IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A Review On Pharmacovigilance In Clinical Trials Ensuring Participants Safety

Gaurav S. Tangade[1], Akash R. Tangde[2], Sanket S. Khedekar[3], Ram S. Gawande[4], Pratiksha A. Dhokane[5]

1,2,3,4,5-Student of Shri Sant Gajanan Maharaj College of Pharmacy, Buldhana 443001MS India

Abstract

The science and practices surrounding the collection, identification, and evaluation of adverse event data are known as pharmacovigilance. Pharmacovigilance's primary goal is to assess a drug's benefit-risk profile in order to improve its efficacy and safety for patient usage. Pharmacovigilance, which gives information regarding adverse drug reactions observed in patients, is crucial to the judicious use of drugs. The Indian pharmaceutical sector ranks third globally in terms of volume and thirteenth globally in terms of value.

Local regulators do not yet require a real-time updating of a drug's cumulative safety profile, despite the global focus on the Development Safety updating Report. Attention must be paid to issues including the need for disclosing general trial results, pregnancy disclosure, and the lax deadline for incidents that result in death or serious injury. Lastly, it is imperative that comprehensive local pharmacovigilance guidelines be developed in accordance with international standards.

Keywords:

Clinical trials, Pharmacovigilance, Eudravigilance, challenches, Future Directions, good Pharmacovigilance Practices, Cohort study,

INTRODUCTION:

Pharmacovigilance may involve ongoing risk and benefit assessments as well as continuous monitoring and assessment of any adverse events that occur during the medication development process in order to ensure the safety of the subjects. (1-2) The particular regulatory guidelines (ICH GCP, USFDA guidelines, etc.) govern the clinical trial process. The evidence base for safe and effective medication approvals by regulatory bodies is provided by clinical studies. The pharmaceutical industry and authorities are attempting to be more engaged in safety reviews due to lengthy development cycles and rising clinical trial expenses. Early safety identification can save a significant amount of development costs in addition to improving patient protection.

Clinical trials must adhere to established guidelines since they include human subjects and must protect the participants' safety, rights, and welfare. These regulations include the International Ethical Guidelines for Biomedical Research Involving Human Subjects published by the Council for International Organizations of Medical Sciences (CIOMS), the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines (3), and consequently the ethical precepts outlined in the Declaration of Helsinki. The Good Clinical Practice (GCP) standard ensures that the rights, integrity, and confidentiality of trial subjects are

protected throughout the conduct, performance, planning, monitoring, recording, auditing, analyses, and reporting of clinical trials. [5]

Sponsors now face more difficulties as a result of the internationalization of clinical studies. Whenever clinical trials are conducted, sponsors are responsible for adhering to local legal and regulatory regulations. For instance, the Clinical studies Directive must be followed when conducting clinical studies inside the European Union [6]. Safety assessment could play a major role in every phase of the drug development life cycle. Thorough safety monitoring and evaluations from pre-clinical to all or any phases of clinical studies are necessary before a medicine is authorized for sale. Pharmaceutical sponsors must sufficiently describe the product's security profile in order to receive regulatory approval and authorization for commercialization. All relevant information regarding the advantages and disadvantages of the product is included on the approved product label. Once the product is on the market, additional information and statistics are obtained from a larger patient population, hence it is imperative that safety awareness be maintained.

There exist scenarios in which the preliminary benefit-risk calculations may become ambiguous due to newly developed safety profiles. Evidence of these can be seen in the significant market withdrawals of Rofecoxib (Vioxx), Rosiglitazone (Avandia), and Troglitazone (Rezulin). In 2005, the US Food and Drug Administration (FDA) published recommendations pertaining to risk management operations, including pre-market risk assessment, post-marketing pharmacovigilance, and pharmacoepidemiologic evaluations. Because of international regulatory agencies, the pharmaceutical industry is using a more comprehensive and integrated approach to safety evaluation in drug development.

What is Pharmacovigilance?

According to the World Health Organization, pharmacovigilance (PV) is a pharmaceutical science that addresses medication safety and involves assessing, detecting, understanding, and preventing adverse effects or drug-related problems. Through the provision of a mechanism for gathering, assessing, and disseminating information on drug safety, PV seeks to strengthen patient safety with regard to medication use. PV activities include tracking authorized medications and investigational pharmaceuticals (IMPs) in order to: Determine any unidentified negative consequences. Recognize variations in the known negative consequences' severity. Evaluate the risk/benefit of a medicine to determine whether action is necessary to improve safety. Ensure that information conveyed to patients and healthcare providers is accurate, and that patient information leaflets (PILs) contain current information [7].

History of Pharmacovigilance:

Approximately 170 years ago, pharmacovigilance began, though it was not yet known by that name. It is a well-organized, socially and commercially significant activity within the professional health system that aims to improve patient safety and quality of life by identifying and tracking the risk to benefit ratio of medications. In order to recall all the steps that have characterized historical evolution, from the initial reports—which are essentially letters or warnings sent by health care professionals to publishers of renowned scientific journals—up to today's ultra-unique structured electronic registries, we report the milestone of pharmacovigilance up to the current scenario in this commentary. Pharmacovigilance aids in the achievement of significant advances in both pharmacology and human health, and the historical phase provides a clear picture of the difficulties that pharmacovigilance will face in the years to come. Hannah Greener, a small child from North England, passed away on January 29, 1848, following the administration of a chloroform anesthetic before to the removal of an infected toenail. Chloroform is a stronger and safer anesthetic that Sir James Simpson discovered and brought into therapeutic practice. Although the reasons behind Hannah's death were looked into in an effort to comprehend what had happened to her, the cause of her death could not be determined. She most likely aspirated her respiratory organs or died from a fatal cardiopathy. The Lancet Journal formed a commission to address this issue after other deaths raised concerns about the safety

of anesthesia among medical professionals and the general public. The panel encouraged medical professionals in England, especially those working in colonies, to report anesthesia-related deaths.

On June 30, 1906, the US Federal Food and Drug Act was created to mandate that medications be pure and devoid of impurities. Furthermore, this body outlawed the use of fraudulent therapeutic indications for medications in 1911. 107 deaths were linked to the usage of sulfanilamide elixir in the USA in 1937; diethyl glycol was used as a solvent in this medication. The manufacturing businesses were unaware of the solvent's toxicity at the time, even though it was thought to be the cause of deaths. The Federal Food, Drug, and Cosmetic Act was created in 1938 as a result, with the intention of improving the public health system. In reality, the new system had the option to perform factory inspections and anticipated that pharmaceuticals should be safe before being approved for sale. Acetylsalicylic acid (ASA) was proposed by Douthwaite as a possible cause of Melena in 1938. Since ASA began to induce GI disorders in 1955, persons who have gastrointestinal ulcers should not take it.

Following the Thalidomide disaster, European Pharmacovigilance underwent a significant shift in 1961. A 1973 retrospective investigation found a link between the use of thalidomide during pregnancy and congenital abnormalities in infants. This tragedy changed the pharmacovigilance system by making the unplanned reporting of adverse drug reactions (ADRs) formal, structured, and regulated. The "yellow card" (YC), a special form designed to systematize unplanned reports of medication toxicity, was established in the UK in 1964. The thalidomide tragedy in Europe prompted the creation of European legislation, culminating in the 1965 EC Directive 65/65.

Following the Thalidomide disaster, European Pharmacovigilance underwent a significant shift in 1961. A 1973 retrospective investigation found a link between the use of thalidomide during pregnancy and congenital abnormalities in infants. This tragedy changed the pharmacovigilance system by making the unplanned reporting of adverse drug reactions (ADRs) formal, structured, and regulated. The "yellow card" (YC), a special form designed to systematize unplanned reports of medication toxicity, was established in the UK in 1964. The thalidomide tragedy in Europe prompted the creation of European legislation, culminating in the 1965 EC Directive 65/65. It is the official European database for tracking and evaluating reports of possible side effects to medications that are being investigated in European clinical trials or that have been approved for sale. A significant shift in European Pharmacovigilance was observed in 2012 with the introduction of new regulations, known as Directive 2010/84/EU.

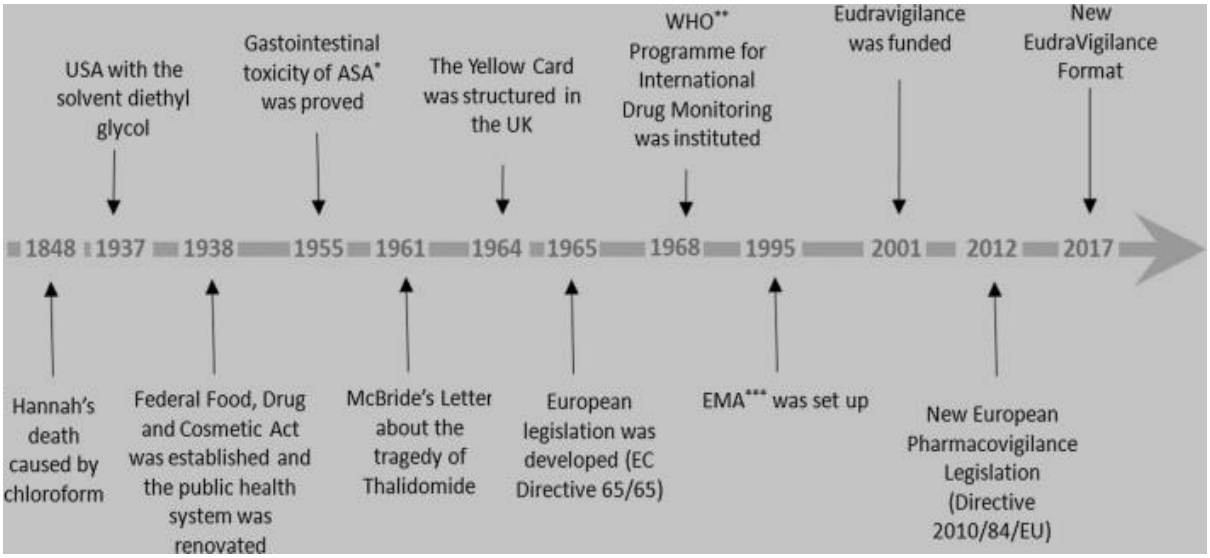

Fig. No. 1: Timeline of the historical evolution of Pharmacovigilance. ASA: acetylsalicylic acid; WHO: World Health Organisation; EMA: European Medicines Agency

Furthermore, the recently established law known as the Good Pharmacovigilance Practices (GVP) takes into account facilitating PV performance. The GVP guideline is separated into two classes: modules that address important aspects of pharmacovigilance and those that are unique to a particular product or group. Biological medicines and vaccines fall under this last category. Additionally, this guideline includes particular chapters devoted to two distinct areas: the geriatric population (P V) and pregnancy and breast-feeding (P III).

The new EudraVigilance format was introduced in November 2017. To help marketing authorizations fulfill their Pharmacovigilance requirements, they will have more access to the EudraVigilance database. Biological medicinal products and vaccines fall into this last category. There are special chapters in this guideline devoted to particular topics, such as geriatric population (P V) and maternity and breast feeding (P III) [8].

Under the guidance of the Indian drug controller, pharmacovigilance was first implemented in India in 1986 with the establishment of an official adverse drug reaction (ADR) monitoring system. India became a member of the Uppsala, Sweden-based World Health Organization (WHO) program. After this failed attempt, the World Bank-funded National Pharmacovigilance Program for India, sponsored by WHO, was put into operation on January 1, 2005. The National Pharmacovigilance Advisory Committee, situated at the Central Drugs Standard Control Organization (CDSCO), New Delhi, was tasked with overseeing it. There are two zonal canters: the North-East centre, which is located in the Aim of pharmacology, and the South-West centre, which is located in the Department of Clinical Pharmacology at Seth GS Medical College and KEM Hospital, Mumbai [9].

The aims of pharmacovigilance are as follows:

The aims of pharmacovigilance are:

• The detection and measurement of adverse drug reactions (ADRs) that were previously unrecognized.

• the determination of patient subgroups that are specifically at risk for adverse drug reactions (ADRs) (the risk relation to dose, age, gender and underlying condition).

• the ongoing assessment of a product's safety during its use to make sure that its advantages and disadvantages continue to be reasonable. This covers safety observation in the wake of noteworthy recently authorized symptoms.

• the relative adverse medication reaction profiles of similar therapeutic class medicines.

• the discovery of improper prescription drug administration.

• the additional clarification of a product's toxicological and pharmacological characteristics as well as the process by which it causes unfavourable medication reactions.

• the identification of noteworthy drug-drug interactions between novel products and co-therapy with commercially available treatments, which might only be discovered after extensive use [10].

To put it briefly, pharmacovigilance seeks to advance knowledge, instruction, and clinical training while also enhancing patient care and safety, public health, and the evaluation of the benefit, harm, effectiveness, and risk of pharmaceuticals.

Objective of Pharmacovigilance:

When a medication is granted a marketing license, not all of its details are available. A new drug's qualities, weighing its advantages and disadvantages, are only determined once enough real-world experience with it has been accumulated.

The reasons for the necessity of Pharmacovigilance are:

• Since preclinical drug development procedures evaluate the safety and efficacy of drugs in animal tests and frequently do not allow the results of animal research to be extrapolated to humans, the information on medication safety gathered during drug development is insufficient.

• It is very challenging to adequately identify actual efficacy, adverse effects, and the whole risk-benefit ratio under actual clinical conditions because clinical trials are evaluated for a limited amount of time and a restricted number of carefully selected patients in carefully selected settings.

• Information is often incomplete or not available on

a) uncommon yet significant responses.

b) Drug use in vulnerable populations (elderly, children, and pregnant women).

c) dangers associated with long-term, frequent usage as well as interactions between drugs and food, drugs and other drugs, and nutritional supplements.

• Less than 5,000 human subjects are exposed to the medicine at the time of licensure. This makes it possible to identify only the most prevalent adverse medication reactions.

• A medication must be administered to a minimum of 30,000 individuals in order to ensure that no patient is overlooked who may experience an adverse drug reaction, which occurs in 1 in 10,000 exposed individuals [11,12].

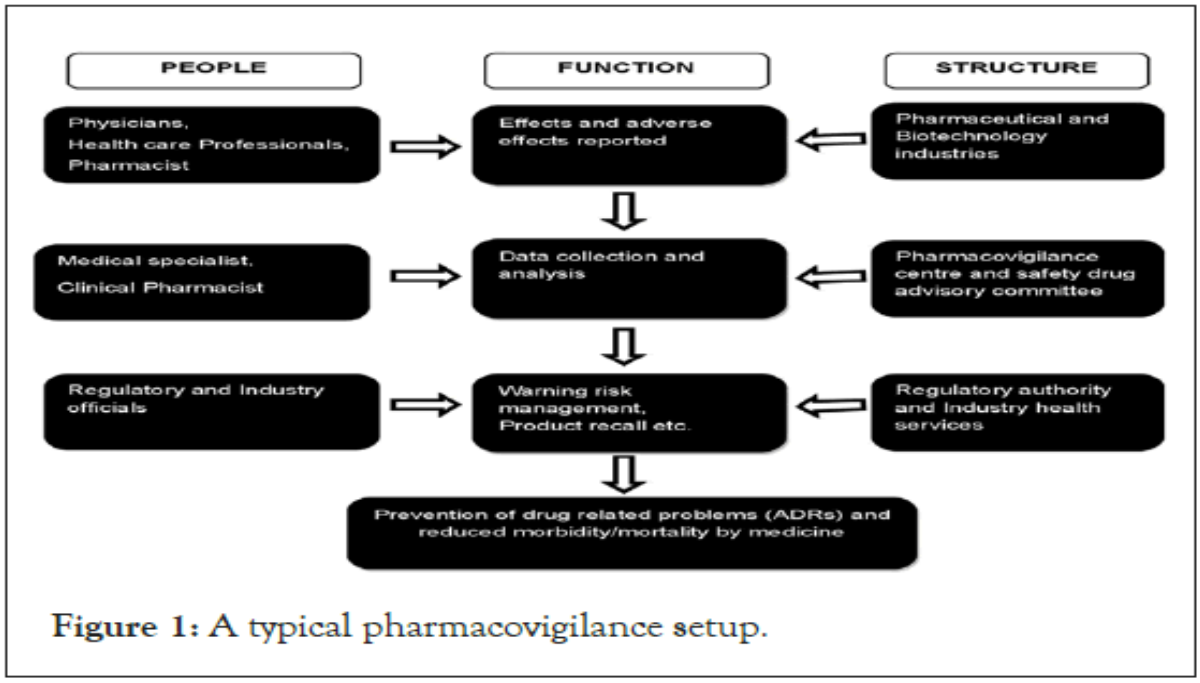

Figure 1: A typical pharmacovigilance setup.

Scope of pharmacovigilance:

The field of pharmacovigilance, which covers chemical, botanical, and biological medications as well as medical devices, is expanding [13,14]. In order to identify and stop any irregularities connected to the suspect product, information about it is gathered from patients and healthcare professionals [15]. As a result, pharmacovigilance addresses serious adverse events, polypharmacy, paradoxical reactions, and pharmacological side effects. It also addresses drug interactions, overdose, poisoning, pharmaceutical errors, failure to vaccinate, irrational use, and lack of efficacy. Pharmacovigilance was first taken into consideration with early WHO technical support in 1972 and continues to be an active, clinical, and experimental principle. Meeting the effects of a greater variety and strength of biological and pharmaceutical therapies, including vaccinations, has been deemed crucial. It's critical that toxic effects and side effects are appropriately communicated to the public, who can observe and evaluate the data in order to fulfill the requirements of the pharmacovigilance contract for its marketed medications.

Fig. No. 2: A typical pharmacovigilance setup.

Data meaning of pharmacovigilance

The science of improving patient care and safety when using medications is called pharmacovigilance, sometimes referred to as drug safety surveillance. It involves gathering, observing, analyzing, and interpreting data from patients and healthcare professionals. According to that perspective, pharmacovigilance can be separated into two phases: premarketing surveillance, which gathers data on adverse drug reactions from preclinical screening and phases I through III clinical trials, and post-marketing surveillance, which gathers data during a drug's post-approval period and entire market life [(16)].

Historically, PV has depended on biological tests or manual case report reviews; however, because of the large volumes and complexity of data that need to be examined, computational techniques that can quickly and reliably identify ADRs have become essential to pharmacovigilance. Computerized adverse drug response detection approaches now rely on large-scale compound databases that hold information on structure, bioassay, and genomics, in addition to extensive clinical data sets like Electronic Medical Record (EMR) databases [(17)].

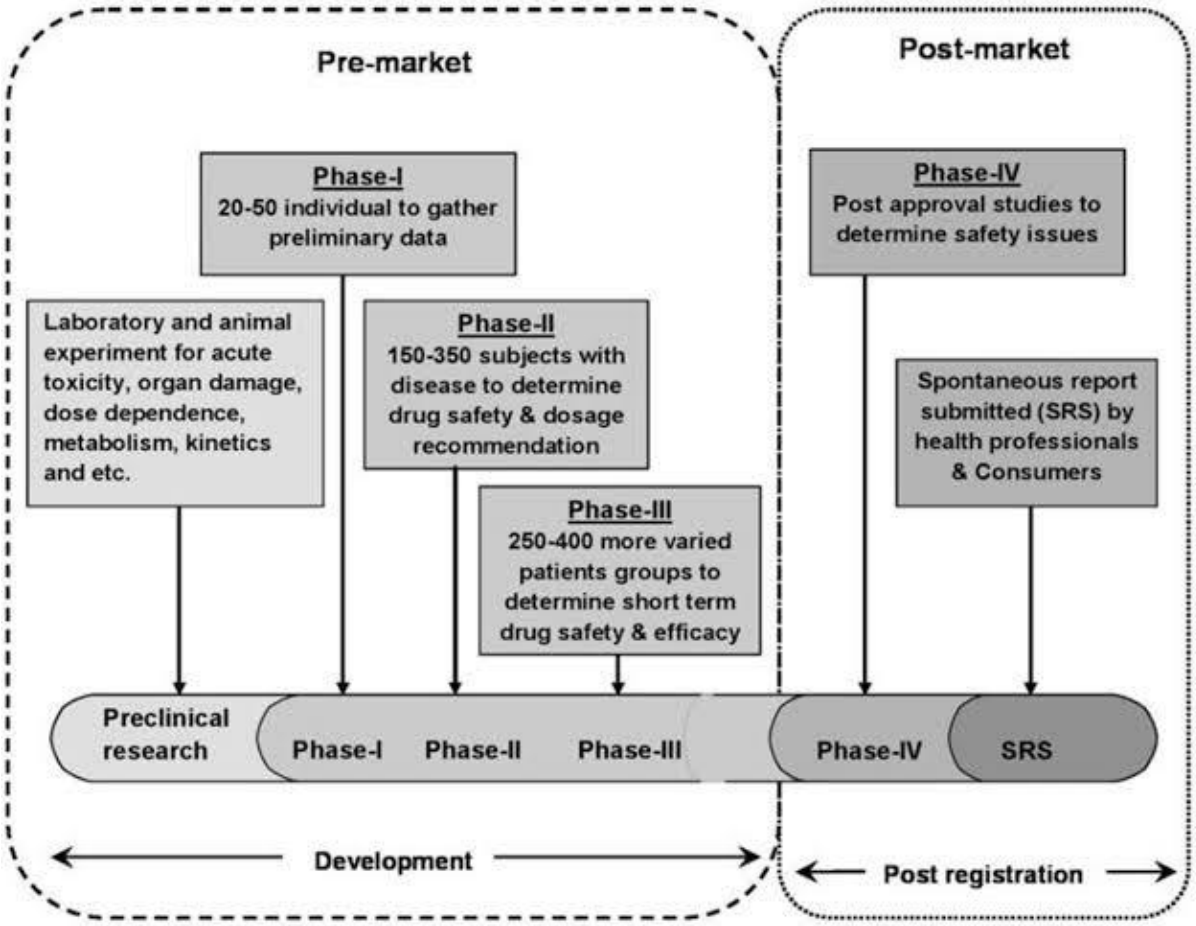

Fig. No. 3: Pharmacovigilance at different stages of drug development

Pharmacoepidemiologic study [18]

The definition of pharmacoepidemiology is "the study of drug use and effects in large populations." It involves using epidemiological techniques to clinical pharmacology problems, typically pertaining to how best to balance a drug's favourable and harmful effects. It also considers other aspects relevant to the real-world use of drugs, such as patient compliance. They are observational in nature rather than experimental. Numerous designs, including as case-control, nested case-control, cohort (prospective or retrospective), case-cross-over, and other models, can be used in pharmacoepidemiologic investigations.

Cohort study:

A cohort study assesses variations in patient outcomes over time by comparing exposed to unexposed patients. A cohort study monitors a group at risk of an event or disease across time to look for signs of the event or disease. Every patient's exposure status is known for the duration of the follow-up period. During follow-up, a patient may be exposed to a medication once and not at another time. Since incidence rates can be computed, the population exposure during follow-up is known. A common practice in exposure cohort studies is to select and track comparative cohorts of interest based on drug use over time. When it's necessary to understand not only the relative risks of adverse events but also their incidence rates, cohort studies come in handy. In a cohort study, several adverse events can potentially be examined with the same data source. But finding enough patients exposed to a medicine of interest (such an orphan medication) or studying extremely uncommon outcomes can be challenging. Similar to case-control studies, cohort studies can use data that was expressly gathered for the study at hand or vast automated databases to identify its patients. Cohort studies can also be used to investigate safety concerns in specific populations (older adults, kids, patients with co-morbid diseases, pregnant women), either by stratifying the cohort if there are enough patients in it or by oversampling these patients.

Case control study:

Individuals with and without diseases are compared in this way. A case-control research identifies cases of a disease (or occurrences). Next, from the source population that gave rise to the cases, controls—that is, patients without the disease or event of interest—are chosen. The controls ought to be chosen so that the exposure prevalence within the control group corresponds to the exposure prevalence within the source population. Next, the exposure status of both groups is compared using the odds ratio, which provides an assessment of the two groups' respective relative risk of disease. Either an existing database or data gathered especially for the relevant study can be used to identify patients. In order to obtain safety information for specific groups, it is possible to categorize cases and controls based on the population of interest, which may include pregnant women, elderly people, or children. Large population-based databases now in existence are a helpful and effective way to quickly provide the necessary drug exposure and medical outcome data for uncommon adverse occurrences. When determining risk factors for adverse events and determining whether there is a correlation between a medicine (or drugs) and a particular rare adverse event, case-control studies are especially helpful. Renal and hepatic dysfunction are examples of risk variables that may alter the connection between drug exposure and adverse event. A case-control study can yield the event's absolute incidence rate under particular circumstances. An incidence rate can be computed if all cases of interest (or a precisely defined fraction of cases) in the attachment area are recorded and the percentage of controls from the source population is known.

Case Report:

A case report in medicine is an in-depth account of a patient's symptoms, signs, diagnosis, course of therapy, and follow-up. Case reports typically describe an uncommon or novel occurrence, though they may also include the patient's demographic description. A review of previous cases that have been reported has been included in some case reports. FDA urges sponsors to engage qualified healthcare professionals to question reports and advises sponsors to make a reasonable effort to gather all information needed for case assessment during initial contacts and any follow-up. This recommendation is particularly strong for serious incidents.

Good case reports include the following elements:

· Description of the adverse event

· Suspected and concomitant product therapy details

· Patient characteristics

· Documentation of the diagnosis of the events

· Clinical course of the event and patient outcomes

Challenges and Future Directions in Pharmacovigilance in Clinical Trials:

Even with improvements in pharmacovigilance procedures, a number of issues still need to be resolved. Furthermore, there are a number of possible avenues for future research that could improve pharmacovigilance in clinical trials even more. The following are some of the main issues and potential paths forward:

Challenges:

International harmonization and standardization: There is still work to be done in order to bring pharmacovigilance methods up to par globally. Inconsistencies can be caused and effective data exchange and analysis can be hampered by differences in laws, reporting standards, and data collection techniques between nations.

Participant rights and ethical considerations: Upholding moral behaviour and defending these rights are constant struggles. Ensuring participant confidentiality, informed permission, and privacy are crucial aspects of gathering, evaluating, and disseminating safety data. It can be difficult to strike a balance between participant anonymity and the demand for data disclosure.

Effective communication and transparency amongst stakeholders, such as researchers, sponsors, participants, and regulatory bodies, are essential. Sustaining trust and confidence in the clinical trial process requires fast and accurate communication of safety information, adverse event reporting, and risk management choices.

Data management and digital innovations: Data management, data privacy, and interoperability are among the issues that arise when digital innovations like wearable technology, mobile health applications, and electronic health records are integrated. It is essential to create reliable systems that can manage and evaluate massive amounts of heterogeneous data while preserving data integrity and privacy.

Data management and digital innovations: When digital innovations like wearable technology, mobile health applications, and electronic health records are incorporated, problems like data management, data privacy, and interoperability come up. Building dependable systems that can handle and assess enormous volumes of diverse data while protecting privacy and data integrity is crucial.

Future Directions:

Proactive identification and control of safety signals by real-time monitoring of safety data made possible by technological advancements in pharmacovigilance. Safety surveillance during clinical trials can be improved by employing real-world evidence, incorporating wearable technology, and continuously monitoring patient data.

Artificial intelligence and machine learning techniques: Automated adverse event detection, signal identification, and risk prediction can be supported by further integrating AI and ML techniques. Large datasets may be analyzed by AI algorithms, which can also spot trends and provide real-time safety alerts. These capabilities enhance the precision and efficiency of pharmacovigilance procedures. Active participation in pharmacovigilance and patient engagement: Active patient participation in pharmacovigilance can improve adverse event reporting and safety reporting. Enhancing data collecting and advancing a more thorough knowledge of medication safety can be accomplished by empowering patients to directly report adverse events, offering patient education and support, and utilizing patient-centered platforms.

Utilization of real-world data and evidence: Combining real-world data (RWD) with real-world evidence (RWE) can offer a more comprehensive understanding of the efficacy and safety of drugs. Utilizing RWD from patient registries, claims databases, and electronic health records can enhance clinical trial data and offer insightful information about the long-term safety profile of investigational medications.

Cooperation and data sharing: The efficacy and efficiency of pharmacovigilance can be increased by fostering greater cooperation and data sharing amongst stakeholders, including as researchers, regulatory bodies, and corporate sponsors. A more thorough understanding of medication safety and the ability to identify possible risks early on can be achieved through the sharing of safety data, adverse event reports, and safety analysis findings.

Informed risk management choices during clinical trials, increased participant safety, and more effective safety signal detection can result from addressing these issues and adopting new directions in pharmacovigilance. through putting participant-centered approaches to pharmacovigilance first, fostering collaboration, and implementing cutting-edge technologies [19].

Conclusion:

For clinical trials to be safe for participants, pharmacovigilance is essential. The significance of pharmacovigilance in clinical trials has been covered in this article, along with important procedures for tracking and disclosing adverse events, preserving data integrity, and weighing the advantages and disadvantages of drugs.

References:

1. Gildeeva GN and Yurkov VI. Pharmacovigilance in Russia: Challenges, prospects and current state of Affairs. J Pharmacovigil. 2016;4:206.
2. Sanaa A, et al. Awareness and Perception of National Pharmacovigilance center among Lebanese Medical Staff. J Pharmacovigilance.2016;4:199.
3. International Conference on Harmonization (ICH). Guideline for Good Clinical PracticeE6(R1),1996.Availableonline:http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_ R1__Guideline.pdf (accessed on 8 October 2010).
4. Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). International Ethical Guidelines for Biomedical Research Involving Human Subjects. CIOMS & WHO: Geneva, Switzerland, 2002.
5. The Declaration of Helsinki. World Medical Association: Somerset West, South Africa, 1996.
6. European Clinical Trials Directive 2001/20/EC. Available online: http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2 001:121:0034:0044:en:PDF (accessed on 09 October 2012).
7. De Carvalho PM et al. Brazilian Regulation in Pharmacovigilance: A Review. Pharmaceut Reg Affairs. 2016;5:164.
8. Giulia Fornasier, Sara Francescon, Roberto Leone & Paolo Baldo. A historical overview over pharmacovigilance.
9. International Journal of clinical pharmacy-40,744-747(2018). V Kalaiselvan, Sushma Srivastava, Abhishank Singh, S K Gupta.Pharmacovigilance in India: Present Scenario and Future Challenges.Drug saf.2019Mar;42(3):339-346.
10. Moore N. The role of clinical pharmacologist in the management of ADRs. Drug safety, 2001; 24(1): 1-7.
11. Kumar D. Pharmacovigilance programme in India: Current status and its perspectives. J Pharmacol Toxicol Studies. 2014; 3:34-36.
12. Pol RP, Somade PM, Chopade AR, Naikwade NS, Dias RJ. Current pharmacy curriculum in India and need for an update. Int J Life Sci Scienti Res. 2017; 3(6):1459-1461.
13. Kumar AP, Bhoopathi D, Sunkara HA, Chalasani SH. An overview of various scales used in causality assessment of adverse drug reactions. Int J Pharm Pharm Sci. 2020; 12(5):1-5.

14. Kumar S, Baldi A. Pharmacovigilance in India: Perspectives and prospects. J Drug Deliv Ther. 2013; 3(4):237-246.
15. Ghewari PS, Salunkhe SS, Bhatia NM, Killedar SG, Chitranagari K. Strategies and current scenario of pharmacovigilance in India. J Adv Drug Deliv. 2014; 1(3):122- 134.
16. Kahn MG, Ranade D. The impact of electronic medical records data sources on an adverse drug event quality measure. J Am Med Inform Assoc. 2010; 17(2):185-191. [Crossref], [Google Scholar], [Pubmed]
17. Kulkarni RD. Reporting systems for rare side eff ects of non-narcotic analgesics in India. Problems and opportunities. Med Toxicol. 1986; 1:110-113. [Google Scholar], [Pubmed]
18. https://asianjpr.com/HTMLPaper.aspx?Journal=Asian Journal of Pharmaceutical Research;PID=2019-9-2-10
19. Gildeeva GN and Yurkov VI. Pharmacovigilance in Russia: Challenges, prospects and current state of Affairs. J Pharmacovigil. 2016;4:206