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## A Review Article On Pharmacovigilance

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### ABSTRACT :

Pharmacovigilance is an important and integral part of clinical research. Pharmacovigilance is “defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines. This addresses what exactly is pharmacovigilance. What do we know of its benefits and risks, challenges and the future hold for pharmacovigilance in Indian medicine. Pharmacovigilance aims to preserve general health by identifying, evaluating, and minimizing health issues to ensure that the benefits of accessible treatments outweigh the potential risks. Concerns with the nature and safety of drugs as noted by medication guidelines. A sound medication policy is required to ensure the safety, viability, and nature of pharmaceuticals as well as the accuracy and applicability of the distribution medication information made available to the general public. Medication guidelines cover a wide range of functions, including authorizing, reviewing manufacturing facilities and channels, item evaluation and enrolment, observing adverse drug reactions (ADR), controlling medication advancement and publicizing, and controlling clinical medication preliminary studies.

**KEYWORDS :** Pharmacovigilance, Medication safety, Drug efficacy, ADRs, Clinical trials.

### 1. INTRODUCTION :

According to the World Health Organization, “Pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problem, particularly long term and short term adverse effects of medicines”<sup>[1]</sup>. Pharmacovigilance is also known as Drug Safety and abbreviated PV or PhV. The etymological roots for the word "pharmacovigilance" are: Pharmakon (Greek word for ‘drug’) and vigilance (Latin word for ‘to keep watch’)<sup>[2]</sup>. Pharmacovigilance greatly focuses on adverse drug reactions (ADRs) which are defined as any reaction to a drug which is harmful and unintended including lack of efficacy used for the prophylaxis, analysis or therapy of illness or for the modification of physiological function<sup>[2]</sup> it is a fundamental component of effective drug regulation systems, public health programmes and clinical practice”<sup>[3]</sup>. Pharmacovigilance supports safe and appropriate use of drugs by a) promoting the detection of previously unknown ADRs and interactions and increases in frequency of known ADRs, b) identifying risk factors for the development of ADRs and c) estimating quantitative aspects of benefit/risk analysis and disseminating information to improve drug prescribing & regulation<sup>[4]</sup>. Pharmacovigilance (PV) was officially introduced in December 1961 with the publication of a letter (case report) in the Lancet by W. McBride, the Australian

doctor who first suspected a causal link between serious fetal deformities (phocomelia) and thalidomide, a drug used during pregnancy: Thalidomide was used as an antiemetic and sedative agent in pregnant women<sup>[5]</sup>. Since very few new drugs were discovered in India and hardly any new drug was launched for the first time in India in the past, there was no major compulsion to have a strong PV system to detect ADRs of marketed products<sup>[6]</sup>. Continuous monitoring of drug effects, side effects, contraindications and outright harmful effects which could result in a high degree of morbidity, and in some cases, even mortality, are essential to maximize benefits and minimize risks. No degree of care and caution at the pre-clinical and clinical testing stages can guarantee absolute safety, when a drug is marketed and prescribed to large populations across the country and outside. Because clinical trials involve several thousands of patients at most, less common side effects and ADRs are often unknown at the time a drug enters the market. Post marketing PV uses tools such as data mining and investigation of case reports to identify the relationships between drugs and ADRs. The drug regulatory agencies have the responsibility of having a well-established PV system to monitor ADRs during the drug development phase and later during the life time of a marketed drug<sup>[7]</sup>.

## HISTORY :

The safety of drugs was not the early concern in the history of drug<sup>[12]</sup>. The thalidomide tragedy of 1960's opened the eyes of drug regulators as well as other concern healthcare professionals to establish a way to ensure drugs safety<sup>[13]</sup>. The milestone in the drug safety was the publication of chloroform related death on the lancet journal for the first time in 1893<sup>[12]</sup>.

- Misfortune of thalidomide (1961) where thalidomide was utilized to treat nausea in pregnant women, infants born suffering from phocomelia which is due to the use of this medication<sup>[14]</sup>.
- The utilization of Practolol (1975) that led to oculomucocutaneous response perceived by U.K. specialists prompted Prescription events monitoring (P.E.M.)<sup>[15]</sup>.
- Pharmacovigilance in india started from 1986. A formal Adverse Drugs Reaction (ADR).
- However no noteworthy growth was made. Afterward in 1997, india joined the World Health Organisation (WHO) And Adverse Drug Reaction (ADR) scrutinizing program based at Uppsala, Sweden but got fail<sup>[2]</sup>.
- Hence, after 2005 WHO supported and World Bank funded National Pharmacovigilance Programme (NPPV) of india was made operational<sup>[8]</sup>.
- In 2002, more than 65 countries have their own pharmacovigilance centres<sup>[9]</sup>. Membership of the WHO for International Drug Monitoring is coordinated by the WHO Collaborating Centre for international drug monitoring, known as the Uppsala Monitoring(UMC)<sup>[10]</sup>.
- Pharmacovigilance is now firmly based on sound scientific principle and is integral to effective clinical practice. The discipline needs to develop further to meet public expectation adopted a resolution (WHA 16.36)<sup>[11]</sup>.
- Sulphanilamide elixir (1937) led to children's poisoning. It was recognized that it was a defect in the formulation, which prompted enhancements in pharmaceutical guidelines<sup>[14]</sup>.

“The sequential pharmacovigilance developments with special reference to india”<sup>[16,5,17]</sup>.

TABLE :-1

| Year    | Developments                                                                                                |
|---------|-------------------------------------------------------------------------------------------------------------|
| 1747    | Very first known clinical trials by James Lind, proving the usefulness of lemon juice in preventing scurvy. |
| 1937    | Death of more than 100 children due to toxicity of sulfanilamide.                                           |
| 1950    | Apalstic anemia reported due to chloramphenicol toxicity.                                                   |
| 1961    | Worldwide tragedy due to thalidomide toxicity.                                                              |
| 1963    | 16th World Health congregation recognize significant to rapid action on Adverse Drug Reactions (ADRs).      |
| 1968    | WHO research project for international drug monitoring on pilot scale.                                      |
| 1996    | Global standards level clinical trials initiated in India.                                                  |
| 1997    | India attached with WHO Adverse Drug Reaction Monitoring Program.                                           |
| 1998    | Initiation of pharmacovigilance in India.                                                                   |
| 2002    | 67th National Pharmacovigilance Center established in India.                                                |
| 2004-05 | India launched National Pharmacovigilance Program.                                                          |
| 2005    | Accomplishment of structured clinical trials in India.                                                      |
| 2009-10 | Pharmacovigilance Program (PvPI) started.                                                                   |

## 1.2 PHARMACOVIGILANCE SYSTEM OBJECTIVES:

- Ameliorate the care of the patient & well-being according to meds utilization.
- To Contribute to the appraisal of the advantage, harm, viability, and hazard of drugs, prompting the avoidance of mischief and boost of advantages, Promote the safe, logical, and more efficient (inclusive of cost-effective) utilization of medication.
- An advance agreement, instruction, and clinical preparation in pharmacovigilance and its powerful correspondence to the general population <sup>[18]</sup>.
- **Monitoring Adverse Effects:** Continues surveillance to detect and evaluate adverse drug reactions (ADRs) that arise during the use of medications.
- **Assessment Of Risk and Benefits :** Analyzing the risk-to- benefit ratio of drugs to ensure that the therapeutic benefits outweigh potential risks or adverse effects.
- **Data Collection and Analysis:** Systematically gathering and analyzing information on medication safety, including reports from healthcare providers, patients, and clinical trials.

• **Risk Management and Mitigation:** Developing strategies to manage and minimize risks associated with medications, such as updating labelling, implementing risk minimization plans, or even withdrawing drugs from the market if necessary.

• **Promoting Safe Use of Medications:** Educating healthcare professionals and patients about the safe and effective use of medications, including appropriate dosing administration, and monitoring.

• **Communication and Information Dissemination :** Facilitating the dissemination of safety information to healthcare providers regulatory agencies, and the public to ensure informed decisions-making about medication use.

• **Regulatory Compliance:** Ensuring compliance with regulatory requirements related to drug safety monitoring and reporting.

• **Post Marketing surveillance:** monitoring the safety of medications after they are approved and made available in the market to identify rare or long-term adverse effects that might not have been evident during clinical trials. It's about promoting, learning, training and clear communication about drug safety to healthcare professionals and the public. It involves recognizing medication- related issues and effectively sharing that information in a way that's easy to understand <sup>[19]</sup>.

### 1.3. KEY GOALS OF PHAMACOVIGILANCE :

- (1) To promote safe, effective, and rational usage of pharmaceuticals.
- (2) To promote awareness among patients and the general public regarding the rational use of medicines via effective communication.
- (3) Enhance patient safety and care in relation to the use of medicines.
- (4) Recognize risks related to meds utilization.
- (5) Take part in comparative evaluation of potentially useful & pharmaceuticals adverse effects which aid improving nature of usage.
- (6) Identify & report suspected ADRs <sup>[20]</sup>.
- (7) Research the efficacy of drug and by monitoring the adverse effects of drugs right from the lab to the pharmacy and then on for many years.
- (8) Pharmacovigilance keeps track of any drastic effects of drugs.
- (9) Improve public health and safety in relation to the use of medicines.
- (10) Contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use.
- (11) Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public <sup>[21]</sup>.

## 1.4. NEEDS OF PHARMACOVIGILANCE :

The forceful marketing of new drug products by pharmaceutical companies and the consequential rapid disclosure over a short period of time of large numbers of patients to them necessitate the formation of a system for global assessment of drug safety concerns. These actions need an effective and efficient pharmacovigilance system that has been realized more than ever to make sure safe use of drugs. There are several rationales for increasing requirement of pharmacovigilance system. The bases of need are as follows:

### 1. Untrustworthiness of pre-clinical safety information.

- Well-controlled environment.
- Appropriate and precise sample size.
- Pressure from various systems to decrease time to authorization <sup>[1]</sup>.

### 2. Altering pharmaceutical marketing policies.

- Aggressive marketing.
- Launch the drug in many countries at a time <sup>[2]</sup>.

### 3. Varying physician's, patient's and other health professional's preferences.

- Increasing use of newer drugs.
- Increasing use of drugs to get better quality of life.
- Shift of manage to self-administered treatment <sup>[22]</sup>.

### 4. Easy convenience.

- Growing conversion of prescription drugs to over the counter drugs
- Easy access to drug information on the Internet <sup>[23]</sup>.

## 1.5. PHARMACOVIGILANCE SCOPE :

- The extent of pharmacovigilance has grown astoundingly as of late and is presently considered to incorporate the accompanying domain

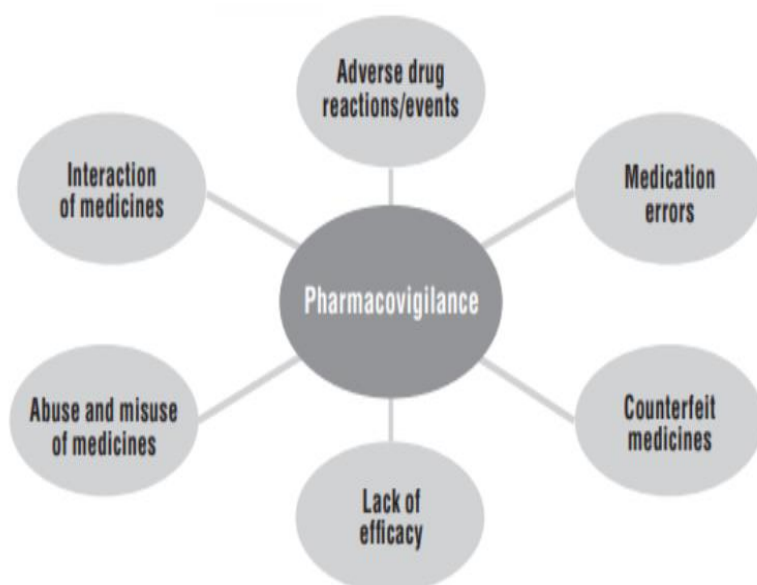
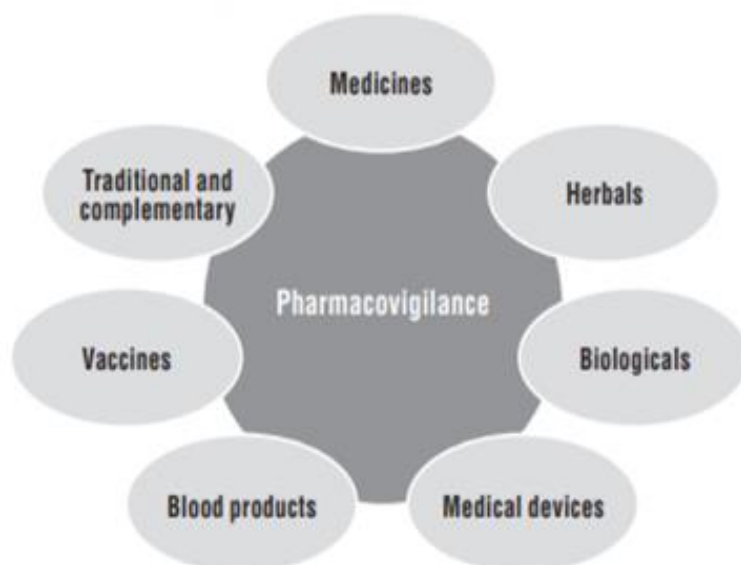


Fig.1.Domains of pharmacovigilance

-Products go past traditional medications and furthermore incorporate natural herbs, other conventional and dietary supplements, vaccines, blood products, and probably clinical gadgets (Fig. 2).

**Fig.2.Products of pharmacovigilance**



-It is vital to have as a primary concern the whole extent of pharmacovigilance and the range of items considered through the development and utilization of a group of pointers to serve as tools for their assessment & observation<sup>[24,25]</sup>.

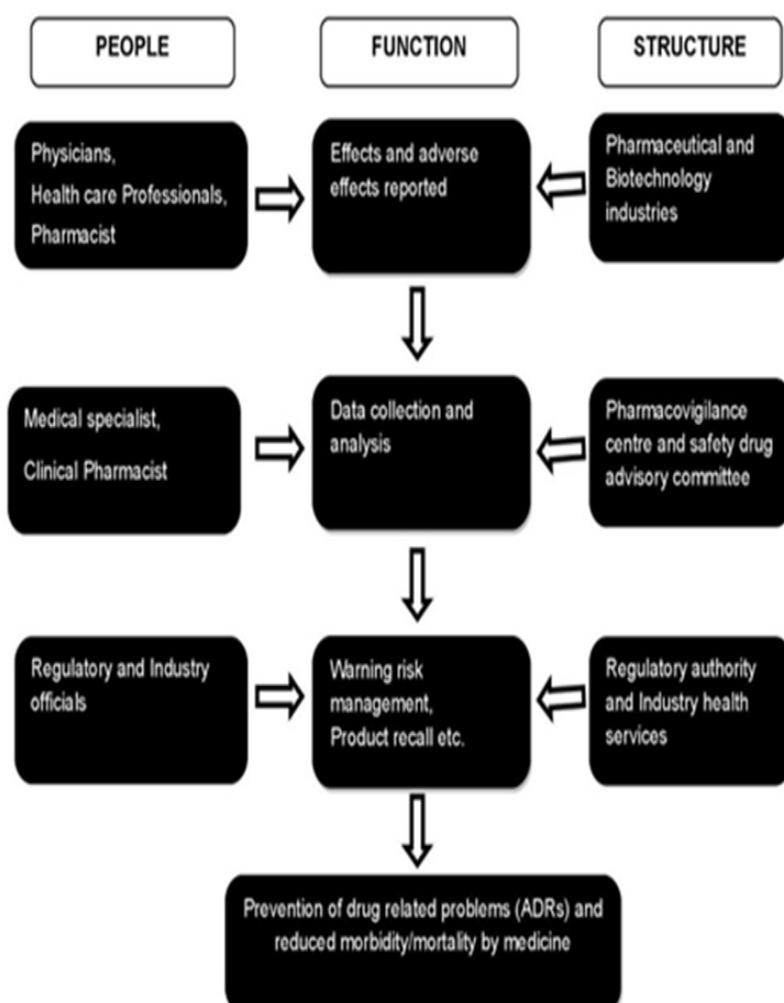


**Fig.3.A typical pharmacovigilance**

## 2. DRUG REGULATION AND PHARMACOVIGILANCE :

Medication safety affairs & pharmacovigilance are essential to everybody where clinical intervention affects his life. Strong medication regulatory configurations establish the national ethos of medication safety & for medication public trust. Besides approving new drugs, medication regulatory authorities have to address these issues:

- a. Clinical preliminaries
- b. All the traditional & complementary medicine, vaccines, etc. Must be safe.
- c. Creating communication lines among all gatherings related to the safety of medications & warranting that these lines are always available & act efficiently, especially at crisis times <sup>[26]</sup>.

Pharmacovigilance programs need strong controller connections to warranty authorities who are quite informed about safety affairs in ordinary practice that might be pertinent to future administrative activity. Regulators comprehend that pharmacovigilance assumes a particular and essential part in guaranteeing the ongoing safety of pharmaceutical items. Pharmacovigilance programs should be upheld enough to accomplish their goals.

To gain acceptance by the national drug regulatory authority, the new medication should pass through three obstacles. Adequate evidence is needed to demonstrate the new medication to be:

- a. It has high quality,
- b. Efficient,
- c. For the purpose that is proposed, it is safe.

While the initial two models should be met before any thought can be given to endorsement, the safety issue is less sure. Safety isn't outright, and it tends to be decided just corresponding to efficacy. There is plausible that uncommon yet genuine adverse effects (for example, those happening with a recurrence of, say, one of every 5,000) won't be identified in the pre- registration advancement of the medication. For instance, deadly blood dyscrasia in 1 out of 5,000 patients cured with a new medication is prone to be perceived later than 15,000 patients have been cured & monitored, given that the foundation frequency of such a response is zero or a causal relationship with the medication is straightforward <sup>[27]</sup> .

## 3. REGULATION OF CLINICAL TRIALS IN INDIA :

Global pharmaceutical companies have found India to be a preferred destination for clinical trials because India's clinical research space and opportunities are very attractive <sup>[28]</sup> . Some of the advantages for clinical trials that India has as are as follows:

- (1) High degree of compliance to international guidelines such as the International Conference on Harmonisation (ICH) / WHO Good Clinical Practice (ICH-GCP) and the regulations lay down by the US Food and Drug Administration.
- (2) Availability of well qualified, English speaking research professionals including physicians.
- (3) Ongoing support and cooperation from the government.
- (4) Lower cost compared to the west <sup>[29]</sup> .
- (5) Increasing prevalence of illnesses common to both developed and developing countries.
- (6) Availability of good infrastructure.
- (7) Changes in Patent Laws since January 2005.

As per a recent report from Federation of Indian Chambers of Commerce and Industry (FICCI), scientific feasibility, medical infrastructure, clinical trial experience, regulations, commercialization potential and cost competitiveness are some of the growth drivers responsible for the metamorphosis of Indian clinical research in the recent past <sup>[30]</sup>. Indian-born contract research organizations (CROs) were able to offer the advantages of understanding the Indian scenario better, provide services at more competitive costs, and having better knowledge of Investigator sites in the country compared to the newer entrants in the market. India's existing favourable regulatory framework and regulations with international standards, increasing awareness of good clinical practice available guidelines and its implementation by clinicians are some of the main reasons propelling the growth of clinical research in India <sup>[31,32]</sup>. The therapeutic area wise distribution of clinical trials and ability of diverse patient population across major therapeutic segments in India is shown in (Figure.4) <sup>[33]</sup>.

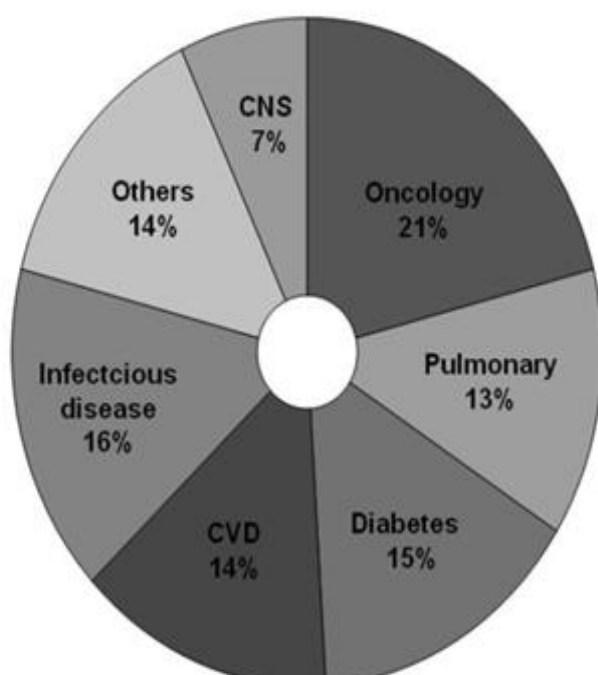


**Fig .4. Therapeutic area wise distribution of clinical trials outsourced to India.**

For policymakers (medication regulators), the changing patterns over late years in the lead of clinical preliminaries present extraordinary and urgent difficulties, especially in guaranteeing that the rights and patients' health and their societies are ensured. In their endorsement of clinical preliminaries, policymakers focus on the efficacy & safety of new medication being scrutinized. Likewise, they should focus on the prevailing norms of care and patient safety related to the proper institutional review boards (I.R.B.s). Prescriptions needed for illnesses like tuberculosis, HIV/AIDS, malaria, and meningococcus meningitis, and those that might have problematic or dubious adequacy, safety profile, require careful observation when previously brought for an enormous scope into societies <sup>[34]</sup>.

Clinical trials progress through distinct phases, with phase I focusing on safety, Phase II expanding to a larger cohort to further assess safety and efficacy, and phase III involving large- scale trials comparing interventions to existing standards of care. The randomized controlled trial the reliability of results by randomly assigning participants to intervention or control groups <sup>[34]</sup>.

| Phases  | Objective                                                                                                                                                     | Participants                                                                       | Dose                                                                         | Duration                                                                                   | End point                                                                                                                                                   | Activities                                                                                                                           | Sample Size                                                                                                                         | Regulatory Approval                                                                                                                                                       |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Phase 0 | To explore drug behavior in human. Asses basic properties like (ADME).                                                                                        | Very small group (10-15 healthy volunteers)                                        | Receive very low dose                                                        | Short duration (typically days)                                                            | Before starting phase 0 trials targeting a diseases progression, a validated test to accurately measure that progression must be in a place (PD end point). | Involve micro dosing where sub therapeutic dose are administered                                                                     | Phase 0 studies are typically small-scale, involving fewer than 15 participants, and the drug is administered for a brief duration. | Phase 0 trials do not require FDA approval and are not formal phase of drugs development. They are exploratory in nature                                                  |
| Phase 1 | Determine safety, dosage range and potential side effects. Understand drug metabolism and pharmacokinetics.                                                   | Small group (22-100 healthy volunteers or individuals with the target conditions). | Focusing on small group to assess treatments safety profile.                 | Several months                                                                             | Phase 1 studies aim to identify side effects, set safe dosages detect organ -related harm through lab test and pin point limiting toxicities.               | Administered escalating doses to establish a safe dosage range. Monitor for adverse effect, pharmacokinetics, pharmacodynamics.      | In the context of phase 1 trial, the sample size typically involve fewer than 20 subjects.                                          | Requires regulatory approval, and data collected is submitted to regulatory authorities.                                                                                  |
| Phase 2 | Phase 2 trials further evaluate safety and begin to assess the drug's effectiveness.                                                                          | Individuals with the condition the drug is intended to treat.                      | Administered at or near the anticipated therapeutic dose.                    | Phase 2 trials may last several months to 2 years                                          | Evaluate efficacy and side effects. Continue to monitor safety.                                                                                             | Assess treatment safety and effectiveness and in more people for a specific condition, gathering, data before larger phase 3 trials. | Involve smaller group, usually less than 50 patients.                                                                               | Approval from agencies like FDA or EMA.                                                                                                                                   |
| Phase 3 | Phase 3 trials confirm effectiveness, monitor side effects and compare the new treatment to standard treatments.                                              | Large groups of patients with the condition the drug is intended to treat.         | Similar to phase 2 administered at or near the anticipated therapeutic dose. | Phase 3 trials can large several years.                                                    | Assess efficacy, monitor side effects, and overall benefits vs. risks. gather additional information about safety.                                          | Test treatment on large groups to confirm effectiveness watch for side effects, compare to standard treatments.                      | Involves 100s to 1000s of participants                                                                                              | Phase 3 trials are big tests for treatment. They check safety, effectiveness and side effects.                                                                            |
| Phase 4 | Phase 4 trials occur after a drug has been approve and is on the market. They aim to gather additional information on long- term risk, benefits, optimal use. | Can involve a large number of patients, millions.                                  | Reflects real world use.                                                     | Phase 4 trials can continue indefinitely, as they monitor the drug in real-world settings. | Evaluate long-term safety and effectiveness. May identify rare or long -term side effects.                                                                  | Phase 4 trials occur post-approval. They assess safety, efficacy, new uses in diverse populations.                                   | Can be very large due to real-world                                                                                                 | Conducted after regulatory approval. Keep in mind that these are general outlines, and specifics can vary depending on the type of treatment and condition being studied. |

TABLE:-2

#### 4. Adverse drug reactions (ADRs) :

An adverse drug reactions (ADRs) can be defined as an unintended and noxious responses to a health product which causes at the doses usually used or tested for the diagnosis, prevention or treatment of a disease or the alteration of an organic function <sup>[35,36,37]</sup>. Though, it is difficult to recognize the causative agent related with the adverse drug reactions (ADRs) encountered because the medicinal preparations generally contain more than ingredients.[38] All drugs are capable of producing adverse drug reactions (ADRs) and whenever a drug is given a risk is taken <sup>[39]</sup>.

❖ **Adverse Drug Reactions (A.D.R.s) Classification :**

**Type A Effects** :- Expanded (augment) pharmacological effect: These are expected effects & it is dose-related; these effects are due to overstated pharmacological impacts. These effects (type A) are common & dose-dependent and may regularly be averted by utilizing dosages that are suitable to the singular patient.

**Type B Effects** :- Unusual effects (idiosyncratic or Bizarre): These are unpredictable effects & it is dose unrelated (Patient responses) typically happen in just a few patients and show few or dose-independent connections. These effects (type B) are uncommon & unpredictable.

**Type C Effects** :- These effects are chronic and refer to medication utilization, frequently for obscure reasons, expanding the recurrence of a "spontaneous" ailment. These effects (Type C) are both common & critical (like malignant) & may affect general well-being. These impacts are incidental & frequently related to prolonging haul impacts.

**Type D Effects** :- These impacts are delay onset effects (dose unrelated) like carcinogenic effects (for example, immunosuppressant) & teratogenic effects (for example, fetal hydantoin syndrome).

**Type E Effects** :- The effect of treatment ends.

**Type F Effects** :- Failure of therapy<sup>[20]</sup>.

➤ **Known drugs adverse effects<sup>[40]</sup>.**

| Drug                     | Adverse Drug Reactions (ADRs)                      |
|--------------------------|----------------------------------------------------|
| Thalidomide              | Phocomelia, Multiple defects                       |
| Methotrexate             | Multiple defects, Foetal death                     |
| Androgen                 | Virilization, limb, esophageal, cardiac defects    |
| Progestins               | Virilization of female foetus                      |
| Silboestrol              | Vaginal carcinoma in teenage female offspring      |
| Tetracyclines            | Discolored or deformed teeth, retarded bone growth |
| Warfarin                 | nose, eye and hand defects, growth retardation     |
| Phenytoin                | Various malformations                              |
| Lithium                  | Foetal goiter, cardiac and other abnormalities     |
| Aspirin/<br>Indomethacin | Premature closer of ductus arteriosus              |

TABLE:-3

## **5. ADVERSE DRUG REACTIONS REPORTING :**

At the point when the adverse response to certain medications is possibly genuine or clinically significant, all medical care laborers, including specialists, pharmacists, attendants, other health care providers, are mentioned to illustrate it. Reporting an adverse drug reaction (A.D.R.s) to pharmacovigilance is important [41].

### **-Spontaneous Reporting System:**

- a) Regionalization.
- b) Repossession of additional information.
- c) Admittance to immensely significant pre and post-marketing data.
- d) Definite medication use information.
- e) Normalized assessment of causality and importance.
- f) Inducement/ Encouragement [41].

### **5.1:- Adverse Drug Reactions (A.D.R.s) Documentation :**

The curriculum of pharmacovigilance passed on an overall spur that all speculated drug-related adverse effects ought to be laid out. Its reports concerned the following.

- 1) All the adverse reactions doubtful or happened to new medications and medications of recent concern.
- 2) Documentation of different medications that cause adverse drug reactions (A.D.R.s) that include death, perilous conditions, inability, hospitalization, and innate irregularities. The critical adverse response of medications ought to be reported within a week. Other data concerning adverse reactions must be reported within eight days. The structure of A.D.R.s may be gathered out of any P.V. place. These forms are reviewed, and the information is passed forward to the regional center & from this point onward, it is pushed to the zonal center. The subtleties were measurably examined & sent to WHO-Uppsala Monitoring advisory group (U.M.C.) [41].

### **5.2 :- Adverse Drug Reactions Reporting Procedure :**

The principal obligation of all P.V. centers is to state whole suspicious adverse reactions related to medication utilization whenever found. These A.D.R.s' information must be reported and organized.

### **5.3 :- Monitoring of Adverse Drug Reactions (A.D.R.s) :**

Monitoring of A.D.R.s is a practice of consistently checking the unwanted effect of utilizing medication. Pharmacovigilance plays a basic pantomime in observing A.D.R.s Drug regulators intrinsically check their marketed medicinal products & enroll every presumed adverse response is distinguished. Use of different medicinal products, clinical gadgets, herbals, cosmetic products, etc. Assuming that and adverse responses are not expressed, it might bring about harmful and dangerous effects of medicinal items. In this manner, appropriately leading adverse drug reaction monitoring projects will assist with lessening the unsafe impacts of medical products [42].

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| Elements in ADR reporting | Reporting Necessary                                  | Others                                    |
|---------------------------|------------------------------------------------------|-------------------------------------------|
| What should be reported   | Adverse reaction of drugs                            | Medication over dose, ph. defect          |
| Who can report (staff)    | Doctors, Pharmacists, Nurses                         | All government and private hospital staff |
| When it can be reported   | Any adverse reaction if noticed                      | --                                        |
| How to report             | Through completely filled yellow form                | --                                        |
| Where it can be reported  | Complete filled ADR form should be submitted to PVPI | --                                        |

**TABLE .4. Adverse Drug Reactions Reporting Procedure**

#### **5.4 :- Adverse Drug Reactions Monitoring Benefits :**

- 1) Monitoring and reporting programs of adverse drug reactions can outfit the following advantages:
  - a) It provides data about the safety & the quality of medications.
  - b) It provides plans for risk management.
  - c) It forestalls the anticipated adverse events and aids in estimating adverse drug reaction adherence.
  - d) It teaches medical services groups, i.e., pharmacists, nurses, & patients, regarding adverse events and initiates the realization of A.D.R.s.
- 2) The primary targets of monitoring adverse drug reactions are:
  - a) Uncover the quality of medications.
  - b) A.D.R.s frequency.
  - c) Recognize hazard factors that lead to adverse events <sup>[42]</sup>.

#### **5.5:- Hazard / Serious Adverse Reaction :**

A hazard / serious adverse event (S.A.E.s) in clinical trials is characterized as any unto- ward clinical event that occurred in any dose:

- 1) Leads to death.
- 2) Is perilous
- 3) Leads to patient hospitalization.
- 4) Prolong patient hospitalization existence.
- 5) Leads to congenital aberration/birth deformity <sup>[28]</sup>.

- Clinical trial investigators are committed to reporting these reactions in clinical review reports. Research recommends that these reactions are frequently insufficiently announced in freely accessible reports <sup>[43]</sup>.

## 6. PHARMACOVIGILANCE AND DRUG SAFETY MONITORING :

Every drug is associated with beneficial as well as undesirable or adverse effect. ADR as defined by WHO is “noxious or unintended response to a drug occurs at a usual dose”<sup>[44]</sup>. ADR is broadly classified as Type A and Type B<sup>[45]</sup>. Type A reaction is associated with the pharmacological actions of the drug and is predictable while Type B reaction is not associated with the pharmacological actions of the drug and is not predictable. It is also known as idiosyncratic reaction. Type A reaction is more prevalent, accounts for more than 80%, than the Type B reaction<sup>[45]</sup>. ADRs are associated with significant morbidity and mortality. Recent estimates suggest ADRs are the fourth to sixth major cause of death in the United States of America (USA)<sup>[46]</sup>. The hospitalization due to ADRs in some countries is about or more than 10%, which means ADRs as a major cause of hospitalization. In addition, it is estimated that 10-20% of the hospital inpatient suffers from ADRs<sup>8</sup>. That's why ADRs is the common clinical problem. Appropriate monitoring of ADRs is the only best way to safeguard the patients and even prevents ADRs<sup>[47]</sup>.

The pharmacovigilance aims to early recognition of previously unknown As, recognition of frequency of known ADRs, identification of risk factors and mechanism of ADRs, quantitative analysis of benefit/ risk ratio and dissemination of safety information for rational drug prescribing regulation. The safety data generated and during the clinical trials is always not enough to rule out all possible adverse effect of the drug, when they introduced in the real world. The major limitations of clinical trial are: animal tests are insufficient to predict the human safety, only selected patients are exposed and limited time frame, limited human subject, in almost all cases less than 5,000, which is favourable to detect only the more common ADR<sup>[44]</sup>. For the detection of rare and very rare ADRs large sample size is required. “Rough estimation of the power to detect adverse events is generally calculated by rule of 3”. For example, to find out the incidence of 1 in 10,000 at least 30,000 people need to be treated with a drug<sup>[45]</sup>. To detect the incidence of 1 in 100,000, we can imagine the sample size, which are almost beyond the scope of clinical trials. This in turn, the safety information available even by the well designed clinical trials is not adequate to answer the safety concern. As a result, the pharmacovigilance; often indicates as post marketing surveillance by pharmaceutical companies, as a systematic monitoring can be an effective ways to identify drug related safety issues throughout the life cycle of any drug.

## 7. SIGNIFICANCE OF PHARMACOVIGILANCE :

When a new drug is presented on the market, there is still plenty of obscure things concerning the safety of this new medication. Different patients utilize these drugs for various ailments, which may be utilizing multiple different medications and should be following various practices and diets, which may unfavourably influence the effect of medication on them. Additionally, a similar medication may vary in the way of its manufacturing. Moreover, adverse drug reactions (A.D.R.s) may likewise happen when medications are brought with conventional and natural meds, which must be observed through pharmacovigilance. Now and again, adverse drug reactions (A.D.R.s) of specific medication may happen just in one nation or locale. To forestall all unjustifiable physic- al, mental and monetary enduring of patients, pharmacovigilance ends up being a significant observing system for medication safety in a country with the help of specialists, drug specialists, attendants, and other health experts of the country<sup>[48]</sup>.

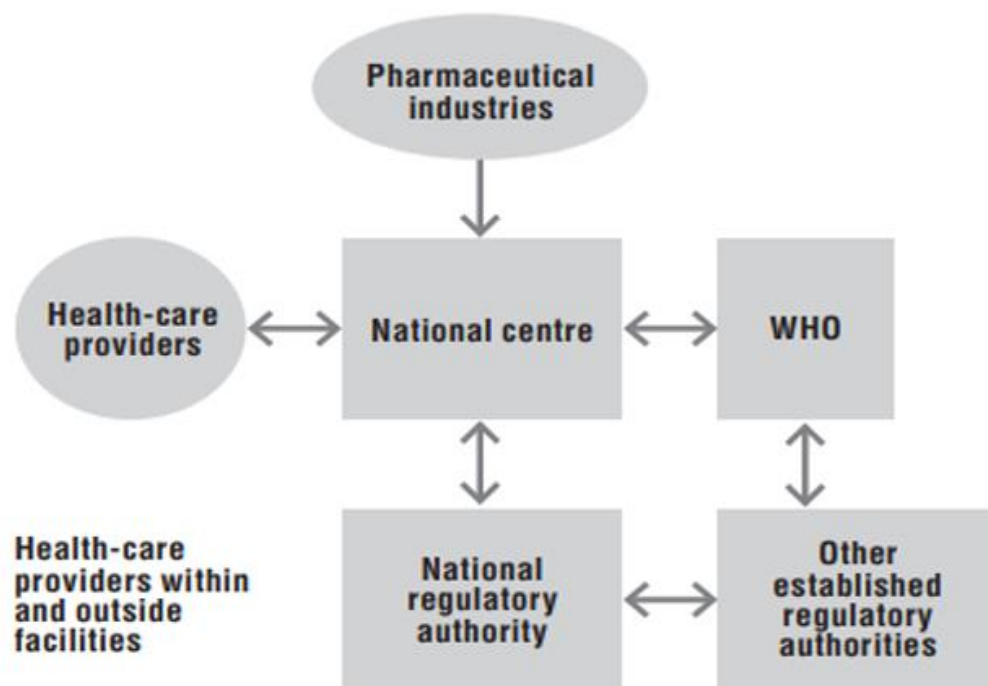


**Fig .4 . Significance of pharmacovigilance**

## 8. METHODS USED IN PV :

Many researchers developed different methods of causality assessment of ADRs by utilizing different criteria like chronological relationship between the administration of the drug and the occurrence of the ADR, screening for non-drug related causes, confirmation of the reaction by in vivo or in vitro tests, and antecedent information on homogeneous events attributed to the suspect drug or to its therapeutic class, etc., to define ADRs in different categories <sup>[49]</sup>. Currently, there is no universally accepted method for assessing causality of ADRs <sup>[50]</sup>. Currently, there are many algorithmic methods of causality assessment but no single algorithm is accepted as the gold standard because of the shortcomings and discordances that subsist between them <sup>[51]</sup>. We would explicate them in short as listed below.

### [A] Dangaumou's French method :

This rule of thumb has been used by the French government agency since 1977. The way of doing thing separates an intrinsic imputability (possible case between abused substance and dispassionate event) from an extrinsic imputability (bibliographical data) by the agency of seven criteria (three connected and four semiological) in two different tables. The criteria are (i) drug challenge, (ii) dechallenge, and (iii) rechallenge by the overall score of four possible categories. The semiological criteria are (i) semiology (clinical signs) using per se (suggestive or other), (ii) favouring component, (iii) arbitrary non-drug- related (none or possible), and (iv) laboratory tests show with three possible outcomes (positive, negative or no test for the event-drug pair). Scores are grouped as possible and dubious <sup>[52]</sup>.

### [B] Kramer et al. method :

This method applies when the offending drug is administered and a single adverse drug event has taken place. Each adverse event is assessed independently and assessment is prepared. One of the advantages of this algorithm is its transparency. However, certain levels of experience, expertise, and time are required to use this method effectively <sup>[53]</sup>.

### [c] Naranjo et al. method (Naranjo scale) :

It is utilized to verify causality in a variety of clinical situations utilizing the categories and definitions of definite, probable, possible, and doubtful. It consists of ten questions which are answered as yes, no and

unknown. The event is assigned to a probability category predicated on the total score after totalling. A total score of  $\geq 9$  is definite, probable is 5-8, possible is 1-4 and doubtful  $\geq 0$ . This scale is more powerful when the adverse event is associated with only one drug, but when multiple drugs are involved or there is any interactions between drugs, this scale fails to identify the offending agent<sup>[54]</sup>.

#### **D) Balanced assessment method :**

This method evaluates a case report on various visual analogue scale (VAS) models that each criterion is fulfilled individually. It has an added advantage that it considers an alternative causative factor as a possibility and not just as a separate factor. Each case is assessed independently by different assessors and the evaluation depends on the assessor's skills knowledge<sup>[55]</sup>.

#### **[E] Ciba-Geigy method :**

Expert consensus meetings have resulted in Ciba-Geigy method. Experts used their clinical judgment to assess adverse drug events and assign causality on a VAS. This method uses a checklist which is composed of 23 questions, which is split into three sections: (i) History of present adverse reaction, (ii) patient's past adverse-reaction history, and (iii) monitoring-physician's experience. This updated method was found to have a high degree of agreement (62%) when compared with valuator's assessments<sup>[56]</sup>.

#### **[F] Loupi et al. method :**

This method developed to assess the teratogenic potential of drug. The first sections of the algorithm sanction for the drug to be omitted if not implicated in the inception of the abnormality. The second section weighs the bibliographical data. The three questions consider alternative etiological candidates other than the drug; chronology of the suspect drug and other bibliographical data, to arrive at a conclusion on causality.<sup>[57]</sup>

#### **[G] Roussel Uclaf causality assessment method :**

This method is used in disease states such as liver and dermatological problems. A retrospect assessment of the reproducibility of this method among four experts had showed a 37-99% agreement rate<sup>[49]</sup>.

#### **[H] Australian method :**

Australian method involves the evidence which helps in to draw the conclusion, such as timing, and laboratory information from case reports presented and the antecedent cognizance on the suspect drug profile is deliberately omitted in the assessment<sup>[58]</sup>.

### **9. CONCLUSION :**

The PV in India has become an important public health issue as regulators, drug manufacturers, consumers, and healthcare professionals are faced with a number of challenges. The PV in India continues to grow, evolve, and improve. India is the largest producer of pharmaceuticals and now emerging as an important clinical trial hub in the world. Apparently, the requirements for professional specialization, a combined view on PGx and clinical requirements are needed. That helps to identify factors that increase the risk of unwanted outcomes from drug therapy and prio to commencing drug treatment and in tailoring drug treatment for individual patients. The PV has also involved in Data Mining Technology in spontaneous reports submit to the national surveillance systems. The PVPI is coordinated at IPC through NCC under the control of Indian Government to generate an independent data on safety of medicines, which will be at par with global drug safety monitoring standards. National and regional PV systems are well-adapted bodies, attuned to the intricate collection and analysis of ADR data that leads to timely alerts and interventions to protect population health. Furthermore, it is responsible in India of entire campaign to improve PV knowledge and increase the number of ADRs reports up to the gold standard level established by the WHO.

The adverse events reported by PV system will potentially benefit to the community due to their proximity to both the population and public health practitioners, in terms of language and knowledge of the lifestyle and habits of patients, enables easy contact with reporters, for example by telephone, Email, text messages by mobile phones. The development of new and effective medicinal products makes a positive contribution to the health and well being of individuals. However, there is a need to improve PV systems to more effectively monitor and take action on for medicinal product safety to help the patients get well and to manage optimally or ideally, avoid illness is a collective responsibility of industry, drug regulators and clinicians and other healthcare professionals. The financial support and future projects should help to achieve a more comprehensive PV activity in India.

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