

Pharmacovigilance safety monitoring in clinical trials

- Pharmacovigilance (PV) is the pharmacological science relating to the detection , assessment ,understanding and prevention of adverse effects, particularly long term and short term side effect of medicines.
- All medicines (pharmaceutical and vaccines) have side effect some are known many are still unknown even this medicine has been in clinical use.
- The importance is to monitor both known and unknown side effects of medicines in order to determine any new information in relation to their safety profile .

- The clinical trial process is regulated by the specific regulatory guidelines (e.g ICH GCP, USFDA guidelines etc).
- Pharmacovigilance looks at all available information to assess the safety profile of a drug
- Pharmacovigilance should also take the benefit of the drug in account.
- Spontaneous reporting depends on the health professional.
- Pharmacovigilance works by
 - ADR Sharing
 - Suspicion Reporting
 - Analysis of Findings

Aim And Objectives of Pharmacovigilance

- Improve patient care and safety.
- Improve public health and safety.
- Encourage safe, rational and appropriate use of drugs.
- Promote understanding, education and clinical training in Pharmacovigilance.
- To identifying new information about hazards as associated with medicines.

Adverse Drug Reactions

- ADR is noxious ,unintended and which occurs a response at doses normally used in humans for Prophylaxis, Diagnosis or Therapy of disease , or for modification of physiological function.....(WHO 1972)
- Type A(Augmented) ADR
- Type B(Bizarre) ADR
- Serious adverse reaction.
- Unexpected adverse reaction.
- Data Analysis Response
- Side effect
 - Any unintended effect of a pharmaceutical product occurring at normal dosage which is related to the pharmacological properties of the drug. e.g. antihistamines producing sedation, anticholinergics producing dryness .

- India is a hub of Global Clinical trials & a destination for Drug Discovery & Development.
- However, whether patients in India receive safe drugs or not is still very much in question Rapid induction of NCEs and high tech Pharma products in the market throw up the Challenges of monitoring Adverse Drug Reactions (ADRs) over large multiethnic population base.
- **Who Should Report Safety Data** [?]
- Physicians
- Pharmacists
- Pharmaceutical companies qualified persons –
(Pharmacovigilance/Regulatory manager)
- Investigational products (clinical trials)
- Post-approval reporting – Individual Case Safety Report (ICSR),
Periodic Safety Update Report (PSUR)
- In many countries patients are encouraged (but not obligated)
to report side effects

- **What to Report?**

- It is important to report serious unexpected ADRs.
- Most cases of unexpected ADRs are associated with medicines newly introduced on the market.
- All suspected adverse reactions.
- Every single problem related to the use of a drug.
- ADRs associated with radiology contrast media, vaccines, diagnostics, drugs used in traditional medicine, herbal remedies, cosmetics, medical devices and equipment.

- **Importance of Pharmacovigilance**

- Complete safety data (especially for unexpected and serious adverse events) can only be captured through Pharmacovigilance.
- It cannot be captured through clinical trials which are conducted in an “artificial environment.”

- **In clinical trials**

- patients are not taking any other medications
- do not have concomitant diseases
- are taking the drug short-term (during the duration of the trials only) and
- are not part of vulnerable groups (e.g., children, pregnant women, elderly, etc.)

Partners in Pharmacovigilance

- The WHO Quality Assurance and Safety : Medicines team
- The Uppsala Monitoring Centre (UMC)
- The National Pharmacovigilance Centers
- Hospitals And Academia
- Health Professionals
- Patients
- Other Partners
 - System of Safety Data Gathering
 - Clinical Trials Healthcare Professionals
 - Pre-Approval Post-Approval Patients
 - National Regulatory Authority Pharmaceutical Companies
 - International Safety Databases

Pharmacovigilance in drug regulation

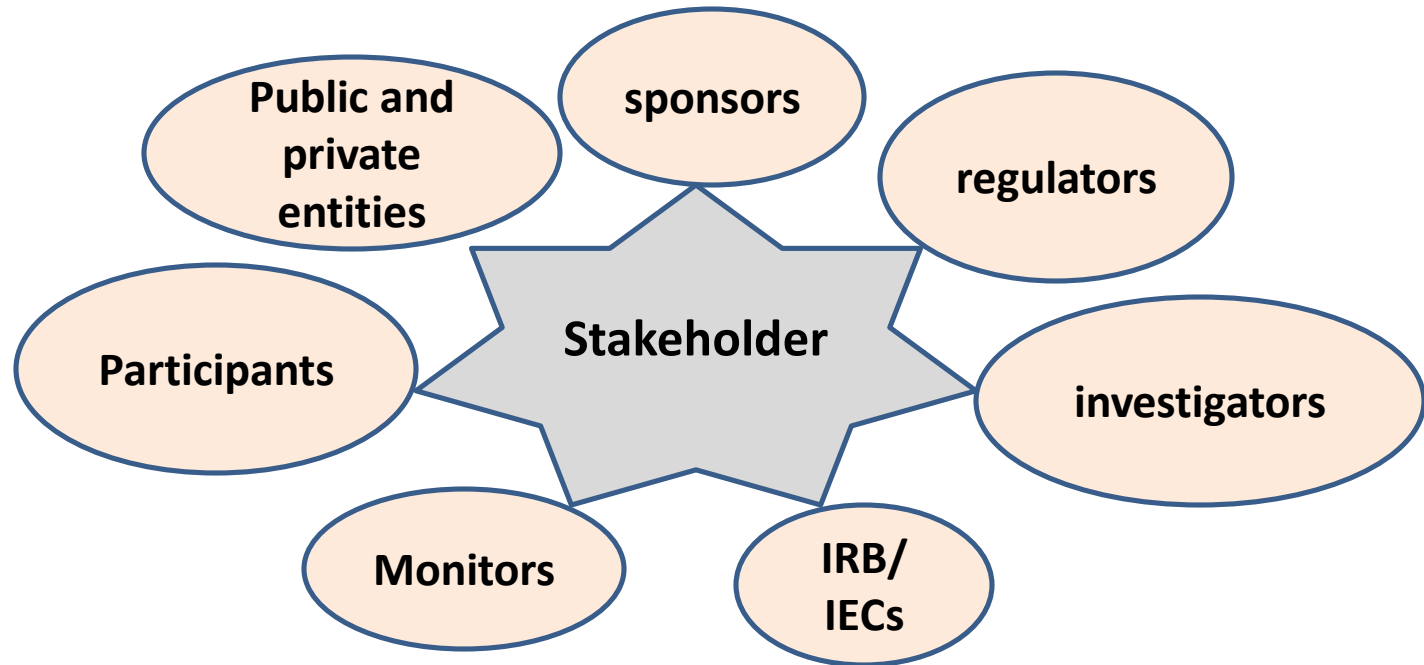
- Clinical Trial Regulation
 - Collection of ADR
 - Monitoring clinical data
 - Reporting of clinical data
- Post Marketing safety Monitoring
- **RaPID** : The RaPID is a PV program which conduct public health program.
 - It provide support to focal point.
 - Focus on RaPID HIV, T.B, Malaria and other program.
 - It is important to encourage and ensure reporting of ADR.
 - It consist of various department for working various type of diseases

- Clinical trials provide the evidentiary basis for regulatory approvals of safe and effective medicines.
- With long development cycles and ever-increasing costs in conducting clinical trials, both the pharmaceutical industry and regulators are making efforts to be more proactive in safety evaluations.
- Early safety signal detection not only leads to better patient protection, but also has the potential to save development costs.

- Since clinical trials are experiments in humans, they must be conducted following established standards in order to protect the rights, safety and well-being of the participants.
- These standards include
 - International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines.
 - International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences.
 - The ethical principles set forth in the Declaration of Helsinki.

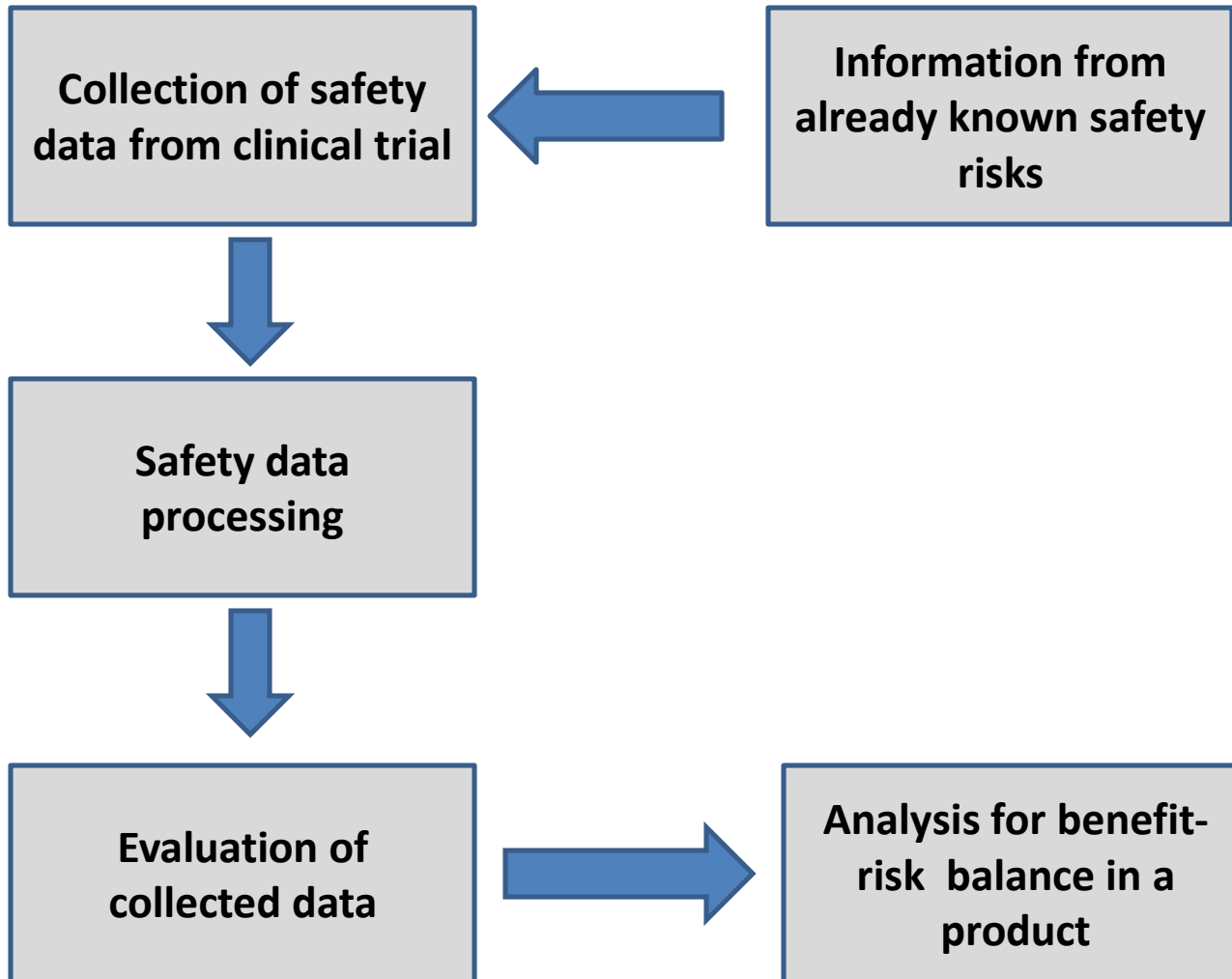
Common Practice in Safety Monitoring

- Stakeholders in Safety Monitoring

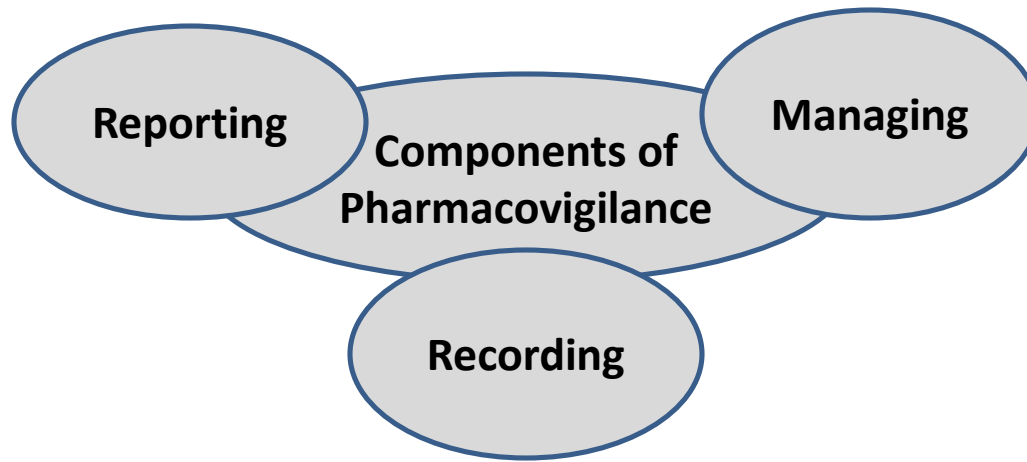


- Communicating Safety Information among Stakeholders
- **Statistical Methods in Safety Monitoring**
 - Methods for Single Arm Trials
 - Methods for Randomized, Controlled Trials
 - Hypothetical Clinical Trial

Basic Framework for Pharmacovigilance During Clinical Trials



- **Components of Pharmacovigilance**



Basic Framework for Pharmacovigilance During Clinical Trials

- Sponsor's responsibilities in Pharmacovigilance
- Reporting
- Protocol in clinical trials
- Guidance in protocol for Pharmacovigilance and safety reporting
- Role of CRF in Pharmacovigilance clinical trial
- Role of IB in Pharmacovigilance clinical trial
- Safety update reports
- To provide the summary of the understanding and management
- Investigator's responsibility in Pharmacovigilance
- Responsibility of IEC/IRB in Pharmacovigilance
- Management of case safety reports during clinical trials
- Risk assessment during clinical trial
- Benefits of risk assessment
- Handling of medication error during clinical trial

Sponsor's responsibilities in Pharmacovigilance:

- Use and adopt Pharmacovigilance procedure(s) to monitor adverse reactions occurring in clinical trials.
- Modifications in protocol due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion criteria, intensification of monitoring);
- Restrictions in study population or indications;
- Changes to the informed consent document relating to safety issues;
- Formulation changes for safety reasons;
- Addition of a special reporting requirement;
- Issuance of a communication to investigators or healthcare professionals;
- plans for new safety trials;
- On going safety evaluation of the investigational medicinal products;
- Immediate notification of finding from the clinical trials that could adversely affect the health of subjects;
- Preparation of various essential documents viz protocol, investigator brochure, case report forms (CRF).
- Reporting of ADRs in Clinical Trial

Protocol in clinical trial

- ICH E6 defines protocol as “a document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.
- The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.”

Guidance in protocol for Pharmacovigilance and safety reporting

- A definition of the expected and unexpected AE
- Specifications of the safety parameters to be studied along with methods and timings for recording and analyzing.
- Standards for expedited reporting with reporting time frames.
- Declaration from the PI that he will ask the study subjects during each scheduled or unscheduled visit about experience of any events or hospitalizations, disability or incapacity since their previous visit.

Role of CRF in Pharmacovigilance clinical trial

- A CRF is “a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject”
- During the clinical trial process all AEs reported are recorded unless otherwise specified in the protocol.
- For routine data collection study protocols clearly define how AEs will be identified, managed, reported and recorded in the CRF.
- From the Pharmacovigilance perspective non serious adverse events are also recorded and reported if their occurrence is important to safety monitoring in a clinical trial.

Role of IB (Investigators Brochure) in Pharmacovigilance clinical trial

- Provides the information to the investigators that facilitate their understanding of the rationale for dosage, dosage frequency/interval, drug administration methods etc.
- Provides procedures for safety monitoring.
- IB acts as an important source document to define the 'expectedness' and 'unexpectedness' of the ADR
- IB serves as the source document for a medicinal product in a country where it is not yet approved for marketing.
- As per ICH GCP 'Investigators Brochure' (IB) is a compilation of the clinical and non clinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects'.

Safety update reports

- Development Safety Update Report (DSUR) should serve as a “stand-alone” document suitable for submission to ethics committees and other stakeholders, if required by local regulations.
- The primary focus should be on the investigational drug (s) and information on comparators is provided only where relevant to the safety of trial subjects.
- SURs present safety profile of an investigational drug and actions proposed (viz early termination of the trial, ongoing status, addition of any extra visit for patient for evaluation of safety etc).
- ICH E2F guidelines on DSUR describe a common standard for annual clinical trial safety reporting among the ICH regions to provide assurance of protection for clinical trial subjects

Objectives of DSUR (development safety update report)

- To provide the summary of the understanding and management of identified and potential risks.
- To provide an update on the status of the clinical investigation/development programme.
- To describe new safety issues.
- To examine whether the information obtained by the sponsor during the reporting period is in accordance with previous knowledge of the product's safety.

Investigator's responsibility in Pharmacovigilance

- The investigator shall report all SAEs immediately to the sponsor except for those that the protocol or IB identifies as not requiring immediate reporting.
- For reported deaths of a subject, the investigator shall supply the sponsor and the Ethics Committee with any additional information requested.
- The sponsor shall keep detailed records of all AEs reported to him by the investigator.
- In blinded clinical trials, Pharmacovigilance role of investigator gets extended to the management of blinded therapy cases.

Responsibility of IEC/IRB in Pharmacovigilance

- IRB/ IEC reviews the essential documents viz trial protocols/amendments, written informed consent forms (and consent form updates), IB and available safety information about the investigational medicinal product.
- IRB/ IEC should be promptly reported for:
 - both serious and unexpected ADRs;
 - any changes or deviations in the protocol to eliminate immediate hazards to the trial subjects;
 - any changes creating an increase in the risks to subjects and/ or changes in the protocol that are affecting the conduct of the trial
 - any new information that may adversely affect the safety of subjects or the conduct of the trial.

Management of case safety reports during clinical trials

- Sponsor has to maintain a detailed record of all AEs that are reported to him by the investigator.
- A detailed analysis for the seriousness, causality and expectedness has to be performed by the sponsor on the individual case safety reports (ICSRs).
- All the collected AEs from all the sites (multicentric trial) need to be assessed so that sponsor can broadly depict the nature and occurrence of the adverse event from the pooled analyses of all participating sites.
- Note: Causality reported by the sponsor on the investigational medicinal product cannot be overruled by sponsor.
- In such circumstances sponsor may comment ('sponsors section' on comments in ADR report) regarding the disagreement. The opinion from both investigator and sponsor should be submitted with the report.

Risk assessment during clinical trial

- If a product is intended to be chronically used and /or has dose-related toxicities.
- If a product's proposed dosing includes a proposed titration scheme.
- When a drug has the potential for AEs which are not likely to be detected or reported by patients.
- If a product is to be studied in pediatric patients, special safety issues should be considered.
- In circumstances when earlier safety data signal an unusual or important concern then in such cases a sponsor may consider reserving blood samples from some or all patients in phase 3 studies.

Handling of medication error during clinical trial

- The medication errors can be minimized by assessing, prior to marketing, common sources of medication errors, which may arise due to the product's inherent properties or because of the inadvertent contribution of the proposed proprietary name, the established name, the proposed labeling and the proposed packaging.
- Medication errors are defined as **any error in the prescribing, dispensing, or administration of a drug, irrespective of whether such errors lead to adverse consequences or not.**

- These errors can occur at any stage of the medication use process.
- During clinical trials, improper dilution or administration techniques, may result in non-optimal dosing.
- These should be carefully examined as warning signs that the product could be subject to dosing errors that may warrant changes in labeling, packaging, or design.

- If errors are not observed in trials, then careful consideration should be given during development to the implications of the design of the product, its packaging, and any device used to administer or deliver the product.
- Any occurrences seen or considered during product development should be documented, reported, and analyzed for potential remedial actions