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DRUG SAFETY MONITORING INTEGRATION OF CLINICAL RESEARCH AND PHARMACOVIGILANCE

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ABSTRACT

Pharmacovigilance is that the science and activities associated with the gathering, detection and assessment of adverse event data.

Major purpose of pharmacovigilance is to gauge the benefit- risk profile of drug for better efficacy and safety to be used in patients. Pharmacovigilance plays a major role in rationale use of drug which provides the information about the adverse drug reactions which Seen in patients. In terms of volume Indian Pharma industry is third largest in world and in terms of value id thirteen largest in world. [1]

India is also known as a hub for clinical research and drug development. There is a requirement of a global and standardized Pharmacovigilance system in India for better safety assessment in India. In drug development process the only priority of clinical trials Is to make sure patient safety during and after the trials. A critical component throughout the drug development lifecycle is Monitoring patient safety. Patient must be treated consistent with the requirements and illness of patient therefore the utmost value Is given to monitoring of patient safety in the least levels of drug development. Such monitoring may be a dynamic process so to Approach safety monitoring. To ensure a systematic approach to safety monitoring pharmaceutical sponsor must work proactively and collaboratively with all stakeholders.

We have to focus upon all the aspects of drug safety in clinical trials including basics of drug Safety, regulatory aspects of drug safety, patient suitability for safety in trials, post marketing safety and causality risk assessment of the drug products. [2]

KEYWORD: *Pharmacovigilance, Clinical-Trails, Safety- Monitoring, Efficacy, Adverse Drug Reaction , Post Marketing Surveillance .*

Aim of Pharmacovigilance (P V)

▪ The determination of patient subgroups that are specifically at risk of unfavourable medication responses (ADRs) (the risk pertaining to dose, age, gender, and underlying illness). The ongoing evaluation of a product's safety while being used to make sure that its advantages as well as disadvantages continue to be reasonable.

▪ How products in the same therapeutic class compare in terms of their adverse drug reaction profiles. Finding and stopping the improper administration of prescription drugs. *[3]*

Pharmacovigilance In clinical trials

▪ To ensure participant safety and an ongoing assessment of risk and benefit, pharmacovigilance may involve the continuous observation and assessment of every unfavourable incident throughout the medication development process.

▪ The majority of safety data taken into account prior to market approval originates from carefully monitored clinical trials The exact regulatory rules (such as USFDA guidelines and ICH GCP) govern the clinical test process. *[4]*

Principal of clinical trials and research

▪ Research and clinical trials are conducted to evaluate hypotheses, increase understanding of the unknown, and conduct research related to public health.

▪ The primary technique for achieving this is data collection and analysis

▪ Principles of clinical trial/research raw conclusions. Clinical trials come in many forms, but they are primarily classified as analytical, observational, or experimental research

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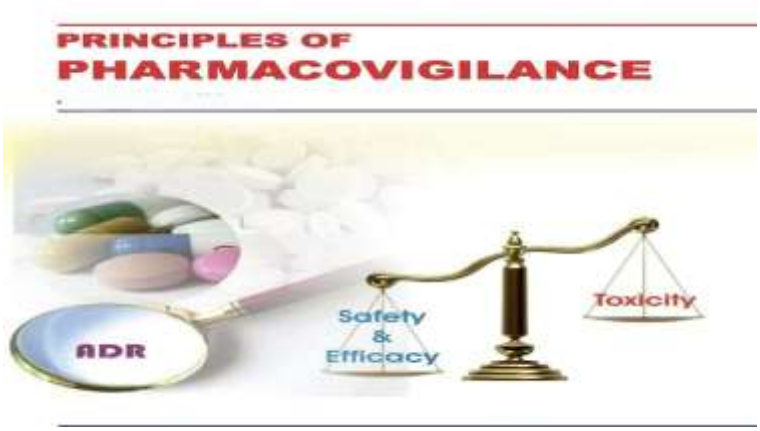

INTRODUCTION

Pharmacovigilance, an integral facet of healthcare and clinical research, encompasses a systematic Approach to monitoring and evaluating adverse effects and safety concerns associated with pharmaceutical products. Rooted in ensuring patient safety, this discipline has evolved significantly Over the years, becoming an indispensable component of the drug development and postmarketing Surveillance processes. The importance of pharmacovigilance is underscored by its pivotal role in Identifying unforeseen or rare adverse events that may not have been evident during the controlled Environment of clinical trials. As a drug progress from preclinical studies to human trials and eventually reaches the market, pharmacovigilance acts as a vigilant guardian, continuously monitoring. [5]

For any untoward effects that may surface in diverse patient populations and real-world settings. An Essential component of pharmacovigilance is the methodical gathering and examination of adverse Event reports. Adverse occurrences might be anything from minor, predictable reactions to serious, Unforeseen, or long-term effects. The classification and understanding of these events are crucial for Distinguishing between normal drug effects and those that pose a genuine risk to patient safety. Next Steps in risk management are based on this classification. The regulatory frameworks set up by international organizations like the European Medicines Agency (EMA), the U.S. Food and Drug Administration (FDA), and other national regulatory authorities are intimately linked to Pharmacovigilance.These organizations establish policies and procedures that control the gathering, Disclosing, and assessment of safety information across the course of a medication's life. Pharmaceutical companies and medical experts must strictly abide by these rules in order to guarantee the ongoing evaluation of a drug's safety profile. Changes in societal expectations and technological Breakthroughs have shaped the growth of pharmacovigilance. Early pharmacovigilance primarily Relied on spontaneous reporting by healthcare professionals and patients. However, contemporary Pharmacovigilance leverages sophisticated data mining techniques, electronic health records, and real-World evidence to proactively identify potential safety signals. As pharmaceutical products become More complex, pharmacovigilance practices are adapting to address the challenges posed by Biologics, gene therapies, and other innovative treatments. The discipline is also increasingly Incorporating patient perspectives, recognizing the value of patient-reported outcomes and insights in Understanding the true impact of drugs on individual. [6]

Fig no.1 Introduction to PV

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Need of work

Drug safety monitoring — also called pharmacovigilance — is essential to ensure that medicines remain safe, effective, and of high quality throughout their use.

Below are the main reasons why it is needed

1. To detect adverse drug reactions (ADRs) Even after clinical trials, some side effects may only appear when the drug is used by a larger and more diverse population. Monitoring helps identify unknown or rare adverse effects.

3.To ensure patient safety Continuous monitoring minimizes harm to patients by identifying and managing risks related to drug use.

3.To maintain a positive benefit–risk balance Drugs should offer more benefit than risk. Safety monitoring helps determine whether a drug's benefits still outweigh its risks during widespread use.

4.To improve prescribing and use of medicines Information from safety monitoring guides healthcare professionals in making better, evidence-based decisions.

5.To support regulatory actions Authorities like the WHO, FDA, and CDSCO (India) rely on safety data to issue warnings, revise drug labels, restrict use, or withdraw unsafe drugs from the market

6.To detect product quality issues Monitoring can reveal problems like contamination, counterfeit medicines, or manufacturing defects. [7]

Preclinical Trials

Preclinical trials (also called non-clinical studies) are conducted before testing a drug in humans to assess its safety, toxicity, and biological activity.

1. Purpose: to determine if the drug is safe and effective enough for human trials.
2. Conducted in: Laboratory tests (in vitro) and Animal studies (in vivo).

Key types of studies

1. Pharmacodynamics – studies how the drug acts on the body.
2. Pharmacokinetics (ADME) – absorption, distribution, metabolism, and excretion.
3. Toxicity studies – acute, sub-acute, and chronic toxicity.
4. Carcinogenicity studies – to check if the drug can cause cancer.
5. Mutagenicity studies – to detect genetic mutations.
6. Reproductive toxicity studies – effects on fertility, pregnancy, and offspring. [7]

Clinical Trials

Clinical trials are research studies conducted to evaluate the safety, efficacy, and effectiveness of medical interventions, including drugs, medical devices, therapies, or diagnostic tools.

They are essential for advancing medical knowledge and ensuring that new treatments are both safe and beneficial for patient.

Clinical trials are prospective biomedical or behavioural research studies on human participants designed to answer specific questions about biomedical or behavioural interventions, including new treatments (such as novel vaccines, drugs, dietary choices, dietary Supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on dosage, safety and efficacy. Clinical trials are systematic research studies conducted to evaluate the safety, efficacy, and effectiveness of medical interventions such as drugs, vaccines, medical devices, and treatment protocols. [8]

Purposes of Clinical Trial's

- Assessing Safety
- Evaluating Efficacy
- Developing Better Treatments
- Preventing Diseases
- Improving Quality of Life
- Advancing Personalized Medicine

Goal's Clinical Trial's

- Aimed at improving medical care, advancing scientific knowledge, and ensuring patient safety.

1) Evaluating Safety
2) Supporting Regulatory Approval
3) Advancing Medical Knowledge
4) Promoting Personalized Medicine
5) Improving Patient Outcomes
6) Exploring Preventive Measures

Phases of Clinical Trial's

1) Preclinical Phase (Before Human Testing)
2) Phase I: First-in-Human Trials
3) Phase II: Efficacy and Safety Trials
4) Phase III: Large-Scale Trials
5) Phase IV: Post-Marketing Surveillance [9]

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Fig no.2 Clinical Trial Phase

1.Preclinical Phase (Before Human Testing)

The preclinical phase is the first stage of research conducted before new drugs, treatments, or medical interventions are tested on humans.

It aims to assess the potential efficacy and safety of a treatment through laboratory and animal studies.

This phase is critical for identifying promising candidates and ensuring they meet safety standards before advancing to human clinical trials.

Objective: -

- Discovery and Target Identification
- Lead optimization
- In Vitro Studies (Cell-Based Studies)
- In Vivo Studies (Animal Testing)
- Formulation Development [9]

2. Phase I: First-in-Human Trials

Phase 1 clinical research is the first stage of human clinical trials in drug development,

Its main objective is to evaluate the safety, dosage, and pharmacokinetics (how the drug is absorbed, distributed, metabolized, and excreted by the body) of a new drug or treatment.

It is typically conducted after preclinical studies, which involve laboratory and animal testing, have shown initial promise regarding the drug's safety and efficacy

Participants: Phase 1 trials typically involve a small number of healthy volunteers (20-100) participant.

OBJECTIVES

Safety: -The primary goal is to assess the safety of the drug, identify any potential side effects or adverse reactions, and determine if the drug. Is safe enough to proceed to the next phase.

Dose-Escalation: -Researchers begin by administering a very low dose of the drug to a few participants and gradually increase the dose in subsequent. Groups to determine the maximum tolerable dose (MTD) and the dose at which side effects become intolerable

Goals of Phase 1

- Safety Profile

The most important goal is to assess the safety of the drug and identify any potential risks or harmful side effects.

- Pharmacokinetics and Pharmacodynamics

Collect initial data on how the drug works in the body. [10]

3. Phase II: Efficacy and Safety Trial

A Phase 2 clinical trial is a critical stage in the drug development process, coming after Phase

1 trial and before Phase 3 trials. The primary focus of Phase 2 is to evaluate the effectiveness of a drug or treatment, continue to assess its safety, and further refine its, Optimal dosage.

Objective

1.Effectiveness (Efficacy)

The main goal of Phase 2 is to assess whether the drug or treatment works as intended in patients who have the condition or disease the drug is meant to treat.

2.Safety (Adverse Effects and Toxicity):

Although Phase 1 trials primarily focus on safety, Phase 2 continues to monitor for any potential side effects or adverse reactions.

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3.Dose Range
Phase 2 studies explore the optimal dose or dosage range that balances effectiveness and safety.

4. Phase III: Large-Scale Trials: -
Phase 3 clinical trials are a critical stage in the development of new drugs, medical devices, or treatments These trials are designed to confirm the effectiveness and safety of an intervention in a larger, more diverse population, and they form the basis for regulatory approval by agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA).

Main Objectives
1.Confirm the efficacy of the intervention
2.Compare the intervention to existing treatments
3. Assess optimal dosing and administration

5. Phase IV: Post-Marketing Surveillance
Post-Phase 3: Post-Marketing Surveillance
This helps detect any long-term or rare side effects that were not evident during Phase 3 trials. Phase 4 clinical trials, also known as post-marketing surveillance trials, occur after a drug or treatment has been approved by Regulatory authorities (like the FDA) and is available on the market. [11]

6. Challenges
1.Underreporting of Adverse Drug Reactions (ADRs):
Many healthcare professionals and patients fail to report side effects, leading to incomplete safety data.
2.Detection of Rare or Delayed Reactions:
Some adverse effects appear only after long-term use or in large populations, making them hard to identify in early stages. [12]
3.Limited Resources and Infrastructure:
Developing countries often lack proper systems, trained personnel, and databases for monitoring drug safety.
4.Data Quality and Accuracy Issues:
Reports may contain incomplete, inaccurate, or inconsistent information, reducing the reliability of safety analysis. [13]
5.Global Variability:
Differences in regulations, healthcare systems, and reporting practices across countries complicate data collection and harmonization.
6.Complex Drug Combinations and Polypharmacy:
Multiple drugs taken together can interact, making it difficult to identify which one causes a particular adverse reaction. [14]

7.Post-Marketing Surveillance Gaps:
After a drug is approved, continuous monitoring is often insufficient, delaying detection of long-term risks.
8.Technological and Analytical Challenges:
Managing and analysing large datasets from various sources (clinical trials, hospitals, online reports) requires advanced tools and expertise. [15]
9.Lack of Public Awareness:
Patients may not recognize or report side effects due to limited knowledge about drug safety reporting systems. [16]

8. **Conclusion**
The information to assess the safety profile of drug is given by pharmacovigilance. Participation of professionals of health care country wide to report adverse drug reaction or adverse events plays a major role in the success of Pharmacovigilance. Current progress in
Pharmacovigilance Is well-marked by increase in use of databases to make the Process more proactive and organized. It must be in everyone's priority to develop safe and effective medicines to patients. During clinical trials monitoring patient safety Is a critical component throughout the drug development [17]

Life- cycle. To ensure a systematic approach of safety monitoring pharmaceutical sponsor must work proactively and collaboratively with all stakeholders. For risk management plans, risk evaluation and minimization strategies. There will be greater demand for more comprehensive and innovative approaches that apply quantitative methods to collecting data from all sources, ranging from the discovery and preclinical through with clinical and post approval stages, As the industry transitions from passive to active safety surveillance Activities. The globalization of clinical trials has posed extra challenges. [18]

A better deal of coordination is required of sponsors to make sure time to time communication of new Safety findings among all stakeholders in all regions. Attempts in building a standard safety data warehouse across all trials in a development program will lay a solid base for integrated safety analyses. [19]

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