

PHARMACOVIGILANCE IN CLINICAL TRIALS

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ABSTRACT

When new therapeutic interventions are developed, clinical trials become an essential part of the drug development process to establish efficacy and safety. However, these trials also expose patient to unknown risks and adverse reaction which can addressed with help of pharmacovigilance. The World Health Organization defines pharmacovigilance as the science of detecting, assessing, understanding, and preventing adverse drug reactions or other drug-related problems. It plays a critical role in ensuring patient safety during clinical trials. Effective pharmacovigilance involves systematic monitoring and reporting of adverse events, maintaining data integrity, and continuously evaluating the benefit-risk balance of investigational products. By integrating ethical principles, Good Clinical Practice (GCP) guidelines, and modern technologies such as electronic data capture, artificial intelligence, and real-world evidence, pharmacovigilance enhances the reliability of clinical research and safeguards patient welfare. This review article highlights the processes, challenges, and future directions of pharmacovigilance in clinical trials, emphasizing its importance in the development of safe and effective medicines.

KEYWORDS: Pharmacovigilance, Clinical trials, Drug safety, Drug Development.

INTRODUCTION

World Health Organization (WHO) explain about **Pharmacovigilance**, that medicines and vaccines have transformed for prevention and to treat the diseases. In addition to their benefits, medicinal products may also have side effects, some of which may be undesirable and / or unexpected. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem.^[1]

All medicines and vaccines are carefully tested in clinical trials to check their safety and effectiveness before they are approved for use because they can show side effects which can be severe in some cases. However, the clinical trial process involves studying of each drug products by selecting them in small number for a short period of time.^[1]

Pharmacovigilance is not limited to the final stage of drug development. It is a process that takes place throughout drug discovery and development, and also within the clinical trial program. In addition, pharmacovigilance should also be carried out even after the drug has entered the market. Safety issues that could emerge at any point during development ought to be detected early to avoid needless exposure of trial participants to possible harm and to prevent squandering resources on medications that are unsafe and ineffective.^[11,19]

Large amounts of data can also make it difficult for safety teams to identify the findings that require immediate attention and many challenges include like differences in regulations between countries, data-quality problems, difficulties in integrating clinical and safety databases, and limitations in emerging technologies such as AI.^[15]

Pharmacovigilance is the science and practice of detecting, assessing, understanding, and preventing adverse drug reactions or other medicine-related problems, now expanded to include herbals, traditional and complementary medicines, blood products, biologicals, medical devices, and vaccines.^[23]

In modern drug development, pharmacovigilance (PV) is not simply a post-approval surveillance mechanism; it is an active safety engine integrated into every phase of human research.^[42] The central mission of pharmacovigilance during clinical development is to continuously evaluate the safety profile of an Investigational Medicinal Product (IMP), protect clinical trial participants from harm, and ensure that the risk-benefit balance remains acceptable as clinical exposure grows.^[35,42]

History of Pharmacovigilance

The history of Pharmacovigilance started 169 years ago, on Jan 29, 1848, when a young girl (Hannah Greener) from the north of England died after receiving chloroform anaesthetic before the removal of an infected toenail. The main objectives of Pharmacovigilance involve exhibiting the effectuality of medicine by observing their adverse impact profile for several years from the research lab to the pharmacy.^[3] The concept of pharmacovigilance developed after the thalidomide disaster in the late 1950s, where thousands of children were born with congenital deformities due to the drug's use in pregnancy.^[9]

Table 1. The sequential Pharmacovigilance developments.

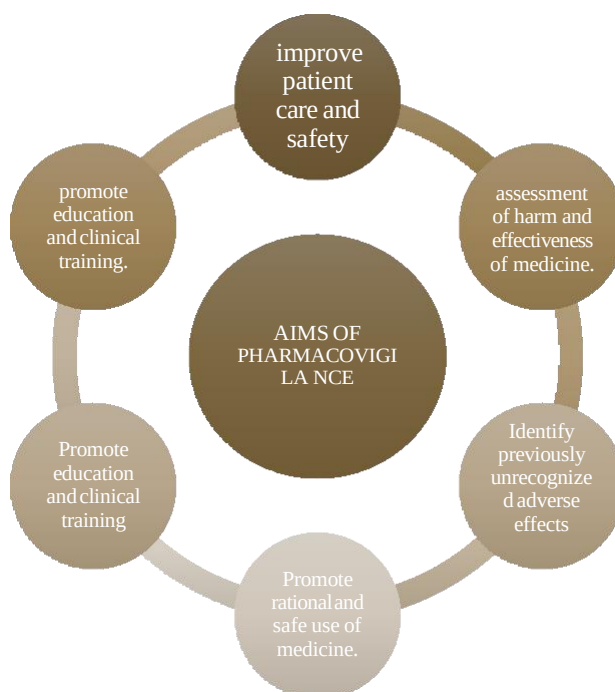
YEAR	DEVELOPMENT
1747	The very first known clinical trials by James Lind proved the usefulness of lemon juice in preventing scurvy.
1937	Death of more than 100 children due to toxicity of sulphanilamide. (Sulphanilamide Disaster)
1950	Aplastic anaemia was reported due to Chloramphenicol toxicity.
1961	Worldwide tragedy due to thalidomide toxicity
1963	16th World Health congregation recognizes significant to rapid action on Adverse Drug Reactions (ADRs).
1968	WHO research project for international drug monitoring on a 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 Centre established in India.

2004-2005	India launched National Pharmacovigilance Program.
2005	The accomplishment of structured clinical trials in India.
2009-2010	Pharmacovigilance Program (PvPI) started .

❖ Pharmacovigilance and safety monitoring

Pharmacovigilance may be a process of continuous monitoring and evaluation of all adverse events during drug development process. Majority of safety information considered before market authorization springs from controlled clinical test. The clinical test process is regulated by the precise regulatory guidelines (e.g. ICH GCP, USFDA guidelines etc). Pharmacovigilance includes detection of adverse effects during the clinical trial and post marketed phases, monitoring and updating the risk-benefit ratio based on relevant findings, prevention or minimization of adverse effects and most important is harmonized communication of these results to the authorised global regulatory authorities for health management in a timely manner ^[4].

❖ The aims of pharmacovigilance are as follows:^[2]



❖ Clinical Research

Clinical research involves combined efforts of many scientists and is characterized by a high level of specificity and complexity. The process usually starts with the research and development phase, during which the new idea is tested in laboratory conditions (in cell cultures or animals) or through computer modelling. Following successful trials, a set of goals, inclusion and exclusion criteria, and an appropriate design of the experiment are determined. In addition, clinical research obligatorily involves ethical issues, namely informed consent, which means that the participants have a clear understanding of all the details of the study and voluntarily agree to participate in it. These factors, together with others, constitute the basics of clinical research performed to gain experience with new treatment approaches and contribute to the improvement of health care services.^[5]

❖ PHARMACOVIGILANCE IN CLINICAL TRIALS

The most important rationale for pharmacovigilance is simple: the safety and well-being of the trial participant is priority for pharmacovigilance. Participants in clinical research may be exposed to medicines for which the safety profiles are not yet fully established. Therefore, pharmacovigilance enables the researcher to identify and assess possible risks, side effects and adverse drug reaction before they become larger problems.^[18] Pharmacovigilance contributes to the quality of clinical-trial data. When appropriately recorded, evaluated, and followed up, safety information contributes to an understanding of the benefit-risk profile of an investigational medicinal product; thus, its inadequate assessment may lead to an inappropriate estimation of risks and benefits of treatment during clinical trials.^[13,18] Moreover, detection of safety signals and elimination of severe drug reactions. The appearance of treatment-emerging adverse events with increased frequency or special interest may indicate new safety issues. Identification and appropriate handling of such events during development can facilitate the sponsor's decision-making on discontinuation or modification of the clinical trial.^[18] Pharmacovigilance is not restricted to the later stages of drug development. Measures to assess and manage safety begin during drug development and continue throughout the clinical trial programme and, later, during the time the medicine is on the market. Early identification of safety problems can help to protect trial participants and may also prevent unnecessary continuation of an unsafe or ineffective development programme.^[11,4]

❖ Adverse Event

According to the ICH E6 guidelines, an **adverse event (AE)** is referred to any unwanted medical occurrence in a patient who has been given a pharmaceutical product, regardless of whether it is directly related to the treatment.

In simpler terms, an AE is any unfavourable or unintended sign, symptom, or disease that appears during the use of an investigational drug. This can include abnormal laboratory findings, unexpected medical conditions, or reactions that happen at the same time as the treatment, even if they are not caused by it.^[4]

❖ Adverse Drug Reaction

The World Health Organization (WHO) defines an ADR as a response to a drug that is noxious, unintended, and occurs at doses normally used for prophylaxis, diagnosis, or treatment. The aetiology of ADRs is complex and multifactorial, arising from pharmacological mechanisms inherent to the drug, patient-related biological variables polymorphisms, (age, comorbidity, sex, genetic concurrent medications), and healthcare system factors (prescribing practices, monitoring quality).^[6] Underreporting of adverse drug reactions remains an important challenge. Some events may not be reported because of lack of awareness, time limitations, uncertainty about causality, or difficulties with reporting systems. Incomplete reporting can reduce the ability of pharmacovigilance systems to identify and evaluate safety signals.^[21]

ADR = adverse drug reaction; SJS = Stevens–Johnson syndrome; PM = poor metaboliser; HPA = hypothalamic-pituitary-adrenal.

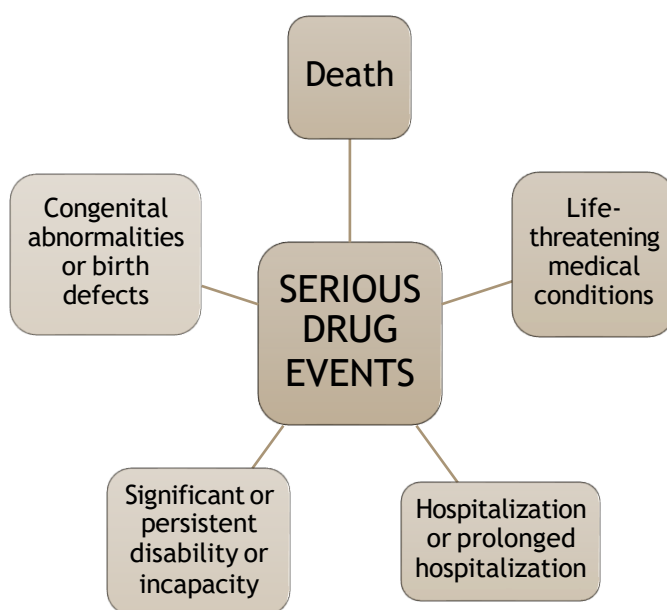
Table 2: Types of Adverse Drug Reaction.

Type	Nomenclature And Characteristics	Example of condition
Type-A	Augmented (dose dependent) Predictable; pharmacological; dose related; most common (~80%)	Morphine — constipation; ACE inhibitor — dry cough; insulin — hypoglycaemia
Type-B	Bizarre (idiosyncratic) Unpredictable; immune mediated or genetic; not dose-related	Penicillin — anaphylaxis; sulfonamide — Stevens–Johnson syndrome

Type-C	Chronic (continuous use) Cumulative dose dependent; may be irreversible	Corticosteroids — osteoporosis; antipsychotics — tardive dyskinesia
Type-D	Delayed onset Latency of months to years; carcinogenic or teratogenic	Thalidomide — phocomelia; Chemotherapy — secondary malignancy
Type-E	End-of-use (withdrawal) On abrupt discontinuation of chronically used drugs	Opioid withdrawal; benzodiazepine seizures; adrenal insufficiency
Type-F	Failure of therapy Therapeutic ineffectiveness; dose- or interaction-related	Oral contraceptive failure with rifampicin; clopidogrel in CYP2C19 PM

❖ Serious Adverse Events

Serious adverse events need to be assessed and reported appropriately since such events might represent an important safety issue.



The quality and accuracy of information for serious cases are mandatory^[22, 27]. The key difference between an adverse drug event (ADE) and an adverse drug reaction (ADR) is that an ADE may not have a proven causal link to the drug, whereas an ADR does.^[26]

❖ Clinical trials phases

Clinical research is all about turning scientific ideas into real improvements in patient care. People who join trials are given clear information about the study's purpose, risks, and benefits so they can make informed choices. Every trial must first be approved by ethics committees and regulators to ensure safety and fairness. Trials move step by step in four phases:

Phase I: First in Human & Safety Profiling.

Target Population: Typically, 20 to 100 healthy volunteers (or specific group of patients such as oncology patients).^[35]

Primary objective: Determine safety, tolerability, pharmacokinetics and pharmacodynamics.^[35]

Clinical Focus: Phase I studies aim to establish the Maximum Tolerated Dose (MTD) and evaluate Single or Multiple Ascending Doses (SAD/MAD).^[35]

Pharmacovigilance Focus: Because people are being exposed to the treatment for the first time, it's vital to watch safety in real time. Safety review committees analyse Dose-Limiting Toxicities (DLTs) before increasing the dose for the next patient group. Rapid identification and Submission of Suspected Unexpected Serious Adverse Reactions (SUSARs) are essential.^[39]

Phase II: Proof of Concept & Efficacy Evaluation

Target Population: 100 to 300 participants living with the target disease or condition.^[35]

Primary Objective: Evaluate short-term therapeutic efficacy and assess common side effects.^[35]

Clinical Focus: Phase II studies explore optimal dosing schedules, therapeutic regimens, and preliminary efficacy (proof-of-concept) while continuously building the safety database.^[35]

Pharmacovigilance Focus: Establishing dose-response curves for adverse events. PV teams assess whether specific side effects correlate with higher doses and monitor preliminary target-organ safety.^[39,40]

Phase III: Confirmatory Pivotal Studies

Target Population: 1,000 to 3,000+ participants across randomized, double-blind, multi-center, and international sites.^[35]

Primary Objective: Confirm clinical efficacy, monitor adverse reactions in broader populations, and establish a long-term safety profile.^[35]

Clinical Focus: Phase III trials compare the investigational drug against the current standard of care or a placebo to prove statistical efficacy and acceptable safety for marketing approval.^[35,37]

Pharmacovigilance Focus: Detection of less frequent adverse reactions, identification of drug-drug interactions, and evaluation of potential safety issues across diverse demographics (e.g., age, sex, ethnicity, comorbidities).^[37,40] Data Monitoring Committees (DMCs) regularly review unblinded safety reports.^[34]

Phase IV: Post-Marketing Safety Surveillance

Target Population: Thousands of patients in real-world clinical practice settings.^[35]

Primary Objective: Monitor long-term safety, rare adverse reactions (e.g., incidence of <1 in 10,000), and efficacy in heterogeneous patient populations over extended periods.^[35,38]

Clinical Focus: Conducted after marketing authorization is granted by regulatory bodies (e.g., FDA, EMA, CDSCO). These studies may be required as Post-Marketing Requirements (PMRs) or Post-Marketing Commitments (PMCs).^[33,36]

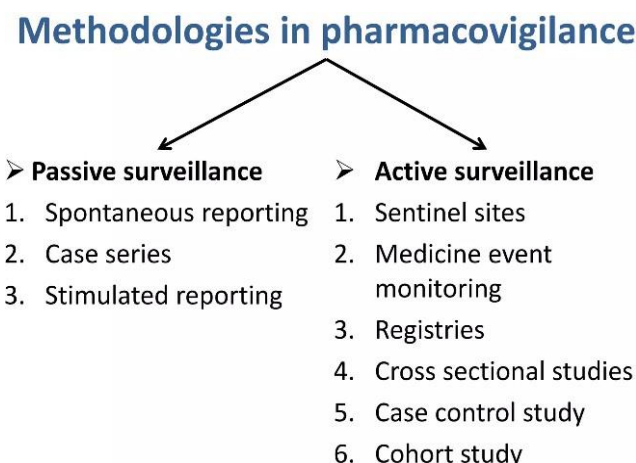
Pharmacovigilance Focus: Spontaneous adverse reaction reporting, signal detection in post-approval databases (such as FAERS), execution of Risk Management Plans (RMP), and Periodic Safety Update Reports (PSURs) / Periodic Benefit-Risk Evaluation Reports (PBRERs).^[38,42]

There is also phase 0 which exists which involves micro dosing study on 10-15 healthy participants in very small groups take a very small dose. This phase is previously conducted on animals but for now it is conducted on human to understand tolerance of dose for phase 1 in human.^[7, 24]

From preclinical phase to phase 3 is known as Research & Development phase mean while phase 4 (post approval) and spontaneous reporting is called as Marketing Authorization.^[8]

❖ Methods Used in Pharmacovigilance

There is a variety of ways in which pharmacovigilance can be used to identify and assess safety problems. Passive surveillance mainly relies on people doctors, patients, or others voluntarily reporting side effects. Spontaneous reporting is one example. It helps to find early safety problems, but the reports can be sometimes unfair or miss many of the cases for trials.^[14,20]



Active surveillance involves more systematic follow-up or monitoring of patients or of defined populations, including reviews of medical records, active follow-up of cohorts of patients, selected populations, registries, and other approaches.^[14]

Among others, there are also cohort, case-control, registry, and database studies that can also prove useful in investigating uncommon, delayed, or long-term outcomes or events.^[14,20] Many researchers developed different methods for assessment of ADR like screening for non-drug related causes, confirmation by in vivo and in vitro test and many more are methods are developed for methodology of pharmacovigilance.^[12]

❖ Artificial Intelligence and Machine Learning

Artificial intelligence and machine learning can analyze large amounts of data and identify patterns that may be difficult to recognize through manual review.

These technologies may support:

- Adverse-event detection
- Signal identification
- Risk prediction
- Data classification
- Automated analysis

However, AI-based systems also face challenges involving data quality, algorithmic bias, explainability, privacy, and regulatory acceptance. Human expertise and appropriate validation remain important.^[21,25,28]

❖ Pharmacovigilance in India

India has developed a formal framework for safety monitoring in clinical research, but the literature also points to areas where further harmonization and clarity are important. The Indian GCP guidelines introduced definitions of adverse events and adverse drug reactions which described the safety-reporting responsibilities of investigators and developer.

The amended Schedule Y in 2005 again study about the legal basis for safety reporting and introduced more specific requirements for reportable serious adverse events, as well as those requiring revising reporting. In addition, the India-specific review identified key challenges associated with inconsistencies in terminology, the need for expedited reporting, reporting during pregnancy, and the need to develop more comprehensive guidelines consistent with international pharmacovigilance practices.^[17]

❖ US Food and Drug Administration (US FDA)

Under the Code of Federal Regulations (CFR), the US FDA enforces strict rules for safety monitoring under Investigational New Drug (IND) applications:



21 CFR 312.32 (IND Safety Reports): Requires sponsors to notify the FDA and all participating investigators of any unexpected serious adverse risk via an IND Safety Report within 15 calendar days. Fatal or life-threatening unexpected risks require reporting within 7 calendar days.^[33]

21 CFR 312.56 (Sponsor Responsibilities): Mandates continuous review of investigational drug safety, protocol compliance, and immediate notification to FDA and Institutional Review Boards (IRBs) if an unreasonable risk to subjects is identified.^[33]

❖ European Medicines Agency (EMA)

The European Union enforces clinical trial safety through unified regulations and centralized reporting tools:



Clinical Trials Regulation (EU) No 536/2014:

Standardizes the submission, assessment, and safety reporting process across all EU/EEA member states using the Clinical Trials Information System (CTIS).^[36]

EudraVigilance Clinical Trial Module (EVCTM): The centralized European database where sponsors must electronically report all SUSARs originating from clinical trials conducted within or outside the European Economic Area.^[38]

Guidance on Investigational Medicinal Products Safety: Requires investigators to report all SAEs immediately to the sponsor and mandates annual reporting via DSURs evaluated by the Pharmacovigilance Risk Assessment Committee (PRAC) when post-marketing safety signals intersect with clinical development.^[36,38]

❖ Central Drugs Standard Control Organisation (CDSCO - India)

India operates under a specialized regulatory structure focused on participant safety, ethics committee oversight, and non-waivable compensation:

New Drugs and Clinical Trials (NDCT) Rules, 2019 (Amended 2023): Governs clinical trial approvals, ethics committee registrations, and safety reporting timelines in India.^[31]

Rule 39 (Reporting of Adverse Events): Mandates that an investigator must report any Serious Adverse Event (SAE) occurring during a clinical trial to CDSCO, the Institutional Ethics Committee (IEC), and The Sponsor within 24 hours of occurrence.^[31,32]



Expedited Causality & Compensation Framework: Sponsors must submit an expedited causality assessment report within 14 days of an SAE [1]. If a trial-related injury or death occurs, the sponsor is legally obligated to pay formula-based financial compensation determined by CDSCO's expert committee, accounting for factors such as age, baseline health, and degree of disability.^[31,41]

Audio-Visual (AV) Consent & SUGAM Portal: Mandates AV recording of informed consent for vulnerable populations and requires submission of trial protocols and safety updates through the CDSCO SUGAM portal.^[31,41]

The textbook included in your references also describes pharmacovigilance as a structured data-processing cycle involving collection, coding, causality and expectedness assessment, quality control, reporting, and data storage.^[16]

❖ Role of Good Clinical Practice (GCP) in Pharmacovigilance

Good Clinical Practice (GCP) provides an ethical and scientific framework for the conduct of clinical trials.

The principles of GCP are important because they aim to ensure that:

- Participants' rights are protected
- Participant safety is maintained
- Confidentiality is respected
- Trial data are reliable
- Research is conducted ethically
- Study procedures are scientifically appropriate

Pharmacovigilance and GCP are closely connected. Effective safety monitoring requires accurate documentation, proper reporting, trained personnel, ethical conduct, and protection of participant information. Therefore, adherence to GCP supports both patient or participate protection and safety also, the reliability of pharmacovigilance data ^[25, 29, 30].

❖ CONCLUSION

The concept of pharmacovigilance was created to collect the necessary amount of information about the safety and effectiveness of drugs. This field of science allows researchers to detect and reduce the risks and side effects of a new drug, as well as carry out all clinical trials in compliance with the principles of ethics and validity. By incorporating the principles of Good Clinical Practice, the practice of pharmacovigilance also entails the application of novel approaches, amongst which is the use of artificial intelligence, as well as compliance with regulatory requirements. Thus, pharmacovigilance contributes to the trust and efficiency of clinical studies conducted globally, as well as the safety and quality of the new drugs being developed. Pharmacovigilance, therefore, appears to be a responsible and necessary undertaking to protect the health and lives of the public.

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