UNIT-IV

Clinical Trials

Points to be covered in this topic

- Developing clinical trial protocols
- Institutional Review Board/Independent Ethics committee formation & working procedures
- Informed consent process & procedures
- GCP Obligations of Investigator, Sponsors & monitoring
- Managing & monitoring clinical trails
- Pharmacovigilance – safety monitoring in clinical trials

Developing 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 and ensures the safety of the trail 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 sponsors.

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

1. General Information
2. Background Information
3. Study Objectives and Purposes
4. Study Design
5. Selection and Withdrawal of Participants
6. Treatment of Participants
7. Assessment of Efficacy
8. Assessment of Safety
9. Statistics
10. Direct Access to Source Data or Documents
11. Quality Control and Quality Assurance
12. Ethics
13. Data Management
14. Financing and Insurance
15. Publication Policy
16. Supplements

Institutional Review Board/Independent Ethics committee formation & working procedures

- ✓ The ICH defines institutional review board (IRB) as a group formally designated to protect the rights, safety and well-being of humans involved in a clinical trail by reviewing all aspects of the trail 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 risks 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.

❑ **An IRB/IEC :**

- Reviews all study-related materials before and during the trial.
- Must operate in accordance with national and/or local regulations, as well as with ICH good clinical practices (GCPs) guidelines.

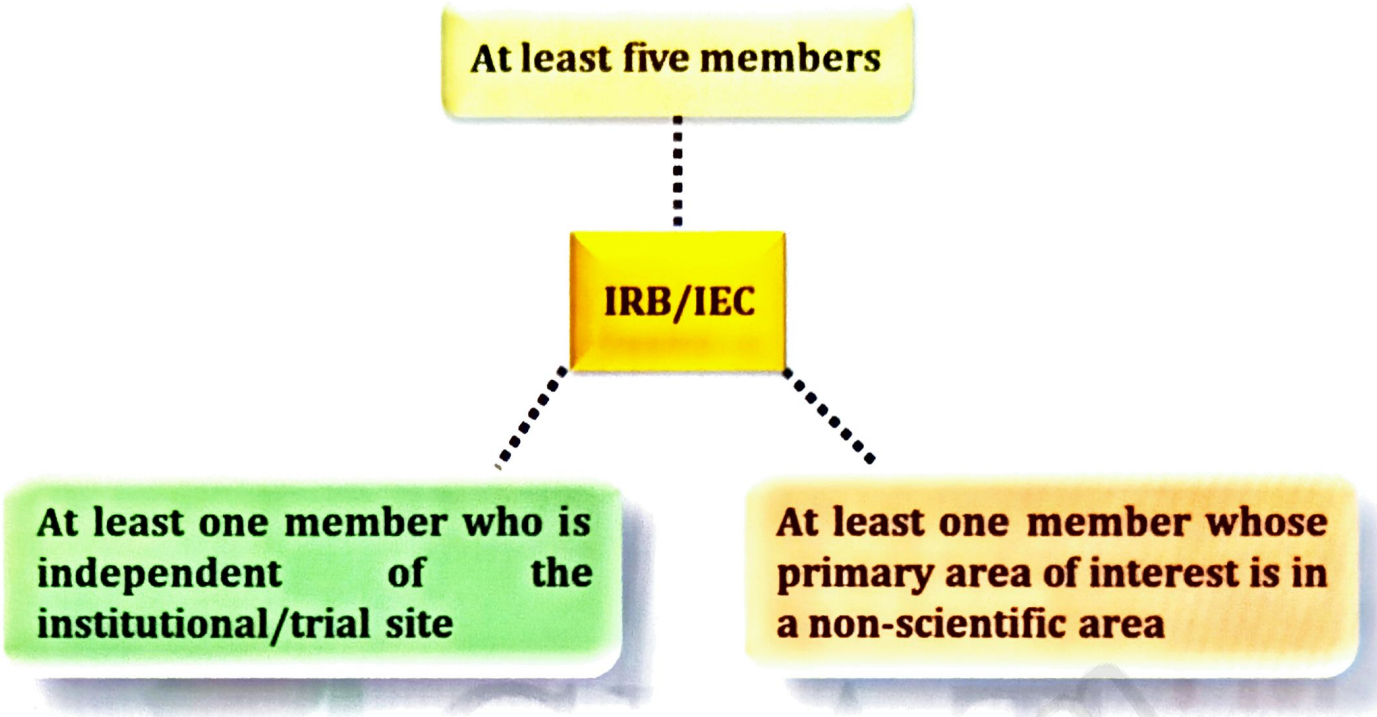
Composition of an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) :

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 non-scientific area.

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



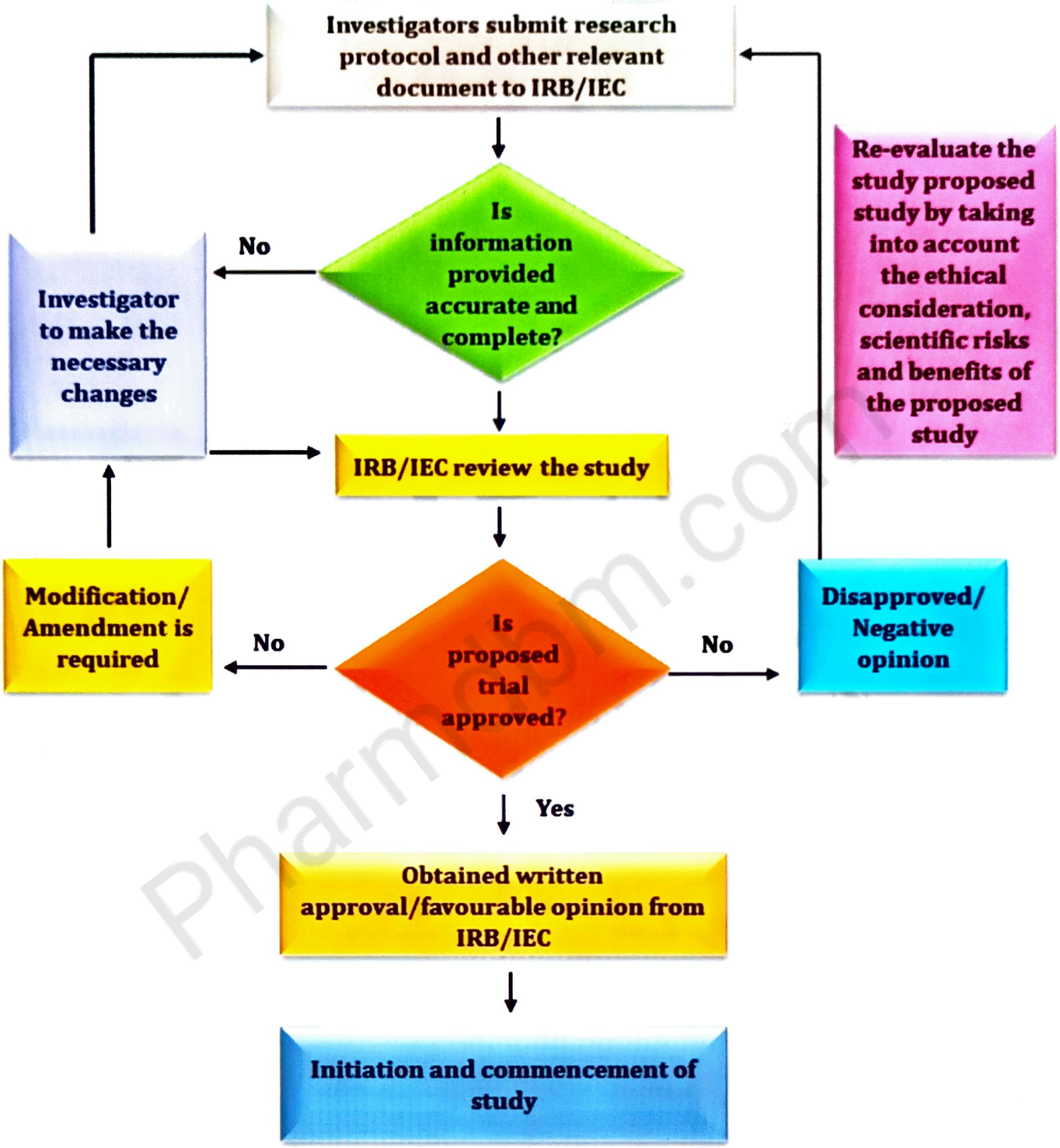
Composition of an Institutional Review Board (IRB)/(IEC)

❑ Procedures

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

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

The flow chart below illustrates the general process to attain an approval to conduct a clinical trial.



- **General process to attain an Approval to conduct a Clinical Trial**

❑ Records :

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

- Written procedures.
- Membership files.
- Submitted documents (protocol related files).
- Minutes of meetings.

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

Informed consent process & procedures

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

❑ 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 provision must apply
- 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 the participation in the study.
- The potential risks and benefits as well as the uncertainties of study participation.
- The participants obligation for the duration of the study.

❑ Comprehension by the participant :

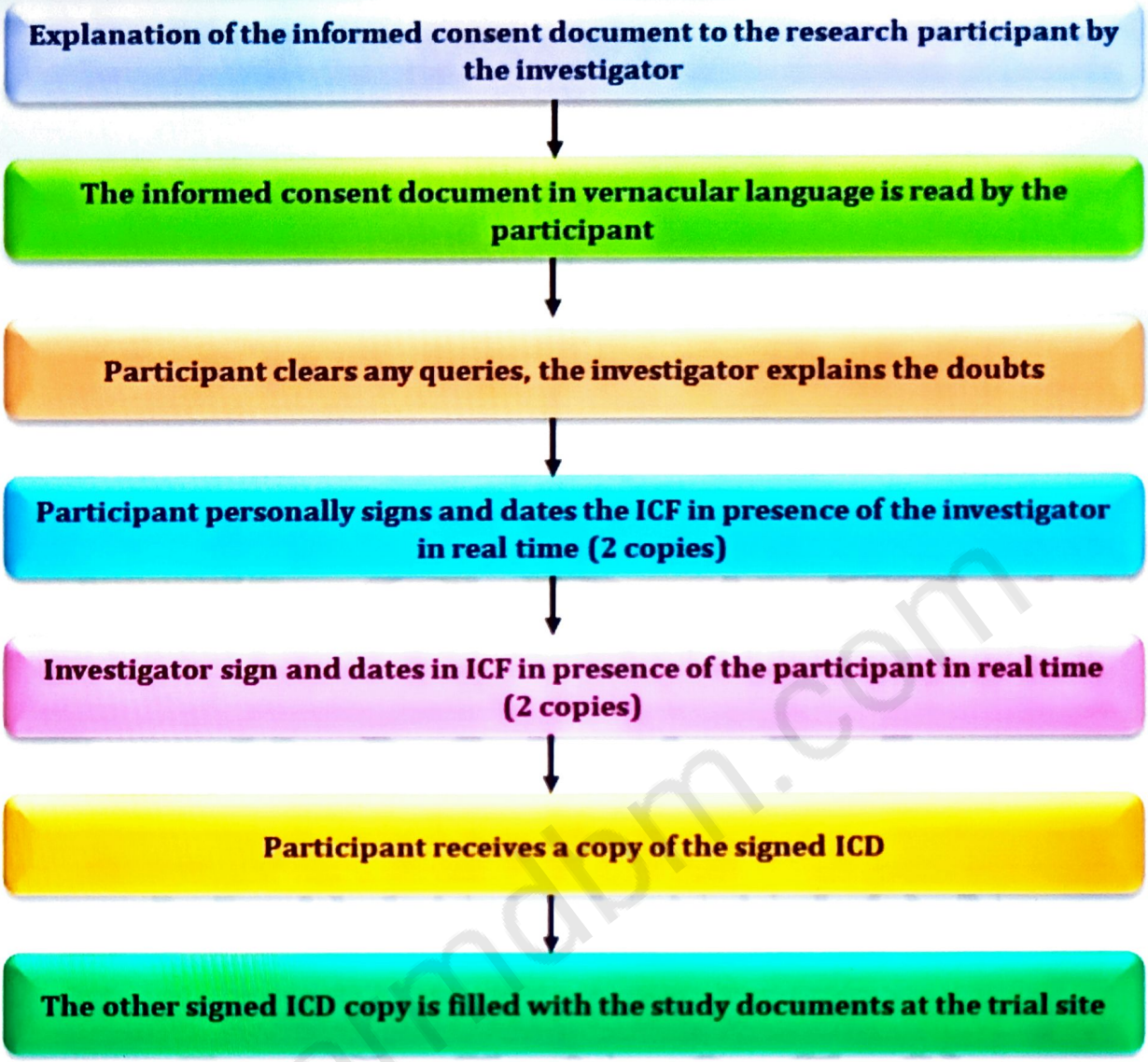
- The potential participant must understand the information disclosed to him or her about the research study.
- The participant is free to ask questions to the study team as take additional time to make a decision regarding participation.
- The research team must be able to evaluate the potential participants ability to understand what his or her participation in the study would involve.

❑ Voluntary Agreement by the Participant :

- The participant must agree to participate in the research study.
- His or her agreement must be voluntary and free from coercion or undue influence.
- The written informed consent form should be signed and personally dated by the subject or by the subjects legally acceptable representatives and by the person who conducted the informed consent discussion.

❑ Right to Withdraw :

- The participant must be informed that he or she has a right to withdraw from the study at any time and for any reason, without penalty or loss of benefits that he or she would otherwise be entitled to receive.
- The research team or principle investigator may terminate participation in a study if it is in the best interest of the participant.



Elements of Informed Consent Required by the ICH Guidelines :

Subjects should include explanation of the following :

1. That the trial involves research.
2. The purpose of the trial.
3. The trial treatments and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subjects responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefits to the subject, the subject should be made aware of this.
9. The alternative procedures or courses of treatment that may be available to the subject, the subject should be made aware of this.
10. The compensation and/or treatment available to the subject for participating in the trial.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. The anticipated expenses, if any, to the subject for participating in the trial.
13. The subject participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14. That the monitors, the auditors, the IRB/IEC and the regulatory authorities will be granted direct access to the subjects original medical records for verification of clinical trial procedures and/or data, without violating the confidentially of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent from, the subject or the subjects legally acceptable representative is authorizing such access.
15. That records identify the subject will be kept confidential and, to the extent permitted by the application laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subjects identify will remain confidential.

16. That the subject or the subjects legally acceptable representative will be informed in a timely manner if the information becomes available that may be relevant to the subjects willingness to continue participation in the trial.

17. The persons to contact for further information regarding the trial and the rights of trial subjects and whom to contact in the event of trial-related injury.

18. The foreseeable circumstances and/or reasons under which the subjects participation in the trial may be terminated.

19. The expected duration of the subjects participation in the trial.

20. The approximate number of subjects involved in the trial.

GCP Obligations of Investigator, Sponsors & monitoring

Principal Investigator (PI)

- Good Clinical Practices (GCP) is an international standard as huge experiments are conducted in several centres and in multiple nations.
- Examiners attentiveness in following GCP has made the difference between a safe and effective trial and an inappropriately developed, a failed trial.
- Using a specified and defined protocol the investigators from various countries may register participants in a trial.

❑ Qualification 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 application regulatory requirements.

❑ 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.

❑ Medical Care of Study Participants (ICH GCP 4.3) :

- All study participants should receive appropriate medical care both for study-related adverse events and all medical conditions unrelated to study participation.
- A qualified physician affiliated with the study should be responsible for all study-related medical decisions.

❑ Communication with Institutional Review Board (ICH GCP 4.4) :

- 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 Board (IRBs).
- A study may not begin prior to obtaining IRB approval.

❑ 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 accordance with the study protocol and federal regulations; and that accountability of the investigational product is maintained.

❑ 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 sponsors.

❑ Progress Reports (ICH GCP 4.10) :

- The investigator should submit written summaries of 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.

❑ Final Study Reports (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.

Sponsor

An individual, company, institution, or organization which takes responsibility for the initiation, management and/or financing of 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 system 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 sponsors may transfer any or all the sponsors 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 sponsors.

❑ Medical Expertise (ICH GCP 5.3) :

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

❑ Study Design and Management (ICH GCP 5.4, 5.5) :

The sponsors 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.
- Ensuring the safety and rights of human participants.
- Planning and conducting the statistical analysis.
- Preparing study reports.
- The sponsors is responsible for selecting the investigators institutions.
- Prior to initiating a trial, the sponsor should define, establish and allocate all trial-related duties and functions.

❑ Investigator Selection (ICH GCP) :

- The sponsor is responsible for selecting the investigator.
- The sponsor should provide the investigator with the protocol and an up-to-date investigators brochure.

❑ Allocation of Responsibilities (ICH GCP 5.7) :

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

❑ Compensation to subject and Investigators (ICH GCP 5.8) :

- The sponsors should provide insurance or should indemnify the investigator against claims arising from the trial, except for claims that arise from malpractice and/or negligence.
- When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirements.

❑ Financing (ICH GCP 5.9) :

- The financial aspects of the trial should be documented in an agreement between the sponsors and the Investigator/Institutional.

❑ Notification/Submission to Regulatory Authorities (ICH GCP 5.10) :

- Before initiating the clinical trials, the sponsor should submit any required applications to the appropriate authorities for review, acceptance and/or permission to begin the trial.

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

- The sponsor should obtain from the principal Investigator (PI)/Institution regarding :

(a) The name and address of the PI's/Institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulation.

(c) Documented IRB/IEC approval/favourable opinion.

❑ Information on Investigational Products (ICH GCP 5.12) :

- When planning trials, the sponsors 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.

Manufacturing packaging, labelling and coding Investigational products (ICH GCP 5.13) :

- The sponsor should determine, for the investigational products, acceptable storage temperature, storage conditions, storage times, reconstitution fluids and procedures and devices for product infusion, if any.

❑ Supplying and Handling Investigational Products (ICH GCP 5.14) :

- The sponsor is responsible for supplying the investigators/institutions with the investigational products.

❑ Record Access (ICH GCP 5.15) :

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

❑ Safety Information (ICH GCP 5.16) :

- The sponsor should promptly notify all concerned investigators/institutions and the regulatory authorities if findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IECs approval favourable opinion to continue the trail.

❑ Adverse Drug Reaction Reporting (ICH GCP 5.17) :

- The sponsor should expedite the reporting to all concerned investigators/institutions to the IRB/IEC, where required and to the regulatory authorities of all adverse drug reaction that are both serious and unexpected.

❑ Monitoring (ICH GCP 5.18) :

- The monitors should follow the sponsors established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

❑ Audits (ICH GCP 5.19) :

- The purpose of a sponsors audit, which is independent and separate from routine monitoring or quality control functions.
- The sponsors audit plan and procedures for a trial audit should be guided by the importance of the trial submission 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 problems.

❑ Non-compliance (ICH GCP 5.20) :

- Non-compliance with the protocol, SOPs, GCP and/or applicable regulatory requirements by an investigator/institution, or by members of the sponsors staff should lead to prompt action by the sponsor to secure compliance.

❑ Premature Termination or Suspension of trial (ICH GCP 5.21) :

- If trail 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.

❑ Clinical Trial/Study Reports (ICH GCP 5.22) :

- Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agencies as required by the applicable regulatory requirements.

❑ Multicentre Trial (ICH GCP 5.23) :

➢ All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority and given approval/favourable opinion by the IRB/IEC.

Monitoring

The purpose 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 trial is in compliance with the currently approved protocol/amendments, with GCP and with the applicable regulatory requirements.

Selection and Qualification of Monitors :

(a) Monitor should be appointed by the sponsors.

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

(c) Monitors should be thoroughly familiar with the investigational products, the protocol, written informed consent form and any other written information to be provided to subjects, the sponsors SOPs, GCP and the applicable regulatory requirements.

Monitor's Responsibilities

The monitors 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.
- Verifying, for the investigational products
- Verifying that the investigator follows the approved protocol and all approved amendments, if any.
- Verifying that written informed consent was obtained before each subject's participation in the trial.
- 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 requirements.
- Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

Monitoring Procedures

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.

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 individuals 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.

Pharmacovigilance – safety monitoring in clinical trials

- Pharmacovigilance is majorly known as drug safety. It is a main integral part of clinical research. Throughout the product life cycle clinical trials safety and post marketing pharmacovigilance plays a critical role.
- The word pharmacovigilance is derived from two words one **Pharmakon** is a Greek word which means **"drug"** and another **vigilare** is a Latin word which means to **"keep awake or to keep watch".**
- Pharmacovigilance is "defined as the pharmacological science relating to the detection, understanding, assessment and prevention of adverse effects, particularly long term and short-term adverse effects of medicines

Aims of pharmacovigilance

- To improve patient care & safety
- To contribute to assessment of benefit, harm & effectiveness of medicine
- To Identify previously unrecognized adverse effects of the drugs
- To Promote rational & safe use of medicine
- To Promote education & clinical training
- To Identify patient related risk factors of ADR such as dose, age, gender
- Any response to a drug which is unintended, occurs at particular doses

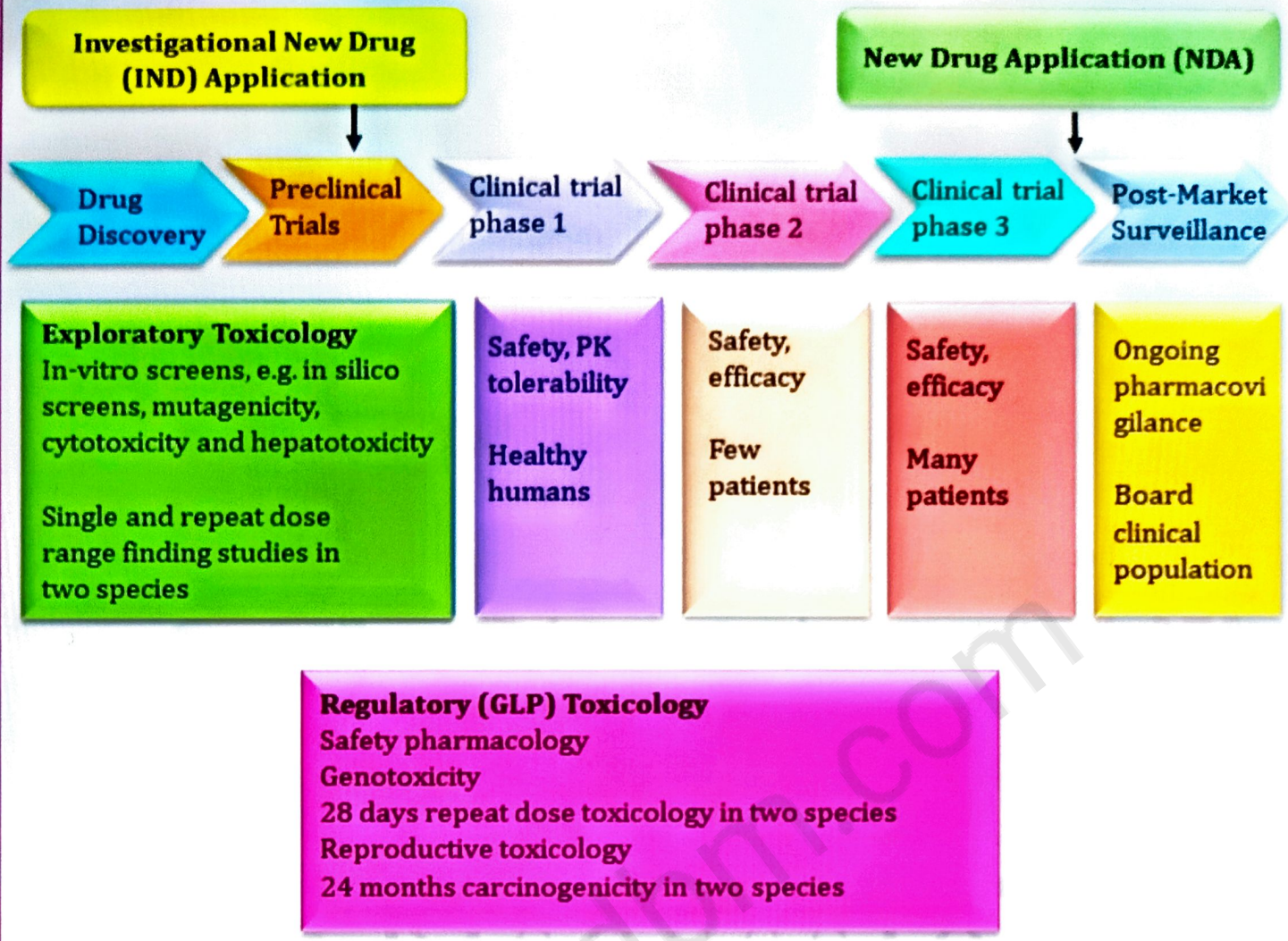
❑ Adverse Drug Reactions

ADR is a response to drug, which alters the normal physiological function of the body, factors which causes ADR includes mainly multiple drug therapy, age & gender.

They are mainly two types of ADR

TYPE A: These are common, predictable, dose dependent, they are seldom fatal

TYPE B: These are uncommon, unpredictable, dose independent; they involve relatively high rates of serious morbidity.



- **Drug Development Process**

Post marketing surveillance

Pharmaceutical drug or medical device is monitored often after it has been released in to the market, Since drugs are approved based of clinical trials which involve relatively small number of people who do not have any other medical complications, post marketing surveillance play an important role to know the ADRs of drugs after they have released in to the market

Approaches by

- Spontaneous ADR reporting
- Prescription event monitoring
- Electronic health records
- Patient Registers

❑ Spontaneous ADR Reporting :

Doctors, health care professionals, they are provided with forms where, they can notify the suspected ADRs they detect, it helps in spontaneous reporting for all the drugs, to pharmacovigilance department. This spontaneous reporting helps to identify many unexpected ADRs, it helps in withdrawal of many marketed drugs, and information being provided which guide safer use of the product. ADRs which occurred by particular drugs should be analyzed and reported, Pharmaceutical manufacturers have to communicate with the doctors at the clinical level regarding the ADRs by

- ❖ Changing Medication formula if necessary
- ❖ Implementing new prescribing procedures
- ❖ Implementing new dispensing procedures
- ❖ Educating the professional staff
- ❖ Educating Patients

❑ Prescription Event Monitoring :

It involves health professionals submitting all the clinical events reported by the patient to the prescribed new drug. This method mainly focuses on studying the safety of new medications that are used by general practitioners in this method. In this method patients being prescribed by drugs are monitored.

❑ Electronic Health Records :

It is a computer stored collection of health information, about one person linked by a person identifier; it represents the basis for healthcare Information system development.

❑ Patient Registers :

To bring together patient records, it is time consuming and less expensive.

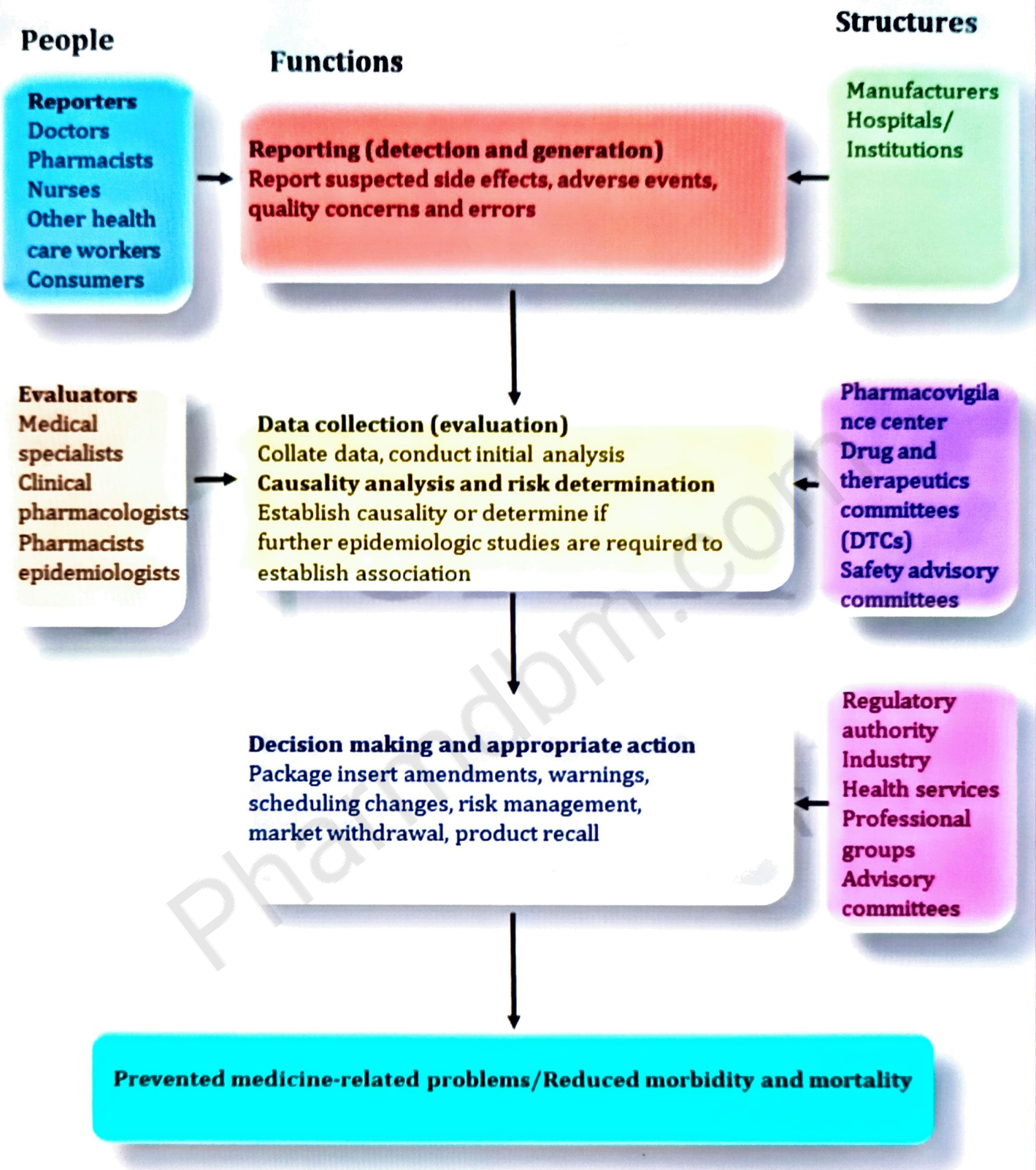


Fig. ADRs Reporting Process

❑ Pharmacovigilance programme of India (PVPI)

It officially starts on 23rd November 2004 at New Delhi, is under the control of CDSCO (Central Drug Standard Control Organization), Directorate general of health services, Indian pharmacopeia commission (Ghaziabad). The program is conducting by NCC (National Coordinating Centre) to ensure that the benefits of use of medicine against the risks.

❑ Objectives:

- To monitor ADRs
- To create awareness among health care professionals about ADRs
- To monitor benefit-risk profile of medicines
- Support the CDSCO