



EUROPEAN COMMISSION
ENTERPRISE and INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

**GUIDANCE DOCUMENTS
CONTAINING THE COMMON PROVISIONS
ON THE CONDUCT OF GCP INSPECTIONS BY COMPETENT
AUTHORITIES OF THE DIFFERENT MEMBER STATES**

**Annex I
TO GUIDANCE FOR THE CONDUCT OF GOOD
CLINICAL PRACTICE INSPECTIONS
Investigator site**

Version: 28 May 2008

This document forms part of the guidance documents containing the common provisions on the conduct of GCP inspections . Please check for updates in the Volume 10 of the Rules Governing Medicinal Products in the European Union.

http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm

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1 INTRODUCTION

This annex compiles specific items that may be verified at the investigator site but their selection will depend on the scope of the inspection and will be established in the local inspection plan. Reference should be made to the relevant GCP, local legal requirements and list of essential documents in determining the documentation which should be present and available for inspection.

2 LEGAL AND ADMINISTRATIVE ASPECTS

The aim is to determine if all legal and administrative aspects of the clinical trial have been accomplished.

The inspector should examine the legal and administrative aspects related to the implementation, progress and termination of the clinical trial. This includes the following points:

2.1 Communication with the IEC (Independent Ethics Committee)

The aim is to:

- Identify the IEC for this site and check whether it provides a statement that it is organised and operates according to GCP and applicable laws and regulations. If applicable, verify the accreditation / authorisation of the IEC by national authorities and the adequate composition of the IEC according to EU requirements as set out in Eudralex Volume 10 and local regulatory requirements.
- Determine whether IEC approval/favourable opinion (signed and dated) was obtained before starting the trial and implementing any amendments at the centre and clearly identifies the trial, the investigator, the documents reviewed and their versions. The same has to be checked for amendments of the protocol, if applicable.
- Determine whether the (coordinating) investigator or sponsor (when appropriate) has maintained copies of all reports submitted to the IEC, when the trial was initiated, and reports of all actions or modifications required prior to the approval/favourable opinion and other notifications.
- Determine whether annual reports have been submitted to the IEC.

If possible according to the local regulations, check the necessary and available written operating procedures.

2.2 Communication with the regulatory authorities

The aim is to check whether notification/ authorisation of the trial, changes to the protocol, information about adverse events, transmission of reports and any exchanges of information have been carried out according to the GCP principles and local regulations.

2.3 Other communications

It may be necessary to check any other required authorisation to perform the trial at the site and whether adequate information about the trial was given to other involved parties at the trial site (director of the institution, pharmacy, etc.). The documentation of insurance and indemnification should be checked.

3 ORGANISATIONAL ASPECTS

3.1 Implementation of the trial at the site

Organisation and Personnel

- Organisation charts (facility management and scientific organisation charts).
- Documentation of delegation of responsibilities by the principal investigator.

- Systems for QA and QC, if available.
- SOP system where available.
- Disaster plans, e.g. handling of defective equipment and consequences.
- Staff – qualification, responsibilities, experience, availability, training programmes, training records, CV.
- Numbers of clinical trials performed and their nature.
- Proportion of time allocated to clinical trial work.

Check the conditions of implementation of the study at the site:

- Contracts between the sponsor and the investigator.
- Qualifications and experience of the investigator's team in the considered clinical area.
- Documentation describing the distribution of duties and functions for the conduct of the trial.
- Compatibility of the workload of the investigator and the staff with the requirements of the study.
- Organisation of the site for the study: organisation chart, GCP training, trial specific training, specific equipment, specific procedures.
- Compliance with the planned time schedule for the study.
- Correct implementation of the correct versions of the protocol and its amendments.

The inspector should also check the dates of the first inclusion/selection of a patient at the site inspected and the last visit of the last patient.

3.2 Facilities and equipment

The aim is to verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the trial. The inspection may include a review of the following:

- Equipment used.
- Facilities.
- Their suitability for the protocol requirements and the characteristics of the study being inspected

For the conduct of the inspection at a laboratory site see Annex II.

3.3 Management of biological samples

The aim is to examine conditions and documentation regarding the management of biological samples, if applicable:

- Collection: person in charge of this task, dates and handling procedures, including labelling.
- Storage of the samples before analysis or shipping.
- Shipping conditions.

3.4 Organisation of the documentation

The aim is to determine whether the **general documentation** (according to Eudralex Volume 10, chapter V, Recommendations on the content of the trial master file and archiving), is available, dated, signed and if applicable how it is archived at the trial site.

Also it should be determined if the following **trial subjects' documents** are available, completed and archived at the trial site:

- Source documents (patient's charts, X-ray, etc.).
- Informed consent documents.
- Case Report Form (CRF).

A sample of data should be verified from the study report and or CRF to the source documents.

3.5 Monitoring and auditing

The following points should be examined, if available:

- Monitoring and follow-up by the sponsor. Number of visits at the site, scope and dates of the visits, content of the monitoring visit reports, where these have been requested from the sponsor. Actions required by the monitor. Monitoring visits log. Monitoring plan and Standard Operating Procedures.
- Audit certificates (from sponsor file).

3.6 Use of computerised systems

If computerised systems have been used for the trial, it will be necessary to ascertain their validation status.

The elements to be evaluated during an inspection of computerised systems used in clinical trials are established in a separate document. Computers may be study specific and supplied by the sponsor (e-CRFs, e-patient diaries, IVRS.). They may be site specific and part of the routine equipment of the site (medical records, on-line laboratory data, ECG recording, etc.).

4 INFORMED CONSENT OF TRIAL SUBJECTS

The aim is to determine whether informed consent was obtained in accordance with EU requirements as set out in Eudralex Volume 10 and local regulatory requirements from an appropriate sample of subjects (patients) (including the subjects/patients whose medical records are reviewed), or the subjects' legally acceptable representative, prior to their entry into the study. This needs to include patients whose medical records are reviewed.

It will be necessary to check:

- The signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC at the time of inclusion of the subjects.
- The information sheet actually used and approved by the IEC, in order to determine whether it includes all the elements requested by the EU requirements as set out in Eudralex Volume 10 and any local regulatory requirements.
- The centre practice for giving a copy of the informed consent to the patient
- Consent for access to medical records by the authorities.

5 REVIEW OF THE TRIAL SUBJECT DATA

The aim is to check whether the investigator team conducted the clinical trial according to the approved protocol and its amendments by source data verification. In the source data verification it will be necessary to evaluate the source records taking into account their organisation, completeness and legibility. The description of the source data inspected should be reported by the inspector. It will be necessary to evaluate whether corrections of the data recorded in the CRF was done according to the EU requirements as set out in Eudralex Volume 10 and the local regulatory requirements (signed and dated by the authorised person and providing justification, if necessary).

For a number of subjects that will be determined within the inspection plan, (the sample might include the first and last patient enrolled, etc.) the following should be checked:

5.1 Characteristics of the subjects included in the clinical trial

The aim is to determine whether the inclusion of the subjects in the trial was performed in accordance with the approved protocol and/or that protocol violations are documented, and also described in the study report.

It should be checked whether:

- Subjects included in the clinical trial existed and participated in the clinical trial.
- Subjects' participation was recorded in their medical records.
- Subjects included fulfilled the inclusion criteria and none of the exclusion criteria stated in the protocol were present. Appropriate medical records must support these criteria.

5.2 Subjects' visits calendar

The aim is to determine whether the subjects' visits calendar established in the protocol was followed. This check will include a review of the dates when the trial visits took place in order to evaluate whether they were done on the correct dates.

5.3 Efficacy and safety assessment data

The aim is to verify whether the efficacy and safety data recorded in the CRF are in agreement with the source data obtained during the trial and whether adequate data management procedures were in place. Data related to endpoints should be compared with source documents, if appropriate, according to the scope of the inspection.

This check will also include whether adverse events recorded in the site records are also recorded in the CRF and were reported to the sponsor, IEC and authorities in accordance with the current regulations.

During the safety data verification, it will be necessary to evaluate the premature discontinuation of treatment and drops outs.

5.4 Concomitant therapy and intercurrent illness

It should be verified whether concomitant therapy and intercurrent illnesses were managed in compliance with the protocol and recorded in the CRF and source documents.

6 MANAGEMENT OF THE INVESTIGATIONAL MEDICINAL PRODUCT(S)

The aim is to verify whether all the activities related to the Investigational Medicinal Product(s) have been conducted according to the protocol and other study documents.

It will be necessary to review the following documents:

- Instructions for handling of Investigational Medicinal Product(s) and trial related materials (if not included in protocol or investigator's brochure).
- Shipping records for Investigational Medicinal Product(s) and trial related material. Receipt date(s) of product delivery and quantity. This record should also contain batch numbers (check correspondence with the information kept at the sponsor site), expiration dates and codes assigned to the product and the trial subject.
- Documentation regarding allocation of treatment, randomisation and code breaking.
- Investigational Medicinal Product(s) accountability at site (pharmacy or investigator):
 - Date and quantity dispensed or returned, identification of recipients (patients' code or authorised person's). This record should contain also batch numbers, expiration dates and codes assigned to the product and the trial subject.
 - Documentation about re-labelling, if applicable.
 - Date and quantity returned to the sponsor. Return receipt: this record should also contain batch numbers, expiration dates and codes assigned to the product and the trial subject.
- Documentation of destruction of the Investigational Medicinal Product (if destroyed at the site): dates and quantity. Documentation or receipt.
- Treatment compliance

- Other activities, as appropriate:
 - Check the suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.).
 - Review of the specific SOPs for this activity from the pharmacy or institution.
 - Check whether there was controlled access to the Investigational Medicinal Product from reception to dispensing.
 - Verification of the labelling for compliance with applicable requirements.

The inspectors should check that where required these documents have been signed and dated by the responsible persons according to the site and/or sponsor SOP and/or applicable requirements related to the management of the Investigational Medicinal Products.

7 REFERENCES

- Directive 2001/20/EC 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.
- Directive 2005/28/EC 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 product.
- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the community code relating to medicinal products for human use, as amended.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
- EUDRALEX Volume 10 - Clinical trials, of the Rules Governing Medicinal Products in the European Union: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol10_en.htm