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SCIENCE MEDICINES HEALTH

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Good Clinical Practice Inspectors Working Group (GCP IWG)

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.