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Inspections

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ANNEX IV TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE EMEA: SPONSOR SITE AND/OR CONTRACT RESEARCH ORGANISATIONS (CRO)
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GCP Inspectors Working Group

Applies to: EMEA, EU/EEA Inspectorates	
Summary of scope: This procedure compiles the main aspects that are to be verified at sponsor site or at a CRO performing sponsor's trial related duties during a GCP inspection requested by the EMEA	
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1 INTRODUCTION

This annex compiles specific items that may be verified at the sponsor site or CROs performing sponsor's trial-related duties.

There could be two different approaches:

- *System inspection*
- *Specific clinical trial inspection*

The selection of the items, which will be inspected, will depend on the scope of the inspection and should be established in the local inspection plan. In general during the inspection an appropriate sample of data/documents/items from specific trials should be checked to confirm the functioning of the process described. Where specific trials form part of the inspection request this sample will come primarily from these trials.

2 SPONSOR OR CRO QUALITY SYSTEM INSPECTION

The aim of this kind of inspection is to evaluate the quality assurance and quality control systems established by the sponsor/CRO in order to assure that clinical trials are conducted and data are generated, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The following items should be reviewed in a sponsor/CRO system inspection:

2.1 Organisation and personnel

The aim is to evaluate if the sponsor/CRO has a well-established organisation for clinical research activities and has a sufficient number of properly qualified and trained personnel for each area.

Review:

- Organisational charts that identify the key personnel in each area.
- The independence of the quality assurance unit.
- The job description, qualifications and training of the individuals involved at any stage of the clinical trial process.

2.2 Facilities and equipment

The aim is to identify and evaluate the facilities used for archiving or investigational medicinal product storage as well as the equipment used. Special attention should be paid to computer systems (hardware, software, communications...), in order to evaluate their validation status, and their adequacy for the requirements of the trial(s) being inspected.

2.3 Sponsor/CRO Operating Procedures

Procedures should be reviewed in order to verify their compliance with GCP standards and applicable regulations.

2.3.1 Implementation and termination of the clinical trial

The aim is to evaluate the procedures established for the implementation and termination of the clinical trial.

Review the procedures for:

- Document preparation: format and content and distribution of protocol, protocol amendments, informed consent documents, investigator brochure, CRF and any other trial documents.
- Investigators selection and training.
- Regulatory compliance: obtaining IEC approval/favourable opinion and necessary authorisations, providing notifications and reports as required by GCP and local regulations.

2.3.2 Monitoring

The aim is to evaluate the system established for monitoring clinical trials.

Determine if procedures include:

- Description of monitoring activities: visits, frequency and extent of data review.
- Content and handling of monitoring reports.
- Agreements for direct access to source documents by the sponsor personnel (or their appointed representatives) and by regulatory authorities and confidentiality of information about subjects.

2.3.3 Investigational Medicinal Product

The aim is to determine if sponsor procedures for different stages of the investigational medicinal product cycle are according to the current GMP, GCP, ICH and local regulations.

Determine if these procedures establish provisions for

- Quality control requirements.
- Manufacturing, packaging and labelling.
- Supplying, accountability, returns and destruction.
- Randomisation and code breaking.

2.3.4 Sample management

The procedures established for handling samples obtained in clinical trials should be reviewed.

2.3.5 Safety and adverse events reporting

The aim is to verify procedures for reviewing and communicating findings that could adversely affect the safety of subjects and the reporting of serious adverse events to regulatory authorities, investigators and IECs, where applicable.

Review procedures for:

- Expedited Adverse Drug Reaction reporting to regulatory authority(ies), investigators and IEC, where applicable.
- Serious adverse events notification by investigators.
- Management of the serious adverse events reported by investigators.
- Safety updates and periodic safety reports.
- Validation of computer systems used.

2.3.6 Data handling and clinical trial report

The aim is to evaluate the system established by the sponsor/CRO for handling the data obtained during the clinical trial and reporting it in the clinical trial report.

Determine if the procedures establish:

- Data handling, data analysis and their control procedures.
- Clinical trial report preparation according to ICH standards.
- Validation of the computerised systems used
- Audit trails (for paper and computer systems).

2.3.7 Documentation archiving

The aim is to determine whether the system established by the sponsor/CRO guarantees that the general documentation which has to be archived at the sponsor/CRO site (according to section 8 of the CPMP/ICH/135/95 Note for guidance on GCP) is available, complete and maintained in good conditions during the period of time established.

Determine if procedures include:

- System for archiving and retrieval of documents.
- Controlled access to the archives.

2.3.8 Sponsor audit and quality assurance system

The aim is to determine if the sponsor/CRO has established an audit system, as part of its own quality assurance system, in order to evaluate its activities related with clinical trials.

It should be determined if the procedures include:

- Audits of key clinical trial processes, including monitoring, data management, safety reporting, clinical study report production, archiving and computer system validation activities.
- Audits of contractors/sub-contractors.

The inspectors should also review:

- The processes for communicating and addressing audit findings, including the format and distribution of audit reports.
- The procedures for dealing with serious and/or persistent GCP non-compliance.
- Audit trails.
- Procedures for generation and implementation of audit programme(s)/plan(s).

2.3.9 Delegation of duties

The aim is to verify the procedures for contracting/subcontracting of trial-related duties.

Inspectors should examine the procedures related with:

- Pre-selection and ongoing assessment of contractor/subcontractors.
- Documentation of duty delegation and its time recording.
- Handling contract amendments.
- Contracts should be reviewed (either specific ones or a sample).

3 SPECIFIC CLINICAL TRIAL INSPECTION

The aim of this type of inspections is to verify if the trial has been conducted, data has been generated, documented and reported in compliance with the protocol, GCP principles and sponsor procedures. The procedures and requirements applicable at the time of the trial should be considered, and compared where relevant to those applying at the time of the inspection.

The specific clinical trial inspections could also be conducted to answer questions listed in the CHMP request for a GCP inspection.

The aspects that should be checked include:

3.1 Implementation and termination of the clinical trial

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

Review:

- Distribution of sponsor's duties or functions.
- Information given to investigators and/or specific training.
- Investigator selection and agreements.
- Fulfilment of regulatory requirements: IEC approval/favourable opinion and necessary authorisations.
- Submission and approval of amendments.
- Critical dates: IEC approval/favourable opinion, regulatory authorisation (where required) initiation of the study, patient enrolment period, closing of the trial sites, termination of the study.

3.2 Monitoring

Check:

- Monitoring plan/SOPs (availability, content and compliance to it).
- Frequency and extent of the monitoring activities made.
- Monitors' qualifications.
- Monitoring visit reports and the review of the reports by sponsor/CRO.
- Corrective actions induced by monitoring visits.

3.3 Investigational Medicinal Product

Check the documentation about:

- Manufacturing, packaging, labelling and quality control.
- Supplying, accountability, returns and destruction (investigational medicinal product tracking system).
- Randomisation and code breaking.
- Blinding.
- Shipment.
- Condition of shipped product on receipt and during storage.

3.4 Safety and adverse events reporting

Check

- Notification, follow up and reporting of serious adverse events and other non-serious adverse events requiring expedited reporting according to protocol.
- Safety updates and their communication.

3.5 Case Report Form data verification

A selected number of CRFs should be checked to verify:

- Adherence with the protocol as well as data accuracy, completeness, legibility and timeliness.
- CRF corrections.
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well as with investigational medicinal product delivery.

3.6 Data handling and clinical trial report (CTR)

Check:

- Data tracking system from CRF to the database.
- Validation of computer systems used.
- Data Management.
- Statistical analysis as established in the protocol.
- Clinical trial report content.
- Quality control applied.
- System for review of CTR, including signatures.

3.7 Clinical trial documentation and archiving

Determine if all essential documents listed in the section 8 CPMP/ICH/135/95 Note for guidance on GCP, are available during the inspection.

3.8 Audit

Determine:

- If the clinical trial was audited and audit reports exist.
- Qualifications of the auditors.

4 REFERENCES

See “Principal documents taken into account for the preparation of procedures for GCP inspections requested by the EMEA”.