GCP/ GMP/ GLP

Module 7 Topic 3

GCP

Good Clinical Practices (GCP) is an international ethical & scientific quality standard for designing, conducting, recording & reporting trials that involve the participation of human subjects

It ensures the RIGHTS, SAFETY, WELL BEING of patients, Designing Clinical Trials or Studies Conducting Monitoring Recording Reporting Analysis

Purpose of GCP To harmonize the regulations and guidelines for the drug development

GCP = Quality data + Ethics

Principles of ICH GCP

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

Principles of ICH GCP

Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks

Principles of ICH GCP

The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society

The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial

Principles of ICH GCP

Clinical trials should be scientifically sound, and described in a clear, detailed protocol

A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion

Principles of ICH GCP

The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s)

Principles of ICH GCP

Freely given informed consent should be obtained from every subject prior to clinical trial participation

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification

Principles of ICH GCP

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s)

Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol

Systems with procedures that assure the quality of every aspect of the trial should be implemented

Integrated Addendum To ICH E6 (R1):Guideline For Good Clinical Practice ICH E6(R2)

Why Amendment?

- Increase in Scale, complexity, and the cost
- Evolution in technology (centralized monitoring) and risk management processes
- Improved and more efficient approaches to clinical trial design, conduct, oversight, recording and reporting while continuing to ensure human right subject protection and reliability of trial results

Glossary

ADDENDUM

Certified copy: A copy (irrespective of the type of media used) of the original record that has been Verified (e.g. by a dated signature or by generation through a validated process) to Have the same information, including data that describe the context, content and Structure, as the original

Monitoring plan : A document that describes the strategy, methods, responsibilities, and requirement for monitoring the trial

Glossary

Validation of Computerized Systems:
A process of establishing and documenting that the specified requirements of a Computerized system can be consistently fulfilled from design decommissioning of the system or transition to a new system. The approach to validation should be based on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results

The Principle Of ICH GCP

ADDENDUM

- After the 10th principle of ICH GCP Addendum that is

  This principle applies to all record referenced in this guideline, irrespective of the type of media used

- After the 13th principle Addendum that is

  Aspect of the trial that are essential to ensure human subject protection and reliability or trial results should be the focus of such system

Investigator Responsibility

ADDENDUM

Adequate Resources

- The investigator is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and function, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and function and should implement procedure to ensure the integrity of the trial-related duties and functions performed and any data generated

Investigator Responsibility

Records and Report

Source data should be attributable, legible, contem-poraneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary(e.g. via an audit trail)

Sponsor Responsibility

ADDENDUM

Quality Management

- Quality management includes the design of efficient clinical trial protocol and tools and procedure for data collection and Processing, as well as the collection of information that is essential to decision making the methods used to assure and control the quality of the trial should be Proportionate to the risk inherent in the trial and the importance of the information collected. Protocols, case report forms and other operational documents should be clear, concise and consistent

Sponsor Responsibility

The quality management system should use a risk-based approach as described below

Critical process and data identification

- The sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results

Risk identification

- Risk should be considered at both the system level (e.g. standard operating procedures, computerized systems, personnel) and clinical trial level(e.g. trial design, data collection, informed consent process)

Sponsor Responsibility

Risk Evaluation

The sponsor should evaluate the identified risks, against existing risk control by considering:

- The likelihood of errors occurring
- The extent to which such errors would be detectable
- The impact of such errors on human subject protection and reliability of trial results

Sponsor Responsibility

Risk Control

- Risk reduction activities may be incorporated in protocol design and implementation, monitoring plans, agreement between parties defining roles and responsibilities, systematic safeguards to ensure adherence to standard operating procedure and training in processes and procedures
- Detection of deviation from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed

Sponsor Responsibility

Risk Communication

- The sponsor should communicate quality management activities to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial execution

Sponsor Responsibility

Risk Review

- Review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience

Risk Reporting

- The quality management approach implemented in the trial and summarize important deviation from the predefined quality tolerance limits and remedial action taken in the clinical study report
(ICH E3. 9.6 Data Quality Assurance)

Trial Management, Data Handling, and Record Keeping

- The sponsor should base their approach to validation of such system on a risk assessment that takes into consideration the intended use of the system and the potential of the system to affect human subject protection and reliability of trial results

Trial Management, Data Handling, and Record Keeping (Contd)

- The SOPs should cover system setup, installation, and use. The SOPs should describe system validation and functionally testing, data collection and handling system maintenance, system security measures, change control, data backup, recovery, contingency planning, and decommissioning. The responsibilities of the sponsor, investigator, and other parties with respect to the use of these computerized system should be clear, and the users should be provided with training in their use

Monitoring

ADDENDUM

- The flexibility in the extent and nature of monitoring described in this section is intended to permit varied approach that improve the effectiveness and efficiency of monitoring
- The sponsor may choose on-site monitoring, a combination of on-site and centralized monitoring, or, where justified, centralized monitoring

Monitoring (Contd)

- On-site monitoring is performed at the sites at which the clinical trial is being conducted Centralized monitoring is a remote evaluation of accumulating data, performed in a timely manner, supported by appropriately qualified and trained persons(e.g. data managers, biostatisticians)
- Centralized monitoring processes provide additional monitoring capabilities that can complement and reduce the extent and/or frequency of on-site monitoring and help distinguish between reliable data and potentially unreliable data

Review, that may include statistical analyses, of accumulating data from centralized monitoring can be used to:

- Identify missing data, inconsistent data, data outliers, unexpected lack of variability
- Examine data trends such as the range, consistency ,and variability of data within and across sites.
- Evaluate for systematic or significant errors in data collection and reporting at a site or across sites; or potential data manipulation or data integrity problems.
- Analyze site characteristics and performance metrics.
- Select sites and/or processes for targeted on-site monitoring.

Monitoring Report

Report of on-site and/or centralized monitoring should be provided to the sponsor(including appropriate management and staff responsible for trial and site oversight) in a timely manner for review and follow-up. Results of monitoring activities should be documented in sufficient detail to allow verification of compliance with the monitoring plan

Monitoring Plan

The plan should also emphasize the monitoring of critical data and processes. Particular attention should be given to those aspects that are not routine clinical practice and that require additional training. The monitoring plan should reference the applicable policies and procedures

Monitoring Report (Contd)

Noncompliance

If noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions

Essential Document For The Conduct of a Clinical Trial

- The sponsor and investigator/institution should maintain a record of the location(s) of Their respective essential document including source documents. The storage system Used during the trial and for archiving (irrespective of the type of media used) should Provide for document identification, version history , search, and retrieval
- Essential document for the trial should be supplemented or may be reduced where Justified (in advance of trial initiation) based on the importance and relevance of the Specific document to the trial

- The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. When a copy is used to replace an original document(e.g. source documents, CRF)

- The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during and after the trial

GMP

Definition:

WHO defines Good Manufacturing Practices (GMP) as "that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization."

Why GMP is important

- A poor quality medicine may contain toxic substances that have been unintentionally added
- A medicine that contains little or none of the claimed ingredient will not have the intended therapeutic effect

QC and QA

- QC is that part of GMP which is concerned with sampling, specifications, testing and with in the organization, documentation and release procedures which ensure that the necessary and relevant tests are carried out
- QA is the sum total of organized arrangements made with the object of ensuring that product will be of the Quality required by their intended use

GMP guidelines

- GMP as per Schedule “M”
- GMP as per WHO
- GMP as per MCA now known as MHRA
- GMP as per TGA
- GMP as per US FDA
- GMP as per ICH guidelines WHO: World Health Organization MHRA: Ministry of Health and Regulatory Affairs TGA: Therapeutic Goods Affairs FDA: Food And Drug Administration ICH: International Conference on Harmonization

Ten Principles of GMP

- Design and construct the facilities and equipments properly
- Follow written procedures and Instructions
- Document work
- Validate work
- Monitor facilities and equipment

Ten Principles of GMP (Contd)

- Write step by step operating procedures and work on instructions
- Design ,develop and demonstrate job competence
- Protect against contamination
- Control components and product related processes
- Conduct planned and periodic audits

List of important documents in GMP

- Policies
- SOP (Standard Operating Procedure)
- Specifications
- MFR (Master Formula Record)
- BMR (Batch Manufacturing Record)

List of important documents in GMP (Contd)

- Manuals
- Master plans/ files
- Validation protocols
- Forms and Formats
- Records

What are cGMPs?

- cGMP refers to the Current Good Manufacturing Practice regulations enforced by the US Food and Drug Administration (FDA)
- cGMP provide for systems that assure proper design, monitoring and control of manufacturing processes and facilities
- Adherence to the cGMP regulations assures the identity, strength, quality and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations

What are cGMPs?

- Adherence to the cGMP regulations assures the identity, strength, quality and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations

Why are cGMP so important

- A consumer usually cannot detect (through smell, touch, or sight) that a drug product is safe or if it will work
- While cGMPs require testing, testing alone is not adequate to ensure quality
- In most instances testing is done on a small sample of a batch (for example, a drug manufacturer may test 1000 tablets from a batch that contains 2 million tablets), so that most of the batch can be used for patients rather than destroyed by testing

Packaging and holding of drugs

- Care shall be taken when using automatic tablet and capsule counting, strip and blister packaging equipment to ensure that all ‘rogue’ tablets, capsules or foils from packaging operation are removed before a new packaging operation is commenced
- There shall be an independent recorded check of the equipment before a new batch of tablets or capsules is handled

Packaging and holding of drugs

Finished pharmaceuticals

- Appropriate specifications for finished products shall include: -
  - The designated name of the product and the code reference
  - The formula or a reference to the formula and the pharmacopoeia reference
  - Directions for sampling and testing or a reference to procedures

Organization and Personnel

- Responsibilities of quality control unit
- Personnel qualifications
- Personnel responsibilities
- Consultants

Building and facilities

- Design and construction features
- Lighting
- Ventilation, air filtration, air heating and cooling
- Plumbing
- Sewage and refuse
- Washing and toilet facilities
- Sanitation
- Maintenance

Equipment

- Equipment design, size and location
- Equipment construction
- Equipment cleaning and maintenance
- Automatic, mechanical and electronic equipment
- Filters

Control of Components

- General requirements
- Receipt & storage of untested components, drug product containers and closures
- Testing and approval or rejection of components, drug product containers and closures
- Use of approved components, drug product containers and closures
- Retesting of approved components, drug product containers and closures

Containers and closures

All containers and closures intended for use shall comply with the pharmacopoeial requirements. Suitable validated test methods, sample sizes, specifications, cleaning procedure and sterilization procedure, wherever indicated, shall be strictly followed to ensure that these are not reactive, additive, absorptive, or leach to an extent that significantly affects the quality or purity of the drug. No second hand or used containers and closures shall be used

Production and process control

- Written procedures; deviations
- Charge-in of components
- Calculation of yield
- Equipment identification
- Sampling and testing of in-process materials and drug products
- Time limitations on production
- Control of microbiological contamination
- Reprocessing

Packaging and labeling control

- Materials examination and usage criteria
- Labeling issuance
- Packaging and labeling operations
- Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
- Drug product inspection
- Expiration dating

Holding and distribution

- Warehousing procedures
- Distribution procedures

Records and reports

- General requirements
- Equipment cleaning and use log
- Component, drug product container, closure and labeling records
- Master production and control records
- Batch production and control records

The inspection for compliance with GMP regulations

- Short description of the self inspection system indicating whether an outside, independent and experienced external export was involved in evaluating the manufacturer's compliance with Good manufacturing Practices in all aspects of production
- Periodic inspection of the garments shall be done by responsible staff

GLP

Objectives of GLP

- GLP makes sure that the data submitted are a true reflection of the results that are obtained during the study
- GLP also makes sure that not to indulge in any fraud activity by labs
- Promotes international acceptance of tests

Principles

- Test Facility Organization and Personnel
- Quality Assurance Programme
- Facilities
- Apparatus, Material, and Reagents
- Test Systems
- Test and Reference Items
- Performance of the Study
- Reporting of Study Results
- Storage and Retention of Records and Materials

Test Facility Organization and Personnel

- Test Facility Management's Responsibilities
- Study Director's Responsibilities
- Principal Investigator's Responsibilities
- Study Personnel's Responsibilities

Test Facility Management's Responsibilities

- Responsibilities of management as defined by these principles of good laboratory practice
- Sufficient number of qualified personnel, appropriate facilities, equipment, and materials are available for the timely and proper conduct of the Study
- Ensure the maintenance of a record of the qualifications, training, experience
- Job description for each professional and technical individual
- Documented approval of the study plan by the Study Director

Study Director's Responsibilities

- Approve the study plan
- Any amendments to the study plan by dated Signature
- Availability of SOPS to the personnel. Raw data generated are fully documented and recorded
- Computerized systems used in the study have been validated
- Sign and date the final report to indicate acceptance of responsibility for the validity of the data
- Ensure that after completion (including termination) of the study, the study plan, the final report, raw data and supporting material are archived

Principal Investigator's Responsibilities

- The Principal Investigator will ensure that the delegated phases of the study are conducted in accordance with the applicable Principles of Good Laboratory Practice
- Knowledgeable Instructions Recording Responsibilities Health precautions

Quality Assurance Programme

- Quality Assurance Personnel
- Study plan contains the information-verification
- Conduct inspections Study-based inspections Facility-based inspections Process-based inspections
- Records of such inspections should be retained

Facilities

- **Test System facilities**
  - Sufficient number of rooms or areas assure the isolation of test systems and the isolation of individual projects involving substances or organisms known to be or suspected of being bio-hazardous
  - There should be storage rooms or areas as needed for supplies and equipment
  - Areas should be available for the diagnosis, treatment and control of diseases, in order to ensure that there is no unacceptable degree of deterioration of test systems

Archive Facilities

- Archive facilities should be provided for the secure storage and retrieval of study plans, raw data, final reports, samples of test items and specimens
- Archive design and archive conditions should protect contents from untimely deterioration
- Handling and disposal of wastes should be carried out in such a way as not to jeopardise the integrity of studies. This includes provision for appropriate collection, storage and disposal facilities, and decontamination and transportation procedures

Apparatus, Material, and Reagents

- Apparatus, including validated computerised systems, used for the generation, storage and retrieval of data, and for controlling environmental factors relevant to the study
- Apparatus used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures
- Apparatus and materials used in a study should not interfere adversely with the test systems

Performance of the Study

- Study Plan
- Content of the Study Plan
- Dates
- Test Methods
- Issues (where applicable)
- Records
- A list of records to be retained
- Conduct of the Study

Reporting of Study Results

- Content of the Final Report
- Identification of the Study, the Test Item and Reference Item
- Information Concerning the Sponsor and the Test Facility
- Dates
- Statement
- Description of Materials and Test Methods
- Results
- Storage

Storage and Retention of Records and Materials

- The study plan, raw data, samples of test and reference items, specimens and the final report of each study
- Records of all inspections performed by the Quality Assurance Programme, as well as master schedules
- Records of qualifications, training, experience and job descriptions of personnel
- Records and reports of the maintenance and calibration of apparatus
- Validation documentation for computerised systems