International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 2 Mar–Apr 2025, pp: 2424-2432 www.ijprajournal.com ISSN: 2456-4494

Innovative Pharmacovigilance Practices for Enhanced Safety in Clinical Trials

Prof. (Dr.) Mohd.Wasiullah[1], Prof.(Dr.) Piyush Yadav[2], Asst.Prof Sushil Yadav[3,] Anita Yadav[4*,] Dileep Kumar Yadav[5]

Date of Submission: 20-04-2025 Date of Acceptance: 30-04-2025

ABSTRACT
Pharmacovigilance is the science and practice of collecting, identifying, and evaluating adverse event data. Pharmacovigilance's primary goal is to assess a drug's benefit-risk profile in order to improve patient safety and efficacy. 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. India is renowned for being a center for medication development and clinical research.For improved safety evaluation in India, a worldwide, uniform pharmacovigilance system is necessary. Ensuring patient safety both during and after clinical trials is the only priority in the medication development process.[1]

Patient safety monitoring is an essential part of the medication development process. Patient safety monitoring is given the highest priority at the lowest stages of drug development since patients must be treated according to their needs and conditions. In order to approach safety monitoring, such monitoring may be a dynamic process. The pharmaceutical sponsor must cooperate and engage proactively with all parties involved to guarantee a methodical approach to safety monitoring.We have to focus upon all the aspects of drug safety in clinical trials including basics of drug safety, regulatory aspects of drug safety, patient suitability for safety in trials, post marketing safety and causality risk assessment of the drug products.

Keywords: Clinical studies, safety monitoring, efficacy, pharmacovigilance, and stakeholders.

I. INTRODUCTION :

Pharmacovigilance may be a process of constant monitoring and evaluation of all adverse events during drug development process, to make sure the security of the participants (subjects) and a continuing assessment of the risk and benefit. 1-4 The clinical trial process is regulated by the specific regulatory guidelines (ICH GCP, USFDA guidelines etc). Clinical trials give the evidential base for regulatory approvals of safe and effective medicines. With long development cycles and ever-increasing costs in conducting clinical trials, both the pharmaceutical industry and regulators are making attempts to be much active in safety evaluations. Early safety detection not only results in better patient protection, but also possible to save lots of development cost. Since clinical trials are experiments in humans, they need to be conducted following established standards so as to guard the safety, rights, and well-being of the participants. These regulation include the International Conference on Harmonization Good Clinical Practice (ICH-GCP) Guidelines , International Ethical Guidelines for Biomedical Research Involving Human Subjects issued by the Council for International Organizations of Medical Sciences (CIOMS) and therefore the ethical principles set forth within the Declaration of Helsinki. GCP is that the "standard for the conducting, performance, planning, monitoring, recording, auditing, analyses and reporting of clinical trials that gives assurance that the info and reported results are believable and accurate which rights, integrity and confidentiality of trial subjects are protected". The globalization of clinical trials has given additional challenges to sponsors. Sponsors are held accountable to suits the relevant local legal and regulatory requirements wherever the clinical trials are conducted. For example, clinical trials conducted within the eu Union are required to be conducted in accordance with the Clinical Trials Directive. Safety evaluation may be a central component altogether stages of the drug development life-cycle. Prior to the marketing authorization of a drug, rigorous safety monitoring and evaluations from pre-clinical to all or any stages of clinical trials are required. Pharmaceutical sponsors got to adequately characterize the security profile of the merchandise so as to get regulatory approval and marketing authorization. The

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Volume 10, Issue 2 Mar–Apr 2025, pp: 2424-2432 www.ijprajournal.com ISSN: 2456-4494

approved product label comprises the necessary information about the product's benefits and risks. The continued vigilance in safety is critical as more data and knowledge is gathered from a broader patient population once the merchandise is on the market. In some cases, new emerging safety profiles may cast the first benefit-risk assessments unsure. These are evidenced in some status market withdrawals, like Troglitazone (Rezulin), Rofecoxib (Vioxx) and Rosiglitazone (Avandia). In 2005, the us Food and Drug Administration (FDA) issued guidance documents on risk management activities, including pre-market risk assessment and post-marketing pharmacovigilance and pharmacoepidemiologic assessments. 9–11 Regulatory agencies round the world and therefore the pharmaceutical industry are taking a more comprehensive and holistic approach to safety evaluation in drug development.

What is Pharmacovigilance

The World Health Organization defines pharmacovigilance (PV) as "It is a pharmacological science which deals with safety of drugs and activityy which concern to assess, detect, understand and prevent adverse effects or the drug-related problem." The aim of PV are to reinforce patient safety concerning medicine use by providing a system to collect, evaluate, and distribute drug safety data. PV activities consist of monitoring approved drugs and investigational medicinal products (IMPs) to: Determine previously unknown adverse effects. Acknowledge changes in the severity of known adverse effects. Assess a drugs risk/benefit to ascertain if action is required to improve safety Guarantee the accuracy of data communicated to health care professionals and patients, and to make sure information contained in patient information leaflets (PILs) is up so far. Pharmacovigilance in clinical trials Pharmacovigilance may be a process of continuous monitoring and evaluation of all adverse events during drug development process, to make sure the security of the participants and a continuing assessment of the risk and the benefit. 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, also referred to as drug safety, is the science of understanding the adverse effects caused by a drug and assessing whether the benefit will outweigh the risk. This 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 significantly, harmonized communication of these results to the affected global regulatory authorities in a timely manner. There are four distinct phases of a drug's clinical trial cycle after animal studies have been completed. Phase I trials scrutinize the pharmacological as well as metabolic actions of a medication when first used by human subjects. These trials involve a very small group (100) of healthy volunteers or volunteers with the targeted disease. The studies are unblinded, uncontrolled and usually last less than one month. Phases II trials observe the efficacy, dose response and tolerance, and adverse effects of the drug. These trials include a larger group of subjects (normally 200-300) with the targeted disease process and have very well defined and controlled inclusion/exclusion criteria. Phase II trials are usually placebo-controlled or activecontrolled comparison studies and last several months. Phase III trials are the final step before the drug developer can apply for marketing authorization. The group of subjects with the targeted disease may range from several hundred to several thousand volunteers who are followed for many years. Phase III trials focus on the drug's safety and efficacy in diverse sub-groups with broader inclusion/exclusion criteria including concomitant medications and concurrent diseases than Phase II trials. The risk-benefit ratio is developed, monitored and updated accordingly. After successful completion of Phase III clinical trials and authorization for marketing, the pharmaceutical company may conduct phase IV trials in order to continue to monitor the drug on a much larger scale and in a less controlled real world environment. Need of Pharmacovigilance.

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Fig-1 Pharmacovigillance

Pharmacovigilance examines which side effects surpass the limits of a medication's effectiveness. Or, to put it another way, it assesses which side effects are worth a patient's risk in relation to how well a medication treats a condition. incomplete data gathered during the drug's pre-marketing period In both the industrialized and developing worlds, ADRS is the primary cause of illness and mortality. In 1994, ADRs were fourth and sixth in the US in terms of causes of mortality. According to some estimates, ADRs could result in 5700 fatalities annually in the UK. 30–70% of ADRs can be avoided. They make patient treatment more expensive and cause patients to lose faith in the medical system.

- Humanitarian concern: Clinical trial safety evidence is insufficient because of certain restrictions (phase 1-3), and animal toxicology is frequently not a reliable indicator of human impacts. small size, confined population (age &sex specific), limiting indications (only specific condition), short duration
- Safe medication use: It has been estimated that adverse drug reactions (ADRs) could result in 5700 deaths annually in the UK.
- Adverse drug reactions are costly.
- Ensuring public trust and encouraging the sensible use of medicine are two ethical concerns.
- It is unethical to fail to disclose a significant reaction.

Adverse drug reaction

A response that is harmful and unintended, occurring at dosages typically used for the prevention, diagnosis, or treatment of illnesses, or for altering physiological functions. The purpose of pharmacovigilance is to identify which adverse events exceed an acceptable threshold relative to a drug’s effectiveness. In simpler terms, it involves evaluating whether the side effects justify the benefits for patients in comparison to the drug's ability to treat a condition. For example, chemotherapy is recognized for causing significant side effects, yet when confronted with life-threatening cancer, The side effects are deemed acceptable when weighed against the possibility of curing a patient. However, if a medication intended to relieve a headache led to similar adverse effects, the danger to the patient would be seen as too high, and the benefits would not be significant enough to warrant the potential harm. According to ICH E6, an adverse event refers to any undesirable medical occurrence in a patient or subject involved in a clinical trial who is given a pharmaceutical product, which is not related to the treatment they received. An adverse event can be described as an unintended and unfavorable response (which may include an abnormal laboratory result), indication, or illness that occurs in relation to the use of a medicinal (investigational) product. serious drug-related incident SAEs are defined as Adverse Drug Reactions or Adverse Events that are linked to death, prolonged hospitalization (if the study was

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on in-patients), inpatient hospitalization (if the study was on out-patients), significant or ongoing disability or incapacity, congenital anomalies or birth defects, or other life-threatening conditions.

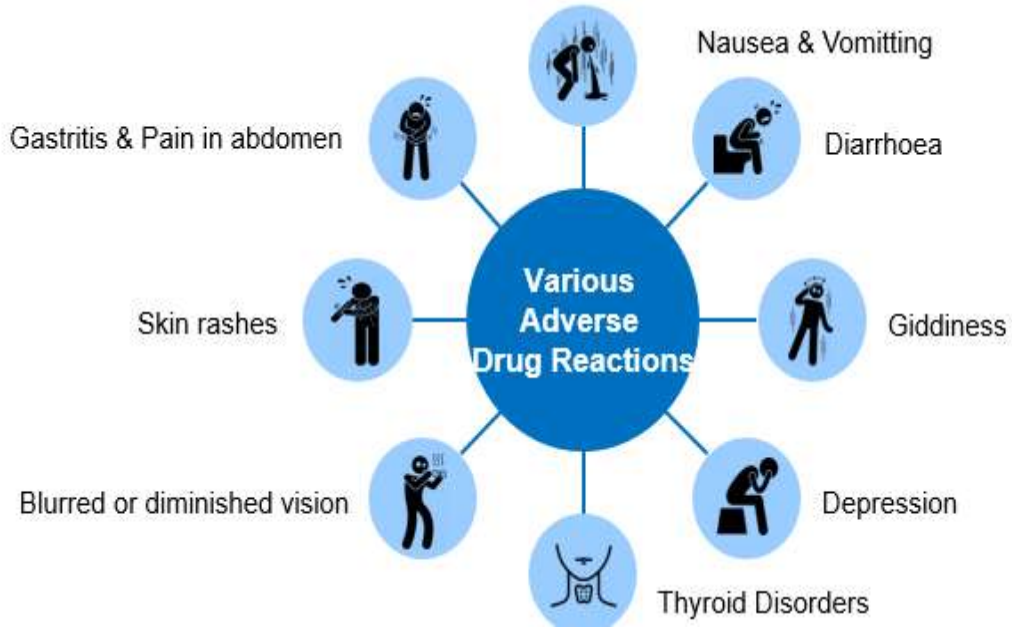

Fig 2Adverse drug reaction

- Death and the threat of death
- Cause hospitalization or prolong an already-existing hospitalization
- Chronic or severe impairment or incapacity; congenital anomaly or birth condition
- Medically significant Serious, unanticipated, suspected adverse response
- Mentioned not the product's core safety data sheet; possible drug connection

Serious vs. severe

Although the term "severe" is typically used to describe the intensity (severity) of a particular event (such as mild, moderate, or severe pain), the event itself may have relatively little medical relevance (such as a bad headache).
investigational therapies, trial procedures, data collection standards, endpoints, and sample size. The protocol also outlines the safety reporting processes, with a particular emphasis on the requirement for expedited reporting of significant adverse occurrences. The purpose of the Informed Consent Form (ICF) is to provide participants in the clinical trial with up-to-date information on the experimental medication as well as the procedures, risks, and advantages. Informed consent is an essential component of the study process. Sponsors are responsible for creating and maintaining clinical databases for the trial's data, as stipulated in

Serious

Seriousness is determined by the actions or results of the patient or event, which are frequently linked to situations that could endanger the patient's life or ability to function.

Common practice in safety monitoring& Stakeholders in safety monitoring

Sponsor: The formulation of the clinical trial protocol is the responsibility of the clinical trial sponsors, which are typically pharmaceutical corporations. The protocol outlines every facet of the study, including the experimental justification, goals, trial population with detailed exclusion and inclusion criteria, administration of the protocol and the ICF. Case Report Forms (CRFs) are instruments created by the sponsor to collect data. These tools are gradually moving away from the conventional paper-based method and toward electronic data gathering modules via the internet. Sponsors are permitted to promptly communicate important safety information to all stakeholders since they have access to all accumulating data.

Subjects

Patients or healthy volunteers who have signed the Informed Consent Form and consent to

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take part in a clinical experiment are known as subjects. The ICF provides crucial safety information together with other information so that the participants can make an informed choice about taking part in the study. Informed permission must be freely provided, free from coercion, and founded on a precise comprehension of the nature of the participation concern. By providing consent, participants authorize the researchers to take their body measurements and medical records in accordance with the protocol. Subjects are encouraged to adhere to the protocol in order to complete the study, although they are free to leave at any moment.

Investigators

Investigators are trained professionals with the necessary training and expertise to provide medical care to trial participants. To examine if they can make an informed choice, researchers identify possible subjects and explain them about the trial. Investigators are expected to adhere to the protocol treatment plan when providing care during the trial. In addition to reporting adverse events, they watch, assess, measure, negotiate, and record all therapy effects. Any problems that endanger the safety and well-being of the trial participants must be reported to the sponsor and their institutional review boards. The conduct of the clinical study and the security of the participants in their care are ultimately the investigators' responsibility and accountability.

Institutional review board/ Ethics committee

The Institutional Review Board (IRB), commonly referred to as the ethics committee, is responsible for safeguarding the welfare and rights of human subjects who are recruited to take part in research protocols that are approved by the organization to which the IRB belongs. Every clinical trial protocol involving human subjects that the specific institution participates in is reviewed by the IRB, which also has the power to approve, disapprove, or mandate protocol revisions. IRBs are also in charge of monitoring current studies to make sure that participants are not put in unnecessary danger and that they provide their free and informed consent. The IRB is also in charge of the education and training of the institution's investigators who participate in clinical research. The majority of members of an IRB are drawn from outside academic communities where research is being done as well as from a wide range of scientific specialties.

DATA AND SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB), sometimes referred to as the Data Monitoring body (DMC), is an expert body that is chartered for one or more clinical trials and is not affiliated with the sponsor. In order to guarantee the ongoing safety of both registered and unregistered participants, the DSMB is authorized to regularly review the data collected from the clinical trial. In order to determine whether there is unquestionable proof of efficacy or not, the DSMB may examine efficacy data at predetermined interim points, thereby ruling out the clinical equilibrium at the start of the experiment. Additionally, DSMB is responsible for informing the sponsor about the trial's ongoing validity and scientific usefulness. A formal DSMB is not required for every clinical experiment. The majority of DSMBs occur in phase 3 double blind randomized studies. Experts in clinical trials, including doctors with the relevant specialization, at least one biostatistician, and perhaps one or more individuals from other fields like biomedical ethics, fundamental science/pharmacology, or law, usually make up the DSMB.

Regulatory authorities

Pharmaceutical sponsors in the US are obliged by law to submit an Investigational New Drug (IND) application to the FDA prior to the start of a first in human clinical trial. To ensure that research participants won't be exposed to excessive risk, the FDA evaluates the IND for safety (usually within 30 calendar days). The FDA provided sponsors and investigators with guidance in 2010 regarding the safety reporting requirements for biological products and human drugs under investigation under an IND, as well as for drugs undergoing bioavailability (BA) and bioequivalence (BE) studies exempt from the IND requirements. The guidelines established globally harmonized definitions and reporting criteria and outlined the agency's expectations for the prompt review, assessment, and submission of pertinent and helpful safety information. The FDA's counterpart in the European Union is the European Medicines Agency (EMA). Applications from pharmaceutical companies are evaluated by a number of scientific committees inside the agency. Although they may function under distinct local rules and regulations, regulatory authorities in various regions of the world will possess comparable authorization.

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Medical community and patients

Clinical trials generate information that benefits the larger medical community and, eventually, the patients by adding to our understanding of the disease and its treatment. For other practitioners utilizing a comparable class of medicines, safety information on one product may be instructive. The Food and Drug Modernization Act (FDAMA), which required clinical trial registration, was passed by the US Congress in 1997. Consequently, ClinicalTrials.gov was established. Following the passage of the Food and Drug Administration Amendments Act (FDAAA) by Congress in 2007, which mandated the certification of additional trial types, the website underwent additional expansion. ClinicalTrials.gov started allowing sponsors and lead investigators to submit clinical study findings in September 2008, in accordance with FDAAA 801. When the results database was first made available, adverse event information submission was optional; however, in September 2009, it became mandatory. Significant advancements in science and greater transparency in clinical research have been made possible by the mandatory necessity for clinical trial registration and the disclosure of trial outcomes.

Communicating safety information among stakeholders

In order to guarantee subject safety in clinical studies, regular communication with the many stakeholders is essential. Clinical trial sponsors are in charge of appropriately monitoring the participants, which includes requiring long-term follow-up as necessary. The protocol, which includes the ICF, outlines the specifics of the assessments as well as the frequency and duration of follow-up. To guarantee a methodical strategy for safety surveillance and monitoring, nearly all pharmaceutical sponsors also have Standard Operating Procedures (SOPs) in place for gathering, processing, reviewing, evaluating, reporting, and communicating cumulative safety data. Overall, the clinical trial's investigators transmit safety information, including adverse events and laboratory results, to a sponsor. However, safety data may originate from sources other than the current clinical trial. Any new risks connected with the use of the investigational drug that arise from the clinical trial or from other sources must be promptly reviewed by the sponsor, who must also notify subjects, investigators, IRBs, and regulatory authorities. One way to implement the necessary procedural changes in light of the improved safety data is to amend the clinical trial protocol. Periodically updating the Investigator's Brochure (IB) is another method of communicating the changing safety information. The investigational drug's clinical and non-clinical data pertaining to the drug's trial in human subjects are compiled in the IB. Its goal is to give the trial's investigators and other participants the information they need to better comprehend the rationale behind and adhere to many of the protocol's essential elements, including the dosage, interval between doses, administration techniques, and safety monitoring protocols.

An RMP serves as the foundation for an action plan for pharmacovigilance and risk minimization actions and includes a description of the drug's significant identified risks, prospective risks, and missing information. The CIOMS VI working group advised forming a multidisciplinary Safety Management Team (SMT) with the sponsor organisation to be in charge of safety surveillance and decision making on risk management and reduction of activities. All safety-related tasks, such as quantitative risk assessment, signal detection, and adverse event of special interest (AESI) identification, must be coordinated by the SMT. Sponsors may decide to designate an internal multi-functional data review team that is not directly involved in the day-to-day trial activities pertaining to the investigational drug to conduct continuous evaluation of the safety data for studies in early phases without DSMBs. On later stage trials, this independent data review panel is permitted to carry out tasks akin to those of the DSMB. The use of the Development Core Safety Information (DCSI) as a summary of the safety concerns found for an experimental medication was approved by the CIOMS VI working group. It was proposed that DCSI be included in the IB's list of suspected adverse effects.

For the purposes of regulatory reporting, any safety concerns or adverse medication reactions included in this paper should be regarded as "anticipated." Accelerated case reporting to regulatory agencies within seven (fatal or life-threatening) or fifteen calendar days is only applicable to suspected adverse drug reactions that are both serious and unexpected. There are a few distinct terms, such as Serious Unexpected Suspected Drug Reaction and Suspected Unexpected Serious Drug Reaction (SUSAR). The CIOMS VI working group recommended that sponsors give the participating investigators and IRBs regular updates on the changing benefit/risk

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profile and highlight significant new safety findings, in contrast to the standard rapid case reporting to regulatory authorities. Local laws in some areas, however, still require expedited case reporting to investigators and IRBs. Additionally, regulatory bodies mandate that safety information be reported collectively rather than case-by-case. Annual IND reports, which comprise aggregate safety data from an experimental drug's whole development program, are required under FDA IND requirements in the United States. A single Development Safety Update Report (DSUR) should be defined and submitted to regulators annually, according to the CIOMS VI working group. Sponsors gather safety data from all pertinent drug studies before submitting New Drug Applications (NDAs) in order to conduct integrated safety evaluations that support the application for marketing authorization. The integration and analysis of safety data have been greatly aided by the common data structure of SDTM (Standard Data Tabulation Model), which was established by the Clinical Data Interchange Standards Consortium (CDISC). Additionally, it enables sponsors to create a safety data warehouse to effectively address safety-related inquiries throughout the medication program. Periodic collective safety analyses and proactive early safety analysis design in a Program Safety Analysis Plan (PSAP) have been suggested as standard industry practices. The PSAP is a representation that will form the base for integrated safety evaluations in an NDA.

Growth of clinical trials industry

From 2021 to 2028, the global clinical trials market is projected to rise at a compound annual growth rate (CAGR) of 5.7%, from its 2020 forecast of $44.3 billion. The expansion of this market is being driven by the increasing prevalence of chronic diseases and the growing need for clinical trials in emerging nations. A growing number of biologics, the need for orphan and customized medications, and the necessity for cutting-edge technology are other factors propelling the industry. The market is thought to be driven by factors like the demand for CROs to perform clinical trials, technological advancements, and the globalization of clinical trials. The market expansion is being supported by the increasing need for CROs to conduct clinical trials in the pharmaceutical industry as a result of their increased experience and the use of cutting-edge technology in clinical trials. Digitization in biomedical research is as well paving the way for market expansion. Using cutting-edge technology like Electronic Data Capture (EDC) helps market players manage patient data, which eventually lowers monitoring costs. By maintaining patient data records and reducing trial process errors through the use of software like e-COA (Electronic Clinical Outcome Assessment), digitization also aids in complying with strict standards.

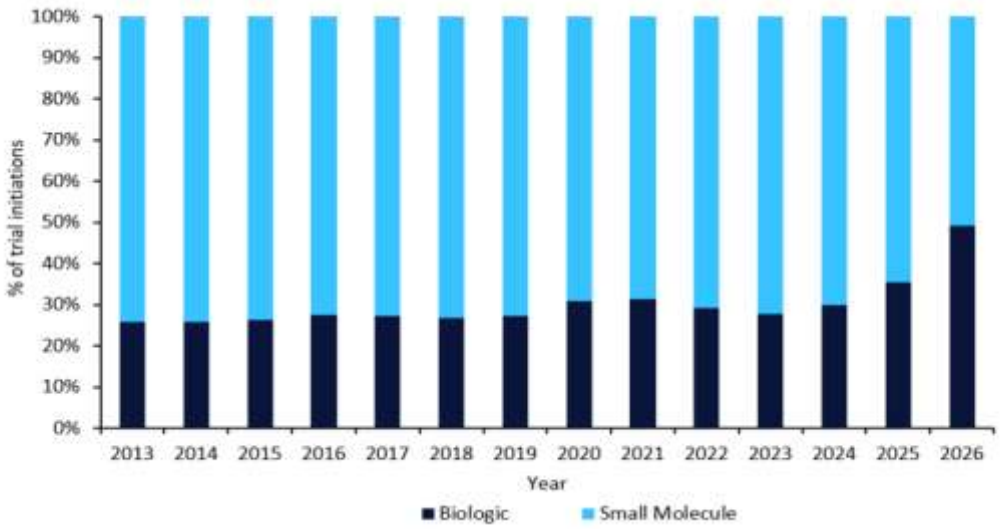

Figure 1: Number of global trials and the proportion in India. Source: The Boston Consulting Group and Business Communications Company data quoted in Mishra

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The global pandemic brought on by the corona virus is another factor propelling the market. Around the world, people's lives, communities, businesses, and industries are being impacted by the rapidly changing threat posed by the COVID-19 pandemic. The current clinical trial ecology has also been negatively influenced by the pandemic. Numerous ongoing trials for different therapeutic areas have been impacted by it. To combat this, however, scientists are working quickly to create novel treatments and COVID-19 vaccines, which is fueling market expansion. Figure 4: Global clinical trials market share, by indication, 2020 (%).The present pandemic is posing a threat and posing challenges to clinical trials aimed at discovering cures and effective treatments for a wide range of illnesses. This pandemic has caused at least 18 pharmaceutical or biotech businesses to report disruptions to a clinical trial. In March, there were roughly 65.0% global average reductions in the enrollment of new patients year-over-year. There was also a 43.0% decline in Japan and an 84.0% decline in India. The U.S. is down with an average of 67.0%. 30 CONCLUSION Pharmacovigilance provides the data needed to evaluate a drug's safety profile. A key factor in the success of pharmacovigilance is the involvement of health care providers nationwide in reporting adverse medication reactions or incidents.

II. CONCLUSION

Detecting, evaluating, comprehending, and preventing adverse drug reactions (ADRs) and other drug-related issues is the main objective of pharmacovigilance, which has become a fundamental component of contemporary healthcare. Pharmacovigilance has developed over time from a reactive approach, in which adverse events were mostly discovered after the product was put on the market, to a more proactive system that integrates a variety of technology advancements meant to improve medication safety. In order to detect ADRs and guarantee patient safety, the conventional pharmacovigilance techniques—such as post-marketing surveillance and spontaneous reporting—have proven essential. These approaches do have certain drawbacks, though, such as delayed signal detection, underreporting, and difficulties in thoroughly monitoring medications across a range of demographics. Pharmacovigilance is changing along with the healthcare industry, and new developments are filling in these gaps. Drug safety monitoring is changing as a result of developments in artificial intelligence (AI), machine learning, big data analytics, and real-world evidence (RWE). By integrating data from electronic health records (EHRs), wearables, patient registries, and other sources, pharmacovigilance systems can now offer a more holistic, real-time view of the safety profile of medications. These advancements allow for more effective and individualized risk management techniques in addition to quicker ADR identification. The field has become more sensitive to the actual experiences of people taking the drugs by emphasizing patient-reported outcomes and boosting direct patient interaction. This change makes safety monitoring more pertinent and makes it possible to evaluate risks and benefits more precisely, which eventually improves patient outcomes. A paradigm change toward more proactive and individualized medication safety monitoring is represented by the incorporation of AI, ML, big data analytics, and RWE into pharmacovigilance. Even though there are still issues with data quality, model interpretability, and integration, further developments in these fields could improve patient safety and optimize treatment.

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