RECOMMENDATION ON THE CONTENT OF THE TRIAL MASTER FILE AND ARCHIVING

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TABLE OF CONTENTS Page

1. Introduction 2
2. Scope 2
3. Documents to be archived 2
4. Quality of essential documents 10
5. Media to be used 10
6. Storage conditions 10
7. Duration for the retention of essential documents 11
8. Destruction of essential documents 11

1. INTRODUCTION

According to Article 15(5) of Directive 2001/20/EC[3] the detailed guidelines on the documentation relating to the clinical trial, which shall constitute the master file on the trial and on archiving, shall be adopted and revised in accordance with the procedure referred to in Article 21(2) in Directive 2001/20/EC.

Directive 2005/28/EC[4] implements in Chapter 4 the detailed guideline on the master file in the trial and archiving, and states that the Commission shall publish additional guidance in order to specify the content of these documents.

This guidance document provides further recommendation on 'The Trial Master File and Archiving', including relevant text from CPMP/ICH/135/95[5] – Note for guidance on Good Clinical Practice.

2. SCOPE

The trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated according to Article 16 of Directive 2005/28/EC.

The essential documents should be filed in an organised way that will facilitate management of the clinical trial, audit and inspection (Sponsor Trial Master File and Investigator and other trial Site Files).

According to Article 17, third paragraph, of Directive 2005/28/EC essential documents should be retained securely prior to archive and then archived for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request.

This document provides guidance on the contents of Trial Master Files and the retention requirements for essential documents held by investigators, sponsors/Contract research Organisations and others involved in the conduct of clinical trials. In particular, this guideline gives details on:

- the minimum set of documents to be retained;
- the quality of documents to be archived;
- minimum standards for storage conditions; media transfer and certified copies
- retention times.

3. DOCUMENTS TO BE ARCHIVED

The documents to be retained in the Trial Master File:
Essential Documents are those documents, which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

[3] [3] OJ L 121, 1.5.2001 p.24

[4] OJ L 91, 9.4.2005, p.13

[5] All parties involved in clinical trials should read and take into account the community guideline Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) (ICHE6).

These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements. Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority (ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

- The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

  1) before the clinical phase of the trial commences,

  2) during the clinical conduct of the trial,

  and

  3) after completion or termination of the trial.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

- Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

Upon request of the monitor, auditor, Ethics Committee, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records according to Community and national legislation..

The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

The essential documents should be located in the file of the investigator and/or sponsor.

3.1 Before the Clinical Phase of the Trial Commences

During this planning stage the following documents should be generated and should be on file before the trial formally starts

3.1.1 Investigator's Brochure

To document that relevant and current scientific information about the investigational product has been provided to the investigator.

- File of the investigator and sponsor.

3.1.2 Signed protocol and amendments, if any, and sample case report form

To document investigator and sponsor agreement to the protocol/amendment(s) and case report form.

- File of the investigator and sponsor

3.1.3 Information given to trial subjects

Informed consent form (including all applicable translations)

To document the informed consent.

- File of the investigator and sponsor.

3.1.3.1 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.

- File of the investigator and sponsor.

3.1.3.2 Advertisement for subject recruitment (if used)

To document that recruitment measures are appropriate and not coercive.

- File of the investigator.

3.1.4 Financial aspects of the trial

To document the financial agreement between the investigator/institution and the sponsor for the trial.

- File of the investigator and sponsor.

3.1.5 Insurance statement (where required)

To document that compensation to subject(s) for trial-related injury will be available.

- File of the investigator and sponsor.

3.1.6 Signed agreement between involved parties,(To document agreements) **e.g.:**

– investigator/institution and sponsor
– investigator/institution and contract research organisation
– sponsor and contract research organisation
– investigator/institution and authority(ies) (where required).

- File of the investigator and sponsor.

3.1.7 Dated, documented favourable opinion of Ethics Committee of the following:

– protocol and any amendments
– case report form (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 favourable opinion

To document that the trial has been subject to Ethics Committees review and given favourable opinion. To identify the version number and date of the document(s).

- File of the investigator and sponsor.

3.1.8 Ethics committee composition
To document that the Ethics Committee is constituted in agreement with Good Clinical Practice.
- File of the investigator and sponsor (where required).

3.1.9 Regulatory authority(ies) authorisation/ approval/notification of protocol
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).
- File of the investigator and sponsor (where required).

3.1.10 Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and/or supporting trial staff to whom investigator tasks are delegated
To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.
- File of the investigator and sponsor.

3.1.11 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 according to the state of the art.
- File of the investigator and sponsor.

3.1.12 Medical/laboratory/technical procedures/tests
To document competence of facility to perform required test(s), and support reliability of results
Certification or
accreditation or
established quality control and/or
external quality assessment or
other validation (where required)
- File of the investigator (where required) and sponsor.

3.1.13 Sample of label(s) attached to investigational medicinal product container(s)
To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects.
- File of the sponsor.

3.1.14 Instructions for handling of investigational medicinal 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 medicinal products and trial-related materials.
- File of the investigator and sponsor.

3.1.15 Distribution records for investigational medicinal product(s) and trial related materials
To document distribution dates, batch numbers and method of distribution of investigational medicinal product(s) and trial-related materials. To allow tracking of product batch, review of distribution conditions, and accountability.

- File of the investigator and sponsor.

3.1.16 Certificate(s) of analysis of investigational product(s)[6]
To document identity, purity, and strength of investigational medicinal product(s) to be used in the trial.
- File of the sponsor and investigator.

3.1.17 Decoding procedures for blinded trials
To document how, in case of an emergency, identity of blinded investigational medicinal product can be revealed without breaking the blind for the remaining subjects' treatment.
- File of the investigator and sponsor (third party if applicable).

3.1.18 Master Randomisation List
To document method for randomisation of trial population
- File of the sponsor (third party if applicable)..

3.1.19 Pre-Trial Monitoring Report
To document that the site is suitable for the trial (may be combined with 3.1.20).
- File of the sponsor.

3.1.20 Trial Initiation Monitoring Report
To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 3.1.19).
- File of the investigator and sponsor.

3.2 During the Clinical Conduct of the Trial

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

3.2.1 Investigator's brochure updates
To document that investigator is informed in a timely manner of relevant information as it becomes available.
- File of the investigator and sponsor.

3.2.2 Any revision to:
To document revisions of these trial related documents that take effect during trial
– protocol/amendment(s) and case report form
– informed consent form
- any other written information provided to subjects
– advertisement for subject recruitment (if used).
- File of the investigator and sponsor.

3.2.3 Dated, documented favourable opinion of the Ethics Committee of the following:
To document that the amendment(s) and/or revision(s) have been subject to the Ethics Committees review and were given approval/favourable opinion. To identify the version number and date of the document(s).

[6] In the EU the Batch release certification should be signed by the Qualified Person can be used

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 favourable opinion continuing review of trial.

- File of the investigator and sponsor.

3.2.4 Regulatory authority(ies) authorisations/approvals / notifications where required for:
To document compliance with applicable regulatory requirements
– Protocol amendment(s) and other documents

- File of the investigator (where required) and sponsor.

3.2.5 Curriculum vitae for new investigator(s) and/or supporting trial staff to whom investigator tasks are delegated (see 3.1.10)

- File of the investigator and sponsor.

3.2.6 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 3.1.11).
File of the investigator and sponsor.

3.2.7 Updates of medical/laboratory/technical procedures/tests
To document that tests remain adequate throughout the trial period (see 3.1.12)
Certification or accreditation or established quality control and/or external quality assessment or other validation.

- File of the investigator (where required)and sponsor.

3.2.8 Documentation of investigational medicinal product(s) and trial related materials distribution

- File of the investigator and sponsor.

3.2.9 Certificate(s) of analysis for new batches of investigational products[7]
(see 3.1.16).

- File of the sponsor.

3.2.10 Monitoring visit reports
To document site visits by, and findings of, the monitor

- File of the sponsor.

3.2.11 Relevant communications other than site visits
To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting
Letters, meeting notes, notes of telephone calls

- File of the investigator and sponsor.

3.2.12 Signed informed consent forms

[7] In the EU the Batch release certification should be signed by the Qualified Person can be used

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 3.1.3).

- File of the investigator.

3.2.13 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.

- File of the investigator.

3.2.14 Signed, dated and completed case report forms

To document that the investigator or authorised member of the investigator's staff confirms the observations recorded

- File of the investigator (copy) and sponsor (original).

3.2.15 Documentation of case report form corrections

To document all changes/additions or corrections made to case report form after initial data were recorded

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- File of the investigator(copy) and sponsor (original).

3.2.16 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.

- File of the investigator and sponsor.

3.2.17 Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and Ethics Committees of suspected unexpected serious adverse reactions and of other safety information

Notification by sponsor and/or investigator, where applicable, to regulatory authorities and Ethics Committees of suspected unexpected serious adverse reactions and of other safety information.

- File of the investigator (where required) and sponsor.

3.2.18 Notification by sponsor to investigators of safety information

Notification by sponsor to investigators of safety information in accordance with 'The detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use'[8]

- File of the investigator and sponsor.

3.2.19 Interim or annual reports to Ethics Committees and authority(ies)

Interim or annual reports provided to Ethics Committees and to authorities.

- File of the investigator and sponsor (where required).

3.2.20 Subject screening log

To document identification of trial subjects who entered pre-trial screening.

- File of the investigator and sponsor (where required).

[8] http://pharmacos.eudra.org.

3.2.21 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.

- File of the investigator.

3.2.22 Subject enrolment log

To document chronological enrolment of subjects by trial number.

- File of the investigator.

3.2.23 Investigational medicinal product accountability at the site

To document that investigational medicinal product(s) have been used according to the protocol.

- File of the investigator and sponsor.

3.2.24 Signature sheet[9]

To document signatures and initials of all persons authorised to make entries and/or corrections on case report forms.

- File of the investigator and sponsor.

3.2.25 Record of retained body fluids/ tissue samples (if any)

To document location and identification of retained samples if assays need to be repeated.

- File of the investigator and sponsor.

3.3 After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in sections 3.1 and 3.2 should be in the file together with the following

3.3.1 Investigational medicinal product(s) accountability at site

To document that the investigational medicinal product(s) have been used according to the protocol. To document the final accounting of investigational medicinal product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor.

- File of the investigator and sponsor.

3.3.2 Documentation of investigational product destruction

To document destruction of unused investigational products by sponsor or at site.

- File of the investigator (if destroyed at site) and sponsor.

3.3.3 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.

- File of the investigator.

3.3.4 Audit certificate

(if available)

To document that audit was performed.

[9] In addition the ‚List of appropriately qualified persons to whom the investigator has delegated significant trial related duties' and which is maintained by the investigator should be retained in the trial master file under this section.

- File of the sponsor.

3.3.5 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.
- File of the sponsor.

3.3.6 Treatment allocation and decoding documentation
Returned to sponsor to document any decoding that may have occurred.
- File of the sponsor.

3.3.7 Final report by investigator to Ethics Committees where required, and where applicable, to the regulatory authority(ies)
To document completion of the trial.
- File of the investigator.

3.3.8 Clinical study report
To document results and interpretation of trial.
- File of the investigator (if applicable) and sponsor.

4. QUALITY OF ESSENTIAL DOCUMENTS

Essential documents should be complete, legible, accurate, and unambiguous.
They should be signed and dated as appropriate.

5. MEDIA TO BE USED

Directive 2005/28/EC states in Article 20 that*: "The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request. Any alteration to records shall be traceable."*

Particular attention should be paid when records are stored on electronic, magnetic, optical, or other non-indelible media. In such cases suitable controls should be implemented to ensure that these records cannot be altered without appropriate authorisation and the creation of an audit trail.

When original records are transferred to other media, for the purpose of archiving, the system of transfer should be validated to ensure that information will not be lost or altered. Such transfers should be certified for accuracy and completeness by someone with appropriate authority (e.g. trial manager), as part of the quality assurance system.

For media that require processing in order to render records into a readable format, the availability of appropriate equipment should be ensured so that this processing can be done.

6. STORAGE CONDITIONS

Storage conditions should ensure that essential records are maintained in a legible condition and can be retrieved upon the request of a regulatory authority. Any change in the location of the stored documentation should be recorded in order to allow tracking.

Adequate and suitable space should be provided for the secure storage of all essential records from completed studies. The facilities should be secure, with appropriate environmental controls and adequate protection from physical damage.

The storage of the sponsor's documentation may be transferred to a sub-contractor (e.g. a commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor (CPMP/ICH/135/95, 5.2.1).

Directive 2005/28/EC Article 19 states "The sponsor shall appoint individuals within its organization who are responsible for archives. Access to archives shall be restricted to the named individuals responsible for the archives". The contract research organisations should also follow this requirement. Withdrawal of essential documents from archives should be under the control of the named individuals responsible for archiving (e.g. archive loans).

An archive index / log should be maintained by the sponsor/contract research organisations to record all trial master files that have been entered into the archive, and to track and retrieve documents on loan from the archive.

The investigator is recommended to make the sponsor aware of the storage arrangements for their essential documents. The ultimate responsibility for the documents to be retained by the investigator/institution resides with the investigator/institution. If the investigator becomes unable to be responsible for their essential documents (e.g. relocation, retirement etc) the sponsor should be notified in writing of this change and informed as to whom the responsibility has been transferred.

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

Storage of personal data is subject to applicable elements of Directive 95/46/EC.

7. DURATION FOR THE RETENTION OF ESSENTIAL DOCUMENTS

Directive 2005/28/EC Article 17 and 18 sets out the requirements for retention of the essential documents and medical files.
The requirements of Annex 1 to Directive 2001/83/EC (as amended by Directive 2003/63/EC) shall be complied with concerning clinical trials submitted in support of marketing authorisations.

Retention times, as laid down in Article 17 of Directive 2005/28/EC, for sponsors' records also apply to the records retained by contract research organisations or other agents of the sponsor, unless arrangements have been made to transfer the documents to the sponsor. Any transfer of ownership should be documented.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for

record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

The sponsor should obtain the investigator's/institution's agreement to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed. The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

8. DESTRUCTION OF ESSENTIAL DOCUMENTS

Sponsors should ensure that essential documents are not destroyed before the end of the periods given in section 7.

The sponsor should notify investigators in writing when their trial records can be destroyed. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.