UNIVERSIDADE D
COIMBRA

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THE IMPORTANCE OF DOCUMENT MANAGEMENT AND THE FUTURE OF CLINICAL TRIALS ARCHIVE

Dissertação no âmbito do Mestrado em Biotecnologia Farmacêutica orientada pelo Professor Doutor Luís Almeida e pelo Professor Doutor Sérgio Simões e apresentada à Faculdade de Farmácia da Universidade de Coimbra.

Setembro de 2018

Faculdade de Farmácia

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ABSTRACT

Clinical Trials are a key part of the development of a new drug, connecting scientific and clinical research and, later, the market.

The clinical part of the trial has a restricted duration, giving place to the documents in the file, to "tell the history of the trial". These documents support the submission to the authorities for the introduction of the test product on the market; and are available at the time of inspection by the competent authorities.

With this dissertation we intend to review the archive of clinical trials. The collection of data on paper or electronically and the application of new technologies to the archive, which will originate new forms of Trial Master Files.

For this, it is important to analyze the advantages and disadvantages of the physical archive, in paper, versus the most recent technologies currently present in the market.

The scale, complexity, and cost of clinical trials are increasing, and the evolution of the technology we see today, coupled with the management of clinical trial documentation, offers new opportunities to increase efficiency and reduce costs.

A clinical trial, in addition to contributing to the innovation of medicine and science, remains an entrepreneurial activity with the need to keep up with the growth and modernization that takes place around it.

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ABBREVIATIONS

CRF: Case Report Form

CRO: Contract Research Organization

DIA: Drug Information Association

EC: European Community

eCRF: Electronic Case Report Form

EEA: European Economic Area

EMA: European Medicines Agency

ePRO: Electronic Patient Reported Outcome

eTMF: Electronic Trial Master File

EU: European Union

FDA: Food and Drug Administration

GCP: Good Clinical Practice

GDPR: General Data Protection Regulation

HER: Electronic Health Record

ICH: International Council for Harmonisation

IMP: Investigational Medicinal Product

IRB/IEC: Institutional Review Board/Independent Ethics Committee

IVRS: Interactive Voice Response Systems

IWRS: Interactive Web Response System

PRO: Patient Reported Outcome

QC: Quality Control

QP: Qualified Person

SOPs: Standard Operating Procedures

TMF: Trial Master File

WMA: World Medical Association

GLOSSARY

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s). [1]

Audit Trail: A process that captures details such as additions, deletions, or alterations of information in an electronic record without obliterating the original record. An audit trail facilitates the reconstruction of the history of such actions relating to the electronic record. [1]

Case Report Form: A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor for each trial subject. [1]

Certified Copy: A copy of original information that has been verified as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original. NOTE: The copy may be verified by dated signature or by a validated electronic process. A certified copy of a source document may serve as a source for a clinical investigation. [1]

Checksums: A checksum is an error-detection method in the transmitter computes a numerical value according to the number of set or unset bits in a message and sends it along with each message frame. [2]

Contract Research Organization: A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions. [1]

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical trial. NOTE: The party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable

regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information. [1]

Good Clinical Practice: A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected. [1]

Inspection: The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies). [1]

Investigational Medicinal Product: means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. [3]

Investigator: A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. [4]

Investigator's Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects. [1]

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. [1]

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [1]

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medicotechnical departments involved in the clinical trial). [1]

Sponsor: An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial. [4]

Trial Site: The location(s) where trial-related activities are actually conducted. [4]

INTRODUCTION

Clinical Trials are "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy." [5]

The clinical trials are a key part of the development of a new drug, connecting laboratory bench with clinical research and, later, the market.

The field of clinical research helps improve and advance medical care through the development of new and better treatments and forms of detecting and preventing diseases. [6]

In 1747, it was performed by the physician James Lind, the one who was considered to be the first controlled assay of the modern era. [7] James Lind, while working as a surgeon on a British Navy ship and knowing the high mortality of scurvy, planned a comparative study among 12 men who had signs of the disease. [7]

The 12 sailors involved in the trial were all accommodated in the same room and had the same basic diet, thus showing the awareness of maintaining constant several factors – clinical condition, environment and diet. [8]

These men were allocated, in the same way, 6 different treatments. The 6 treatments used were: 1,1 liters of cider; 25 milliliters of dilute sulfuric acid; 18 milliliters of vinegar; half a pint of sea water; two oranges and one lemon; and a medicinal paste made with garlic, mustard seed, radish root and gum myrrh. Of the 6 treatments, the one that showed the most positive effects was the one that used oranges and lemons. [8] This way, the citrus fruits became part of the diet of the sailors. [7]

Since 1747 clinical trials have been improved and subject to change, both in design and in the field of ethics and regulation.

Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology

do exist. A brief description of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below.

In phase I, the drug or experimental treatment is administered to a small group of healthy (20-80) people. [9] At this phase, safety is evaluated, the safe dosage range is determined for the human being and the side effects are identified. [10]

Phase II involves a greater number of participants living with the condition to which the new drug or treatment is intended. [9] In this phase the efficacy and safety of the drug or experimental treatment is evaluated. [10]

In phase III requires a larger group of people (up to 3000) with the condition to which the new drug or treatment is intended. [9] This phase is used for investigators to confirm efficacy, monitor side effects and compare new therapies with existing ones for the same condition. [10]

Phase IV implicates thousands of participants and are post-marketing studies. [9] At this phase, additional information on the safety, efficacy and use of the drug or experimental treatment is obtained. [10]

Clinical trials involve a complex series of steps from the beginning with the protocol design, recruitment, follow-up, data collection, analysis, until the final results. An important component of this process is the archiving of documents created as the study progresses. This activity is often neglected, although it is a legal and regulatory requirement. The archiving of documents can be labor intensive and expensive, but should be planned and accomplished with same attention every other aspect of the clinical trial. [11]

Dinnett et all (2018) stated that archiving, in context of clinical research, is the secure storage of essential documents[11] which are defined as "documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced". [4]

According to Article 57 of Clinical Trials Regulation (EU) No 536/2014 "The clinical trial master file shall at all times contain the essential documents relating to that clinical trial". [3] A Trial Master File (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". [12]

Initially, clinical trials were performed with paper-based processes [4], including the construction and maintenance of TMF. However, because clinical trials are large and complex processes, involving many departments and partners, the maintenance of paper TMF becomes difficult. [12] For these reasons, it is common to hear auditors and inspectors complaining about incomplete TMFs, lack of audit trails, miss of data integrity and poor supervision of sponsors. [13] With the advancement of technology, electronic TMF (eTMF) has emerged, which some organizations are currently using to solve the problem. However, this new approach to TMF raises new challenges and issues. [12]

During the conduction of the clinical part of the trial, the source documents naturally arise. They are original documents, data and records that document "the existence of the subject and substantiated integrity of the trial data collected, which includes original documents related to the trial, medical treatment, and history of subject". Contained in source documents are the source data. Source data are "all information in original records and certified copies of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial". [4] As with TMF, source data was traditionally recorded in paper documents. [14]

One of the most common inspection and audit findings in investigator site inspections is absence of reliable, accurate and adequate source documentation (essential documents), [15] as can be seen in the European Medicines Agency (EMA)'s Annual Report of the Good Clinical Practice Inspectors Working Group 2016 (see Figure 1 and Table 1).

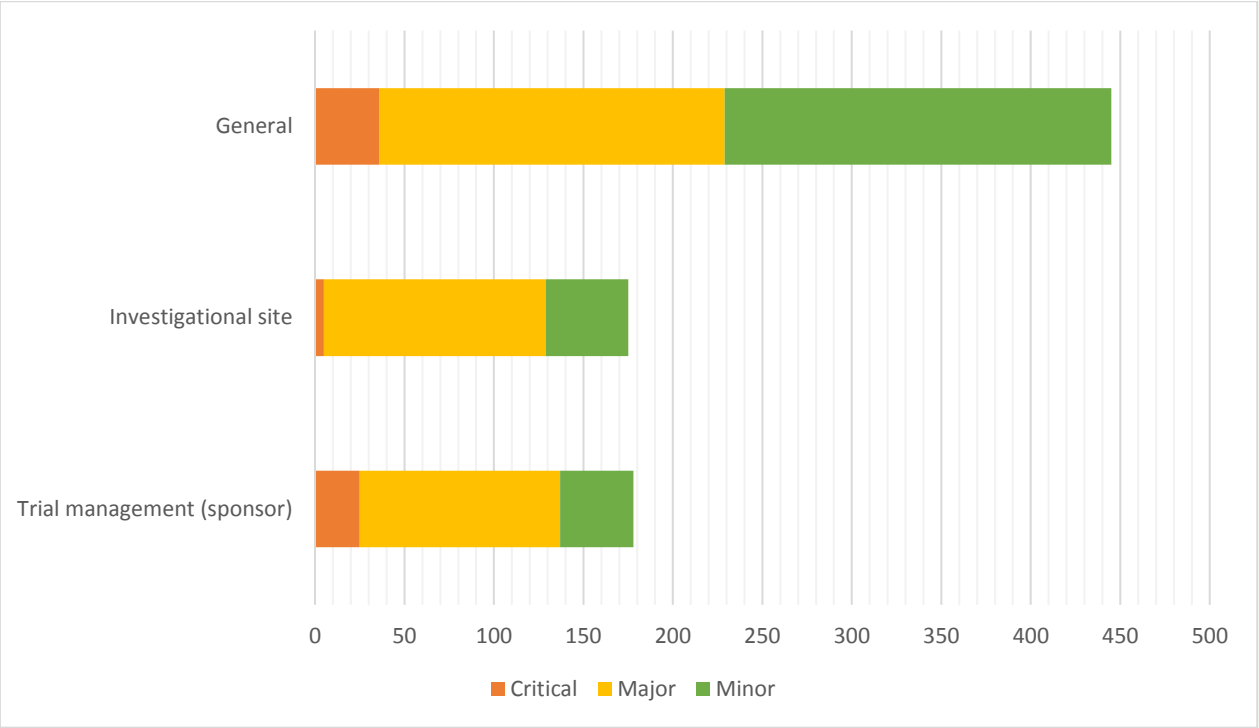

Figure 1: Number of findings per sub-category of the top 3 main categories graded by critical, major and minor. (adapted from Annual report of the Good Clinical Practice Inspections Working Group, 2016) [16]

Table 1: Number of findings in the sub-category general, graded by critical, major and minor. (adopted from Annual report of the Good Clinical Practice Inspections Working Group, 2016) [16]

		Inspected Deficiencies			Inspected Deficiencies Total
Deficiency Category Name	Deficiency Sub-category Name	Critical	Major	Minor	
General	Contracts/agreements	4	22	11	37
	Direct access to data	2	6	2	10
	Essential documents	19	79	87	185
	Facilities and equipment	-	3	16	19
	Organisation and personnel	2	18	16	36
	Qualification/training	2	16	24	42
	Randomisation/Blinding/Codes IMP	1	11	6	18
	Standard Operating Procedures	2	17	19	38
	Source documentation	4	21	35	60
General total		36	193	216	445

The attributes for good documentation were first described by the FDA – ALCOA: attributable, legible, contemporaneous, original and accurate. [15] These attributes have evolved and EMA has added a few more - complete, consistent, enduring and available when needed. [14]

During the clinical trial "All clinical trial information shall be recorded, processed, handled, and stored by the sponsor or investigator, as applicable, in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected in accordance with the applicable law on personal data protection". [3]

Clinical trials are a very sensitive area, from the data collected, to the results obtained up to the trial subjects themselves. Consequently, in clinical research there is great concern with ethical and regulatory issues, as announced by the first ICH GCP principle "Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement (s)". [4]

For some time there was no formal statement of ethical principles, or regulatory requirement to guide clinical research. Before to World War II, the investigators depended on national policies or followed their own personal ethical guidelines. After the atrocities committed by medical researchers in Germany, the Nuremberg Code was established in 1947, followed by the Declaration of Geneva of World Medical Association (WMA) in 1948, which define the ethical duties of physicians. Both documents influenced the creation in 1964 of the Declaration of Helsinki by WMA, which is a formal statement of ethical principles published to guide the protection of human participants in clinical research. [17] The first version of the ICH GCP E6 Guideline was finalized in 1996, and was amended in 2016. [18] The purpose of this Guideline is to "provide a unified standard for the European Union, Japan, the United States, Canada, and Switzerland to facilitate the mutual acceptance of data from clinical trials by the regulatory authorities in these jurisdictions". [4]

According to the ICH (2016) "A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion". [4]

Above all the IRB/IEC must safeguard the rights, safety, and well-being of all trial subjects. [4]

The IRB / IEC should review a proposed clinical trial within a reasonable time and document their views in writing, where it should be clearly identified the clinical trial, the revised documents and one of the following options: [4]

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval / negative opinion;

- termination/suspension of any prior approval/favourable opinion.

Documents submitted to the IRB / IEC for review of the trial proposal are the essential documents as stated before, such as: trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g., advertisements), written information to be provided to subjects, Investigator's Brochure, available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities. [4]

The investigator/institution, before to initiate any clinical trial, must have written and dated approval/favourable opinion from the IRB/IEC of the trial protocol, written informed consent form and updates, recruitment procedures, and any other written information to be provided to subjects trial. [4]

"A clinical trial may be initiated only if the Ethics Committee and/or the competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored." [5]

The approval of clinical-trial is the responsibility of the national competent authorities and EMA performs a key role assuring that the standards of GCP are applied across the European Economic Area in cooperation with the Member States. [19]

In clinical research, the training of the individual involved in the trials is very important as stated in principle 2.8 of the ICH GCP E6 "Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)". [4]

As a trainee in Blueclinical's Phase 1 clinical trials unit I was allocated the Archive where I came across with the documentation of the clinical trials. I also came across the various aspects of the archive, from the regulatory aspects to the logistics and motivated me to deepen this theme in order to work according to the best clinical practices.

1. TRIAL MASTER FILE

1.1. TMF Purpose, Structure and Organization

"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" (EMA/15975/2016). Another purpose of the TMF is to demonstrate, through the documents it contains, compliance with the protocol and with the Regulation in force. [3]

Typically, the TMF is composed of the sponsor TMF, maintained by the sponsor or by a CRO, when the sponsor chooses to outsource this function, and the investigator TMF, managed by the site. [12]

The better efficient way to manage a large volume of data is to structure and organize it. Placing content in its own structure makes it easy to find and retrieve information at a later date. [20]

In this way, the sponsor TMF and the investigator TMF must be established at the beginning of the trial (Figure 2). [12]

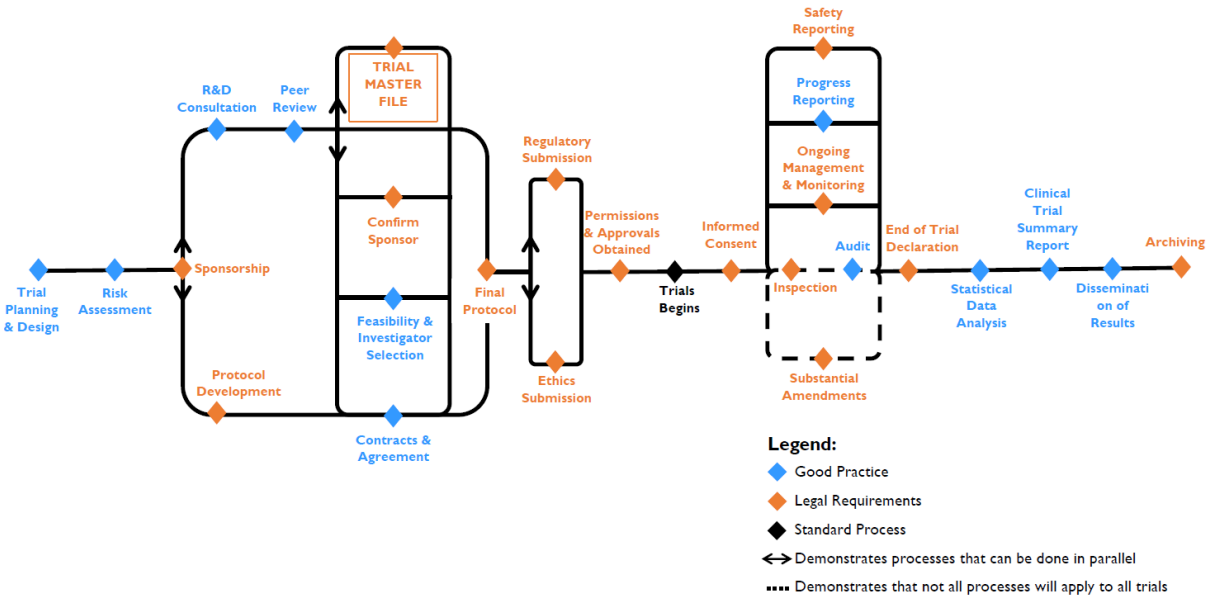

Figure 2: The Clinical Trials Routemap – Trial Master File (adapted from The Clinical Trials Toolkit – Routemap, 2013) [21]

The sponsor and the investigator should also define and record the location of the documentation to be considered for the construction of each TMF, once, normally various departments, organizations and systems are involved in the study, in order to the more

efficient and organized process. [12] This initial organization of the TMF is also important for segregating documents that are created and maintained only by the sponsor or only by the site. An adequate indexing for TMF and a clear electronic file naming system for eTMF should be provided to the auditors and inspectors in order to assist in locating the documents. Documentation should be archived in the TMF in the appropriate section, in sequential order of dates, to facilitate the provision of a clear audit trail. [12]

Adopt standardized structures of the TMF facilitates collaborate with external parties, audits and inspections and export eTMF to other systems. One of the standard models adopted, for example by Montrium, is the TMF Reference Model, from the Drug Information Association. [20] Montrium is the industry leading provider of cloud-based collaborative and compliant document and quality management system. [22]

The TMF Reference Model supplies standardized taxonomy and metadata and describes a reference definition of TMF content using standard nomenclature. The Model can be adapted to an electronic or paper TMF. [23]

When the sponsor transfers any or all of the sponsor's trial-related duties and functions to a CRO, the ultimate responsibility for the quality and integrity of the trial data continues to reside with the sponsor. The function of CRO is to implement quality assurance and quality control [4] and as "Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing". [4]

Contract certain duties and tasks to a CRO, can increase the complexity of the TMF. [13] When there is co-sponsorship there must be an agreement for TMF based on the responsibilities of each co-sponsor. The contract agreed between all parties should describe, in detail, the arrangements for the TMF, which are: [12]

- 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 eTMF 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.

During the clinical trial, all essential documents and records that are generated are the responsibility of the investigator/institution and should be contained in the investigators TMF. [12] The TMF must be updated "at all times" so that it is possible to verify the conduct of the trial and the quality of the data generated during the trial. [3]

When it is necessary to make "any changes to the contents of the master archive of clinical trials it must be traceable" [3] creating an audit trail that allows a reconstruction of the history of such changes. [1]

1.2. TMF contents – Essential Documents

"A TMF is the collection of essential documents". [12] As referred to in Article 57 of the Regulation, essential documents must be available and accessible when requested by Member States. [3] The essential documents are the documents monitored by the sponsor [3] audited by independent auditors of the sponsor and inspected by the competent authorities of the Member States, in order to verify the conduct of the clinical trial and the integrity of the data generated [4]. "Essential documents should be complete, legible, accurate, unambiguous and signed and dated as appropriate". [12]

The TMF maintained by the investigator and the sponsor may not have the same content, which is due to the different responsibilities of both the investigator and the sponsor. [3]

The documents considered essential are listed in section 8 of ICH-GCP E6. [4] This list also indicates where the essential documents are to be archived, in the investigator/institution TMF, in the sponsor TMF or both, also defining the purpose of each essential document (Annex I). [4] Within this list the various documents are divided into 3 sections conforming to the stage of the clinical trial in which they are generated: section 1: **before the clinical phase of the trial commences; section 2: during the clinical conduct of the trial; section 3: after completion or termination of the trial. [4]** However, this list should not be considered a checklist for TMF. [12]

In fact, for each study the essential documents "should be supplemented or may be reduced when justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial". [4]

This justification is based on risk assessment, where adaptations are identified and where they can be applied. These adaptations may make some of the documents specified in the ICH-GCP E6 guideline (annex I) not relevant to that clinical trial. [24]

Article 57 of the Regulation makes it clear that the TMF of the trial must take "into account all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial ". [3] The adaptations resulting from risk assessment may affect the content of TMF. Examples of these adaptations are: [24]

- combining of documents, where one document serves several purposes (for example: screening logs and recruitment logs, signature and delegation logs);
- absence of documents (for example: Investigator Brochure as the Summary of Product Characteristics is being used instead).

For certain clinical trials, there may be a need for additional documents, which are not present in the ICH-GCP E6 guideline list. [12] In this case, the sponsor and / or investigator will include these additional documents in the TMF. [12]

Any documentation created during the clinical trial that helps to reconstruct and evaluate the conduct of the trials should be archived in the TMF, whether or not it is

mentioned in the ICH-GCP E6 guideline. [12] Examples of essential documents that are not mentioned in section 8 of ICH-GCP E6: [12]

- forms, checklists and reports generated from quality system procedures;
- Qualified Person (QP) certification of the IMP;
- method validation report for analysis of IMP or metabolite(s) in clinical samples;
- documentation to demonstrate validation of trial-specific builds of computer systems (for example: electronic Case Report Form (e-CRF)).

If superseded versions exist of documents required for the reconstruction of the clinical trial, they should be included in the sponsor TMF. [12] The investigator TMF must also include the superseded versions in order to be able to reconstruct without recourse to the sponsor TMF, with evidence of receipt, review, approval (if necessary) and implementation by the investigator. [12] In order for the size of the investigator TMF to be reduced, a version of tracked change that includes all changes can be archived. [12]

1.3. Electronic TMF

An electronic TMF serves the same purpose, organization, structure and basic requirements as a paper TMF. "The Regulation does not differentiate between paper and electronic TMFs". [12]

Recently, have witnessed a transition from a paper TMF to an eTMF, it has been a growing process for several sponsors. With this transition, the goal is to have complete, up-to-date eTMFs where you can store documents and review eTMF remotely from anywhere, resolving auditors and inspectors complaints about incomplete TMFs, missing audit trails, lack of data integrity, and poor sponsor oversight. [13]

Electronic TMFs have to enable appropriate security and reliability in order to ensure that no loss, alteration or corruption of data and documents occurs. [12] The e-TMF is a document management system containing, normally, all the necessary controls listed below: [12]

- user accounts;
- secure passwords for users;

- a system in place locking/protecting individual documents or the entire e-TMF (for example: 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 (for example: randomisation codes).

The eTMF should be validated to demonstrate that the functionality is appropriate for purpose, with formal procedures prepared to manage the process of eTMF. [12] These 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. [12] All the team involved in the conduct of the clinical trial and that uses the system should receive appropriate training. [12]

When different TMF systems are associated to facilitate the clinical trial conduct (for example, a CRO, through its eTMF system, uploads documents into the sponsor's eTMF system) the process for transferring documents should be robust and should be validated in order to avoid failure of transferring parts or the entire content of the original TMF without loss. [12]

In order for documents to be displayed in sequential order, they must have included the date and time of their creation, as well as the date of uploading. The version of each electronic document must also be present, the same applies if these documents are printed. [12]

Metadata is information that pertains to each document present in eTMF. [20] This information is attached to the document and captures various information, such as the author, creation or upload time, document status, among others. [20] "Metadata is the backbone of an intelligent eTMF". [20] The metadata supports the search function, workflows, and other critical functions in the system, allowing you to automate much of the TMF. [20]

In a separate location and/or media there should be stored a back-up of the e-TMF. [12] Periodically, there should be test recovery or restorations to confirm the on-going availability of the data. [12]

1.3.1. Benefits of an eTMF

The use of an eTMF during a clinical trial has several benefits, which increases the potential of this being successful. These benefits are: [13]

- Real-time tracking of documents;
- Easy access to search and finds documents;
- Increase of TMF compliance;
- Cost-effectiveness;
- Inspection readiness;
- Lower storage costs;
- Lower storage space.

For a paper TMF there are a lot of manual collection of the documents. In an eTMF system, access to the eTMF can be provided and each partner can upload the document directly into the eTMF, or create an area for centralized processing. [20] Using an eTMF with document collaboration capabilities, there is always access to the latest version of the document. Version history is part of the audit trail that will be used by the inspectors. [20]

Through these characteristics an eTMF is obtained where it is possible to "Real-time tracking of documents" and that will always be "Inspection readiness". [13]

1.4. Scanning or Transfers to Other Media

In accordance with Article 58 of the Regulation, the "media used to archive the content of the clinical trial master file shall be such that the content remains complete and legible" during the retention period. [3] Special attention should be paid to records

stored on electronic, magnetic and optical media. [12] With this media should be implemented suitable controls, so that these records cannot be changed without authorization and also allow the creation of audit trail. [12]

Sometimes using eTMF and electronic archiving requires scanning of paper records so that electronic copies of those documents can be created. When exist scanning documents in the eTMF, they must be a certified copy generated through a validated process to produce an exact copy of the original. [12] If the original documents of a paper TMF are transferred to an electronic format, this process must also be validated to ensure that all information remains the same as the original, without being lost or altered. [12] Validation should accomplish the following process steps: [12]

- approval for scanning;
- transportation of the records to the location of scan;
- preparation and scanning of the records;
- indexing and assignment of metadata;
- import of the scanned 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 scanned hosted/archived records;
- deletion of scanned hosted/archived records.

As part of the validation should be process in place for regular QC checks of scanned and indexed documents in the e-TMF. The QC checks should include the following quality features: [12]

- accuracy of the metadata attributed to the document;
- quality of the image (suitable resolution, readability, legibility, reproduction of color, 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 increment legibility are acceptable (provided that the limits of what can be changed are clearly specified). [12] Using scanning processes to remove or add material to the image is not acceptable, such as adding or remove the header of a document, or using 'cut and paste'. [12]

Sponsors must assure that essential documents are not destroyed by the end of the required retention time. [12] However, if certified copies were transferred to an eTMF, the original documents could be destroyed before the end of the retention time. [12] But the earlier destruction of documents is only possible if the eTMF is in accordance with the regulatory requirements, so that inspectors do not need to request any original paper documents. [12]

The sponsor together with the investigator must decide whether certain documents that legally require a signature, such as written informed consent of trial participants and contracts must be destroyed or maintained. [12] These decisions should consider the legal implications if these documents are necessary for provide legally recognized evidence. [12]

2. SOURCE DATA AND SOURCE DOCUMENTS

2.1. Purpose Source Data and Source Documents

According to EMA (2010) the "Collection of accurate clinical trial data is essential for compliance with Good Clinical Practice" [14]

Source documents are essential documents of the clinical trial (ICH-GCP E6 section 8 - annex I). [4] The source documents are the original documents, data, and records generated during the clinical conduct of the clinical trial and may be of different types, such as: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. [4]

Contained in source documents are source data. Source data are original records or certified copies that contains all information the clinical findings, observations, or others activities related clinical trial. [4]

Any instrument used to generate, capture, transfer, manipulate or store data (paper or electronic) should ensure that the data are captured in accordance with the clinical trial protocol. [14]

According to the list of essential documents of ICH-GCP E6 (annex I), the purpose of the source documents is "to document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject". [4] Other purpose of source documentation in a clinical trial is the reconstruction of the trial, it should enable an independent observer to reconfirm the data. [15] The source documents are the tool which confirms the eligibility criteria of the subject and document the progress from the signing of the informed consent until the trial subject ends the clinical trial. [15]

It is the responsibility of the sponsor to securing agreement from all involved parties to assure direct access to all trial related sites, source data/documents and reports with

the purpose of monitoring and auditing by the sponsor and inspection by regulatory authorities. [4]

The source documents should not be under the exclusive control of the sponsor (ICH GCP 8.3.13 – annex 1). [4] The original source documents they must be maintained by the investigator, or have a certified copy of documentation. [14]

The sponsor continues responsible for the quality of the study data and for assure that procedures, system controls and contracts/agreements are available to defend this quality. The investigator must ensure the accuracy, completeness and legibility of the data reported to the sponsor in the all reports and Case Report Forms (CRFs). [14]

After a source data transfer from the paper to an eCRF a quality control should be done [14], because when the information present in the source documents is transcribed for the CRF/eCRF, the data should be consistent with the source documents. If there are discrepancies, these should be explained. [4]

Source documents, such as TMF, must present an audit trail whenever changes are made, as referred to in ICH GCP E6 "changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary". [4] The source documents should only be changed with the knowledge and/or approval of the investigator. [14]

"The source document should allow for accurate copies to be made." (EMA/INS/GCP/454280/2010) When making a copy of the source data, the process used must ensure that it is an exact copy, which preserves all the data and metadata of the original. [14]

The source documents contain sensitive information about trial subjects and therefore "the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)." [4]

2.2. Electronic Records

In the conduct of clinical trials, are being used more and more computers and electronic systems for the data management, analysis, laboratories and reporting by and to the sponsor or CRO. [14] In medical records it is not a well-established practice, but the use of computers and electronic systems is increasing for the capture of clinical data (as an eCRF) or for electronic patient diaries. [14]

A variety of software and hardware is used, and also several systems, such as: LAN (Local Area Network); WAN (Wide Area Network); mobile devices, web-based systems; Interactive Voice Response Systems (IVRS); Interactive Web Response System (IWRS). [14] A LAN system is implemented at a single site and machines are connected to each other. A WAN system consist of a networked system that operates in multiple sites. Sites could be in a single city, country or various countries. [25] IVRS is used by the site administrators to interact with a database by pressing keypad buttons on a phone. [26] The IWRS works the same way, but uses a computer. [26] These systems are used, for example, to register new subjects and to the randomization. [26]

When the clinical trial is conducted in institutions that use electronic health record systems, the sponsor should determine whether this system meet the requirements of GCP. [14] The evaluation should consider "the potential harm to trial subjects and patient rights and to the data integrity of the trial." [14] If, at the end of the evaluation, the systems are not conform with the GCP requirements, action must be taken before the trial site initiation. [14] Some examples where the systems of the trial site did not meet with the GCP requirements: [14]

- "Investigator controls may be absent in systems where non-trial healthcare professionals at the investigator site or other location may alter the health records. In this instance the sponsor assessment on the impact to the trial should include whether there is an audit trail of changes made. If there is an audit trail, then a chronological assessment of what was known at the time of a trial decision is possible and therefore the absence of investigator control may have little impact. However, if an audit trail is not available,

additional process controls, such as a signed and dated print outs, will have to be introduced to maintain the information."

- "The monitor, auditor and inspector should have direct access to trial subjects' entire electronic health records whilst the trial site staff should ensure that the medical records of patients who are not trial subjects should not be accessible."
- "Whenever copies of electronic health records are provided for the purpose of monitoring/ auditing/inspecting the monitor/auditor/inspector should be able to verify that this copy is a complete and accurate copy of the electronic health record."

The sponsor, when use electronic trial data handling and/or remote electronic trial data systems, must validate the systems and ensure that they comply with your requirements for completeness, accuracy, reliability, and consistent intended performance. [4] Sponsor should also, certify that the systems are designed to documented any data changes (create an audit trail); and a list of individuals who are authorized to make data changes should be maintained and the system must be secure to prevent unauthorized access. [4] An adequate backup of the data should be maintained by the sponsor. [4] The blinding, if any, has to be maintained during data entry and processing. [4]

When electronic source documents are used in a clinical trial one of the major concerns is the "risk of obsolescence". [27] Obsolescence to media, software or file format. [27] To counter this risk and guarantee that essential information continues complete and retrievable throughout the retention period, a migration to another systems is important. The migration procedures must be validated. [27]

In computerized systems it is even more important to ensure the integrity of the data (than on paper), since the software upgrades or data migration to another electronic system occurs. [4]

2.3. Principles of Good Documentation Practice

Several attributes are used to ensure the quality of the data collected in the source documents during the clinical trial. The FDA was the first to describe these attributes

through the acronym ALCOA - Attributable, Legible, Contemporaneous, Original and Accurate. [15] Later, the EMA added some more attributes for the source documents [15], they are: Complete, Consistent, Enduring and Available when needed. [14]

- Attributable

  The person who documented the data must be registered by the system. This person must have a unique identification, such as a signature, password, or username. [14]

- Legible

  Readable at the independent reviewer [14] and signatures identifiable [15].

- Contemporaneous

  The information must be documented in the correct time, along with the flow of events. [15] For example, the recording of a clinical observation should be documented at the same time as when the observation occurred. [14] If is not registered at time, the chronology of events should be recorded. [14]

  Should be defined and justified an acceptable amount of delay. [14]

- Original

  The first record made by the appropriate person, produced by the subject or by the investigator. [14]

- Accurate

  Precise, consistent and real representation of facts. [15] The data capture process should be validated in order to ensure that they are generated high-quality data. [14]

- Complete

  Complete up to that point in time. [15] All data necessary are available. [28]

- Consistent

  Demonstrate the needed attributes consistently. [15] The data capture process should also ensure that all data required are captured in a consistent manner. [14]

- Enduring

  Data must be accessible for an extended period of time [28] – retention time.

- Available when needed

  The documents should be available for review of physicians and for auditors and inspectors. [15] "Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records." [4]

Given the global nature of clinical trials, these principles should be applied at international level. [14]

3. THE ARCHIVE

3.1. Archive

The archive is "the physical or electronic facility designated for the secure retention and maintenance of archived materials, including the operation of that facility under the control of an archivist". [27]

An archive must be designed and constructed to contain the materials to be archived, assuring their integrity. [27] A building, room, fire-resistant safe, filing cabinet or other can be considered as a physical archive, provided that the following aspects are considered: [27]

- prevent unauthorized access to the documents (locks or electronic entry systems);
- withstand the elements of weather. (for example: risk of flooding);
- water pipes in or near the archive area should be avoided;
- installation of automated fire detection system, and an automated fire suppression system;
- use of naked flames, or other open heat sources, within or around the archives must be prohibited. (use of electrical appliances should be reduced);
- should be made a risk assessment relating of pests (for example: rodents and insects).

When it comes to an electronic archive, naturally the design and construction are different from the physical archive, of the paper. When a process of archive electronic records is being developed, it must ensure the usability, reliability, integrity, authenticity and accuracy of the data generated, and that the systems used are secure and do not allow loss, alteration or unauthorized access. [29] When developing such systems, consideration should be given to "risk of obsolescence" of the storage media, a concern in the long-term retention of documents, as it was stated before. [27]

The form of archiving (paper or electronic) documents must be decided before they are generated. These decisions have implications in the form of archiving, record generation, and process validation. [29]

During the archive process there are several roles and responsibilities. The sponsor, before to initiating a clinical trial, must define, establish and allocate all trial related duties and functions. [27] In relation to the archive, the responsibilities of the sponsor are:

- agree the format in which all records will be maintained throughout their lifecycle; [27]
- ensure that the materials required to support their studies are retained and maintained in conditions that ensure its integrity and continued access; [27]
- maintain contact with the organization that archives his materials; [27]
- ensure procedures are established for making materials available for inspection; [27]
- determine the investigators capability to retain trial material in appropriate and suitable conditions; [27]
- inform the investigator, in writing, of the need for material retention including timeframes; [27]
- ultimately, ensuring that records that support the data submitted to regulatory authorities are retained and available when required. [29]

In case of the sponsor contracted an CRO or Electronic Data Capture vendor, should ensure that the third party understands their responsibilities. [27] The responsibilities must be agreed between the two parties before the beginning of the trial and included in the contractual agreement. [27]

It is part of the role of the investigator to comply with the contract with the sponsor and to understand the importance of good records management practices. [27] It is part of his responsibilities as an investigator: [27]

- accountability for the trial materials throughout their lifecycle;
- take appropriate measures to minimize risk of loss, damage or destruction of materials;
- inform the sponsor, in writing, of any changes in contact details/personnel who have control of the archived trial material;
- the investigator is unable to provide suitable storage for the trial materials, a contract archive facility may be used (inform the sponsor of the location of the material);

- ensure procedures are established for making materials available for inspection;
- appoint an individual as the archivist.

The investigator also can contract a CRO or Electronic Data Capture vendor, and just like the sponsor, should assure that the third party understands their responsibilities and these should be described in a contract between the two parties. [27]

The archivist is responsible for the day-to-day operation and management of the archive in accordance with SOPs of the company, GCP and any contractual obligations. [27] The role of archivist does not need to be dedicated exclusively to the archive, it can combine with other roles. [27] The archivists should receive appropriate training. [27] They are responsible for: [27]

- ensuring that the archive is operated in accordance with specific archiving documentation, SOPs and work instructions for their organization;
- monitoring the conditions within the archive and addressing any issues arising;
- indexing, identifying and managing materials deposited into the archive;
- controlling access to the archives and archived material in accordance with defined procedures;
- managing, tracking and documenting material retrieval, loan, transfer and destruction.

According to Jones (2014) "Material cannot be considered to have been archived unless it comes under the control of an archivist." [27]

In case of electronic materials, archiving is usually responsibility of the IT staff, provided the regulatory requirements relative to the archive are attended. [27] The IT staff also should receive appropriate training. [29] It is part of their responsibilities as an IT staff: [29]

- maintaining and supporting the software, hardware and IT infrastructure;
- maintaining system configuration;
- performing routine backups of the system or overseeing automated backups at defined intervals;
- providing technical support to the business managers and users;
- undertaking technical aspects of the computer systems validation.

The sponsor and the investigator have responsibilities to protect clinical trial records and subjects confidentiality. [29]

3.2. Archiving and Retention Period of TMF and Source Documents

As referred in Article 58 of the Regulation, the TMF "shall be archived in a way that ensures that it is readily available and accessible, upon request, to the competent authorities". [3]

At the end of the clinical part of the trial, the TMF remains, and it is with its content (including the source documents) that the assay supervision is performed, for such, the TMF has to be properly archived (Figure 3). [12]

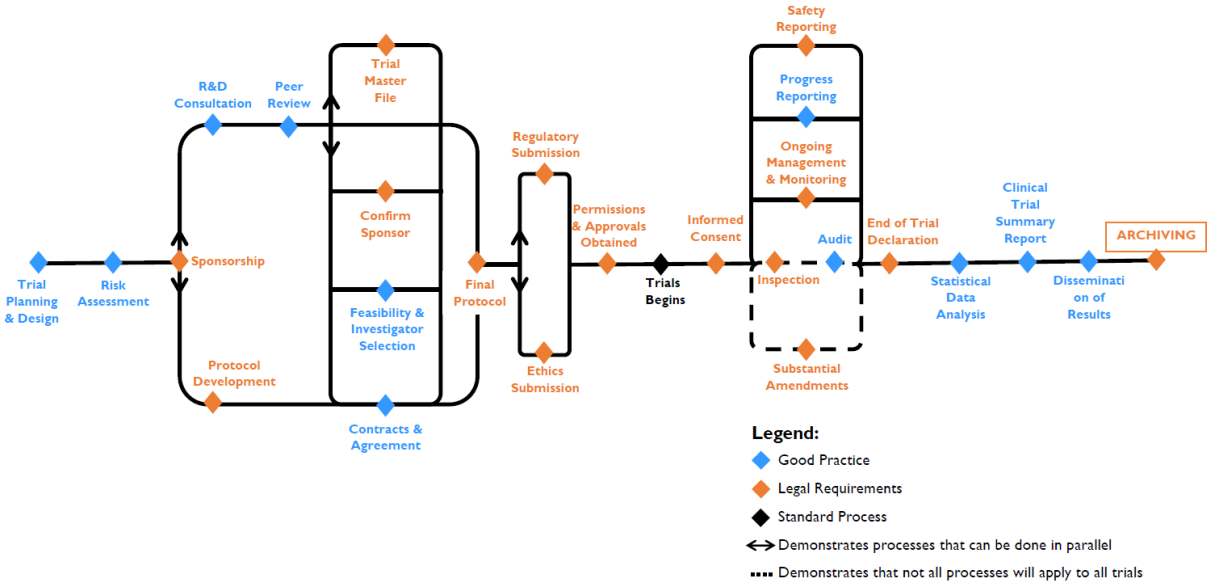

Figure 3: The Clinical Trials Routemap – Archiving (adapted from The Clinical Trials Toolkit – Routemap, 2013) [21]

In order to ensure that the TMF is properly archived, file access must be restricted. As for eTMF, in addition to restricted access, it must be protected against unauthorized changes, in order to maintain the authenticity of the archived data. [12]

With regard to the sponsor TMF, article 58 of the Regulation states that "the sponsor shall appoint individuals within its organization to be responsible for the archive. Access to archive shall be restricted to those individuals". [3] The named individuals responsible

for archiving should control the exit of essential documents from archive. [12] These individuals should receive proper training. [12]

An archive index/log of all the TMFs that have entered the archive must be kept in order to track and retrieve documents requested from the archive. [12]

These procedures should also be used by CROs. [12]

In the case of subcontracting a CRO, the sponsor is responsible for ensuring that the documentation generated by the CRO is archived. The CRO may choose to have certified copy of the documents it generated. (EMA/15975/2016)

The sponsor can subcontract the documentation archive, for example to a commercial archive, but the last responsibility belongs to the sponsor. [12] The sponsor is responsible for the quality, integrity, confidentiality and retrieval of the documents. [12]

The sponsor must be informed by the investigator of the archive agreement for his essential documents, in the same way that the sponsor must inform the investigator, in writing, of the need for retention of these documents. [12] The sponsor also must inform the investigator when the retention of documents is no longer necessary, when the retention time ends. [12] In case the investigator becomes unable to assume responsibility for the essential documents, the sponsor must be notified in writing of the change and informed to whom this responsibility has been transferred. [12]

All such information must be described in a contract or similar document, signed by both parties. [12] The investigator can use the commercial archive for the TMF and, in some cases also be an option for the source data, but the last responsibility belongs to the investigator. [12] The source documents archiving involves a special care with data protection and confidentiality, since they contain sensitive information about the subjects. [14]

Concerning the archive of electronic records (eTMFs and eSource Documents), it is important to ensure that future access is maintained, since the media used to store the data has the risk of deteriorating or becoming obsolete. [12] In order to maintain the future access, it is necessary to maintenance the system (hardware and software) or migration into a new format (for example: floppy disc to a hard drive) to assure continual access. [12] The capacity to read the media should be regularly checked, because the

individual bits of the documents can become corrupted. [29] This degradation can be induced by an archive transfer and environmental impacts (such a temperature and humidity). [29] The bit level integrity must verify through the use of checksums. [29]

The documentation must be properly archived in a way that the integrity is maintained over the long retention time required.

For clinical trials conducted in accordance with Regulation (EU) No 536/2014 "unless other Union law requires archiving for a longer period, the sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial". [3]

Although the Regulation (EU) No 536/2014 already entered into force, "the timing of its application depends on the development of a fully functional EU clinical trials portal and database, which will be confirmed by an independent audit". [30] The Regulation (EU) No 536/2014 "becomes applicable six months after the European Commission publishes a notice of this confirmation. The entry into application of the Regulation is currently estimated to occur in 2019". [30]

Therefore, there are still clinical trials conducted under Directive 2001/20/EC. [12]

For these tests, according to Directive 2005/28/EC, the "sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion". [31] The sponsor and the investigator can retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the two. [31]

The clinical trial data used to marketing authorization, according to Directive 2003/63/EC, must to be kept during: [32]

- "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 authorization in the EC and 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".

It is stated in the Directive 2003/63/EC that "the sponsor or other owner of the data shall retain all other documentation pertaining to the trial as long as the product is authorized. 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; audit certificate(s), if available. The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorized." [32]

Medical files of subjects, as laid down in Regulation [3], Directive 2005/28/EC [31] and Directive 2003/63/EC [32], must be retained in accordance with national legislation. "Retention periods apply regardless of the format of the record." [29]

3.2.1. Commercial Archives

The use of a commercial archive requires evaluation of the suitability of the facilities before to their use and a continuous evaluation after being contracted. [12] A formal contract should be signed between sponsor/investigator and the commercial archive that details conditions of service to be provided. [27] Agreement must include: [27]

- specific location of archive facilities to be used;
- process for authorizing use of alternative archive facilities;
- transfer of material to and from the archive;
- chain of custody of materials;
- access rights to stored material;
- storage conditions within the archive facility and required monitoring;
- period of storage;
- method of retrieval/access;
- method of return/disposal including authorization requirements;
- service level agreements in relation to the services provided.

The contract archive should have documented procedures for its operations, records of recruitment and staff training. [27]

When the sponsor arranges the commercial archiving of the investigator TMF on behalf of the investigator, consideration must be given to data protection and confidentiality (unauthorized access) so: [12]

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

3.3. Archive Storage Conditions – Paper and Electronic

The storage area should be adequate to maintain the content of the TMF complete and legible throughout the clinical trial conduct and the required period of retention, in order to be able to provide to the monitors and competent authorities when requested. [12] This storage area must be a facility secure, with appropriate environmental controls and adequate protection from physical damage. [12] When evaluating an area for TMF retention purposes, so as not to compromise the physical integrity of materials or the integrity of the data the following should be considered: [12]

- security (access the storage facility and documents);
- location (consider what risks are there, for example: water, fire or other environmental impacts such as – excessive temperature, humidity, sunlight, contamination (dust, smoke etc.), pests (rodents, insects etc.));
- size (appropriate shelving to accommodate the expected documentation and ease of access).

The sponsors should assess the storage conditions at the investigator site for the archive of the investigator TMF. [12]

The electronic records must be archived in order to ensure their reliability, and usability at all times and should be backed up. [29]

When the TMF of the clinical trial is paper-based, and stored physically, locating specific documentation is a manual process. This manual process requires an individual resource for physically retrieve the trial documents needed. [20] However, when TMF is stored electronically (eTMF), it's simpler to strike a few keywords and find the documents needed, 'sparing' an individual resource. [20]

Stiles (2014) stated that "Electronic records simply left or locked away on a computer or computerized system does not constitute an electronic archive." [29]

The time that the electronic record is to be retained must be entered in consideration at the moment of selecting the storage media to be used for archiving. [29]

3.4. Disaster Recovery

An archive, physical or electronic, is subject to several risks, such a fire, flood, pest infestation, structural damage (forced entry of the archive by unauthorized persons) [27] and hackers (electronic archive). In the archive should be in force a disaster recovery plan. [27] This plan should describe the steps to be taken in case of damage or inaccessibility to the archive/archived materials. [27] The disaster recovery plan should be determinate by an evaluation of the risks to which the archive may be exposed, and the risks can be dependent on the archive location and environment. [27] The "A Guide to Archiving" recommended that a disaster recovery plan includes: [27]

- outline of building, including location of different archived materials;
- process for recovery and/or restoration of lost or damaged materials and re-establishing the security of the archive;
- names and telephone numbers of appropriate personnel;
- who can be contacted outside of normal working hours;
- whereabouts of equipment to support recovery;
- restoration of archive materials (for example: dehumidifying equipment and wrapping materials);

- roles of the emergency services;
- define who may access the archive in an emergency;
- the access to the archive by employees will be denied while there is a risk to health and safety;
- records that should be made to document the disaster and recovery effort;

In the electronic archive, the disaster recovery plan, should including backup of all data and kept in a separate location. [27]

Establish contract with the organizations specialist in recover and/or restore damaged archived materials, may be useful in case of the disaster. [27]

In order to be given the best response in the event of a disaster, the disaster recovery plans should be reviewed and tested periodically, to confirm they are suitable for purpose. [27] Persons involved in the implementation of this plan must receive appropriate training. [27]

3.5. Process of the Archive

3.5.1. Submission of Materials for Archiving

According to Jones (2014) "There should be documented procedures in place which define the processes for archiving of trial materials, including checks for completeness, timeframes for submission to archive, delegation of responsibility for submission of material to the archive etc." [27]

The documents should be archived immediately on completion of the clinical trial, or ongoing basis. [27] Should be agreed and documented the maximum period for the transfer of materials to the archive after the completion of the clinical trial. [27]

When the trial documents are submitted to the archive, must be verify by archivists in order to confirm that they correspond with the information provided. [27] The completeness of the files should verify through the standard TMF contents list, defined at the beginning de clinical trial. [27] The acceptance of the trial documents must be documented by the archive staff to supply a traceable chain of custody record. [27]

When an electronic record is submitted to archive there are particularities to consider, such as the identification of the records. The metadata for the electronic records must be easily identified, located and retrieved. [29] The verification of the successful and complete transfer of the electronic records depend of the system used (simple systems - counting the size and number of files transferred; complex systems - rigorous process of data sampling). [29] These particularities are usually defined during system setup, but in some situations is necessary the assistance of IT staff to complete the archiving process. [29]

3.5.2. Retrieval and Transfers of Archived Material

Trial documents that have been archived may need to be retrieved, for example for the inspection by Regulatory Authorities. [27] The procedures for retrievals documents from archive, must include: [27]

- "details of management controls related to access to archived materials (e.g. which materials can be accessed by whom, any authorization needed to support removal of materials from the archive)";
- "reasons for which materials may be removed from the archive (referred to as loans)";
- "timeframe within which the removed material should be returned to the archive";
- "how the Archivist identifies any materials that have not been returned within the specified timeframe";
- "mechanisms to ensure the return of these materials by the person to whom they had been loaned".

When the trial documents return to the archive, should be identified, by the person to whom the documents were loaned, the changes or additions that were made. [27] The archive must maintain the records of all trial documents loans and the returns. [27] In electronic archive, not necessary to maintain a record of accesses to archived trial material, if security controls of system impede that the documents being removed (for

example: copy is downloaded for viewing purposes), or the systems prevent changes in documents. [27]

Sometimes is necessary to transfer archived trial documents to another location, when there is, for example, relocation of archive facilities or transfer between systems to prevent obsolescence or deterioration of storage media or format (electronic records). [27] The materials transferred should described in documentation of the chain of custody, this must include details of the materials, details of the receiving facility and means of transfer. [27]

3.6. Destruction of Material

The sponsor and the investigator should take measures to prevent accidental or premature destruction of trial documents. [27]

When the period of the retention time comes to an end, the sponsor notify investigator, in writing, that their clinical trial records can be destroyed. [33] The sponsors must assure that essential documents are not destroyed before the end of the periods of the retention time. [33] To managing the destruction of the clinical trial documents must be defined procedures, that include: [27]

- "processes for identifying materials that have reached the end of their retention period";
- "approvals needed for the destruction to occur";
- "the method by which the destruction will be carried out whilst ensuring the materials confidentiality is maintained";
- "records of destruction that should be retained".

For electronic records the process of destruction must stipulate if the destruction is relating to removal the "pointer" to the files or to physical electronic records. [29] For example: archived records encrypted - an acceptable way of destroying the records is destruction of the encryption key; portable digital medium (CDs, DVDs, USB devices, hard drives) - appropriate means to render such media unusable. [29] In any cases, must have

a mechanism to assure that electronic records are not recoverable, such a destruction all backups of the trial data. [29]

For destruction of the investigator site documents, must be obtained the approval from the sponsor and the investigator. In some circumstances, in the case that either party is not available to approve the destruction, the other party can authorize, since the retention criteria has been fulfilled, and the records of attempts to contact the other party should be retained. [27]

3.7. Access to the Archive

"Access to archives shall be restricted" to individuals appoint by the sponsor and investigator. [3] Access to an archive must be restricted to the Archivist, archiving staff and other named individuals [27], either in the physical or electronic archive. In case of electronic archive, the access to the archive by archivist may require the use of log-on with password or access levels restricted according to the records classification. [29] The access list should be review regularly and the visits by anyone not on the list must be record and these records maintained. [27] In electronic archive, this access are controlled by an audit trail. [29]

In the electronic archive, the access of the documents is, many times, a copy (read-only copy - "viewing") of the electronic records. [29] Thus, this is not a loan, such happen of the records in paper, but the supplies of a copy of the record. [29] These facts are an advantage, once the original records does not leave the archive and there is less likely to be altered, damaged and loss integrity of the document.

It is important to define user roles in eTMF for each study, when various studies occur at one time. [20] Over the course of a clinical trial the TMF and eTMF will collect vast quantity of sensitive information and this information will archiving it in the correct locations. [20] Due its sensitive nature, it's important that only authorized personnel can access and view this information. [20] Everyone who has access to the TMF to add or remove documentation should be controlled at all times. Before and during formal

archive, the entire TMF should be managed securely, in order to prevent accidental or premature loss of documents, alteration or destruction. [12]

3.8. Closure of an Archive

When a investigators site closes, the destiny of the archived material has to defined. [27] Sometimes there is the possibility that the material can be transferred to another archive within the same organization. [27] When closing down an archive owned by a third party, the sponsor should be contacted, to advice on the transfer or disposal of materials archived. [27] Examples of what might happen: [27]

- Sponsor request that materials are returned to them. To guarantee the validity of the clinical trial data, it might be necessary for the sponsor to collect copies of relevant non-trial specific material.
- Sponsor request that materials be transferred to another storage location (specified by the sponsor). It might be fundamental for the sponsor to obtain copies of relevant non-trial specific, that would be necessary to support the trial data.
- Sponsor may instruct the third party to destroy some, or all their archived materials.

Until it is defined what course is given to the archived materials, these must be maintained in a secure manner to safeguard their future integrity. [27]

4. DATA PROTECTION

Data protection is an issue of great importance due to the sensitive information produced during the clinical trials.

"Rapid technological developments (…) have brought new challenges for the protection of personal data" [34], and the increasing use of information technology in pharmaceutical development it was no exception. [14]

Personal data is "any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person". [34]

The collection and sharing of personal data have increased significantly. [34] The data protection must be technologically neutral and should not depend on the techniques used, must be apply to processing of personal data by automated means and manual processing. [34]

"The processing of personal data of data subjects who are in the Union by a controller or processor not established in the Union should also be subject" to the Regulation (EU) 2016/679, Known as the General Data Protection Regulation (GDPR) [34]

The processing of personal data for archiving scientific research purposes should be subject to appropriate safeguards for the rights and freedoms of the data subject. "The processing of personal data for scientific purposes should also comply with other relevant legislation such as on clinical trials" (Regulation (EU) No 536/2014). [34]

5. SUBJECT'S PROTECTING CONFIDENTIALITY

The new General Data Protection Regulation (GDPR) determines the processing of personal data and rules relating to the free movement of personal data and entered into force on the 25th May 2018.

Personal data shall be "processed in a manner that ensures appropriate security of the personal data, including protection against unauthorised or unlawful processing and against accidental loss, destruction or damage". [34]

All personal data of Trial subjects or other natural persons including Investigator or other individuals involved in the Trial, collected in relation to the Trial shall be handled in accordance with all Applicable Regulations, including, but not limited to the GDPR. The Site of the Clinical Trial shall not supply any Personal Data to the Sponsor or to the CRO which is not requested by them or otherwise required to be disclosed for the proper performance of the Clinical Trial or is obtained without the respective Trial subject's or other natural person's (as applicable) explicit consent to such supply.

The parties involved in the collection and processing of the Personal Data, should implement appropriate administrative, technical, and physical security to protect Personal Data. This protection is important in order to prevent "a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed" ('personal data breach'). [34]

The parties involved, in addition to ensuring protection of Personal Data, must ensure that their personnel involved in the processing of Personal Data have information about the confidential nature of the Data, that it has received adequate training on its responsibilities and that it has written confidentiality agreements.

Some measures that contribute to the protection of personal data are the anonymisation of the data of the clinical trial subjects and, on the other hand, the restricted access to the electronic systems through passwords and different levels of access.

6. FUTURE OF CLINICAL TRIALS ARCHIVE

The clinical trials, until recently, were performed in a largely paper-based process. [4] The subject's data were recorded in paper and the TMF were the collection of essential documents in paper. All this large amount of paper documents generated in an assay needed physical facilities, which were suitable so that they could be archived. The long retention periods to which trial documents are subject, make the archiving period (of the TMFs and paper source documents) to have high costs and are often outsourced to commercial archives for lack of space in the sponsor's or the site investigator’s archive. [13]

Presently, with the advances in use of electronic data recording and reporting and eTMF facilitate implementation of other approaches to conduct, oversight, recording and reporting, for example centralized monitoring, while ensuring human subject protection and reliability of clinical trial results. [4]

The eTMFs are increasingly being the preferred option for managing clinical trial documentation, however many organizations are still not familiar with eTMF systems. [20]

In the near future, all "data collection is expected to be immediate, seamless and extremely convenient" and "the majority of patient data collected will be delivered directly from the patient to the electronic health record (EHR)". [35] Progressively, trial subjects use wearable and implantable devices in their daily lives. [35] The trial subjects receive real-time updates and reminders about their clinical trial participation responsibilities, and will have access to their EHRs. [35] And the investigation professionals receive real-time progress reports and summary data on clinical trial performance and quality. [35]

The archive of clinical trials must keep up with the constant changes in clinical research. As sponsors and investigators adopt electronic data collection systems and eTMFs to manage the large amount of documentation generated during a trial, the archives begin to abandon their traditional closet and shelves facilities to become a set of electronic systems. These electronic archives will become more and more common.

7. CONCLUSION

The scale, complexity, and cost of clinical trials are increasing. The evolutions of the technology and managing clinical trial documentation provide new opportunities to increase efficiency and reduce the cost. [4]

"One of the major cost drivers is the mismanagement of trial documentation". [36] Although the rate of the adoption the eTMF systems is rising, many organizations still thinking in "paper". [36] Sometimes, the "workflow follows paper principles but gets shared and captured in electronic format, resulting in redundancies and inefficiencies". [36]

The transition from paper TMF to an eTMF is an evolution that generates great efficiencies and cost savings for the organization. [36]

A well-kept TMF or eTMF help with efficient clinical trial management and ease the reconstruction of the conduct of the trial during the audit or inspection process. [37] In order for these to be well-kept the sponsor or investigator must define who is responsible for placing each document type in the TMF / eTMF, that way, during an audit or inspection, no incomplete TMFs / eTMFs will be found.

One of the most important activities in clinical trials, which is also a legal and regulatory requirement, is the archiving of essential documents, although this activity is sometimes neglected.

A successful archive must meet a number of requirements, such as access control, consider the environmental conditions, the media used and the risk of them becoming obsolete (in the electronic archives), so that archived essential documents keep integrity throughout the required retention period.

The archiving of TMFs and paper source documents, during retention periods are usually outsourced, involve higher costs and making access to these trial documents difficult. [13] During the archiving of eTMFs and electronic source documents, the biggest problems are related to the compatibility between software systems and the risk of obsolescence of the archival media of the trial documents. [13]

Lack of understanding of basic GCP principles and applicable regulation may have a negative impact on the conduct of the clinical trial and the quality of results.

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ANNEX

Annex I- Essential Documents for the Conduct of a Clinical Trial [4]

Table 2: Before the Clinical Phase of the Trial Commences (adapted from Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 2016)
During this planning stage the following documents should be generated and should be on file before the trial formally starts [4]

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.1	INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	NFORMATION GIVEN TO TRIAL SUBJECT - INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	X	X
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
	-ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4	FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5	INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:	To document agreements		
	- investigator/institution and sponsor		X	X
	- investigator/institution and CRO		X	X (where required)
	- sponsor and CRO			X
	- investigator/institution and authority(ies) (where required)		X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.7	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
8.2.8	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.10	CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	X	X
8.2.12	MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14	INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.2.15	SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17	DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	MASTER RANDOMISATION LIST	To document method for randomisation of trial population		X (third party if applicable)
8.2.19	PRE-TRIAL MONITORING REPORT	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator’s trial staff (may be combined with 8.2.19)	X	X

Table 3: During the Clinical Conduct of the Trial (adapted from Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 2016)

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available. [4]

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.1	INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X
8.3.2	ANY REVISION TO: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.3	DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favourable opinion - continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
8.3.4	REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.5	CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.3.6	UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7	UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.9	CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.3.10	MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		X
8.3.11	RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12	SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.14	SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	DOCUMENTATION OF CRF CORRECTIONS	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X
8.3.17	NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18	NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19	INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.3.20	SUBJECT SCREENING LOG	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	SUBJECT ENROLMENT LOG	To document chronological enrolment of subjects by trial number	X	
8.3.23	INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	SIGNATURE SHEET	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X
8.3.25	RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)	To document location and identification of retained samples if assays need to be repeated	X	X

Table 4: After Completion or Termination of the Trial (adapted from Integrated addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2), 2016)

After completion or termination of the trial, all of the documents identified in Sections 8.2 and 8.3 should be in the file together with the following. [4]

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.1	INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	

	Title of Document	Purpose	Located in Files of	
			Investigator/ Institution	Sponsor
8.4.4	AUDIT CERTIFICATE (if available)	To document that audit was performed		X
8.4.5	FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		X
8.4.7	FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)	To document completion of the trial	X	
8.4.8	CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	X