new owner shall be responsible for data retention and archiving (Directive 2005/28/EC Article 18). For TMFs that are returned to the archive or where a transfer of ownership took place, a check is recommended to be undertaken of the contents to ensure all the originally archived records remain present. It is recommended that at investigator sites/institutions were there are many investigator TMFs being managed, a person is appointed with archiving responsibilities.

8.3. Pre-archive checks

Prior to the storage of the TMF, it should be checked to ensure it is complete and that all necessary documentation has been filed appropriately (Recommendations on the content of the trial master file and archiving Section 3).

The sponsor is recommended to have a system to identify all trials conducted and the archive arrangements for the TMF for those trials, particularly if the organisation sponsors many trials and an external archive facility is being used. The system would ideally track TMF documentation to and from the archive facility (particularly important where contract archives are being used) and, where

appropriate, such as for large organisations, location of the TMF documentation on site when temporarily removed from the archive. The system/process would be controlled or overseen by the named archivist.

8.4. Storage areas/conditions

The storage area for the TMF records must be appropriate to maintain the documents such that they remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request (Directive 2005/28/EC Article 16 and 17 and Recommendations on the content of the trial master file and archiving Section 6). The areas to be considered when assessing a suitable storage facility are recommended to at least include:

- Security – how accessible are the documents, are there locks in place on doors/cupboards, what is the risk of unauthorised access, are there windows on the ground floor etc?
- Location - what risks are there from water (burst pipes, flood), fire (what activities take place in the room next door/above/below), what runs in the ceiling/floor void etc?
- Size – is the archive facility large enough and have the appropriate shelving to accommodate the expected documentation?
- Environmental – are there risks from excessive temperature, humidity, sunlight, contamination (dust, fumes, smoke etc)?
- Pests – are there risks from rodents, insects etc?

It is essential that sponsors also make a documented assessment of the storage conditions at the investigator site for the investigator site file and that the investigator provides this information (Recommendations on the content of the trial master file and archiving Section 6).

8.5. Subcontracting archiving

The storage of the TMF may be 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 and investigator for their part of the TMF (Directive 2005/28/EC Article 7[1], Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4, 4.9.5 and 5.2.1 and Recommendations on the content of the trial master file and archiving Section 6). Therefore, they should undertake an assessment of the suitability of the facility prior to use and continue assessment once the organisation has been contracted. It is recommended that there is a formal contract in place between the sponsor/investigator organisation and the archive company. Where the contract facility is a company with several document storage locations, it is recommended that the sponsor/investigator ensures they are made aware of the storage location of their TMF, as some contracts allow the archive company to move documents between their facilities. The contract is recommended to include provisions for the situation of the subcontractor going out of business.

8.6. Archiving of investigator TMF by the sponsor

The investigator should retain control of the documentation contained in the investigator TMF and the investigator TMF should never be sent to the sponsor organisation (Directive 2005/28/EC Article 17, Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 4.9.4, 8.2-8.4, Recommendations on the content of the trial master file and archiving Section 3.1-3.3). This requirement does not mean that a sponsor cannot arrange the external archiving of the investigator TMF on behalf of the investigator, which is acceptable, subject to the following being implemented. As the investigator TMF contains

subject information, consideration should be given to data protection and confidentiality with respect to unauthorised access (Directive 2005/28/EC Article 5, Directive 2001/20/EC1 Article 3 [2] c and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 2.11):

- the archived arrangements are formally agreed and documented between the sponsor and investigator or health care institution;
- a formal procedure is in place such that the documents are only released from the external archive with the approval of the investigator or institution and this is tested for robustness. 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 go directly between the investigator site and an archive facility independent of the sponsor, thereby ensuring that the sponsor does not have uncontrolled access to the investigator files.

8.7. Electronic archiving

The use of electronic systems for such activities as data management, statistical analysis, reporting, trial management systems and eTMFs means that electronic documentation and data are likely to need to be retained. The data may be on a server or on transportable media, e.g. media drives/pens drives, Compact Discs, tapes etc. The following is recommended to be considered with respect to electronically archived data:

- it could be subject to back up (with the back up media stored in a separate location);
- storing the data in differing formats on different types of media (or even on the same media from different manufacturers.);
- access to archived data should be suitably restricted;
- the electronic documents or data that have been archived must be protected from unauthorised changes to maintain authenticity (Recommendations on the content of the trial master file and archiving Section 5);
- future access to records and data should be maintained (processes to overcome media, software and hardware becoming obsolete) (Recommendations on the content of the trial master file and archiving Section 5);
- periodic test retrieval or restores to confirm that ongoing availability of the data is being maintained;
- where data is required to be migrated to new media or a new format, then the transfer/migration of data to a new media/format should be validated (Directive 2005/28/EC Article 5, Recommendations on the content of the trial master file and archiving Section 5 and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.3) (no loss, changes or corruption to the data or meta data and that authenticity is maintained).

8.8. Destruction of original paper

As stated, the EU legislation and guidance does require the documents to be readily available, complete, legible and contain traceability of any changes made. Sponsors should ensure that essential documents are not destroyed before the end of the required retention periods (Recommendations on the content of the trial master file and archiving Section 8); however, transfer of the document to an eTMF repository (either during the trial or for archiving) could enable earlier destruction of the paper

original in case where the eTMF system would have all the characteristics as defined above. Experience of eTMFs to date, however, has not yet provided sufficient evidence that inspectors would not need to request some original paper records for inspection and thus early, complete destruction of such records is not recommended currently.

In this regard, destruction of paper original documents with wet ink signatures (e.g. letters, contracts, consent forms) by the sponsor or investigator would be of particular higher risk to destroy than the following examples and this is recommended to be considered by the sponsor when deciding if and what to destroy.

- 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.
- A paper document may be a copy of an original located elsewhere (e.g. investigator's signed CV from the Investigator TMF), thus if required, a copy could be obtained.
- Documents that do not have wet ink signatures, thus the electronic version is an exact 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).

9. Problems found with trial master files from GCP inspections

The following summarises some of the issues that have been found from GCP inspections

- Organisation was unable to provide a full TMF (paper and electronic) for inspection purposes on request of the GCP inspectors. In some cases resulting in additional inspection days required. This is often as a result of the contents being restricted to the contents of Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 Section 8 documents. The organisation should be aware of the locations within the organisation (and that includes all the global locations) of all the documentation that comprises the TMF and situations arise where there is complete lack of clarity on what constituted the TMF for the trial. This includes issues with the location of documents that are common across several clinical trials (for example, the investigator's brochure).
- The paper TMF structure (poor indexing etc.) did not facilitate timely review to evaluate the conduct of the trial.
- The sponsor provided an "artificial TMF", thus failed to provide adequate direct access. Inspectors have in the past been provided with an 'artificial TMF or 'snapshot' which consisted of a copy of the official TMF being used and led to issues with documentation not being consistent with that of the official TMF.
- Staff that were put forward as "system users" for eTMF were also unable to locate documents requested by the inspector.
- Failure to fully document and perform effective QC checks on documents uploaded into eTMF – the result being that the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were missing pages, incorrect documents, poor quality scans.
- Incorrect documents located in the TMF and eTMF – for example from other trials.
- There was poor, often repetitive, sometimes incorrect labelling of files, resulting in excessive time wasted opening and closing pdf documents in the eTMF when attempting to locate documents.

- There was no accurate record with the details of documents sent to contractor for uploading into eTMF.
- There was a failure to document activities to allow reconstruction of the trial conduct. All the records that were produced from following the organisations SOPs or other activities (e.g. training, Project Team Meetings) were not filed.
- The organisation did not provide adequate equipment for the inspector to review the eTMF. Lap tops with tiny screens did not facilitate the review and were not comparable (e.g. in size) with paper.

10. References

[i] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 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 (Official Journal L 121, 1/5/2001 p. 34 - 44)
[ii] Directive 2005/28/EC of 8 April 2005 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 (*Official Journal L 91*, 9/4/2005 p. 13 - 19)
[iii] Recommendation on the content of the Trial Master File and archiving July 2006. Volume 10 Rules Governing Medicinal Products in the European Union
[iv] Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Volume 10 Rules Governing Medicinal Products in the European Union
[v] Q&A GCP EMA:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000016.jsp&mid=WC0b01ac058002 96c5&jsenabled=true
[vi] EMEA/P/24143/2004 'Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework'
http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500004011.pdf
[vii] Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Community code relating to medicinal products for human use
[viii] PIC/S publication/recommendation, PI 011-3 "Good Practices for Computerised Systems in Regulated "GXP" Environments (PI 011-3) Sept 2007. Secretariat of the Pharmaceutical Inspection Convention c/o EFTA Secretariat 9-11, rue de Varembé, CH - 1211 Geneva 20, http://www.picscheme.org and (INS-GCP-3 Annex III to Procedure for conducting GCP inspection requested by the EMEA- Computerised Systems http://www.emea.europa.eu/Inspections/GCPproc.html)
[ix] EMA GCP Inspectors Working Group Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials (EMA/INS/GCP/454280/2010)
[x] Detailed guidelines on good clinical practice specific to advanced therapy medicinal products 03/12/2009 ENTR/F/2/SF/dn D(2009) 35810