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ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

The rules governing medicinal products
in the European Union

Volume 10

Clinical trials

Notice to applicants

July 2006

Edition (First Edition)

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- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*)

- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*).

FOREWORD

This Notice to Applicants - Clinical Trials - (NtA) is a compilation of legislative and guidance documents in the field of clinical trials and has been prepared by the European Commission, in consultation with the competent authorities of the Member States and the European Medicines Agency. This Notice has no legal force and does not necessarily represent the final views of the Commission. In case of doubt, therefore, reference should be made to the appropriate Community legislation. It is important when reading this text to appreciate that the legal requirements of the Directives must be met and that this Notice presents the harmonised views of the Member States on how those requirements may be met.

The resulting size of the NtA -Clinical Trials- has been divided into following parts:

- Chapter I deals with applications for a clinical trial
- Chapter II deals with safety monitoring and reporting of adverse reaction developing during clinical trials.
- Chapter III deals requirements for the manufacturing and import authorisation
- Chapter IV deals qualification of inspectors and inspection procedures
- Chapter V provides information on the modalities for non-commercial trials, the recommendation for the trial master file and archiving, the guideline on the datafields from the European clinical trials database (EudraCT) that may be included in the European Database on Medicinal Products, Questions and Answers and CPMP/ICH/135/95 guideline on good clinical practice
- Chapter VI provides the relevant legislation for clinical trials and manufacturing and importation of investigational medicinal products

General Pharmaceutical legislation may be consulted in EudraLex Volume 1 pharmaceutical legislation consists of all Directives and Regulations.
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev1.htm

GENERAL INFORMATION

The application dossier for the commencement of a clinical trial, to be submitted to the competent authorities of the Member States and the Ethics Committees, consists of administrative information and the necessary demonstration of quality, safety and efficacy of the investigation medicinal product.

For applications submitted in accordance with Article 8 and Article 9 of Directive 2001/20/EC, applicants should clearly indicate under which conditions the application is made (competent authority or Ethics Committee).

Each volume of the dossier should be sequentially paginated throughout, in Arabic numerals, legible and suitably bound. Each volume should be clearly identified. Particular care should be given to proper and consistent cross-referencing throughout the dossier.
If spectra or photographic material are supplied in the dossier, legible copies and photographs should be supplied in each copy submitted.

Full copies of all bibliographical references should be provided, translated if necessary.

CHAPTER I APPLICATION AND APPLICATION FORM

Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial
October 2005 Revision 2

Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use
February 2006 Revision 1

Detailed guidance on the European clinical trials database (EUDRACT Database)
DG Enterprises releases the: 'Detailed guidance on the European clinical trials database (EUDRACT Database) ' as required by Article 11 and Article 17 of Directive 2001/20/EC,
CT 5.1 Amendment describing the development of EudraCT Lot 1 for 1 May 2004 and CT 5.2 EudraCT core dataset.
April 2004

CHAPTER II MONITORING AND PHARMACOVIGILANCE

Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
March 2006 Revision 2

Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance – Clinical Trial Module)
as required by Article 11, Article 17 and Article 18 of Directive 2001/20/EC revision 1.
April 2004

CHAPTER III INFORMATION ON THE QUALITY OF THE INVESTIGATINAL MEDICINAL PRODUCT

Good manufacturing practices
ANNEX 13

Manufacture of investigational medicinal products July 2003

Community basic format for manufacturing authorisation
Community basic format for manufacturers/importers

Committee for Human Medicinal Products:
Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials

CHAPTER IV RECOMMENDATION ON INSPECTIONS

RECOMMENDATIONS ON THE QUALIFICATIONS OF INSPECTORS VERIFYING COMPLIANCE IN CLINICAL TRIALS WITH THE PROVISIONS OF GOOD CLINICAL PRACTICE
July 2006

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1. Introduction

Article 15 of Directive 2001/20/EC[1] requires the Commission to draw up detailed guidelines on the qualification of inspectors to verify compliance of the clinical trial with the provisions of Good Clinical Practice. These detailed guidelines are implemented by Chapter 5 Directive 2005/28/EC[2].

Articles 21 and 22 of Directive 2005/28/EC provide details on the qualifications and training of inspectors for the verification of Good Clinical Practice.

The present document provides further recommendations on qualifications and training of Good Clinical Practice inspectors.

2. Scope

These recommendations are relevant to the qualifications for inspectors who conduct inspections of clinical trial to verify compliance with Good Clinical Practice

3.1 APPOINTMENT OF INSPECTORS

The inspectors should be officials of/or appointed by the Member States in accordance with national regulations and follow the provisions for the national competent authority.

All inspectors should be competent to carry out their assigned duties and should receive appropriate training.

3.2. PERSONAL QUALITIES

The personal skills of an inspector are important in helping to achieve the objectives of the inspections.

During an inspection, the inspector should facilitate the exchange of information. Inspectors need to remain objective during the inspection and in this context should answer questions or provide clarification but avoid entering into the role of a consultant.

4. EDUCATION AND TRAINING

4.1. Education

The level of education should allow good communication with all persons involved with the clinical trails.

The inspector should have demonstrated competence in clearly and fluently expressing concepts orally and in writing in their officially recognised language. In Member States where English is not the officially recognised language, the inspector should preferably also be able to read English.

The inspector should be familiar with basic medical terminology.

[1] OJ L 121, 1.5.2001 p.24
[2] OJ L 91, 9.4.2005, p.13

Where applicable and in some circumstances, the inspector may need to become familiar with the health care and regulatory systems of other countries.

To be able to act as lead inspector in inspections requested by the Committee for Human Medicinal Products and co-ordinated by European Medicines Agency (Agency) and to participate in the ongoing co-operation and harmonisation of procedures in the Community, the inspector should in addition be able to write and speak English.

4.2.Training

The inspectors should have undergone training to the extent necessary to ensure their competence and skills required for planning, carrying out and reporting inspections.

The training and experience should be documented individually and evaluated within the requirements of the applicable quality system of the competent authority/ inspectorate.

Based on the tasks assigned to the inspector, training is recommended to provide knowledge and understanding of:

- knowledge and understanding of Good Clinical Practice;
- knowledge of and training in working according to national and European guidelines for inspections;
- training in inspection technique, acquired by attending relevant course(s) and accompanying and being guided by qualified Good Clinical Practice inspectors, and participating as an observer when relevant during Good Manufacturing Practice and Good Laboratory Practice inspections;
- training in administration procedures required for managing an inspection, such as planning, organising, communicating or providing feed back to inspectees;
- knowledge and understanding of current technology, computer systems, information technology, data handling and archiving;
- requirements for laboratory facilities, analytical instrumentation, handling of samples and analyses, pharmacokinetics;
- training in evaluation of findings and reporting;
- the general principles of Quality Management Systems;
- review and design of clinical trials and processes, including protocol and Case Report Form design;
- the basic requirements for production e.g. labelling, storage and quality control, and distribution of investigational medicinal products;
- medical writing.

Prior to assuming responsibility for performing Good Clinical Practice inspections a new inspector should have gained experience by participation as team member in inspections led by experienced Good Clinical Practice inspectors. Preferably, the inspector should start with national Good Clinical Practice inspections as a member of a team and then deal progressively with more complex Good Clinical Practice inspections. Training is a prerequisite to be able to act as a team leader and/or reporting inspector in international inspections requested by the Committee for Human Medicinal Products and co-ordinated by Agency.

4.3. Management capabilities

The inspector should through suitable means demonstrate knowledge and capability of using the necessary management skills required in execution of an inspection, i.e. planning, announcing, conducting and reporting of an inspection.

4.4. Report writing

The inspector should document and demonstrate his/her capacity to write inspection reports according to national requirements as well as according to the EMEA system for inspections requested by the Committee for Human Medicinal Products.

4.5. Formation of inspection teams

It is up to the Member State to ensure that clinical trials are inspected in line with Directive 2001/20/EC and to that effect it may be necessary to form a team to ensure the presence of skills necessary for specific inspections.

5. MAINTENANCE OF COMPETENCE

According to Article 21(3) and (4) of Directive 2005/28/EC the competence should be maintained. This should be documented by the Member States competent authorities/inspectorate.

6. HARMONISATION IN THE COMMUNITY

In order to promote harmonisation in the Community in the interpretation of the Good Clinical Practice principles and compliance, the management of Good Clinical Practice inspections in the Member States facilitate training activities, including on the job training, at national and international levels.

Consultations with the staff of other Good Clinical Practice inspectorates and joint inspections or training visits are useful and should be encouraged.

Where possible, management should also facilitate the exchange of information and practical experience gained by inspectors in the fields of Good Laboratory Practice and Good Manufacturing Practice, especially in those parts that are closely related to Good Clinical Practice, e.g. laboratory facilities, computerised data recording and analyses and requirements in relation to medicinal products for investigational use.

RECOMMENDATION ON INSPECTION PROCEDURES FOR THE VERIFICATION OF GOOD CLINICAL PRACTICE COMPLIANCE

July 2006

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1. INTRODUCTION

Good Clinical Practice inspections are performed in order to verify protection of the rights and welfare of trial subjects, compliance with the provisions of Good Clinical Practice and the quality of data generated in clinical trials.

This document should be read in conjunction with Article 15(5) of Directive 2001/20/EC and Chapter 6 of Directive 2005/28/EC.

2. SCOPE

This document specifies and provides guidance on the minimum requirements for Good Clinical Practice inspection procedures to verify compliance with Good Clinical Practice in accordance with the requirements of Directive 2001/20/EC and Directive 2005/28/EC.

3. DEFINITIONS

Deviation from Good Clinical Practice or non-compliance with Good Clinical Practice: failure to satisfy the prescribed requirements.

Finding: a failure to comply with the prescribed requirements recorded during the inspection and supported by appropriate factual evidence

Good Clinical Practice Inspection Services Group: This group provides expert advice and support to the Community, its members, the European Commission, the European Medicines Agency and its scientific committees and other parties as required on matters related to Good Clinical Practice and inspections. It draws its membership from representatives of the Good Clinical Practice inspectorates of the Member States and the European Medicines Agency Inspection Sector.

4. COMPONENTS

4.1. Administrative structure and documentation

According to provisions of Directive 2001/20/EC, Directive 2005/28/EC and Regulation (EC) No. 726/2004 the Member States, the Commission, and the Agency have different roles further elaborated below.

Member States should:

- establish the legal and administrative framework within which their good clinical practice inspections operate, including provisions that inspectors of the competent authority of the other Member States also have access to the clinical trial sites and data, on request and where appropriate.

- provide for sufficient resources and should in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice.
- establish relevant procedures that should include
    - the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures;

    - appointment of experts for accompanying inspectors in case of need;
    - requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State;
    - arranging inspections in third countries.
- maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up

According to Article 29 of Directive 2005/28/EC in order to harmonise the conduct of inspections by the competent authorities of the different Member States, guidance documents containing the common provisions on the conduct of those inspections shall be published by the Commission after consultation with the Member States.

These guidance documents should normally be developed by the Good Clinical Practice Inspection Services Group on the request of the Commission. Appendix I provide the topics covered by these guidance documents.

Member States enter in the EudraCT database a reference to the inspections carried out on conformity with Good Clinical Practice according to provisions of Article 11 and Article 15.1 of Directive 2001/20/EC and the guidance referred to in these articles.

To foster international understanding and liaison, Member States should inform the Commission, the Agency and other Member States of the national requirements relating to the adoption of Good Clinical Practice, the legal administrative framework for Good Clinical Practice inspections and the contact point(s) for Good Clinical Practice inspections.

The Agency in conjunction with the Good Clinical Practice Inspection Services Group should within the remit of Regulation (EC) No. 726/2004:

- establish the inspection procedures for inspections requested by the Agency;

- establish a Good Clinical Practice inspection program for clinical trials. The scope and extent of the program, the powers under which it is conducted, and the categories of inspections should be described;

- establish, in conjunction with the Good Clinical Practice Inspection Services Group, the processes for the request, conduct, reporting and follow-up of the GCP inspections. This is carried out through the inspectorates of the Member States;

- establish the process for contracting the conduct of inspections to the inspectorates of the Members States in accordance with the agreements established between the Agency and the Competent Authorities of the Member States;

- publish documents providing criteria which form the basis for the Good Clinical Practice compliance program, including information on the legal or administrative framework within which the program operates and references to published acts, normative documents (e.g. regulations, codes of practice) after validation by the Good Clinical Practice Inspection Services Group;

- maintain records of the inspections requested, the reports and their follow-up;

- establish a process for arranging inspections in third countries.

At the request of the Agency, within the framework of its powers as provided for in Regulation (EC) No. 726/2004 , or of one of the Member States concerned, and following consultation with the Member States concerned, the Commission may request a new inspection should verification of compliance with the Directive 2001/20/EC reveal differences between Member States.

4.2. Confidentiality

According to Article 21(1) of Directive 2005/28/EC inspectors, appointed by the Member States pursuant to Article 15(1) of Directive 2001/20/EC, shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements.

Inspectors of the Member States may have access to personal medical data and commercially valuable information and, on occasion, may even need to remove/take copies of sensitive documents from a clinical trial site or refer to them in detail in their reports.

Member States shall according to Article 30 of Directive 2005/28/EC lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts. With regard to personal data, the requirements of Directive 95/46/EC of the European Parliament and of the Council (1) shall be respected.

Inspection reports shall be made available by the Member States to the recipients referred to in Article 15(2) of Directive 2001/20/EC, in accordance with national regulations of the Member States and subject to any arrangements concluded between the Community and third countries.

National regulations can make provisions for other recipients to receive the inspection reports, for example the (principal) investigator or the people responsible for the site/activities inspected, or the applicant for a Marketing Authorization/Marketing Authorization Holder.

For inspections carried out in to the context of Article 23(2) of Directive 2005/28/ECthe Agency should make provision for the maintenance of confidentiality, by their personnel involved and by the inspectors and by experts including inspectors who undertake the tasks of inspection and assessment on behalf of the Agency and its scientific committees. And ensure that inspection reports are made available to the recipients referred to in article 15(2) of Directive 2001/20/EC, in accordance with EU regulations and national regulations of the Member States and subject to any arrangements concluded between the community and third countries.

4.3. Follow-up to inspections

When an inspection has been completed, the inspector should prepare an inspection report, provided to recipients presented in section 4.2.

According to Article 12 of Directive 2001/20/EC where a competent authority has objective grounds for considering that the sponsor or the investigator or any other person/party involved in the conduct of the trial no longer meets the obligations laid down, it shall forthwith inform

him in writing thereof, indicating the course of action which he must take to remedy this state of affairs. The competent authority concerned shall forthwith inform the Ethics Committee in writing, the other competent authorities, and the Commission of this course of action.

Where a Member State has objective grounds for considering that the conditions in the request for authorization referred to in Article 9(2) of Directive 2001/20/EC are no longer met or has information raising doubts about the safety or scientific validity of the clinical trial, it may suspend or prohibit the clinical trial and shall notify the sponsor thereof. Such decision might be based on or caused by inspection findings. Before the Member State reaches its decision it shall, except where there is imminent risk, ask the sponsor and/or the investigator for their opinion, to be delivered within one week. In this case, the competent authority concerned shall forthwith inform the other competent authorities, the Ethics Committee concerned, the Agency and the Commission of its decision to suspend or prohibit the trial and the reasons for the decision.

Member States may also take action through the courts, where warranted by circumstances and where national legal provisions so permit.

Where applicable, if deviations are found which may affect the authorization of a clinical trial site, the competent authority should inform the authority responsible for the site authorisation.

Where an inspection is conducted as part of the inspection programme for the centralised procedure, the Agency and Commission should take action where major or critical deviations from Good Clinical Practice principles are found during or after an inspection, with recommendation to Member States which may take administrative or legal actions on their territories in accordance with national regulations. Member States are recommended to take administrative action in a harmonised manner.

APPENDIX 1: TOPICS TO BE COVERED BY PROCEDURES

This Appendix provides the topics to be covered by the guidance documents, referred to in section 5.1. This set of guidance documents will be developed by the Good Clinical Practice Inspection Services Group and will be published by the Commission. These guidance documents may be customised or updated as required to address the needs of the scope of inspections, advances in inspection practices or advances in the conduct of clinical trials and/or advances in investigational medicinal products.

Procedures for national inspections are adopted by the Member States; in order to achieve harmonization amongst the EU inspectorates, Member States should ensure that the national procedures concerning topics covered by the guidance documents developed and adopted by the Good Clinical Practice Inspection Services Group, are consistent with those guidance documents and encompass the topics included. These national procedures are also applicable to marketing authorisations via the mutual recognition process.
Procedures involving marketing authorisations via the centralised procedure are adopted by the Good Clinical Practice Inspection Services Group, and are consistent with the guidance documents referred to in section 5.1 and encompass the topics included.

Table I: Topics to be covered by the generic set of procedures

Selection of the trials/sites to be inspected - context of assessment of applications for marketing authorisation - surveillance of clinical trials in Member States
Coordination / co-operation with other organisations involved in assessing Good Clinical Practice requirements
Preparation of Good Clinical Practice inspections
Conduct of Good Clinical Practice inspections
Preparation of Good Clinical Practice inspection reports
Record keeping and archiving of documents obtained or resulting from the Good Clinical Practice inspection
Actions taken after completion of Good Clinical Practice inspection
Communication on Good Clinical Practice inspections and findings

CHAPTER V ADDITIONAL INFORMATION

Draft guidance on 'specific modalities' for non-commercial trials referred to in the Commission Directive 2005/28/EC laying down the principles and detailed guidelines for good clinical practice

(To be included after finalisation)

RECOMMENDATION ON THE CONTENT OF THE TRIAL MASTER FILE AND ARCHIVING

July 2006

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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 M**onitoring 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 S**igned 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.

Guideline on the data fields from the European clinical trials database (EudraCT) that may be included in the European database on Medicinal Products
(To be included after finalisation)

QUESTIONS AND ANSWERS
In order to give more and detailed information to requirements set in the legislation on clinical trials a document called "QUESTIONS AND ANSWERS" has been prepared. It concerns interpretation of the sponsor and the legal representative in a clinical trial. It also gives advice in relation to EudraCT database and questions in relation to the application

Good Clinical Practice
Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95 - adopted July 96)
EudraLex Volume 3C Efficacy 3CC1A

CHAPTER VI LEGISLATION

Directive 2001/20/EC OF the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (*Official Journal L 121, 1/5/2001 p. 34 - 44*)

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (*Official Journal L 91, 9/4/2005 p. 13 - 19*)

Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use (*Official Journal L 262, 14/10/2003 p. 22 - 26*).