CLINICAL TRIALS

Introduction to Clinical trials:

Clinical trials are a type of research that studies new tests and treatments and evaluates their effects on human health outcomes. People volunteer to take part in clinical trials to test medical interventions including; drugs, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments and preventive care.

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials. It also serves to protect the rights, integrity and confidentiality of trial subjects.

It is very important to understand the background of the formation of the ICH-GCP guidelines as this, in itself, explains the reasons and the need for doing so.

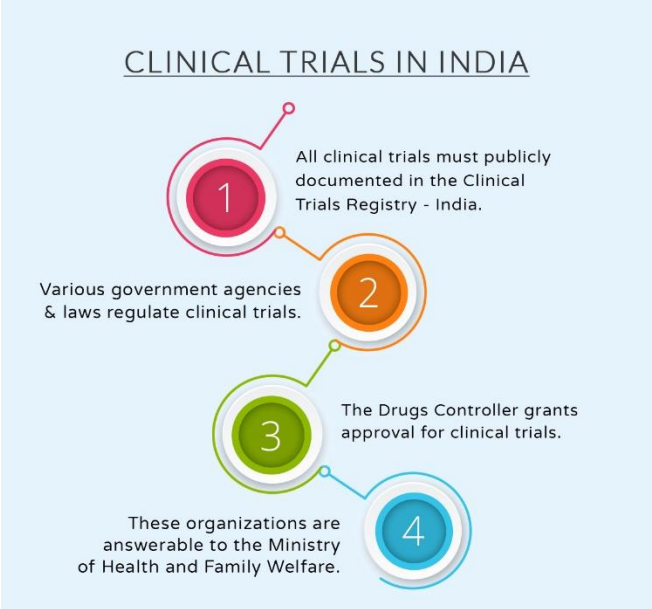
❖ DEVELOPMENT OF CLINICAL TRIAL PROTOCOLS:

Every clinical investigation begins with the development of a clinical protocol. The protocol is a document that describes how a clinical trial will be conducted (the objectives, design, methodology, statistical considerations and organization of a clinical trial) and ensures the safety of the trial subjects and Integrity of the data collected.

The clinical trial should be carried out in accordance with a written protocol agreed upon and signed by the investigator and the sponsor. Any changes subsequently required must be similarly agreed on and signed by the investigator and sponsor and appended to the protocol as amendments.

The protocol, appendices and any other relevant documentation should state the aim of the trial and the procedures to be used.

- The reasons for proposing that it should be undertaken on humans.
- The nature and degree of any known risks.
- The groups from which it is proposed that trial subjects be selected and the means for ensuring that they are adequately informed before they give their consent.



According to the ICH Good Clinical Practice guidelines, a protocol should include the following topics:

1. General Information:

- Protocol title, identifying number, version number and date.
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person authorized to sign the protocol and the protocol amendments for the sponsor.
- Names and titles of the investigators responsible for conducting the study and the address and telephone number of the trial sites.
- Name, title, address and telephone number of the sponsor's medical expert.

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- Name, title, address and telephone number of the qualified physician who is responsible for all study related medical decisions.
- Names and addresses of all institutions involved in the study (Including clinical laboratories and other medical or technical departments).
- Addresses and telephone numbers of all clinical laboratories and/or institutions involved in the trial.

2. Background Information:

- A description of the study is addressed, as well as its public health significance.
- Findings from clinical or non-clinical studies may be significant to the proposed study.
- Summary of the known potential risks and benefits to human participants.
- A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).
- Description of the study population.
- References to relevant literature and data.
- If the study involves the use of an investigational product or therapy: Name and description of the investigational product or therapy. Description of and justification for the route of administration, dosage, dosage regimen and treatment period(s).

3. Study Objectives and Purposes:

A detailed description of the major (primary) and minor (secondary and exploratory) objectives and the purpose of the trial.

4. Study Design:

The scientific integrity of the study and the credibility of the data obtained from the study largely depend on the study design. This section of the protocol should describe:

- Primary and secondary endpoints to be measured and how they will be measured.
- Study type (e. g. double-blind), with a schematic diagram of the study design, procedures and stages.
- Measures that will be taken to avoid or minimize bias (e. g. randomization, blinding).
- Dosage and dosage regimen, dosage form, packaging and labelling of investigational products.
- Expected duration of participant participation, sequence and duration of all study periods, including follow-up.
- "Stopping rules" or "discontinuation criteria" for individual participants, parts of the study and the entire study.
- Accountability procedures for the investigational product, including the placebo and comparator.
- Maintenance of study treatment randomization codes and procedures for breaking codes.

5. Selection and Withdrawal of Participants:

- Criteria for inclusion and exclusion of participants.
- Procedures for withdrawal of participants:
- When and how to withdraw participants from the study/ Investigational product treatment.
- Type and timing of data to be collected for participants who withdraw from the study.
- Whether and how participants are to be replaced.
- Follow-up for participants withdrawn from trial treatment.

6. Treatment of Participants:

A. Pharmacological treatment:

- Names of all products to be administered.
- Doses.
- Dosing schedules.
- Method(s) of administration (i. e. oral, intramuscular).
- Other medications or treatments permitted (including rescue medication) and not

permitted (including rescue medication) and not permitted before and/or during the study.

B. Other interventions (i.e., chiropractic, physical therapy, social therapy, behavioural therapy, counselling):

- Name of intervention (i. e. Motivational interviewing, cognitive Behavioural Therapy).
- Frequency of sessions.
- Duration of each session.
- Method of each intervention (i.e., individual, group).
- Treatment adherence.

C. All interventions:

- Period(s) of intervention, including follow-up periods for participants in each group.
- Procedures for monitoring participant compliance.
- Identification of who will administer an intervention.

7. Assessment of Efficacy:

This section describes the methods that will be used to determine the success of the treatment, including:

- Criteria for determining the treatment's effectiveness.
- Methods and timing for assessing, recording and analysing the effectiveness criteria

8. Assessment of Safety:

This section describes how the study will be monitored and how adverse events will be dealt with.

- Specification of safety criteria.
- Methods and timing for assessing, recording and analysing the safety criteria.
- Procedures for obtaining reports of adverse events and illnesses experienced by participants during the study period and for recording and reporting these events including expedited reporting procedures.
- Type and duration of follow-up of participants who experience adverse events.

9. Statistics:

This section describes the strategy for analysing the data collected during the study including:

- Statistical methods to be employed, including the timing of any planned interim analyses.
- Total number of participants to be enrolled.
- Reason for the Choice of sample size, including reflections on the power of the study and clinical justification.
- Level of significance to be used.
- Criteria for termination of the study.
- Procedure for accounting for missing, unused and false data.
- Procedures for reporting deviations from the statistical plan.
- Selection of participants to be included in analysis.

10. Direct Access to Source Data or Documents:

The sponsor should ensure that the protocol or other written agreement specifies that study investigators or institutions will permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source data or documents.

11. Quality Control and Quality Assurance:

A detailed quality assurance plan describing the set of standards and controls that are in place to confirm that the execution of each step follows the agreed-upon plan is usually submitted as a separate document. The protocol should, however, provide a general description of the quality assurance methods.

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12. Ethics:

This section should describe ethical considerations relating to the study and measures taken to protect human participants and maintain confidentiality of study data.

13. Data Management:

The data management plan describes the procedures that will ensure data integrity throughout the study and at all study sites, including:

- A description of the data system design and development.
- Data collection methods and activities.
- Methods of data entry and editing.
- Procedures for data monitoring, reporting and transfer.
- Data recipients and procedures for data dissemination.

14. Financing and Insurance:

This section describes how the study will be financed and insured. In some research networks, these issues are addressed in a separate agreement and need not be included in the protocol.

15. Publication Policy:

This section describes the policies and procedures relating to publication of findings from the study. In some research networks, policies and guidelines are established for research for the publications planning process.

The trial results will also be published on public website. This website will not identify participants, but will provide a resource for clinical trial participants and those seeking clinical trial involvement, to inform themselves.

16. Supplements:

This section supplies any additional information that may be required, depending on the nature of the research. For example, the informed consent template, the therapy manual, a patient information handbook, etc. may be included as attachments.

❖ **INSTITUTIONAL REVIEW BOARD (IRB) / INDEPENDENT ETHICS COMMITTEE (ICE):**

The ICH defines an institutional review board (IRB) as a group formally designated to protect the rights, safety and well-being of humans involved in a clinical trial by reviewing aspects of the trial and approving its start-up.

IRBs can also be called independent ethics committees (IECs).

An IRB/IEC reviews the appropriateness of the clinical trial protocol as well as the risk and benefits to study participants. It ensures that clinical trial participants are exposed to minimal risks in relation to any benefits that might result from the research.

▪ Composition of an Institutional Review Board (IRB)/ Independent Ethics Committee (IEC):

An IRB/IEC should have a reasonable number of members who have collectively assumed sufficient expertise and experience to review and evaluate the scientific, medical and ethical aspects of a research proposal.

It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a non- scientific area.

(c) At least one member who is independent of the institution/trial site.

Procedures:

The IRB/IEC should establish a document in writing and follow its procedures, which should include:

I. Determine composition and source of authority under which it is established.
II. Schedule, notify members and conduct meetings.
III. Conduct initial and continuing review.
IV. Determine frequency of continuing review.
V. Provide expedited review mechanism for minor changes.
VI. Specify that no subject may be enrolled and no deviation prior to approval.
VII. Specify that investigator promptly report protocol changes or deviations, increased risks to subjects, ADRs (serious and unexpected), new information related to subject safety.
VIII. Promptly notify in writing the investigator/ institution about its decisions, reasons for its decisions and procedures for appeal.

Records:

Maintain all relevant records at least three years after completion of the trial.

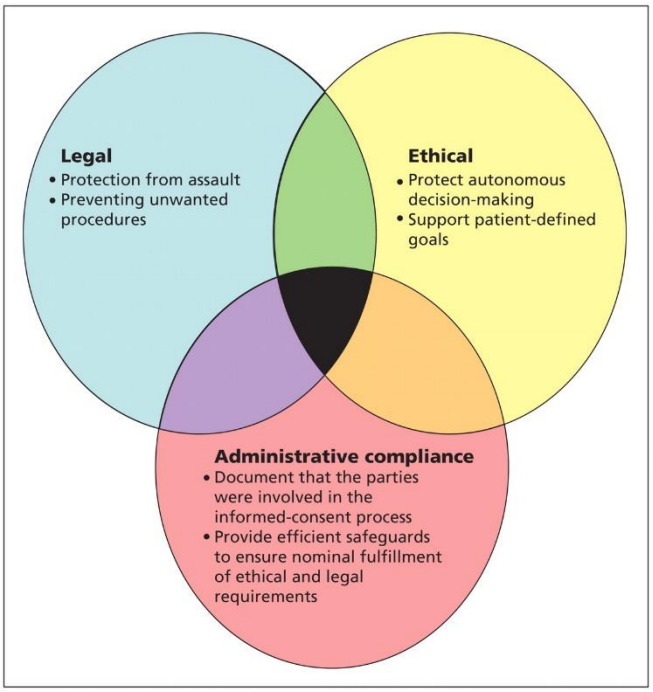
a) Written procedures.
b) Membership files.
c) Submitted documents (protocol related files).
d) Minutes of meetings.

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

❖ **Introduction to Informed consent (IC):**

Informed consent (IC) is an ongoing process of communication and mutual understanding between a patient and investigator which is then demonstrated by the patient's voluntary agreement to enter a clinical trial.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.



Capacity to Give Informed Consent:

Before the informed consent process can begin, the potential participant must be deemed capable of understanding his or her actions and making a reasoned decision.

If the person lacks the capacity because he or she is a minor, is ill, or for any other reason, special provisions must apply (such as; a life-threatening emergency), or the person may not be included in the study.

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A person who has a court-appointed legal guardian or who has been determined by a court to be legally incompetent cannot sign an Informed Consent Form even if he or she has the capacity to make a decision.

Disclosure of all Relevant Information:

The research team must disclose all relevant information about the study to the potential participant. The information disclosed must be sufficient to enable the potential participant to make an informed reasoned decision about whether to participate.

This information generally includes:

- The purpose of the study.
- The nature of the procedure or intervention that is being studied.
- Reasonable alternatives for participation in the study.
- The potential risks and benefits as well as the uncertainties of study participation.
- The participants obligations for the duration of the study.

Comprehension by the Participant:

The potential participant must understand the information disclosed to him or her about the research study.

The participant is free to ask questions to the study team as well as take additional time to make a decision regarding participation.

❖ **GCP Obligations: Investigators, Sponsors, Monitors**

A. SPONSOR:

An individual, company, institution, or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

Quality Management (ICH GCP 5.0)

The sponsor should implement a system to manage quality throughout all stages of the trial process.

Sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results.

QA and QC Quality Assurance and Quality Control (ICH GCP 5.1)

The Sponsor is responsible for implementing and maintaining quality assurance and quality control systems to ensure that studies are conducted and documented in compliance with the protocol, GCP and regulatory requirements.

Transfer of Trial-Related Obligations (ICH GCP 5.2)

The Sponsor may transfer any or all of the Sponsor's trial-related duties and functions to a Contract Research Organization (CRO). However, the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

Any trial-related duties and functions that are transferred to and assumed by a CRO are specified in writing.

Medical Expertise (ICH GCP 5.3)

The Sponsor is responsible for designating appropriately qualified medical personnel to advise on trial-related medical questions or problems.

Study Design and Management (ICH GCP 5.4, 5.5)

The Sponsor is responsible for designating qualified individuals to carry out all stages of the study process, including:

- Designing the protocol.
- Supervising the overall conduct of the study.
- Managing and verifying the study data.

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- Ensuring the safety and rights of human participants.
- Monitoring study performance.
- Planning and conducting the statistical analysis.
- Preparing study reports.
- The sponsor is responsible for selecting the investigator(s)/institution(s).
- Prior to initiating a trial, the sponsor should define, establish and allocate all trial-related duties and functions.

Investigator Selection (ICH GCP 5.6)

The sponsor is responsible for selecting the investigator. The sponsor should provide the investigator with the protocol and an up-to-date Investigator's Brochure.

- The sponsor should obtain the investigator's agreement.
- To conduct the trial in compliance with GCP.
- To comply with procedures for data recording.
- To permit monitoring, auditing and inspection.
- To retain the trial-related essential documents until the sponsor informs the investigator these documents are no longer needed.
- The sponsor and the investigator/institution should sign the protocol or an alternative document, to confirm this agreement.

Allocation of Responsibilities: (ICH GCP 5.7)

Prior to initiating a trial, the sponsor should define, establish and allocate all trial related duties and functions.

Compensation to Subjects and Investigators: (ICH GCP 5.8)

The sponsor should provide insurance or should identify the investigator against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

Financing (ICH GCP 5.9)

The financial aspects of the trial should be documented in an agreement between the sponsor and the Investigator/institution

Notification/Submission to Regulatory Authorities (ICH GCP 5.10)

Before initiating the clinical trial, the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement should submit any required application(s) to the appropriate authorities for review, acceptance and/or permission (as required by the applicable regulatory requirement(s) to begin the trials.

Any notification/submission should be dated and contain sufficient information to identify the protocol.

Confirmation of Review by IRB/IEC (ICH GCP 5.11)

The sponsor should obtain from the Principal Investigator (PI) /institution regarding:

- The name and address of the PIs/Institution's IRB/IEC.

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- A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.
- Documented IRB/IEC approval/favourable opinion upon changes in any aspect of the trial.

The sponsor should obtain from the Pl/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favourable opinion and of any withdrawals or suspensions of approval/favourable opinion.

Information on Investigational Products (ICH GCP 5.12)

When planning trials, the sponsor should ensure that sufficient safety and efficacy data from non-clinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration and in the trial population to be studied.

The sponsor should update the Investigator's Brochure as significant new information becomes available.

Manufacturing, Packaging, Labelling and Coding investigational Products: ICH GCP 5.13)

I. The sponsor should ensure that the investigational product(s) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP and is coded and labelled in a manner that protects the blinding, if applicable.

II. The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions, storage times, reconstitution fluids and procedures and devices for product infusion, if any.

III. The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

IV. In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency.

Supplying and Handling investigational Products: (ICH GCP 5.14)

The sponsor is responsible for supplying the investigator(s)/ Institution(s) with the investigational product(s). The sponsor should:

- Ensure timely delivery of the investigational product(s) to the investigator(s).
- Take steps to ensure that the investigational product(s) are stable over the period of use.
- Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

Record Access (ICH GCP 5.15)

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator provides direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection.

The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review and regulatory inspection.

Safety Information (ICH GCP 5.16)

The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authorities of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's an approval/favourable opinion to continue the trial.

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Adverse Drug Reaction Reporting (ICH GCP 5.17)

The sponsor should expedite the reporting to all concerned investigator(s)/ institutions to the lRB/IEC where required and to the regulatory authorities of all adverse drug reactions (ADRs) that are both serious and unexpected.

Such expedited reports should comply with the applicable regulatory requirements and with the ICH Guideline for Clinical Safety Data Management. The sponsor should submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

Monitoring (ICH GCP 5.18)

Monitors should be appointed by the sponsor: The monitors should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial. The monitor should submit a written report to the sponsor after each trial- site visit or trial-related communication.

Audit (ICH GCP 5.19)

The purpose of a sponsor's audit is independent and separate from routine monitoring or quality control functions. The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial. the level of risks to the trial subjects and any identified problem(s).

Non-compliance: (ICH GCP 5.20)

Non-compliance with the protocol, SOPs, GCP and/or applicable regulatory requirement(s) by an investigator/Institution, or by a member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

If the monitoring and/or auditing identifies serious and/or persistent non-compliance on the part of an investigator/ institution, the sponsor should terminate the investigator's/ institution's participation in the trial. When an investigator's/Institution's participation is terminated because of non-compliance, the sponsor should notify promptly the regulatory authorities.

Premature Termination or Suspension of a Trial (ICH GCP 5.21)

If a trial is prematurely terminated or suspended the sponsor should promptly inform the investigators/institutions and the regulatory authorities of the termination or suspension and the reasons for the termination or suspension.

The IRB/IEC should also be informed promptly and provided the reasons for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirements.

B. PRINCIPAL INVESTIGATOR (Pl)

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and maybe called the principal investigator.

The PI retains ultimate oversight responsibility even when specific tasks are delegated to other site research staff. Additionally, PI responsibilities include:

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- Documenting the delegation of study responsibilities to qualified and adequately trained research staff.
- Supervising study performance and overseeing the performance of study staff at the research sites.
- Ensuring that Participants' well-being and safety are protected.
- All study procedures are conducted at the research sites in accordance with the protocol and GCP.
- Preparing a communication plan for all staff involved in the study.
- Overseeing investigational product accountability.

Qualifications and Experience (ICH GCP 4.1)

- The PI must be qualified by education, training and experience to assume responsibility for the proper conduct of the study.
- If the study involves the use of an investigational product be thoroughly familiar with the appropriate use of that product as described in the study protocol.
- Be aware of and remain in compliance with GCP and applicable regulatory requirements.
- Maintain a list of qualified people to whom he or she delegates significant study-related duties.

Adequate Resources (ICH GCP 4.2)

The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s) and their trial-related duties and functions.

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 functions, the investigator/Institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

Medical Care of Study Participants (ICH GCP 4.3)

All study participants should receive appropriate medical care both for study-related adverse events and for all medical conditions unrelated to study participation.

A qualified physician affiliated with the study should be responsible for all study-related medical decisions.

The participants primary care physician should be informed about the participant's involvement in the study, provided that the participant: • Has a primary care physician. • Agrees that the primary care physician may be informed.

Communication with the institutional Review Board (ICH GCP AA):

The PI is identified to the designated IRB. Before and during a study, the PI must comply with all requirements of the designated Institutional Review Boards (IRBS). A study may not begin prior to obtaining IRB approval.

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Compliance with the Protocol (lCH GCP 4.5)

The PI is responsible for ensuring that the study is conducted in compliance with the research protocol. He or she should ensure that all protocol violations are identified, documented and reported in accordance with sponsor and IRB requirements.

Repeated protocol violations may indicate that protocol amendments, procedural Changes, or additional training are needed.

Use of Investigational Products (ICH GCP 4.6)

If the study involves the use of an investigational product, the PI is responsible for ensuring that the investigational product is used only in accordance with the study protocol and federal regulations; and that accountability of the investigational product is maintained. For clinical investigations that use a controlled study of the drug, the PI may be required to have a medical license.

When the PI is not required to have a medical license, responsibility for receiving or administering certain drugs, reviewing safety events and making independent medical decisions is delegated to qualified medical personnel, such as physicians, physician's assistants, nurse practitioners, or other qualified/licensed medical professional. research using the controlled drugs.

These delegated responsibilities are documented in the site's delegation of responsibilities log and the staff assigned may serve as a sub-investigator. Consult local regulations and oversight authorities on medical license requirements for conducting research using the controlled drug.

Randomization and Blinding (ICH GCP 4.7)

The PI is responsible for ensuring that the study's procedures, if any, for randomization and blinding are followed.

Informed Consent (ICH GCP 4.8)

The PI is responsible for ensuring that procedures for obtaining and documenting informed consent comply with GCP and with the ethical principles originating in the Declaration of Helsinki.

Records and Reports (ICH GCP 4.9)

The PI is responsible for ensuring the accuracy, completeness, legibility and timeliness of all study data that are reported to the Sponsor.

Progress Reports (ICH GCP 4.10)

The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

The investigator should promptly provide written reports to the sponsor.

Safety Reporting (ICH GCP 4.11)

All serious adverse events (SAEs) must be reported immediately to the Sponsor. The immediate reports should be followed promptly by detailed, written reports.

The PI must also comply with regulatory requirements to report serious adverse events to the IRB and regulatory authorities.

Premature Suspension or Termination of Study (ICH GCP 4.12)

If the study is suspended or stopped early for any reason, the PI is responsible for:

- Promptly informing all study participants.
- Ensuring that all participants receive appropriate therapy and follow-up.
- Complying with all requirements to inform regulatory authorities.

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Final Study Report (ICH GCP 4.13)

On completion of the study, the PI is responsible for providing:

- All required reports to the Sponsor and regulatory authorities.
- A summary of the study outcome to the Institutional Review Board.

C. MONITORING

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/ amendments, with GCP and with the applicable regulatory requirements.

Selection and Qualifications of Monitors

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP and the applicable regulatory requirement(s).

Monitor's Responsibilities

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site: Acting as the main line of communication between the sponsor and the investigator.

Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment and staff, are adequate to safely and properly conduct the trial and remain' adequate throughout the trial period.

Verifying, for the investigational product(s)

(a)That storage times and conditions are acceptable and that supplies are sufficient throughout the trial.

(b)That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).

(c) That subjects are provided with necessary instruction on properly using, handling, storing and returning the investigational product(s).

(d)That the receipt, use and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(e) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(f) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(g) Verifying that written informed consent was obtained before each subject's participation in the trial.

(h) Ensuring that the investigator receives the current Investigator's Brochure, all documents and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(i) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(j) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution and have not delegated these functions to unauthorized individuals.

(k) Verifying that the investigator is enrolling only eligible subjects.

(l) Reporting the subject recruitment rate.

(m) Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.

(n) Verifying that the investigator provides all the required reports, notifications, applications and submissions and that these documents are accurate, complete, timely, legible, dated and identify the trial.

(o) Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other.

The monitor specifically should verify that:

1. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

2. Any dose and/or therapy modifications are well documented for each of the trial subjects.

3. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

4. Visits that the subjects fail to make, tests that are not conducted and examinations that are not performed are clearly reported as such on the CRFs.

5. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

Monitoring Report:

(a) The monitor should submit a written report to the sponsor after each trial- site visit or trial-related communication.

(b) Reports should include; the date, site, name of the monitor and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant Findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

Extent and Nature of Monitoring:

- The sponsor should ensure that the trials are adequately monitored.
- The sponsor should determine the appropriate extent and nature of monitoring.
- The determination of the extent and nature of monitoring should be based on considerations such as; the objective, purpose, design, complexity, blinding, size and endpoints of the trial.
- In general, there is a need for on-site monitoring, before, during and after the trial: however, in exceptional circumstances, the sponsor may determine that central monitoring in conjunction with procedures such as; investigators' training and meetings and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP.

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- Statistically controlled sampling may be an acceptable method for selecting the data to be verified.
- The sponsor should develop a systematic, prioritized, risk-based approach to monitoring clinical trials.
- The flexibility in the extent and nature of monitoring described in this section is: intended to permit varied approaches 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. The sponsor should document the rationale for the chosen monitoring strategy (for e.g., in the monitoring plan).
- 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 (for 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:

(a)Identify missing data, inconsistent data, data outliers, unexpected lack of variability and protocol deviations.

(b)Examine data trends such as the range, consistency and variability of data within and across sites.

(c) 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.

(d)Analyse site characteristics and performance metrics.

(e)Select sites and/or processes for targeted on-site monitoring.

❖ PHARMACOVISULANCE:

Pharmacovigilance Program of India (PvPI)

The Central Drugs Standard Control Organisation (CDSCO), New Delhi, under the aegis of Ministry of Health & Family Welfare, Government of India has initiated a nation-wide pharmacovigilance programme in July, 2010, with the All-India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordinating Centre (NCC) for monitoring Adverse Drug Reactions (ADR) in the country to safe-guard Public Health.

Scope and Objectives:

- To create a nation-wide system for patient safety reporting.
- To identify and analyse new signal from the reported cases.
- To analyse the benefit – risk ratio of marketed medications.
- To generate evidence-based information on safety of medicines.
- To support regulatory agencies in the decision-making process on use of medications.
- To communicate the safety information on use of medicines to various stakeholders to minimise the risk.
- To emerge as a national centre of excellence for pharmacovigilance activities.

CLINICAL TRIALS

- To collaborate with other national centres for the exchange of information and data management.
- To provide training and consultancy support to other national pharmacovigilance centres across globe.
- To promote rational use of medicine.

Safety Monitoring in clinical trial:

Drug safety monitoring is a risk mitigation exercise in which the ADRs caused by therapeutic drugs, biologicals or devices can be explored, prevented or minimized. It is the process of identifying expected and unexpected adverse reactions resulting from the use of medicines in the post-marketing phase.

It is known, that the medicines developed for treatment of diseases, have also side effects, sometimes dangerous for life. There are no absolutely safe medicines! Moreover, the use of medicines in a wide exposition may cause various adverse reactions of drugs (ADR) which were not registered during clinical trials because of the limited quota of the patients. Revealing, registration and analysis of the ADR (Pharmacovigilance) are necessary for the subsequent specification of the drugs' indications, contra-indications, side effects, dosages, etc.

"Health care institutions, drugstores, institutions and the organizations which are consuming and using medicines, are obliged to inform the authorized governmental body about all cases of development of unknown adverse reactions immediately".

Other relevant issues:

• substandard medicines

• medication errors

• lack of efficacy reports

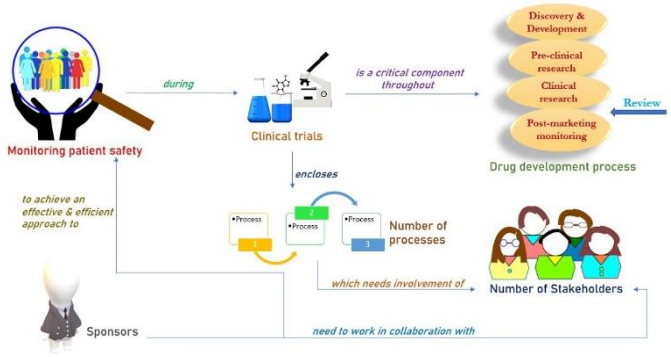
• use of medicines for indications that are not approved and for which there is inadequate scientific basis

• case reports of acute and chronic poisoning

• assessment of drug-related mortality

• abuse and misuse of medicines

• adverse interactions of medicines with chemicals, other medicines, and food.



Report Form:

The Report Form has four sections:

A. INFORMATION ABOUT PATIENT

This section includes the personal information of the patient:

- Name, surname (may be encoded in purpose of keeping confidentiality)
- Age or date of birth.
- Sex
- Weight

B. ADVERSE DRUG REACTION OR MANUFACTURING PROBLEM

This section is for the description of the adverse drug reaction or manufacturing problem and includes the following information:

- Marking of adverse reaction or manufacturing problem.

- Date of event.
- Date of report
- Motivation for sending the report (death, life-threatening, hospitalization, disability, congenital anomaly, other)
- Description of adverse reaction or manufacturing problem
- Used diagnostic methods
- Short description and peculiarities of the disease.
-

C. SUSPECTED DRUG(S)

This section is for pointing out the suspected drug or drugs that are related to the adverse reactions. The section includes the following information:

- Name, drug form, manufacturer, batch
- Dose
- Indications for use
- Duration

D. INFORMATION ABOUT THE REPORTER

This information has to be introduced completely; in case it is necessary to contact the reporter for getting detailed data of the case. The section includes the following information:

- Name, address, phone
- Profession
- Occupation

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Subject: pharmaceutical Regulatory Science

Class: Final Year B. Pharm

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