



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, implementation and legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
ENTR/F/2 D(2002)

**DETAILED GUIDELINES ON THE TRIAL MASTER FILE AND
ARCHIVING.**

Comments are expected before 16 September 2002

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DETAILED GUIDELINES ON THE TRIAL MASTER FILE AND ARCHIVING.

Draft agreed for release for consultation – 12 June 2002

1. BACKGROUND

The European Directive on Clinical Trials requires the publication of detailed guidance on 'The master file on the trial ' and 'Archiving' (Directive 2001/20/EC, Article 15.5).

This document provides guidance for sponsors and investigators on requirements on trial master files.

2. REFERENCES

Trial Master File: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Section 8.

Archiving: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
Sections:
3.4, Ethics Committees,
4.9.4 to 4.9.7, Investigator / Institution
5.5.6, 5.5.7, 5.5.8, 5.5.11, 5.5.12, 5.6.3, 5.15, Sponsor / CRO

Directive 2001/83/EC Annex 1

Manufacturing: Annex 13 to EU GMP regulations -
'Manufacture of Investigational Medicinal Products'

3. PRINCIPLES

The documents which individually and collectively permit evaluation of the conduct of a clinical trial and the quality of the data produced, are defined as essential documents according to CPMP/ICH/135/95. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with applicable regulatory requirements. They should be filed in an organised way that will facilitate management of the clinical trial, audit and inspection (Trial Master File).

Essential documents must be retained (archived) for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request.

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.

4. DOCUMENTS TO BE ARCHIVED

Section 8 of CPMP/ICH/135/95 defines the minimum set of documents to be archived.

In addition:

Section 4.1.5 also refers to the investigator site delegation list/log.

Section 5.1.3 refers to quality control records

Section 5.11.1.b refers to statements that Independent ethics committees are

organised and operate in accordance with GCP.

Responsibilities for ensuring that these documents are archived are identified in the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)

Sections:

3.4, Ethics Committees,

4.9.4 to 4.9.7, Investigator / Institution

5.5.6, 5.5.7, 5.5.8, 5.5.11, 5.5.12, 5.6.3, 5.9, 5.15, Sponsor / CRO

5. QUALITY OF ESSENTIAL DOCUMENTS

Essential documents should be complete, legible, accurate, unambiguous, authentic and, as appropriate, certified after verification.

CPMP/ICH/135/95, sections 5.1.1 and 5.1.3 state the responsibilities of the sponsor for implementing quality assurance and quality control to assure the quality of essential documents.

6. MEDIA TO BE USED

The media used to store essential documents should ensure that these documents will be promptly available, complete and legible throughout the required period of retention.

Any alteration to records should be traceable, particular attention needs to be paid when records are stored on electronic, magnetic, optical, or other non-indelible media, in which case 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 copied or transferred to other media for archiving, the system of copying or transfer should be validated to ensure that information will not be lost or altered. Such copies or transfers should be certified for accuracy and

completeness by someone with appropriate authority, as part of the quality control procedure.

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.

7. STORAGE CONDITIONS

Storage facilities and their maintenance should reflect relevant EU and national standards. They should ensure that essential records are maintained in a legible condition and can be retrieved promptly. Any change in the ownership and location of the documentation should be documented in order to allow tracking of the stored records.

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 fire, flood and unauthorised access.

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 retrievability of the documents resides with the sponsor (CPMP/ICH/135/95, 5.2.1).

The function of storage and archiving should be specified and the role assigned to identified archivist(s). Access to archives should be restricted to authorised personnel.

An archive index / log should be maintained by the archivist(s) to record all essential documents that have been entered into the archive, and to track and retrieve documents on loan from the archive.

The investigator should make the sponsor aware of the storage arrangements for the documents. If the investigator becomes unable to store their essential documents, the sponsor should be notified in writing so that alternative storage arrangements can be agreed. If the investigator is no longer able to maintain custody of their essential documents, the sponsor should be notified in writing and the investigator/institution see to it that appropriate arrangements can be made.

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 EU Directive 95/46/EC.

8. DURATION FOR THE RETENTION OF ESSENTIAL DOCUMENTS

8.1 TRIALS TO BE INCLUDED IN REGULATORY SUBMISSIONS

8.1.1 SPONSOR'S RESPONSIBILITIES

The requirements of Annex 1 to Directive 2001/83/EC shall be complied with.

In addition the GCP requirements apply CPMP/ICH/135/95 section:

The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

If the sponsor discontinues the clinical development of an investigational medicinal product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in the EU and until there are no pending or contemplated marketing applications in the EU/EEA or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the sponsor

Record retention times for sponsors apply also 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.

8.1.2 INVESTIGATOR / INSTITUTION RESPONSIBILITIES

CPMP/ICH/135/95 section:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in the EU and until there are no pending or contemplated marketing applications in the EU or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or by agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

In addition the requirements of Annex I of Directive 2001/83/EC shall be complied with.

8.2 TRIALS WHICH ARE NOT TO BE USED IN REGULATORY SUBMISSIONS

It is the responsibility of the sponsor to consider whether the results of a trial will or may be included in a marketing authorisation application and to take the necessary steps to ensure appropriate retention of the essential documents. Essential documents of the sponsor and investigator, from trials which are not to be used in regulatory submissions should be retained for at least 5 years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirement(s) or by agreement with the sponsor.

8.3 INDEPENDENT ETHICS COMMITTEES' RESPONSIBILITIES

The IEC/IRB should retain all relevant records for a period of at least 3 years after completion of the trial and make them available on request from the regulatory authority (ies). These documents should be retained for a longer period if required by the applicable regulatory requirement(s).

9. DESTRUCTION OF ESSENTIAL DOCUMENTS

The reasons for destruction of essential documents should be documented and signed by a person with appropriate authority. This record should be retained for a further 5 years from the date that the essential documents were destroyed.

The sponsor should notify investigators in writing when their trial records can be destroyed.