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Good Clinical Practice Inspectors Working Group (GCP IWG)

# ANNEX I
# TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: INVESTIGATOR SITE

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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 can be established in the local inspection plan. Reference should be made to the Regulation (EU) No 536/2014, relevant GCP, national regulatory requirements and list of essential documents in determining the documentation, including electronic documents, which should be present and available for inspection. As the Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference v for further information).

# 2. Legal and administrative aspects

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

The inspectors should check whether the authorisation of the clinical trial and its further modifications, the trial safety reporting and any other required authorisation/ notifications/ exchange of information have been carried out according to GCP principles, legal obligations and the applicable regulatory requirements.

In the case of EU investigator sites, the Member State decision on the authorisation of the trial and substantial modifications, as well as other clinical trial notifications and exchanges of information will be available from the EU clinical trial system for their further verification at the investigator site. The decision on the authorisation takes into consideration the ethical review by the ethics committee which shall be performed in line with the Member State legislation. Therefore inspectors should examine any specific Member State conditions related to the ethical review outlined in the decision that may require further verification at the site.

For sites outside the EU a separate ethical opinion from the authorisation of the trial may be required and available at the site for verification.

In both cases the following aspects should be considered, as applicable, for examination at the investigator site in relation to the ethics committee review:

- Identify the Independent Ethics Committee (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 and independence of the IEC according to national regulatory requirements[1].
- Determine whether IEC approval/ favourable opinion (signed and dated) was obtained before starting the trial and implementing any modifications at the centre and clearly identifies the trial, the investigator, the documents reviewed and their versions. The same has to be checked for modifications of the protocol and implementation of any urgent safety measures, 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. If possible according to local regulations, check the necessary and available written operating procedures.

[1] Third country inspection should take into account national regulatory requirements, as applicable.

- Determine whether annual reports have been submitted to the IEC, if applicable.

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*

Inspectors should examine the following elements:

Organisation and personnel:

- Organisation charts (facility management and scientific organisation charts).
- Documentation of delegation and acceptance of responsibilities by the principal investigator.
- Systems for QA and QC, if available.
- Standard Operating Procedure (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.

The following points should be examined regarding the implementation of the study at the site:

- Contracts between the sponsor (or Contract Research Organisation (CRO)) 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.
- Regulatory authorisation to start the trial and supply the IMP.
- Compliance with the planned time schedule for the study.
- Correct and timely implementation of the correct versions of the protocol, informed consent form and amendments.
- First patient first visit (inclusion or selection) and last patient last visit.

## *3.2. Facilities and equipment*

Inspectors should verify the proper use, adequacy and validation status of procedures and equipment used during the performance of the trial. A tour of the facilities can be considered, if applicable (e.g. the clinic, pharmacy, lab processing area). The following points should be examined:

- Equipment used.
- Equipment maintenance, service and calibrations.
- 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 and for phase I units see Annex V.

### *3.3. Management of biological samples*

Inspectors should 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*

Inspectors should determine whether the general documentation and trial participants' documents (according to the guideline "GCP compliance in relation to the Trial Master File (TMF)" in Eudralex Volume 10, chapter V), is available, dated, signed and, if applicable, how it is archived at the trial site.

### *3.5. Monitoring and auditing*

Points to consider, if available:

- The 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 SOPs.
- Audit certificates (from sponsor file).

### *3.6. Use of computerised systems*

The elements to be evaluated during an inspection of computerised systems used in clinical trials are established in a separate document (Annex III – computer systems). Computers may be study specific and supplied by the sponsor (eCRFs, ePRO, IRT). 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 participants

Inspectors should determine whether the informed consent was obtained in accordance with EU requirements as set out in in Chapter V of Regulation (EU) No 536/2014 and national regulatory requirements and guidelines in Eudralex Volume 10, by examining an appropriate sample of trial participants (including the trial participants whose medical records are reviewed), or the trial participants' legally acceptable representative, prior to their entry into the study. This needs to include patients whose medical records are reviewed.

Points to consider:

- The signed and self-dated (by the trial participant 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 trial participants.
- 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 in Chapter V of Regulation (EU) No 536/2014, in Eudralex Volume 10 guidelines and in any national regulatory requirements[2].
- The centre practice for giving a copy of the informed consent to the patient.
- Consent for access to medical records by the authorities.
- Documentation in the source data of the process of obtaining the initial informed consent and subsequent consent to updates, including paediatric assent and emergency consent, if applicable.

# 5. Review of the trial participant data

Inspectors should check whether the investigator team conducted the clinical trial according to the approved protocol and its modifications 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 can be reported by the inspector. It will be necessary to evaluate whether corrections of the data recorded in the case report form (CRF) was done according to the EU requirements as set out in Eudralex Volume 10 guidelines and the national regulatory requirements2 (signed and dated by the authorised person and providing justification, if necessary).

For a number of trial participants (the sample might include the first and last patient enrolled, etc.) the following points should be examined:

## *5.1. Characteristics of the trial participants included in the clinical trial*

Inspectors should determine whether the inclusion of the trial participants 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.

Points to consider:

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

[2] Third country inspection should take into account national regulatory requirements, as applicable.

### *5.2. Trial participants' visits calendar*

Inspectors should determine whether the trial participants' 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*

Inspectors should 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 drop outs.

### *5.4. Concomitant therapy and intercurrent illness*

Inspectors should verify 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.

Points to consider:

- 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 and unauthorised auxiliary 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 participant.
- Visual appearance of IMP and comparators used, if still available at the site
- Documentation regarding allocation of treatment, randomisation and code breaking of investigational medicinal products.
- Investigational and unauthorised auxiliary 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 participant.
  - 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 participant.

- Documentation of destruction of the investigational medicinal product (if destroyed at the site): dates and quantity. Documentation of 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 receipt 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


i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. Commission Implementing Act on Detailed arrangements for clinical trials inspection procedures including the qualifications and training requirements for inspectors, pursuant to Article 78(7) of Regulation (EU) No 536/2014.

iii. 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.

iv. 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.

v. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

vi. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the Rules Governing Medicinal Products in the European Union.

vii. Annex II to Guidance for the conduct of GCP inspections – clinical laboratories.

viii. Annex III to Guidance for the conduct of GCP inspections – computer systems.

ix. Annex V to Guidance for the conduct of GCP inspections – phase I units.

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# ANNEX II
# TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: CLINICAL LABORATORIES

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# 1. Introduction

This guidance may be applied to the inspection of laboratories that perform the analysis or evaluation of human samples collected as part of a clinical trial.

As the Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference vii for further information).

As there is already a large volume of guidelines and other documentation already available in relation to inspections applicable to laboratories, this guidance presents merely a general outline of the elements that should be taken into account when inspecting such laboratories.

The following aspects should be assessed during an inspection:

# 2. General aspects

## *2.1. Background*

2.1.1. Scope of work and delegated responsibilities.

2.1.2. Accreditation status of the laboratory (the methods) e.g. GLP, GMP, ISO, EN. The accreditation status of the laboratory is not assessed, nor considered to be essential for clinical sample analysis, but may support the presence of a formalised quality system.

2.1.3. Fulfilment of national requirements of accreditation (where required).

2.1.4. Relevance of accreditation in the context of clinical trial(s).

2.1.5. Proportion of work in connection to clinical trial sample analysis.

## *2.2. Organisation and Personnel*

2.2.1. Organisation charts (facility management, scientific organisation charts, quality assurance (QA) reporting lines).

2.2.2. Systems for quality assurance (QA) and quality control (QC), including programmes for internal audits.

2.2.3. Standard Operating Procedure (SOP) system appropriate to the work to be conducted including relevant supporting systems.

2.2.4. Disaster recovery and business continuity.

2.2.5. Staff – qualifications, responsibilities (i.e. via job description and/or delegation), experience, availability, training programmes and competency assessment, training records, CV.

## *2.3. Contractual arrangements*

2.3.1. Procedures, e.g. for contracts and sub-contracts, protocol, protocol modifications, definition of source data, agreements for reporting.

2.3.2. Specification of methods and procedures.

2.3.3. Access and availability for monitoring, audit and inspection.

2.3.4. Data recording, handling and archiving.

2.3.5. Security and protection of trial participant confidentiality.

2.3.6. Standards of work – i.e. compliance with ICH GCP, applicable national legislation.

2.3.7. Serious breach reporting.

2.3.8. Informed consent requirements (if not managed elsewhere) – presence of, withdrawal or amendment of consent, notification of changes, coverage of sample analysis.

2.3.9. Expedited trial participant safety reporting requirements and protection of blinded data.

### *2.4. Facilities/ Premises*

2.4.1. Suitability and adequacy of premises (fit for purpose) – e.g. adequate degree of separation of work areas to avoid mix-ups, contamination and interference.

2.4.2. Environmental conditions, e.g. temperature, airflow and air pressure, microbiological contamination (where relevant).

2.4.3. Security and safety, e.g. fire, water and pest control.

2.4.4. Suitability for intended use (e.g. laboratory areas, archive, sample storage areas) with appropriate controls (access, fire prevention, pest control).

### *2.5. Apparatus/ Equipment, Materials, Reagents*

2.5.1. Apparatus available, in good working order and complies with relevant specifications (calibration, validation, maintenance).

2.5.2. Quality of general supplies including tap water, analytical water, gases etc.

2.5.3. Records of operation, maintenance, and calibration of laboratory systems and supported by relevant risk assessments and justification to demonstrate fitness for intended use.

2.5.4. Records associated with method validation.

2.5.5. Materials and reagents are prepared, labelled, documented and stored under appropriate conditions and adherence to expiry dates. Labels for reagents indicate their identity, source, concentration and expiry dates.

2.5.6. Apparatus and materials used do not alter to any appreciable extent the samples.

2.5.7. Definition of source data and source documents, retrieval and archiving. Data generated by electronic systems including data capture, transfer, retention and archiving, restoration, ability to inspect and reconstruct.

## 3. Trial related aspects

*The inspection should also include review of all aspects applicable to the clinical trial, e.g. as listed under section 2.*

## *3.1. Handling of samples*

### 3.1.1. Pre-examination

- Samples obtained from trial participants in the clinical trial, date and time (where relevant for the analysis), identification, labelling, prior storage and shipping conditions, preparation, storage.
- Consideration for patient confidentiality in label details (where applicable, for example at laboratories remote from the investigator site).
- Consideration for any blinding constraints.
- Documentation of receipt (date and time), identification, condition, re-labelling (i.e. bar coding) and storage of samples by identifiable person.
- Confirmation received by the analytical laboratory that the samples were subject to appropriate handling and transfer prior to receipt for analysis i.e. storage at the clinical site and transfer/shipping to the laboratory.
- Documented procedures for acceptance or rejection of samples for analysis.
- Aliquoting.
- Distribution of samples for examination.
- Documented procedures for ensuring traceability.

### 3.1.2. Examination

- Compliance with protocol and specified validated test methods.
- Traceability and identification of samples and controls.
- Recording of data, documentation of acceptance and release of results.
- Handling of non-conformance, repeat analysis/ re-analysis, and results within critical/ alert ranges.
- Supporting data e.g. equipment, storage conditions, etc.
- Competence, training and experience of personnel.
- Reconstruction of laboratory activities during the analysis.

### 3.1.3. Post-analysis

- Data management, statistical analysis and reporting.
- Long term storage (where required), retrieval and destruction of samples.

## *3.2. Material and methods*

3.2.1. Material and methods according to the specification stated in the protocol/ contract and/or required according to Ph Eur or other applicable pharmacopeial standards.

3.2.2. Validation status of the methods, appropriate setting of limits of detection/ quantification, precision/accuracy, known inferences and specific control measures.

# 4. Reporting of laboratory results

*Various systems for reporting of results may be required according to the protocol/ contract e.g. report per sample (i.e. for immediate consideration in medical care of the trial participant) or on an integrated basis (i.e. to be used in the trial report). This will affect the procedures used by the laboratory and during the inspection.*

## *4.1. Procedures for reporting and evaluation of results and for data transfer*

## *4.2. Systems for alerting results that are unexpected and/or significant deviations from pre-specified limits*

## *4.3. Transcription of raw data into the report*

4.3.1. Identification of laboratory.

4.3.2. Unique identification and localisation of the trial participant.

4.3.3. Identification of investigator.

4.3.4. Date and time of sample collection, and time of receipt.

4.3.5. Date and time of examination and release of report.

4.3.6. Source of primary sample type and any comments of its quality.

4.3.7. Description of the analysis and of its results.

4.3.8. If applicable, detection limit, uncertainty of each measurements, and reference intervals.

4.3.9. Where appropriate, interpretation of results and other comments.

4.3.10. Identification of the person releasing the report.

## *4.4. Attribution of review and release of the report(s) to the responsible personnel*

## *4.5. Procedures for alterations and amendments of reports*

## *4.6. Procedures for complaints and corrective actions*

# 5. Quality assurance

## *5.1. Integrity of data reported by internal QA/QC and/or sponsor's QA/QC personnel (audit certificate)*

# 6. References


i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. 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.

iii. 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.

iv. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the Rules Governing Medicinal Products in the European Union.

v. Reflection paper on guidance for laboratories that perform the analysis or evaluation of clinical trial samples, EMA/INS/GCP/532137/2010.

vi. Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2.

vii. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

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# ANNEX IV
# TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: SPONSOR AND CRO

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# 1. Introduction

This annex compiles specific items that may be verified at the sponsor site or the Contract/Clinical Research Organisations (CROs) performing sponsor's trial-related duties.

There could be two different approaches:

- *System inspection (developed under Section 2).*
- *Specific clinical trial inspection (developed under Section 3).*

The selection of the items that will be inspected will depend on the scope of the inspection and should be established in the local inspection plan. In general, an appropriate sample of data/documents/items from specific trials should be checked during the inspection, 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.

As the Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference iv for further information). Risk proportionate approaches applied to a trial may affect the content of the TMF, in the sense that some documents may be combined or absent, depending on the risk adaptations performed and in line with the risk assessment and mitigation plan.

# 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 adequately for the purpose of ensuring trial participant rights and safety and data generated in clinical trials is recorded, handled, reported and stored in compliance with the protocol, GCP and applicable regulatory requirements to ensure robustness and reliability.

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

## *2.1. Organisation and personnel*

Inspectors should 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*

Inspectors should identify and evaluate the facilities (e.g. archiving, investigational medicinal product storage) as well as the equipment used. Special attention should be paid to computer systems (hardware, software, communication, etc.), 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*

Inspectors should evaluate the system for standard operating procedures and associated documents (e.g. forms, templates, policies). Individual 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

Inspectors should evaluate the procedures established for the implementation and termination of clinical trials.

Review the procedures for:

- Document preparation: format and content and distribution of protocol, protocol modifications, 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 as required by EU requirements as set out in Eudralex Volume 10 and national regulatory requirements.

### 2.3.2. Monitoring

Inspectors should evaluate the system established for monitoring clinical trials.

Determine if procedures include:

- Description of risk proportionate approach to monitoring, if applicable.
- Description of the rationale for chosen monitoring strategy in trial specific monitoring plans: planning, frequency, extent and nature of monitoring activities (visits, data review, etc.), monitoring responsibilities, etc.
- Description of on-site and central monitoring activities.
- Content, handling and follow up 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 trial participants.
- Training and oversight of monitors (e.g. co-monitoring, issue escalation, resourcing).

### 2.3.3. Investigational Medicinal Product

Inspectors should determine if sponsor’s procedures for different stages of the investigational medicinal product cycle are in accordance with current EU GMP and GCP requirements.

Determine if these procedures establish provisions for:

- risk proportionate approach to IMP management, if applicable;
- quality control requirements;
- manufacturing, packaging and labelling;
- storage and transport;
- supplying, accountability, returns and destruction;
- randomisation and code breaking;
- validation of computer systems used.

### 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

Inspectors should verify procedures for reviewing and communicating findings that could adversely affect the safety of trial participants and the reporting of serious adverse events to regulatory authorities, investigators and IECs, where applicable.

Review procedures for:

- risk proportionate approach to safety and adverse events reporting, if applicable;
- identification of AE/SAE/SUSAR by the investigator and/or sponsor;
- 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;
- preparation, implementation and use of IB and RSI, ongoing safety monitoring/profiling, handling of information from DSMBs, if applicable;
- validation of computer systems used.

### 2.3.6. Non-compliance

The procedures established for handling significant non-compliance in clinical trials should be reviewed (e.g. review and submission of potential and actual serious breaches, including log, confirmations for decisions, outcomes and CAPAs).

### 2.3.7. Data handling and clinical study 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 study report.

Determine if the procedures establish:

- data handling, data analysis and their control procedures;
- clinical study report preparation according to ICH standards;
- validation of the computerised systems used;
- audit trails (for paper and computer systems).

### 2.3.8. Documentation archiving

The aim is to determine whether the system established by the sponsor/CRO guarantees that the essential documentation which has to be archived at the sponsor/CRO site (according to Eudralex Volume 10, chapter V, GCP compliance for trial master file (TMF)) is available, complete and maintained in good conditions during the period of time established. Risk proportionate approach applied to a trial may affect the content of the TMF.

Determine if procedures include:

- system for archiving and retrieval of documents. The storage system (irrespective of the media used) should provide for document identification, search and retrieval;
- controlled access to the archives/electronic systems.

### 2.3.9. 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 to 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);
- risk based quality management, if applicable.

### 2.3.10. 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 contracts and contract amendments;

- oversight of any trial-related duties and functions performed by contractors/subcontractors;
- project management and general oversight of the trial both internally and externally.

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, applicable regulatory requirements and sponsor procedures. The procedures and requirements applicable at the time of the trial should be considered and compared where relevant to those applicable at the time of the inspection.

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

The aspects that should be checked are:

## *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. Oversight of any trial-related duties and functions in-house and performed by contractors/subcontractors.
- 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 modifications, urgent safety measures, serious breaches, review of protocol deviations
- 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:

- Description of risk proportionate approach to monitoring, if applicable.
- Monitoring plan/SOPs (availability, content and compliance with it).
- Frequency and extent of the monitoring activities made.
- Monitors' qualifications.
- Monitoring visit reports and the review of the reports by sponsor/CRO.
- Central monitoring activities and the review of the reports by sponsor/CRO.

- Corrective actions induced by monitoring visits.

## *3.3. Investigational Medicinal Product*

Check:

- Risk proportionate approach to IMP management, if applicable.
- Manufacturing, packaging, labelling and quality control.
- Supplying, accountability, returns and destruction (IMP tracking system).
- Randomisation and code breaking.
- Blinding.
- Shipment, including regulatory authorisation for IMP supply.
- Condition of shipped product on receipt and during storage.
- Validation of computer systems used.

## *3.4. Safety and adverse events reporting*

Check:

- Risk proportionate approach to safety and adverse events reporting, if applicable.
- Notification, follow up and reporting of serious adverse events and other non-serious adverse events requiring expedited reporting according to the protocol.
- Safety updates and their communication.
- Preparation, implementation and use of IBs and RSI, ongoing safety monitoring/profiling, handling of information from DSMBs, if applicable.
- Validation of computer systems used.

## *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 and audit trail.
- Correspondence of the dates of first patient included and last patient with the dates of the study initiation and completion as well with investigational product delivery.

## *3.6. Data handling and clinical study report*

Check:

- Data tracking system from CRF to the database.
- Validation of computer systems used.
- Data management.

- Statistical analysis as established in the protocol.
- Clinical study report content.
- Quality control applied.
- System for review of clinical study report, including signatures.

### *3.7. Clinical trial documentation and archiving*

Determine if all essential documents listed in the Eudralex Volume 10, chapter V, GCP compliance for trial master file (TMF) and other essential documents for the specific trial are available and retrievable during the inspection. Risk proportionate approach applied to a trial may affect the content of the TMF.

### *3.8. Audit*

Determine:

- if the clinical trial was audited and if the audit reports exist;
- qualifications of the auditors.

## 4. References


i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. Commission Implementing Act on detailed arrangements for clinical trials inspection procedures including the qualifications and training requirements for inspectors, pursuant to Article 78(7) of Regulation (EU) No 536/2014Directive 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.

iii. 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.

iv. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.

v. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the Rules Governing Medicinal Products in the European Union.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

02 May 2022
EMA/INS/GCP/183077/2022
Good Clinical Practice Inspectors Working Group (GCP IWG)

# ANNEX VI
# TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: RECORD KEEPING AND ARCHIVING OF DOCUMENTS

| | |
|---|---|
| Adopted by GCP Inspectors Working Group (GCP IWG) | 29 April 2022 |

| | |
|---|---|
| **Keywords** | ***GCP inspection, record keeping, archiving, documentation*** |

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# 1 Introduction

The scope of this document is to provide guidance for the record keeping and archiving of documents in relation to all Good Clinical Practice ("GCP") inspections carried out by the competent authorities of Member States of the European Union on behalf of the EMA in the context of a centralized procedure.

An inspection file is an organised body of records produced or received during the performance of the GCP inspection and which contains all correspondence concerning the inspection, documents submitted by the sponsor and/or applicant and the documents retrieved and copied during the inspection.

The Lead Inspectors ("LI") participating in an inspection have to open local inspection files, which content is described in appendix 1.

A central file should be also kept by the Reporting Inspector ("RI"), which content is described in appendix 2.

Local standard operating procedures ("SOPs") concerning the management of documents are not affected by this procedure, except where it is more stringent.

# 2 Management of the inspection files

## *2.1 Responsibilities*

The LIs and RI should establish the local and the central inspection files, respectively, immediately after appointment. The general layout of these files should be in accordance with the format as described in the appendices to this procedure.

All entries in the files should be made or completed at the time each action is taken and should be added in chronological order within the sections of the appendix.

All ensure that all copies of relevant data/documents are routed to the RI so that the information can be incorporated into the Central Inspection File and filed properly during the conduct of the inspection.

Locally collected information by all participating inspectors (validated copies of relevant data/documents, etc.) is filed into the local Inspection file(s) according to the procedures of the concerned inspectorates. A copy of all local information that is of a general importance or reflects on the whole of the inspection is sent to the RI to be incorporated into the Central Inspection File, in particular documents which are evidence in inspection findings that might adversely affect the rights, safety and/or wellbeing of the trial participants and/or the quality and integrity of data.

## *2.2 Storage*

The local inspection files are preserved by the concerned inspectorates while the central inspection file, where applicable, has to be maintained at the reporting inspectorate.

It is the responsibility of the involved inspectorates to store the inspection files under conditions that prevent accidental or premature destruction of the documents according to national requirements.

The inspection files should be stored safely in a suitable archive for the whole retention period and only authorised personnel shall have access to the archives.

Documents may be stored electronically, onto human readable media or other new media as changes in technology demand. If documents are to be archived using electronic or optical media, the methods for transferring the data to these media should be validated. A suitable backup-strategy must be implemented to prevent loss or destruction of data. There must be a possibility to generate hardcopies throughout the period of retention.

## *2.3 Confidentiality and security*

Each concerned authority is responsible for ensuring the correct application of applicable data protection requirements.

On reasonable request of a Member State inspectorate, the EMA or the Commission, the documentation could be made available for review whenever not accessible on the EU clinical trial system at the time of request. Access will not be provided to parties other than the Commission, the EMA or the Competent Authorities or the duly appointed experts of these parties, unless otherwise is indicated by legislation[1].

Whenever an authority grants access to the inspection file(s) or parts thereof, this access should be recorded. If copies of documents are required these may be provided, subject to confidentiality, to the parties mentioned above. The parties in receipt of the documents then bear full responsibility for ensuring their continued confidentiality.

## *2.4 Retention period and destruction*

The inspection files should be maintained for at least 25 years or as determined by national requirements, whichever retention period is longer. After this time, the inspection files could be removed from the archives for destruction. The signature of the person who is responsible for the destruction of the inspection file and the date of the destruction has to be recorded and should be kept in the archives for unlimited time.

[1] Such as national legislation on Freedom of Information.

# APPENDIX 1: FORMAT OF A LOCAL INSPECTION FILE

## *1. Table of contents*

## *2. Communication*

- With requesting party.
- With the participating inspectors and, where applicable, Reporting Inspector.
- With assessors.
- With applicant/sponsor with inspectees.
- Others.

## *3. Trial related documents[2]*

Provided by the applicant/sponsor (as applicable, a note to file is accessible on the EU clinical trial system):

- Protocol and amendments.
- Clinical study report.
- Investigator's brochure.
- Blank patient informed consent forms.
- Patient listings and audit trails.
- Other.

## *4. Inspection related documents*

- Inspection request/announcement.
- Inspection team composition.
- Contracts.
- Planning documents (such as, but not limited to, inspection plan, agenda etc.).
- Other.

## *5. Locally collected information of general importance*

- Documents retrieved or copied during the inspection.

[2] Multiple copies of documents from the applicant/sponsor may be sent to each member of the inspection team. One copy has to be retained in the Local and Central Inspection File as required by Appendix 2 of this Procedure. Therefore the concerned inspectorates could decide on the destruction or the return of those documents. The destruction or return of documents has to be recorded in the Inspection File.

## *6. Inspection Reports*

- Inspection Report(s) (that was/were sent to the inspectee(s) for comments).
- Response of the inspectees.
- Inspection Report (final version) or close-out documents of the inspection.
- Integrated Inspection Report (final version), where applicable.

# APPENDIX 2: FORMAT OF THE CENTRAL INSPECTION FILE

## *1. Table of contents*

## *2. Communication, if applicable*

- With requesting party.
- With lead inspector(s) and participating inspectors.
- With assessors.
- With applicant/sponsor.
- With inspectees.
- Others.

## *3. Trial related documents*

Provided by the applicant/sponsor (as applicable, a note to file is accessible on the EU clinical trial system):

- Protocol and amendments.
- Clinical study report.
- Investigators brochure.
- Blank patient informed consent forms.
- Patient listings and audit trails.
- Other.

Provided by assessor:

- Clinical study report (if applicable).
- Assessment reports.
- List of questions.
- Response to the list of questions.
- Other.

## *4. Inspection related documents, if applicable:*

- Inspection request.
- Inspection team composition (central and for each selected site).
- Contracts.
- Planning documents (such as, but not limited to, inspection plan, agenda etc.).

- Other.

## *5. Locally collected information of general importance*

- Documents retrieved or copied during the inspection.

## *6. Inspection Reports*

- Inspection Reports (including the responses of the inspectee(s)) and evaluation of Integrated Inspection Report (final version).

# APPENDIX 3: REFERENCES AND RELATED DOCUMENTS

i. Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

ii. Commission Implementing Act on Detailed arrangements for clinical trials inspection procedures including the qualifications and training requirements for inspectors, pursuant to Article 78(7) of Regulation (EU) No 536/2014.

iii. 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.

iv. 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.

v. EUDRALEX "Guidelines for Clinical Trials", Volume 10 of the Rules Governing Medicinal Products in the European Union.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Good Clinical Practice Inspectors Working Group (GCP IWG)

# ANNEX VII
# TO PROCEDURE FOR CONDUCTING GCP INSPECTIONS REQUESTED BY THE CHMP: BIOANALYTICAL PART, PHARMACOKINETIC AND STATISTICAL ANALYSES OF BIOEQUIVALENCE TRIALS

| | |
|---|---|
| Adopted by GCP Inspectors Working Group (GCP IWG) | 29 April 2022 |

| | |
|---|---|
| **Keywords** | ***GCP inspection, bioanalytical part, pharmacokinetic and statistical analyses of bioequivalence trials*** |

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# 1. Introduction

Bioequivalence trials are comprised of several parts:

- a clinical part, where the test and the reference products are administered to the trial participants and where biological samples (generally plasma or serum, possibly blood, urine or any other suitable matrix) are collected from the trial participants. This part is not addressed in this document;
- a bioanalytical part, where the concentration of the active moiety and/or its biotransformation product(s) in these biological samples is measured;
- the pharmacokinetic analysis, where pharmacokinetic parameters derived from these concentrations are calculated;
- the statistical comparison of the pharmacokinetic parameters obtained for the test and the reference products.

This annex compiles specific items that may be verified during the inspection of the bioanalytical part and of the pharmacokinetic and statistical analyses of bioequivalence trials. The selection of items to be inspected will depend on the scope of the inspection and should be detailed in the inspection plan.

The documents and data relating to the following topics are generally reviewed during the inspection:

- Storage of the biological samples.
- Validation of the bioanalytical method.
- Performance of the assays.
- If requested, pharmacokinetic and statistical analyses of the trial data.

As the Regulation (EU) No 536/2014 provides the basis for the application of a risk proportionate approach to the design and conduct of clinical trials, inspectors should take this into account during the inspection when such an approach is implemented in the conduct of the clinical trial inspected. Risk adaptations should be clearly described and justified in a risk assessment and mitigation plan (see reference iv for further information).

# 2. Bioanalytical part of bioequivalence trials

## *2.1. General organisation of the site*

### 2.1.1. Activity

The main points to consider are the following:

- Nature of the activities carried out at the laboratory.
- Proportion of bioequivalence trials in this activity.
- Command of the analytical methods used, particularly for complex methods.

### 2.1.2. Personnel

The main points to consider are the following:

- Organisation charts, valid at the time of the inspection and at the time when the inspected trial was conducted.
- Number and categories of people employed.
- Qualification, training and experience of the personnel.
- Individual workload of people involved.

### 2.1.3. Quality assurance system

The main points to consider are the following:

- Quality assurance system in place at the laboratory.
- Existence, availability, accessibility and validity of standard operating procedures ("SOPs").
- List of SOPs used for the trial.
- SOP awareness by people in charge.

### 2.1.4. Installations and equipment

The suitability of the facilities and equipment available, their appropriateness for the activity of the laboratory and for the bioequivalence trial inspected should be checked during the inspection.

### 2.1.5. Archiving of documentation

The main points to consider are the following:

- Nature of the documents kept.
- Place of archiving.
- Access control to that place.
- Conditions of storage and of protection of the documents.
- Person responsible for the archives.
- Documentation of file movements.
- Duration of retention of the files.
- Where applicable, loan arrangements.

## *2.2. Sample tracking*

### 2.2.1. Receipt

General aspects relating to sample handling at the facility may be inspected including:

- Responsibilities for receipt and handling of biological samples.
- Organisation of the receipt system, including outside workdays/ hours.
- Sample registration.
- Controls performed on receipt.

The points to consider specifically for the inspected trial(s) are the following:

- Dates and times of receipt of the samples, and acknowledgement of receipt.
- List of samples received for each dispatch.
- Shipment conditions (temperature).
- Condition of the samples on receipt.
- Any anomalies noted.
- Known sample stability (see validation report).

### 2.2.2. Storage

The following points should be checked for the samples collected for the inspected trial:

- Storage conditions of the trial samples.
- Compliance of these conditions with the protocol and the conditions used during method validation.
- Assessment of the risk of confusion between samples.
- Identification of the freezer(s) used.
- Temperature records of the freezer.
- Calibration of the thermometer and its traceability to national/international standards.
- Alarms and other surveillance measures.
- Labelling of the samples, if they are still available.
- Documentation of freeze/thaw cycles undergone by the samples.

### 2.2.3. Destruction

Check the date of destruction or return of the samples.

## *2.3. Sample analysis*

### 2.3.1. Bioanalytical method used

- **Method description**

Check the consistency of the trial report with the SOP describing the bioanalytical method and other documents available.

- **Equipment**

The main points to consider regarding the equipment used (including balances and pipettes) are the following:

  - Identity of the equipment (make, model).
  - Availability of the equipment. If the equipment is no longer visible at the site at the time of the inspection, review the documentation that could show that the equipment needed was indeed available when the trial was conducted.
  - Availability of instructions for use.
  - Compliance with specific conditions necessary for the trial, if any.
  - Documentation relating to the qualification, checks, and maintenance of the equipment.

- **Reagents**

The main points to consider are the following:

  - Labelling of reagents, including the expiry date.
  - Traceability of the reagents used.
  - Compliance with specific storage conditions, if any.

- **Reference substances**

The main points to consider are the following:

  - Availability and contents of the certificates of analysis.
  - Expiry dates.
  - Storage conditions.
  - Conditions for access to reference substances.

- **Calibration, control samples**

The main points to consider are the following:

  - Dates and conditions of preparation of the stock and working solutions and of the calibration and control samples, and the number of aliquots prepared for each sample.
  - Accuracy of the calculation of nominal concentrations.
  - Conditions and duration of storage of the stock solutions, working solutions, calibration and control samples, compared to their stability, as described in the validation report.

- Matrix used, including the anticoagulant, if any.
- Storage conditions on the blank matrix before use (temperature, duration, freeze/thaw cycles).

The main points to consider regarding the calibration for each run are the following:

- Number of calibration samples.
- Response function used, including weighting, if any.
- Acceptance criteria for the calibration curve.
- Criteria for exclusion of calibration samples.

### 2.3.2. Development of the method

A quick overview of the origin and of the development of the bioanalytical method can be helpful to identify critical steps in the procedure.

### 2.3.3. Method validation

The main points to consider are the following:

- Validation protocol.
- Dates of the validation.
- Adequate documentation of all operations.
- Completeness of the validation report, when compared to the various experiments performed.
- Consistency of the validation report with the source documents.
- Chromatogram integrations.
- Gaps in the injection sequence.
- Variations in the internal standard response.
- The settings and contents of the audit trail.
- The exclusion of calibration samples, if any.

The main validation parameters are the following:

- Stability:
  - of the stock solutions;
  - of the samples (bench-top, freeze/thaw cycles, long term);
  - if applicable, of extracted samples before their injection.
- Specificity / selectivity.
- Accuracy.
- Precision.
- Limit of quantification.

- Response function.
- Carry-over.
- In case of mass spectrometric methods: matrix effect.
- Effect of a dilution, if applicable.
- If applicable, effect of the anticoagulant, if the anticoagulant used for the preparation of the calibration and/or QC samples is different from the anticoagulant used to collect samples during the trial.

### 2.3.4. Assays

The main points to consider are the following:

- Nature and completeness of the documentation available.
- Adequacy of the documentation of all operations.
- Completeness of the analytical report.
- Number, date and composition of the analytical runs.
- Identification of samples and tubes.
- Assessment of the risk of sample mix-ups.
- Assessment of the risk of sample cross-contamination.
- Chromatogram integrations.
- Calculation of the concentrations.
- Compliance with pre-defined criteria for the exclusion of calibration samples.
- Criteria of acceptance of the runs, and compliance with pre- established criteria.
- Audit trail settings and information recorded in the audit trails.
- Gaps in the injection sequence.
- Variations in internal standard response.
- Practicalities of repeat analysis and the criteria for choosing the result to be reported.
- Maintenance of blinding, if required by the protocol.
- Practicalities of data transfer.
- Consistency of the analytical report with the source documents.
- Maintenance of blinding until the end of the bioanalytical phase, if applicable.

# 3. Pharmacokinetic and statistical analyses

## *3.1. Pharmacokinetics*

The main points to consider are the following:

- Quality system in place.
- Identity, qualification and responsibilities of the personnel involved.
- Software used.
- Practicalities and control of data entry.
- Sampling times used.
- Method used for calculation of pharmacokinetic parameters.
- Selection of data for the calculation of the terminal half-life, if applicable.
- Consistency of the raw data with the trial report.

It is helpful to recalculate the pharmacokinetic parameters before the inspection.

## *3.2. Statistical analysis*

The main points to consider are the following:

- Quality system in place.
- Identity, qualification and responsibilities of the personnel involved.
- Software used.
- Practicalities and control of data entry.
- Data line listings and tables of results.
- Consistency of the raw data with the calculated pharmacokinetic parameters and with the trial report.

The statistical analyses can be repeated before or during the inspection if needed.

# 4. References

As bioequivalence trials are clinical trials, all reference texts applicable to the inspection of clinical trials are applicable to the inspection of their bioanalytical part, including GCP.

i. Guideline on the investigation of bioequivalence (CHMP/EWP/QWP/1401/98 Rev.1/ Corr).

ii. Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1/ Corr. 2).

iii. Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (EMA/INS/GCP/532137/2010).

iv. Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.