# INSPECTION/AUDIT AT CLINICAL LABORATORIES

# REFERENCES

- Guidelines on Good Clinical Practice (ICH E6: Good Clinical Practice: Consolidated guideline CPMP/ICH/135/95)
- Annex II to Procedure for Conducting GCP Inspections Requested by the EMA: Clinical Laboratories (INS/GCP/3/II)
- Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples (adopted February 2012)
- GLP (but referred to the pre-clinical studies!!!!!)
- GCLP (i.e. WHO)

## GCLP REPRESENTS A BRIDGE BETWEEN GLP & GCP

- Good Clinical Laboratory Practice (GCLP) applies those principles established under GLP for data generation used in regulatory submissions relevant to the analysis of samples from a clinical trial. At the same time it, ensures that the objectives of the GCP principles are carried out.
- GCLP outline the principles and procedures to be followed by medical laboratories involved in patient care and/or clinical research so as to provide consistent, reproducible, auditable, and reliable laboratory results which contribute to good patient care and promote a positive attitude toward testing from a patient's perspective.

# GCP AUDIT/INSPECTIONS: CLINICAL LABORATORIES

- GENERAL ASPECTS
- TRIAL RELATED ASPECTS
- REPORTING
- QUALITY ASSURANCE

# GENERAL ASPECTS

- Background/Accreditation/National Requirements
- Organisation and Personnel
- Contractual arrangements
- Facilities/Premises
- Apparatus/Equipment, Material, Reagents

# GENERAL ASPECTS - BACKGROUND/ACCREDITATION/NATIONAL REQUIREMENTS

- Authorization according to National Requirements
- **(GCP § 8.2.12)** MEDICAL/LABORATORY/TECHNICAL PROCEDURES/TESTS

– certification or

– accreditation or

– established quality control and/or external quality assessment or

– other validation (where required)

(To document competence of facility to perform required test(s), and support reliability of results)

# GENERAL ASPECTS - ORGANISATION

- Organisation charts (facility management and scientific organisation charts) – clear responsibilities for oversight.
- Roles and responsibilities established and documented prior to the initiation of analytical work.
- Systems for QA and QC, including programmes for internal audits.
- SOP system (distribution, availability including holidays etc., audit-trail, clinical trials, archiving etc).

# GENERAL ASPECTS - PERSONNEL

- Personnel appropriately qualified (education and experience) and trained.
- Job descriptions detailing the individual's role and responsibilities.

# GENERAL ASPECTS - TRAINING

- GCP training of personnel commensurate with their roles and responsibilities.
- Periodic GCP refresher training (especially important following changes to regulations and associated guidance documents).
- Appropriate level of technical training prior to their participation in the analysis or evaluation of clinical trial samples.
- Information about relevant parts of clinical protocol.
- Validation of personnel.

# GENERAL ASPECTS – CONTRACTUAL ARRANGEMENTS

- Contractual agreements between relevant parties should be in place prior to the initiation of any work.
- It is advisable to review the contract, the relevant sections of the clinical trial protocol and the work instruction prior to the initiation of laboratory analysis or evaluation.
- Contract should be at an adequate level of technical detail (work instruction attached to the main general agreement).
- Responsibilities clearly distributed.
- The laboratory's quality system should include a documented procedure for the drafting, agreement, review and revision of contracts.

# GENERAL ASPECTS – CONTRACTUAL ARRANGEMENTS

- A formal contract is not required in situations where the laboratory is part of the sponsor organisation. However, a service level agreement or other internal documents, which detail the roles and responsibilities of both parties (including lines of communication and timelines), should be in place.
- Work of Internal Labs of the hospital could be included in the main agreement for the clinical trial.
- Procedure for analysis: routine vs clinical protocol specific.

# GENERAL ASPECTS – CONTRACTUAL ARRANGEMENTS

Main topics to be agreed:

- Definition of source data.
- Agreements for data transmission.
- Agreements for reporting.
- Methods and procedures (including sample handling).
- Agreed access and availability for monitoring, audit and inspection.
- Data recording, handling and archiving.
- Security and protection of subject confidentiality.

# GENERAL ASPECTS – FACILITIES/PREMISES

- Suitability & Adequacy. Suitable size, construction and location to meet the requirements of the work being performed.
- Environmental conditions.
- Adequate degree of separation of different activities to assure the proper conduct of the work.
- Security & Safety. Procedures for decontaminating laboratories and their equipment should be considered where relevant.

# GENERAL ASPECTS – APPARATUS/EQUIPMENT, MATERIAL, REAGENTS

- Apparatus available, in good working order and compliant with relevant specifications.
- Prior to use, analytical equipment should be subject to an appropriate level of user acceptance testing, by a suitably qualified person to demonstrate that the equipment is fit for its intended purpose.
- Apparatus should be periodically inspected, cleaned, maintained and calibrated according to standard operating procedures or the manufacturer's manuals.
- Quality of general supplies including tap water, analytical water, gases etc.

# GENERAL ASPECTS – APPARATUS/EQUIPMENT, MATERIAL, REAGENTS

- Records of operation, maintenance, justification and calibration.
- Records of the validation for the methods used for the measuring equipment and apparatus (including computerised systems). Log books.
- Materials and reagents are prepared, labelled and stored under appropriate conditions and adherence to expiry dates. Labels for reagents indicate their identity, source, concentration and expiry dates.
- Apparatus and materials used do not alter to any appreciable extent the samples.
- Definition of source data and source documents, retrieval and archiving. Data generated in automatic systems e.g. listings, graphs, record traces or computer printouts are archived.

# GENERAL ASPECTS – COMPUTER SYSTEM

- All computerised systems used for the capture, processing, reporting and storage of data should be developed, validated and maintained in ways which ensure the validity, integrity and security of the data.
- List of existing systems. For each computerised system, the components (e.g. hardware and software) which constitute the system should be clearly defined.
- Computerised systems should be sited in appropriate locations. Consideration should be given to environmental conditions and other external factors which may adversely impact on the systems performance.
- Re-validation.
- Disaster recovery/system failure procedures should be considered for all computerised systems.

## TRIAL RELATED ASPECTS - MATERIAL AND METHODS

- Analysis should be performed using appropriately validated methods (appropriately setting of limits of detection/quantification, precision/accuracy, known inferences and specific control measures) with defined acceptance criteria where appropriate.
- Relevant storage stability data must be available if samples are to be stored prior to analysis.
- Routine system suitability tests, such as the analysis of quality control (QC) samples, should be considered and included in the analytical methodology as required.
- It is important that analytical factors that may potentially affect clinical trial results are considered.

# TRIAL RELATED ASPECTS - HANDLING OF SAMPLES

- Samples obtained from subjects in the clinical laboratory, (date and time), identification (anonymisation, decoding), labelling, conditions, preparation, storage.
- Documentation of receipt (date and time), identification, condition, re-labelling and storage of samples by identifiable person.
- Procedures for acceptance or rejection of samples for analysis.
- Aliquotting and distribution for examination.
- Storage retrieval and destruction of samples.

## TRIAL RELATED ASPECTS - EXAMINATION

- Compliance with protocol and specified test methods.
- Availability in the Lab of a copy of the full clinical trial protocol (and amendments) or, at least, of the sections of which are relevant to the work).
- Availability of work instructions.
- Traceability and identification of samples and controls.
- Recording of data and acceptance and release of results.
- Handling of non-conformance, repeat analysis / re-analysis, and results within critical / alert ranges.

## TRIAL RELATED ASPECTS - SAFETY OF TRIAL PATIENTS

- The safety of trial patients or subjects takes precedence over any other aspect of the trial.
- Consequently, prior to the initiation of laboratory work, lines of communication should be established with the sponsor, or their representative, and with the investigators, to ensure that any issues that may impact on patient/subject safety are reported without delay.
- Under most circumstances normal ranges should be established for safety tests prior to the start of analysis. If clinically significant deviations from these ranges are recorded, a mechanism should be in place to communicate this information to the sponsor or their representative and to the investigator as quickly as possible.

## TRIAL RELATED ASPECTS – REPEAT ANALYSIS

- Repeat analyses should only be undertaken in accordance with a documented policy.
- Such a policy may be detailed in a standard operating procedure, or if there are specific requirements for a particular trial, this information may form part of the contract or work instruction.
- It is never acceptable to selectively report data; consequently, the rationale for performing the repeat analysis and the reason for the selection of the data points that will be reported should be transparent and should be documented.
- Adequate investigations should be performed in order to support decisions for repeat analyses.

# REPORTING

- Procedures for reporting and evaluation of results and for data transfer.
- Systems for alerting results that are unexpected and/or significant deviations from pre-specified limits.
- Transcription of raw data into the report.
- Attribution of review and release of the report(s) to responsible personnel.
- Procedures for alterations and amendments of reports.
- Procedures for complaints and corrective actions.

# QUALITY ASSURANCE

- Quality systems should be developed which include in-process quality control procedures and independent quality assurance audits designed to ensure data integrity and safeguard patient safety and confidentiality.
- QA programmes should always be designed to assure compliance with the relevant European Union Directives, associated guidance and the facility's internal policies and SOPs.
- It would be inappropriate for members of the organisation who are directly involved in generating trial data to be involved in a quality assurance programme (independence of quality assurance processes).

# QUALITY ASSURANCE

- It is recommended that quality assurance activities include, but are not limited to the following:
- Regular facility audits to ensure that the laboratory and associated equipment used to conduct analysis or evaluation of clinical trial samples remain fit for purpose.
- Periodic review of the laboratory's quality systems, including control of standard operating procedures and/or laboratory policies, archiving and the maintenance of training records.
- The audit of technical procedures and methodologies used to conduct the analysis or evaluation of clinical trial samples.

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# QUALITY ASSURANCE

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- Audit of critical analytical phases.
- Audits performed to assess the conduct of routine and repetitive processes which are common to all trials such as; sample receipt, sample storage, temperature monitoring, pipette and balance controls, and cleaning procedures.
- Audit of documentation generated during the validation of computerised systems or analytical equipment.
- Complete review of data sets and reports before they are sent to the sponsor to confirm that the analysis or evaluation of the clinical trial samples has been conducted and reported in accordance with the protocol, the contract/agreement, the work instruction and in compliance with the principles of GCP.