



Pharmacovigilance Safety Monitoring in Clinical Trials

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Received: 07-06-2021; Revised: 19-08-2021; Accepted: 26-08-2021; Published on: 15-09-2021.

ABSTRACT

Pharmacovigilance is that the science and activities associated with the gathering, detection and assessment of adverse event data. Major purpose of pharmacovigilance is to gauge the benefit- risk profile of drug for better efficacy and safety to be used in patients. Pharmacovigilance plays a major role in rationale use of drug which provides the information about the adverse drug reactions which seen in patients. In terms of volume Indian Pharma industry is third largest in world and in terms of value it is thirteen largest in world. India is also known as a hub for clinical research and drug development. There is a requirement of a global and standardized pharmacovigilance system in India for better safety assessment in India. In drug development process the only priority of clinical trials is to make sure patient safety during and after the trials. A critical component throughout the drug development life-cycle is monitoring patient safety. Patient must be treated consistent with the requirements and illness of patient therefore the utmost value is given to monitoring of patient safety in the least levels of drug development. Such monitoring may be a dynamic process so to approach safety monitoring. To ensure a systematic approach to safety monitoring pharmaceutical sponsor must work proactively and collaboratively with all stakeholders. We have to focus upon all the aspects of drug safety in clinical trials including basics of drug safety, regulatory aspects of drug safety, patient suitability for safety in trials, post marketing safety and causality risk assessment of the drug products.

Keywords: Pharmacovigilance, Clinical trials, safety monitoring, efficacy, stakeholders.

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DOI:

10.47583/ijpsrr.2021.v70i01.002



DOI link: <http://dx.doi.org/10.47583/ijpsrr.2021.v70i01.002>

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) Guidelines⁵, 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.⁶ 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”.⁷ 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.⁸

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 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 activity 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.¹²

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).¹³

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 active-controlled 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.¹⁴

Need of Pharmacovigilance

Pharmacovigilance analyse which adverse events cross the line of drug’s efficacy. Or in other words we can say it determines which side effects are worth the risk to patients compared with how effective they are at treating a disease. Incomplete information collected during the pre-marketing phase of drug ADRs are leading cause of morbidity and mortality in both developing and developed world. ADRs were 4th-6th commonest cause of death in the US in 1994 It has been suggested that ADRs may cause 5700 deaths per year in UK 30-70% ADRs are preventable. They increase cost of patient care and loss of patient confidence in health care system.

- Humanitarian concern: Animal toxicology is often not a good predictor for human effects-Evidence of safety from clinical trials insufficient due to some limitations (phase 1-3): limited size, narrow population (age & sex specific), narrow indications (only specific disease), short duration
- Safe use of medicine: It has been suggested that ADRs may cause 5700 deaths per year in UK.
- Adverse drug reactions are expensive
- Promoting rational use of medicine
- Ensuring public confidence
- Ethical concern: Not reporting is serious reaction is unethical.¹⁵

Adverse drug reaction

A response which is noxious and unintended and which occurs at doses normally used in human for the prophylaxis, diagnosis or therapy of diseases or for



modification of physiological function. The role of pharmacovigilance is to determine which adverse events cross the line of a drug's efficacy. In other words, analyzing which side effects are worth the risk to patients compared with how effective they are at treating a disease. For instance, chemotherapy is known to cause some very serious side effects but when faced with life-threatening cancer, these side effects are considered acceptable given the potential to cure a patient. However, if a drug used to cure a headache caused similar side effects, the risk to the patient would be considered too great and the benefit not substantial enough to justify the potential damage.¹⁶

Adverse event

ICH E6: An Adverse event is any undesirable medical event in a patient or clinical investigation subject administered a pharmaceutical product and that does not have any relationship with this treatment.¹⁷

An Adverse event can also states as an unfavorable and unintended reaction (including an abnormal laboratory finding), indication, or disease temporally associated with the use of a medicinal (investigational) product.¹⁸

Serious drug event

SAE is defined as an Adverse Event or Adverse Drug Reaction that is associated with death, inpatient hospitalization (in case the study was being conducted on out-patients), prolongation of hospitalization (in case the study was being conducted on in-patients), persistent or significant disability or incapacity, a congenital anomaly or birth defect, or is otherwise life threatening.

- Death
- Life threatening
- Result in hospitalization/ prolongs existing hospitalization
- Persistent or significant disability or incapacity
- Congenital abnormality or birth defect
- Medically significant

Serious, unexpected, suspected adverse reaction

- Serious
- Not included in product core safety data sheet
- Suspected link to the drug

Serious vs. severe

Severe is mostly used to account the intensiveness (severity) of a specific event (as in mild, moderate, or severe pain) the event itself, however, may be of comparatively minor medical significance (such as severe headache).

Serious is based on patient / event action or outcome criteria commonly associated with events that pose to patient's life threatening or functioning.¹⁹⁻²²

Common practice in safety monitoring

Stakeholders in safety monitoring

Sponsor:

Clinical trial sponsors, normally pharmaceutical companies, are obligated for development of the clinical trial protocol. The protocol mark out every aspect of the research, by taking consideration of the rationale for the experiment, objectives, trial population with elaborated exclusion and inclusion criteria, investigational therapies administration, trial procedures, data collection standards, endpoints and sample size. The protocol too details the safety reporting procedures, especially on the demand for accelerated reporting of serious adverse events. The Informed Consent Form (ICF) is utilized to reveal current information about the investigational drug and about the procedures, risks and benefits for subjects who participate in the clinical trial. Critical part of the research process is Informed consent. In constituent to the protocol and the ICF, sponsors are accountable for assembling and maintaining clinical databases for the data collected in the trial. Sponsor has designed Case Report Forms (CRFs) as data collection tools. These tools are gradually based on electronic data capture modules through the internet rather than the traditional paper-based way. With access to all accumulating data, sponsors are authorized to report key safety information to all stakeholders in a timely fashion.

Subjects

Subjects are patients or healthy volunteers who agree to participate in a clinical trial and have signed the Informed Consent Form. with else information, the ICF gives important safety info so the subjects can take an informed decision on whether to participate in the trial. The informed consent must be given freely, without compulsion and must be based on a clear-cut understanding of what participation concern involves. By giving consent, subjects give permission to the investigators to collect health information and body measurements as per the protocol. While by encouraging the subjects to follow the protocol to trial completion takes place, subjects can withdraw at any time. The reason for withdrawing the consent is not necessary by the subjects. In a phase 1 clinical trial, when the drug is first used in healthy humans, healthy volunteers are paid for their time and willingness to be exposed to unknown risks. Later phase trials are generally conducted in patients with the disease of interest, and payments to these subjects for participation are disputatious. The important concern is the payment could be coercive or serve as undue incentive guiding to impaired assessment on trial participation.²³

Investigators

Investigators are qualified individuals who are skilled and experienced to give medical care to subjects registered in the trial. Investigators determine potential subjects and educate them about the trial participation to see that if



they can make an informed decision. While the trial is ongoing, investigators are supposed to follow up to the protocol treatment plan in delivering care. They observe, evaluate, measure, negotiate and document all effects of treatment, including the reporting of adverse events. They are responsible for informing their institutional review boards and the sponsor of any issues that pose a threat to the safety and wellbeing of the trial subjects. Investigators are eventually accountable and responsible for the conduct of the clinical trial and for the safety of the subjects under their care.

Institutional review board/ Ethics committee

The Institutional Review Board (IRB), also well known as the ethics committee, is charged with protecting the rights and welfare of human subjects enlisted to participate in research protocols conducted under the endorsement of the institution to which the IRB is affiliated. The IRB reviews all clinical trial protocols concern human subjects that the particular institution is involved with and has the authority to approve, disapprove or require modifications to the protocols. IRBs have the further responsibility of reviewing ongoing research to ensure continued diligence that subjects are not placed at undue risk and they give unforced, informed consent to the subjects. The training and education of investigators at the institution who take part in clinical research is also a responsibility of the IRB. Members of an IRB mostly come from a wide range of scientific disciplines and from outside academic communities in which research is being conducted.²⁴

DATA AND SAFETY MONITORING BOARD

The Data and Safety Monitoring Board (DSMB), also known as data monitoring committee (DMC), is an expert committee, independent of the sponsor, chartered for one or more clinical trials. The authorization of the DSMB is to review on a regular basis the collecting data from the clinical trial to ensure the continuing safety of current participants and those yet to be registered. The DSMB may review efficacy data at pre-defined in meantime points to assess whether there's irresistible evidence of efficacy or the lack thereof, such that the clinical equilibrium at the beginning of the trial is not justified. DSMB has the additional responsibilities to send word to the sponsor regarding the continuing validity and scientific merit of the trial. Not all clinical trials need a formal DSMB. DSMBs are most frequent in double blind randomized phase 3 trials. Members of the DSMB typically consist of clinical trial experts, including physicians with the appropriate specialty, at least one bio statistician and possibly person(s) from other disciplines, such as biomedical ethics, basic science/pharmacology or law.

Regulatory authorities

In the US, preceding to the initiation of a first in human clinical trial, pharmaceutical sponsors requisite to submit an Investigational New Drug (IND) application to the FDA as required by law. The FDA reviews the IND (typically within 30 calendar days) for safety to guarantee that

research subjects will not be subjected to unreasonable risk. In 2010, the FDA issued guidance to sponsors and investigators on safety reporting necessitate for human drug and biological products that are being investigated under an IND and for drugs that are the subjects of bioavailability (BA) and bioequivalence (BE) studies that are free from the IND requirements. The guidance stipulated to the agency's expectations for timely review, evaluation and submission of relevant and useful safety information and implemented internationally harmonized definitions and reporting standards. The European Medicines Agency (EMA) is the Eu Union's FDA equivalent. The agency has several scientific committees that carry out the assessment of applications from pharmaceutical companies. In other parts of the world, regulatory authorities will have similar authorization, but may operate under different local laws and regulations.²⁶

Medical community and patients

Clinical trials create data that contribute to the body of knowledge about the treatment and the disease that benefit the wider medical community and, ultimately, the patients. Safety info of one product may be informative to other practitioners using a similar class of agents. In 1997, the US Congress passed the Food and Drug Modernization Act (FDAMA), demanding clinical trial registration. ClinicalTrials.gov was created as a result. The website was further expanded in 2007 after the Congress passed the Food and Drug Administration Amendments Act (FDAAA), which required more types of trials to be certified. In September 2008, as required by FDAAA 801, ClinicalTrials.gov began to permit sponsors and principal investigators to submit the results of clinical studies. Submission of adverse event info was optional when the results database was released and became required in September 2009. The compulsory requirement on clinical trial registration and the revelation of trial results are significant achievements in advancing science and increasing transparency in clinical research.²⁷

Communicating safety information among stakeholders

Time to time communication with the various stakeholders is critical to ensure subject safety in clinical trials. Sponsors of clinical trials are responsible for monitoring the subjects suitably, including the requirement of long-lasting follow up as appropriate. The protocol (including the ICF) specifies the details of the evaluations, the oftenness and the length of follow-up. In addition, almost pharmaceutical sponsors have Standard Operating Procedures (SOPs) in place to collect, process, review, evaluate, report and convey accumulating safety data to ensure a systematic approach for safety surveillance and monitoring. In overall, safety information, consist of adverse events and laboratory findings are reported to a sponsor by investigators conducting the clinical trial. However, safety information may come from origin outside the immediate clinical trial. The sponsor is required to readily review all information related to the safety of the drug and to update subjects, investigators, IRBs and regulatory authorities of



any new risks associated with the use of the investigational drug that originate from the clinical trial or from other sources. Amending the clinical trial protocol is one approach to apply procedural alterations that are essential given the updated safety information. Another way to convey the evolving safety information is through the periodic update of the Investigator's Brochure (IB). The IB is a compiling of the clinical and non-clinical data on the investigational drug that are related to the study of the drug in human subjects. Its motive is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for and their compliance with numerous key features of the protocol, such as the dose, dose interval, methods of administration and safety monitoring procedures. The IB should be reviewed at least annually and revised as essential in compliance with the sponsor's written procedures and the local requirements. A new safety finding that represents a important risk to study subjects should be communicated to the investigators immediately, along with an update to the IB and potentially to the protocol and the ICF. For trials where DSMBs are in place, sponsors should also communicate important safety findings to the DSMBs employed to administrate clinical trials of the same or similar investigational drug(s). In different situations, DSMBs may being possession of critical safety information and they will requisite to follow the DSMB charter and the protocol to make recommendations to the sponsor with respect to its safety findings and whether the trial should continue as planned. The aim of safety monitoring in clinical trials is to identify, evaluate, minimize and appropriately manage risks. In Europe, Risk Management Plans (RMPs) are needed by the EMA as part of the drug approval process. An RMP consist of a summary of important identified risks of the drug, potential risks and missing information, which function as the basis for an action plan for pharmacovigilance and risk minimization activities. The CIOMS VI working group recommended establishing 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. The SMT is accountable for coordinating all safety-related activities including quantitative assessment of risks, signal detection and identification of adverse events of special interest (AESIs). For trials in earlier stages without DSMBs, sponsors may choose to appoint an internal multi-functional data review team removed from the direct everyday trial operations related to the investigational drug to carry out ongoing review of the safety data. This independent data review team is authorized to perform similar functions as the DSMB on later stage trials. The CIOMS VI working group supported the use of the Development Core Safety Information (DCSI) as the summary of the identified safety issues for an investigational drug. DCSI was suggested to be a part of the IB that defines the list of suspected adverse reactions. Safety issues or adverse drug reactions involved in this document should be considered "expected" for regulatory

reporting purposes. Only suspected adverse drug reactions that are both serious and unexpected are subject to accelerated case reporting to regulatory authorities in either seven (fatal or life-threatening) or 15 calendar days. Somewhat different terminologies exist, including Suspected Unexpected Serious Drug Reaction (SUSAR) or Serious Unexpected Suspected Drug Reaction. Opposite to the routine expedited case reporting to regulatory authorities, the CIOMS VI working group suggested sponsors provide periodic updates of the evolving benefit/risk profile and highlighting important new safety information to the participating investigators and IRBs. However, in some regions, accelerated case reporting to investigators and IRBs are still needed by local regulations. Regulatory authorities also require reporting of safety info in the aggregate rather than the individual cases. In the US, the FDA IND regulations need annual IND reports, which include aggregate safety information across the entire development program of an investigational drug. CIOMS VI working group suggested defining a single Development Safety Update Report (DSUR) for submission to regulators on an annual basis. For submission of New Drug Applications (NDAs), sponsors collect safety information from all relevant trials of the drug to perform integrated safety analyses in support of the filing for marketing authorization. The common data structure using SDTM (Standard Data Tabulation Model) defined by Clinical Data Interchange Standards Consortium (CDISC) has widely facilitated the safety data integration and analyses. It also gives ability to the sponsors to build a safety data warehouse to better respond to safety related queries across the entire drug program. Proactive early designing of safety analyses in a Program Safety Analysis Plan (PSAP) and periodic collective safety analyses have been recommended as standard industry practices. The PSAP is a representation that will form the base for integrated safety analyses in an NDA.

Growth of clinical trials industry

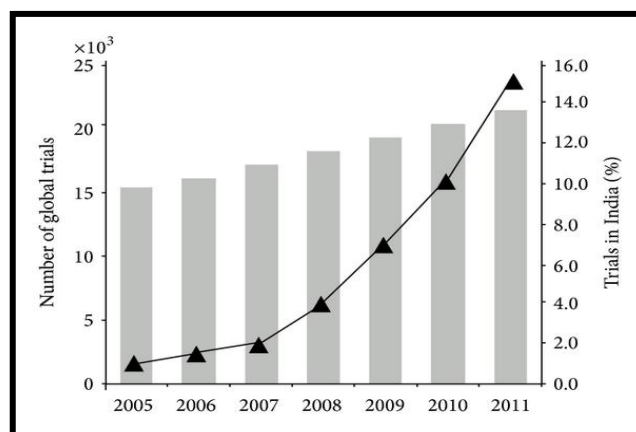


Figure 1: Number of global trials and the proportion in India. Source: The Boston Consulting Group and Business Communications Company data quoted in Mishra.²⁷

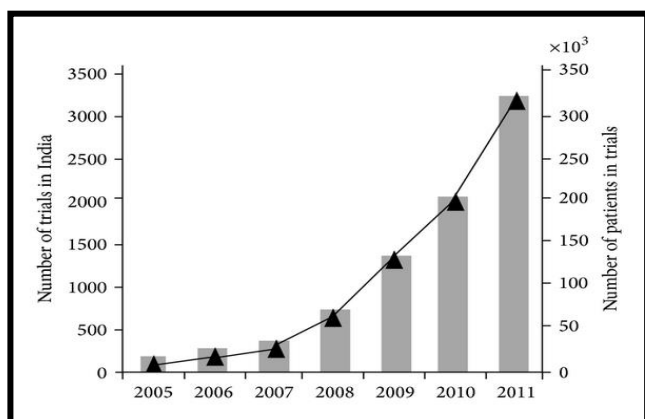


Figure 2: Number of trials and patients in India. The Boston Consulting Group and Business Communications Company data quoted in Mishra ²⁸

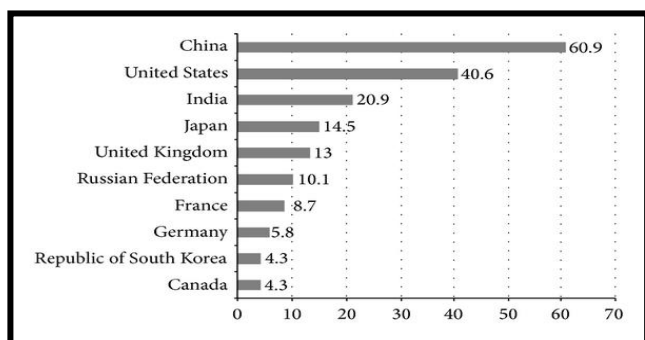


Figure 3: Most attractive locations for future foreign R & D in UNCTAD survey, 2005–2009 (percent of responses).²⁹

The global clinical trials market possibility was estimated at 44.3 billion in 2020 and is expected to expand at a compound annual growth rate (CAGR) of 5.7% from 2021 to 2028. The increasing pervasiveness of chronic disease and the rising demand for clinical trials in developing countries is fueling this market's growth. The market is also driven by a rising number of biologics, the need for custom-made medicines and orphan drugs, and the demand for advanced technologies. Factors such as globalization of clinical trials, technological evolution, and demand for CROs to conduct clinical trials are further estimated to drive the market.

The growing demand of CROs for conducting clinical trials in the pharmaceutical sector due to the expanded expertise of CROs and the adoption of advanced technologies in clinical trials is supporting the market growth. Digitization in biomedical research is as well paving the way for market growth. Incorporating advanced technologies such as Electronic Data Capture (EDC) aid market participants in handling patient data that ultimately decrease monitoring cost. Digitization also helps in meeting stringent regulations by upholding patient data records that reduce the trial process errors through the adoption of software such as e-COA (Electronic Clinical Outcome Assessment).

The market is also driven by the emergence of the global pandemic triggered by coronavirus. The promptly evolving

threat due to the outbreak of COVID-19 is impacting lives, communities, businesses, and industries around the world. The pandemic has also destructively impacted the current ecosystem of clinical trials. It has affected numerous ongoing trials for various therapeutic areas. However, to overcome this, researchers are speedily trying to develop innovative therapeutics and vaccines against COVID-19, which is supporting market growth.

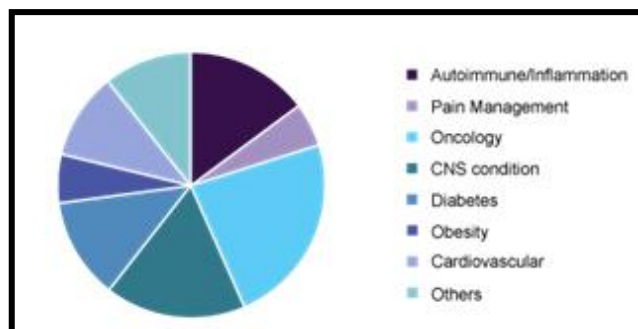


Figure 4: Global clinical trials market share, by indication, 2020 (%).

The current pandemic is building a threat and acting as difficulty in the clinical trials for finding effective treatments and cures for a myriad of diseases. At least 18 pharma or biotech companies have reported disturbance to a clinical trial due to this pandemic. In March, there were around 65.0% global average reductions in the enrollment of new patients year-over-year. 84.0% decrease in India and a 43.0% decrease in Japan were also observed. The U.S. is down with an average of 67.0%.³⁰

CONCLUSION

The information to assess the safety profile of drug is given by pharmacovigilance. Participation of professionals of health care country wide to report adverse drug reaction or adverse events plays a major role in the success of pharmacovigilance. Current progress in Pharmacovigilance is well-marked by increase in use of databases to make the process more proactive and organized. It must be in everyone's priority to develop safe and effective medicines to patients. During clinical trials monitoring patient safety is a critical component throughout the drug development life-cycle. To ensure a systematic approach of safety monitoring pharmaceutical sponsor must work proactively and collaboratively with all stakeholders. For risk management plans, risk evaluation and minimization strategies. There will be greater demand for more comprehensive and innovative approaches that apply quantitative methods to collecting data from all sources, ranging from the discovery and preclinical through with clinical and post-approval stages, As the industry transitions from passive to active safety surveillance activities. The globalization of clinical trials has posed extra challenges. A better deal of coordination is required of sponsors to make sure time to time communication of new safety findings among all stakeholders in all regions. Attempts in building a standard safety data warehouse across all trials in a development program will lay a solid

base for integrated safety analyses. Innovative statistical methods can be applied to gain the efficiency in reviewing a large volume of safety data, to determine safety trends and to establish prospective monitoring guidelines.

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30. Clinical Trials Market Size, Share & Trends Analysis Report By Phase (Phase I, Phase II, Phase III, Phase IV), By Study Design (Interventional, Observational, Expanded Access), By Indication, By Region, And Segment Forecasts, 2021 - 2028 Published Date Jan 2021.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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