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Mini Review

Pharmacovigilance Safety Monitoring in Clinical Trails

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ABSTRACT

Monitoring patient safety during clinical trials is a critical component throughout the drug development life-cycle. Pharmaceutical sponsors must work proactively and collaboratively with all stakeholders to ensure a systematic approach to safety monitoring. The regulatory landscape has evolved with increased requirements for risk management plans, risk evaluation and minimization strategies. As the industry transitions from passive to active safety surveillance activities, there will be greater demand for more comprehensive and innovative approaches that apply quantitative methods to accumulating data from all sources, ranging from the discovery and preclinical through clinical and post-approval stages. Statistical methods, especially those based on the Bayesian framework, are important tools to help provide objectivity and rigor to the safety monitoring process. Pharmacovigilance (PV) is a scientific activity which keeps constant watch on the drug throughout its life cycle. In India, Indian Pharmacopoeia Commission (IPC) and National Coordination Committee (NCC) through the Central Drug Standard Control Organization (CDSCO) cordially regulate the PV activity. To build a potential PV system in India, Pharmacovigilance Program of India (PvPI) have been proposed and implemented by the Indian government in 2010. The accurate detection and reporting of ADR is a heart of this system.

Keywords: Clinical trial; Safety monitoring; Data and Safety Monitoring Board (DSMB); Sequential Probability Ratio Test (SPRT); Bayesian methods

Abbrivations: PV: Pharmacovigilance; ADR: Adverse Drug Reactions; AE: Adverse Event

INTRODUCTION

Clinical trial data should be able to potentially reflect the safety and effectiveness of a drug for the successful launching of product in the market. Generally the clinical trials are carried in limited number/controlled population and only the common adverse effects can be traced. But, the reaction which develops after long duration and occurs in a specific individual remains undetected. This may be due to the presence of individual genotype and specific physiological conditions. Any medicine is said to be safe only when its benefits are greater than associated risk. So to determine the complete safety profile of medicine/drug a constant and continuous monitoring in a diverse population is essential which is possible in terms of pharmacovigilance deals with the complete study of drug related adverse effects and other problems. "Pharmakon" means "Drug" and "Vigilance" means "to keep watch or alert". Broadly speaking, all chemicals other than the food that can alter biological systems are called as drugs. However, if it produces harmful or toxic effect then it is regarded as a poison. Thus every drug is poison depending on the dose and use. The noxious and unintended reactions occurring at normal therapeutic dose are named as Adverse Drug Reactions (ADRs) [1]. While the untoward events occurred during drug therapy having no relation with its use is called adverse event adverse effect [2].

Aim of pharmacovigilance

The aims of pharmacovigilance are as follows

- To improve patient care and safety.
- To contribute to assessment of benefit, harm and effectiveness of medicine.
- To identify previously unrecognized adverse effects of the drugs.
- To promote rational and safe use of medicine.
- To promote education and clinical training.
- To identify patient related risk factors of adverse drug reaction such as dose, age, gender.

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• Any response to a drug which is unintended occurs at particular doses.

• To diagnose or therapy of disease, or for the modification, of physiological function. Pharmacovigilance helps in removal of approved and licensed products from the market because of clinical toxicity, which is caused by adverse drug reactions in the body. Below is a short note on adverse drug reaction.

Objective of pharmacovigilance

Not everything is known about a medicine when it receives its license for marketing. The merits of a new drug, balancing its beneficial and its untoward effects become established only after sufficient experience has been gained from its use in real practice. The reasons for the necessity of Pharmacovigilance are:

• Information on drug safety collected during drug development is incomplete as preclinical drug development processes involve the evaluation of drug safety and efficacy in animal experiments and often it may not be appropriate to extrapolate the results of animal experiments to human.

• Clinical trials are evaluated for limited duration and limited numbers of carefully selected patients in carefully selected settings and so it is extremely difficult to accurately determine actual efficacy, adverse effects and total risk-benefit ratio under actual clinical setting.

• Information is often incomplete or not available on

a) Rare but serious reactions.

b) Use of drugs in vulnerable groups (pregnant women, children, geriatric).

c) Risks of long term, repeated use and drug-drug, drug-food, drug-nutritional Supplement interactions.

• At the time of licensing, the drug is exposed to less than 5,000 human subjects. This allows only the most common adverse drug reactions to be detected.

• At least 30,000 people are required to be treated with a drug to be sure not to miss at least one patient with adverse drug reactions which has an incidence of 1 in 10,000 exposed individual [3,4].

Scope of pharmacovigilance

Pharmacovigilance is a booming concept which deals with chemical, botanical, and biological medicines including medical devices [5,6]. The information about suspect product is collected from healthcare providers and patients to detect and prevent abnormalities associated with it [7]. Therefore Pharmacovigilance deals with adverse effects of drug, poly-pharmacy, paradoxical reactions, and severe adverse events. It also covers vaccination failure, irrational use, and lack of efficacy, drug interactions, poisoning, overdose, abuse, medication errors and misuse of drug. The principle of pharmacovigilance was considered early from 1972 WHO technical support and stays an energetic, clinical and experimental principle. It has been set important to meet the consequences of wider range and potency of pharmaceutical and biological medicines including vaccines. When adverse effects and noxious appear, it is important that they are interpreted and interacted effectively to the public that has the observation to analyze the information to satisfy the pharmacovigilance contract for its marketed products as per regulations (Figure 1) [8].

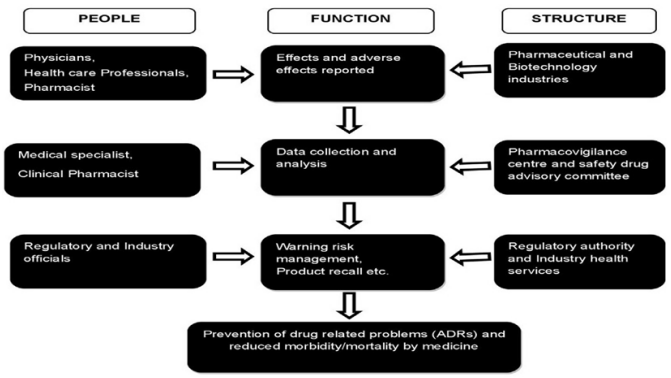

Figure 1: A typical pharmacovigilance setup.

Partners in pharmacovigilance

Management of the issues related to the use of medicines demands close and effective association between the key stakeholders in the Pharmacovigilance. The people responsible should jointly anticipate, elucidate and respond to the continually enhanced demands and expectations of the public, health administrator policy officials, politicians and health professionals. However, there is little prospect of this happening in the absence of strong and comprehensive systems which make such associations possible. The obstacles typically encompass lack of training, resources, political support, and especially scientific infrastructure. Understanding and tackling these are a necessary prerequisite for future development of the science and practice of pharmacovigilance [9].

Pharmacovigilance is the responsibility of everyone so that all drugs can be used safely. Furthermore, the Ministry of Health or its equivalent in any country of the world is not only responsible for monitoring drug safety but also needs commitment and collaboration between the different Pharmacovigilance partners.

A comprehensive list of these 'partners' includes:

• Healthcare professionals

a) Prescribers

b) Nurses

c) Pharmacist

• Patients

• Hospitals and academia

• Pharmaceutical Industry

• The WHO quality assurance and safety (Medicines Team)

• Uppsala Monitoring Center (UMC)

• National Pharmacovigilance Centers (NPC)

• Others partners of pharmacovigilance

Healthcare professionals

Safe medication use is critical for physicians, dentists, pharmacists and nurses. They have the responsibility to be vigilant of their patients of any issues related with drug therapy including,

a) Nature of the disease,

b) Purpose of medication, and

c) Any potential risks involved in its use.

They also have an additional responsibility to ensure that their patients have an adequat understanding of the nature of the treatment(s) they are taking.

Prescribers: It is a prerequisite that all involved in the process of prescribing of medicines have some knowledge of the potential adverse drug reaction so that an assessment of the balance between the beneficial and harm is considered before a drug is prescribed, dispensed and administered to a patient. Any medication or any kind of treatment should take in consideration all these factors including, the individual patient and their predisposition to drug toxicity. The intention of the prescriber is to use a medicine to help the patient, not harm them, as they hope all drugs used are without any risk. This should facilitate the key recognition that if the patient develops any undesired signs and symptoms it may be drug related and eventually turn out to be due to an adverse drug reaction [10]. Therefore, all the members of the healthcare team are required to be aware of the importance of adverse drug reaction reporting and that they are competent to provide practical information for reporting of adverse drug reaction They should have a familiarity with the policy and procedures of adverse drug reaction reporting and guidance as to how and when to report and where to actually send it.

Nurses: Traditionally nurses did not report adverse drug reaction. But some new developments for adverse drug reaction reporting have taken place for nurses and as they are now also able to prescribe drugs in some countries such as united states of America and the united kingdom as such prescribers they have the responsibility to report adverse drug reaction For example, in the united kingdom some nurses after October 2002 played a valuable part in the improvement of Pharmacovigilance by adverse drug reaction reporting [11,12]. A little later, in the Sweden, nurses could report adverse drug reaction and so contributed to the improvement of public health by the detection of suspected adverse drug reaction [13]. Currently, the contribution of nurses to the rate of reporting.

In some countries is quite significant, for example, Sweden 12%, Canada 16% and in the UK 21%. In contrast, the spontaneous nurse reporting in the Italian database is still lower than that in other countries. It is quite clear that nurses do represent an important and valuable source of reporting for adverse drug reaction.

Pharmacist: A pharmacist, in a dispenser of medicines, is in a "cornerstone position", he/she should be fully aware of any suspected adverse drug reaction. The pharmacist specifically focuses in making a contribution to adverse drug reaction reporting.

Patients

In 2005, the reporting system for suspected adverse drug reactions by patients to the regulatory authorities started in the UK (United Kingdom) via using (YCS) Yellow Card System. In 2009, adverse drug reaction reporting by patients in the UK (United Kingdom) Sweden, Australia and the USA (United States of America) were in the range of 18% to 20%, submitted using three major methods: postal, internet and telephone to provide assessment awareness. These methods were found fitting for the UK (United Kingdom) general population and indicated that the awareness was low and could be improved [14,15]. In the study by Van Grouchiest and Berg, 2004, which examined the role of patients in reporting adverse drug reactions, they concluded that, because patients have a positive value and involvement in drug therapy, their concern regarding possible adverse effects is a major factor in possible adverse drug reactions reporting. As a consequence, patients' reports on adverse drug reaction should be accepted albeit with care as is now done in the UK(united kingdom) The literature, as yet, does not provide any major results in relation to the detection of adverse drug reactions by patients, more recent studies are required to show their contribution worldwide. In any system where patients have taken medicines, their views and options about their therapy can be of great knowledge for adverse drug reactions reporting. It is, however, a difficult problem to address. Often, because of the brevity of the physician's consultation process, patients have little time to understand any warnings that may be given about the potential problems of their treatment(s). It could be argued that the inclusion of the patient's information leaflet should avoid such difficulties. However, this applies to people whose first language is English and, when they are used in Saudi Arabia, where many people who use the medicine do not read a high level of English, their value is very difficult if not impossible to assess. On the other hand, in a study by Hughes et al. adverse drug reaction reporting by patients was not considered by pharmacovigilance centers to be equivalent to those of the health care professionals as many of adverse drug reaction patient reports were incorrectly filled in, so increasing the overall work load for little gain [16].

Hospitals and academia

Collaborations between the pharmaceutical industry, academia and drug regulatory authorities has led to the development of pharmacovigilance as a clinical discipline. Only a small number of medical institutions provide medical student education related to adverse drug reaction during their curricula in pharmacology. So, the majority of healthcare professionals may graduate without an adequate background regarding drug adverse drug reactions Therefore, academic centers of pharmacology and pharmacy should provide knowledge of adverse drug reaction to healthcare professionals and the public by; training, teaching and research. In many schools of health and medical institutions the topic is still neglected. Consequently, there is a still greater need for integration of Pharmacovigilance by clinical practice so as to affect a system for adverse drug reaction monitoring to protect public health as suggested by WHO 10 years ago.

Pharmaceutical industry

Every company in the pharmaceutical industry has a vital role to play in the provision and supervision of drug safety and they must inspect all drug related information, from drug development to patient use, and should also consider the assessment of the safety of the drug and monitoring system. An important role exists in communication between the pharmaceutical company and drug regulatory authority that leads to an improvement by exchanged information [17].

The WHO quality assurance and safety: Medicines team

The provision of guidance and support to countries regarding drug safety matters is a function of the Quality Assurance and Safety: Medicines Team within World Health Organization (WHO). The purpose of the department is stated to be: "to help save lives and improve health by closing the huge gap between the benefit that essential drugs have to offer and the reality that for millions of people–particularly the poor and disadvantaged–medicines are unavailable, unaffordable, unsafe or improperly used". Clearly,

the purpose of Quality Assurance and Safety for Medicines team is "To ensure the quality, safety and efficacy of all medicines by strengthening and putting into practice regulatory and quality assurance standards". Hence, pharmacovigilance needs to be applied to all related health technologies, including medicines, vaccines, blood products, biotechnology, herbal medicines and traditional medicines.

Uppsala Monitoring Center (UMC)

During early 1960s, after the infamous event of 'Thalidomide disaster', various national schemes for collecting information concerning emerging drug hazards were implemented, and, in 1968, the world health organization set up an international drug monitoring programme. 10 years later, in 1978, the UMC was started and was made responsible for leading and managing this programme. Working with the world health organization collaborating centre for international drug monitoring UMC, world health organization promotes Pharmacovigilance at the country level 23, and encourages the participation in the world health organization programme for international drug monitoring. In addition, world health organization still highlights the importance of collaboration and communication at local, regional and international levels, so as to ensure pharmacovigilance delivers the necessary protection to the public this scheme was 86, and all these provided the necessary data for the world health organization programme with the collaborating centre in Uppsala, Sweden. This contrasts with the initial established national reporting system for adverse drug reaction which was for only 10 countries. In March 2010, the number of countries had grown to 97 and in addition there were a further 33 countries as "associate members" [18]. At the end of 2010, the number had increased to 134 countries and they were all part of the world health organization Pharmacovigilance Program. More recently, In May 2012, the number now stands at 142 countries. It can be seen that the Kingdom of Saudi Arabia (KSA) has been a member of the WHO IDMP since 2009.

On 30 March 2010, new information from the Uppsala monitoring Centre website showed that the global adverse drug reaction database they maintain for the WHO programmer contains 5 million adverse drug reaction reports from all the countries who are members of the WHO programmer. In 2011, the UMC-WHO, which managed the global database of Individual Case Safety Reports (ICSRs) and consists of reports of ADRs which were received from national centers in the WHO network database, is called "VigiBase". It currently contains over 6 million descriptions of individual cases which make a significant contribution to promoting global adverse drug reaction awareness. This information about adverse drug reaction is extremely useful and helpful as, unfortunately, many hospital admissions are caused by drug use. The Uppsala Centre can therefore clarify any problems should they occur. The Uppsala Center, to function effectively, requires constant new information about ADRs, where and when they occur [19].

The National Pharmacovigilance Centers (NPC)

In addition, most (MOHS) Micro graphically Oriented Histographic Surgery in their own countries can support pharmacovigilance National Centers fully or at least in part by comparing expenditure of medication with the NPC policies and regulatory guidelines.

In addition, The International Conference for Drug Regulatory (ICDRA) at their Annual Meetings of National pharmacovigilance provides an unparalleled opportunity for the WHO programme for International Drug Monitoring to be comprehensively and adequately discussed.

Others partners of pharmacovigilance

The media, advocacy groups, and lawyers can help in the contribution directly or indirectly to the creation of policies and legislation on pharmacovigilance by cooperation and communication with the proper authorities.

Method of pharmacovigilance

Pharmacovigilance methods that can be employed in specific circumstances are based upon de the local situation, experience, expertise, and resources available to achieve these objectives.

Active surveillance

This method depends on active follow-up of patients after treatment, and all adverse reactions are detected either by asking patients directly or by screening the patient records.

Cohort event monitoring

Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies generally are used to compare exposed patients to unexposed patients or one exposure to another [20]. Cohort studies have many advantages. They are the best way to ascertain both the incidence and natural history of disorder, temporal sequence between cause and outcome is usually clear, useful in investigation of multiple outcomes that might arise after a single exposure, useful in the study of rare exposure. It also has some disadvantages such as selection bias is built into such studies, follow up can be difficult [21]. Cohort event monitoring can be done with different epidemiological designs as follows:

Observational: This means that the studies are "non-interventional and are undertaken in real life situations. Patients are not selected according to any criteria: all patients who receive treatment are included until the desired cohort size is achieved. Patients of all ages, those with other diseases and those on other medicines are included in this. Treatment is given according to the usual local guidelines [22].

Prospective: This means that CEM is planned before the patients are treated and treatment is monitored until the end of the program, or until they cease to receive treatment for whatever reason.

Inceptional: In this every patient is followed-up for adverse events from the time of commencement of their treatment.

Dynamic: In this new patients are added as the study continues until such time as there are sufficient numbers in the cohort.

Longitudinal: In this the occurrence of any events in patients are observed over a period of time until the end of the programme, or until they cease to receive treatment with the monitored medicines.

Descriptive: In this all events are identified and described, their frequency is measured and their distribution in different subgroups of interest in the cohort is recorded and analyzed [23].

Sentinel Sites: Active surveillance can be achieved by reviewing medical records or interviewing and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported

adverse reactions from these sites. The selected sites can provide information, such as data from specific patient subgroups that would not be available in a passive system and information on the use of a drug can be targeted at sentinel sites.

Registries: A registry is a patient list presenting with the same characteristics. This characteristic can be a disease (disease registry) or a specific drug exposure. Pregnancy is also recorded as an event as part of the cohort event monitoring study. This helps to estimate the exposure to medicines during pregnancy [24].

Deaths: As part of cohort event monitoring, all deaths can be recorded, and their causes assessed by verbal autopsy. Where possible the data will be cross-tabulated with data from governmental records of deaths. In a study done by U. Mehta, they have carried out confidential enquiry into malaria related deaths which proved to be useful tool for identifying the preventable factors, health system failures, and adverse events affecting the malaria case management [25].

Data meaning of pharmacovigilance

Pharmacovigilance also known as drug safety surveillance is the science of enhancing patient care and patient safety regarding the use of medicines by collecting, monitoring, assessing, and evaluating information from healthcare providers and patients. In that view, Pharmacovigilance can be divided into two stages such as premarketing surveillance information regarding adverse drug reaction is collected from preclinical screening and phases I to III clinical trials; and post-marketing surveillance data accumulated in the post approval stage and throughout a drug's market life shown in Figure 1 [26].

PV has relied on biological experiments or manual review of case reports; however, due to the vast quantities and complexity of data to be analyzed, computational methods that can accurately detect ADRs in a timely fashion have become a critical component in pharmacovigilance. Large-scale compound databases containing structure, bioassay, and genomic information, as well as comprehensive clinical data sets such as Electronic Medical Record (EMR) databases, have become the enabling resources for computerized adverse drug reaction detection methods (Figure 2) [27].

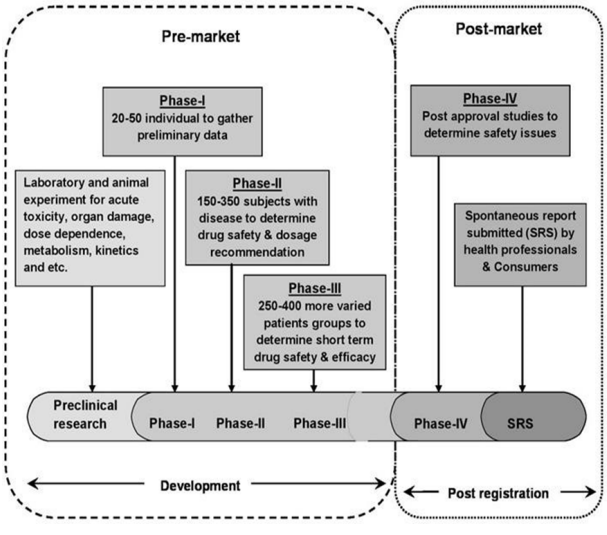

Figure 2: Pharmacovigilance at different stages of drug development.

Pharmacovigilance program in India

In India, consideration for the surveillance of adverse drug reactions developed relatively late, as traditionally there was no concept of surveillance of medicines in the country. Even though pharmacovigilance is still in its infancy, it is not new to India. It was not until 1986 when a few physicians, mainly from academic institutions, called for greater attention to be devoted to the potential adverse effects of prescription medicines and rational prescribing of medicines. This led to the formation of the first adverse drug reaction monitoring program consisting of 12 regional centers, each covering a population of 50 million, but was unsuccessful. Nothing much happened until a decade later when India joined the WHO Adverse Drug Reaction Monitoring Programme based in Uppsala, Sweden in 1997. Three centers for adverse drug reaction monitoring were identified, mainly based in the teaching hospitals: A National Pharmacovigilance Center located in the Department of Pharmacology.

All India Institute of Medical Sciences (AIIMS), New Delhi and two WHO special centers in Mumbai (KEM Hospital) and Aligarh (JLN Hospital, Aligarh). These centers were to report adverse drug reactions to the drug regulatory authority of India. The major role of these centers was to monitor adverse drug reaction to medicines marketed in India. However, they were non-functional as information about the need to report adverse drug reaction and about the functions of these monitoring centers never reached the prescribers and there was lack of funding from the government.

This attempt was unsuccessful, and hence, again from 1 January 2005, the WHO-sponsored and World Bank-funded National Pharmacovigilance Program (NPVP) for India was formulated NPVP structure [28]. The NPVP, established in January 2005, was to be overseen by the National Pharmacovigilance Advisory Committee based at the Central Drugs Standard Control Organization (CDSCO). Two zonal centers, the South-West (SW) zonal center (located in the Department of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai) and the North-East (NE) zonal center (located in the Department of Pharmacology, AIIMS, New Delhi) were to collect the information from all over the country and send it to the committee as well as to the Uppsala Monitoring Centre (UMC) in Sweden [29].

Three regional centers would report to the Mumbai center and two to the New Delhi one. Each regional center, in turn, would have several peripheral centers (24 in total) reporting to it. The program had three broad objectives. The short-term objective was to foster a reporting culture, the intermediate objective was to involve large number of healthcare professionals in the system in information dissemination, and the long-term objective was for the program to be a benchmark for global drug monitoring. However, this program also failed [30]. Recognizing the need to restart the NPVP, in a brainstorming workshop jointly organized by the Department of Pharmacology, AIIMS and CDSCO in late 2009, the framework of the new and current program was formulated. The program, now rechristened as the Pharmacovigilance Programme of India (PVPI) was initiated by the Government of India on 14th July 2010 with the AIIMS, New Delhi as the National Coordination Centre (NCC) for monitoring ADRs in the country for safe-guarding public health. In the year 2010, 22 ADR monitoring centers including AIIMS, New Delhi was set up under this programme [31]. To ensure implementation of this program in a more effective way, the NCC was shifted from the AIIMS, New Delhi to the

Indian Pharmacopoeia Commission (IPC), Ghaziabad, and Uttar Pradesh on 15th April 2011 [32]. The main aim of the NCC at IPC is to generate an independent data on the safety of medicines, which will be at par with global drug safety monitoring standards (Figure 3).

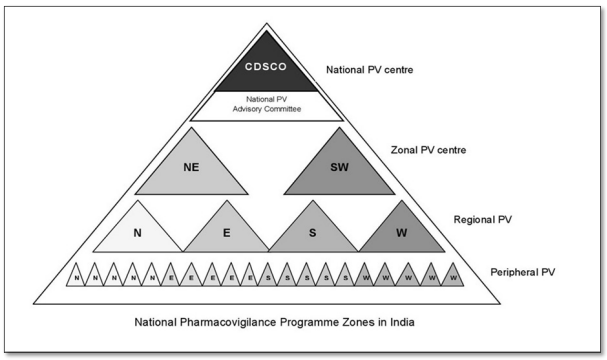

Figure 3: National pharmacovigilance program zone structure.

Clinical trials in India

Global pharmaceutical companies have found India to be a preferred destination for clinical trials because India's clinical research space and opportunities are very attractive [33]. Some of the advantages for clinical trials that India has as are as follows:

- High degree of compliance to international guidelines such as the International Conference on Harmonization (ICH)/WHO Good Clinical Practice (ICH-GCP) and the regulations lay down by the US Food and Drug Administration.
- Availability of well qualified, English speaking research professionals including physicians.
- Ongoing support and cooperation from the government.
- Lower cost compared to the west 36.
- Increasing prevalence of illnesses common to both developed and developing countries.
- Availability of good infrastructure.
- Changes in Patent Laws since January 2005.

As per a recent report from Federation of Indian Chambers of Commerce and Industry (FICCI), scientific feasibility, medical infrastructure, clinical trial experience, regulations, commercialization potential and cost competitiveness are some of the growth drivers responsible for the metamorphosis of Indian clinical research in the recent past [34]. Indian-born Contract Research Organizations (CROs) were able to offer the advantages of understanding the Indian scenario better, provide services at more competitive costs, and having better knowledge of Investigator sites in the country compared to the newer entrants in the market. India's existing favorable regulatory framework and regulations with international standards, increasing awareness of good clinical practice guidelines and its implementation by clinicians are some of the main reasons propelling the growth of clinical research in India [35,36]. The therapeutic area wise distribution of clinical trials and availability of diverse patient population across major therapeutic segments in India is shown in Figure 4.

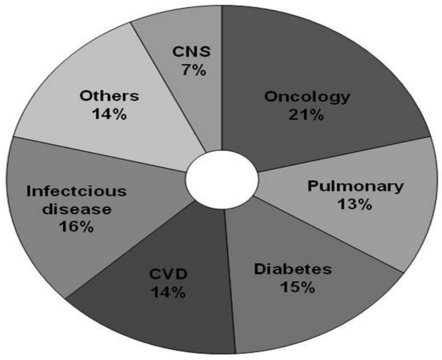

Figure 4: Therapeutic area wise distribution of clinical trials outsourced to India.

Agencies involved for clinical research regulation in India

For the purposes of clinical trials, regulatory approvals include any approvals by government or health authorities regarding any research that includes human subjects. Additional approvals will be necessary if the research involves the use of an FDA regulated product (Table 1).

Table 1: Role of various regulatory agencies.

S. No.	Agencies	Role of agencies
1	Drug Controller General of India (DCGI)	Implementation the National Pharmacovigilance Program (NPP) in India.
2	Central Drug Standard Control Organization (CDSCO)	Operate under the supervision of the national pharmacovigilance advisory committee to recommend.
3	Department of Biotechnology (DBT)	Provides product evaluation and validation through support for limited and large scale field trials for agriculture product and clinical trial for health care product.
4	Ministry of Environment and Forests (MOEF)	Project advisory committee approves guidelines for making data entries of the information provides by the environmental experts through the field trial for agricultural products and clinical trials for health care product.
5	Indian Council of Medical Research (ICMR)	Brought out policy statement on ethical consideration involved in research on human subject in 1980 revised these guideline in 2000 as the ethical guideline for biomedical research on human subject.
6	Central bureau of narcotics	Closely monitor all clinical trials require additional narcotics compliance relating to storage import-export quoties and movement of the investigational drug.
7	Ministry of Health and Family Welfare (MHFW)	An autonomous body for setting of standard for drug, pharmaceuticals and healthcare devices and technologies in India.
8	National pharmacovigilance advisory committee	Collates, analyzes and archives adverse drug reaction data for creating healthy environment for the regulatory authorities to analyze the drug to be marketed in India.

Services enhancing pharmacovigilance activity in India

Services enhancing pharmacovigilance activity in India are as follows:

Helpline facility for the assistance of adverse drug reaction reporting: Considering the use of telecommunication and phone connectivity in India, PvPI-NCC launched a toll free helpline number (1800 180 3024) on 11 October, 2013 which helps to increase the involvement of the patients, stakeholders and public in adverse drug reaction reporting. This attempt created awareness and improved data collection from all parts of the country, which was very difficult previously.

After receiving the adverse drug reaction data an acknowledgement message used to drop to the sender. This message facility creates positive impact and builds confidence in public which ensures honest and timely reporting of adverse drug reaction for enhancing drug safety [37,38].

Android mobile application for adverse drug reaction reporting: In developing countries due to lack of basic facilities and easy going procedures results in under-reporting of adverse drug reaction which is a serious concern. India is growing at faster rate in (IT) Information Technology sector which is a great opportunity to utilize for public health. India has 1.27 billion populations out of which approximately 77.58% of people are using mobile phones and getting information on single click. Considering the huge internet connectivity it was more appropriate to introduce the concept of reporting and communication of adverse drug reaction with pharmacovigilance program in India, stakeholders and population through smart phones. For easy and faster reporting of adverse drug reaction, national cadet corps pharmacovigilance program in India had developed a mobile app in association with NSCBMC (Netaji Subhash Chandra Bose Medical College), Jabalpur, on 22 May 2015. This approach was much inspiring to several Clinical Research Organizations (CRO's) or companies to create and own user friendly adverse drug reaction reporting app and websites.

Feedback form for Health Care Professionals Pharmacovigilance (HCPs): A feedback form from the health care professional is collected at the pharmacovigilance program in India to ensure smooth running of pharmacovigilance activity. Health care professional can write their views, problems and suggestions to the pharmacovigilance authority by filling a prescribed form available on the official website. Taking feedback from health care professional creates good impact amongst them and boost ups the pharmacovigilance process.

Feedback form for consumer: Some private organizations have the feedback form on their official sites for consumer. Consumer can directly report adverse drug reaction suggestions and any other problems related to the product by filling a respective feedback form, via email or post.

Safety data reporting of ongoing marketed product

PSUR (Periodic safety update reports) is provision to check the safety of marketed product. In India, it is mandatory for Marketing Authorization Holders (MAHs) to submit PSUR to CDSCO twice a year for 2 consecutive years. For the first time in December, 2013 the representatives from MAHs, CDSCO, and NCC-PvPI were participated in an interactive session on "Review of PSURs/Post Marketing.

Surveillance data and PV Planning of Marketed Products" held at New Delhi. Aim of this meeting was to enhance the participation of MAHs in pharmacovigilance program in India.

Availability of ADR reporting form in vernacular languages: India is a multi-linguistic nation hundreds of languages spoken in India. Due to this reason flexibility in language is required to ease the process of adverse drug reaction reporting. The final goal of PV system is to ensure the safety of medicine among the population. By considering population growth and number, patients or general public can submit adverse drug reaction spontaneously by filling suitable form available in their convenient language. This vernacular languages facility was started on 1 Aug. 2014, at NCC-PvPI. Patient or his/her representative/relatives are promoted to fill the form (Medicines Side Effect Reporting form for Consumers" i.e. blue form) or E-mail at pvpi.compat@gmail.com. This form is available in Hindi, Marathi, Bengali, Kannada, Assamese, Odiya, Telugu, Tamil, Malayalam and Gujarati languages and can be downloaded from official website of IPC www.ipc.gov.in [39].

Educational courses and training program on Pharmacovigilance: For the enhancement of the pharmacovigilance activity, proper education and training related to pharmacovigilance activity throughout the country is essential. To fulfill this criteria the NCC has recognized nine medical institutes that can provide PV training which are situated at regional level particularly in major cities like Mumbai, Mysore, Chandigarh, Kolkata, Bhopal, Ahmedabad, Rishikesh, Hyderabad. In addition some Indian universities have adopted pharmacovigilance as B Pharmacy subject which will boost the pharmacovigilance knowledge, create awareness and build new personnel to enhance the drug safety. Several private institutions are also providing certificate course of pharmacovigilance. Separate pharmacovigilance journals are available which continuously highlight the current trend in pharmacovigilance.

Collaborations with various government and private hospitals: Every year pharmacovigilance program in India signs memorandum of understanding with various eligible hospitals and health care institution to enhance reporting and the pharmacovigilance activity. 250 authorized reporting centers approved in India till Jan 2017 from various states. A special notification on pharmacovigilance program in India website is available viz. The interested government and private medical colleges and corporate hospitals to become an adverse drug reaction monitoring centers, please furnish the 'Letter of Intent' and submit us round the year.

Collaborations with Central Drug Standard Control Organization (CDSCO): Pharmacovigilance program in India is working closely with collaborations with central drug standard control organization zonal offices and other health authority of India. Collaborations with central drug standard control organization know that pharmacovigilance activity assure safety of medicine in India. It takes opinion of national cadet crops before making regulatory decisions. The NCC in collaboration with other national and international organizations promotes safety of medicines excellent pharmacovigilance Centre in India. To know the global scenario and building of strong pharmacovigilance system in India, PvPI-NCC works in association with the WHO-UMC based in Sweden.

Collaboration with WHO-Uppsala monitoring centre (UMC) and other health authorities: (WHO) World Health Organization is the topmost health regulatory authority in the world [40]. This authority frames guideline and provides technical support to greater than 130 countries in the world. Final goal of pharmacovigilance is to develop.

WHO-UMC regulations following activity

Training of the HCPs and related staff at the pharmacovigilance

program in India-NCC and AMC throughout the country. Ensures use of vigi-flow software at pharmacovigilance program in India. Access to vigi-flow, which contains worldwide medicines safety data and early information about potential safety hazards of medicines (worldwide data). Technical support to stakeholders in matters published and distributed by pharmacovigilance program in India–NCC regularly.

Pharmacovigilance program in India-national cadet corps work in association with following authorities: Drug Controller General of India (DCGI), CDSCO, Department of Biotechnology (DBT), Ministry of Environment and Forests (MOEF), Indian Council of Medical Research (ICMR), Central Bureau of Narcotics(CBN), Ministry of Health and Family Welfare (MHoFW), National Pharmacovigilance Advisory Committee (NPAC), (AEFI) An Adverse Event Following Immunization, Immunization Technical Support Unit (ITSU).

Future of pharmacovigilance

Below are a few challenges to pharmacovigilance

a) Pharmacovigilance should consider the negative comments at least level and should enhance the awareness of safety towards public.

b) Complicated risk-benefits decisions are responsible and likely to increase the use of formal-decision analysis.

c) Pharmacovigilance should be made aware in a culture of scientific development. It needs a proper and right supports from various preparations, a good academic base and wider availability of training and resources.

d) Systematic analysis of pharmacovigilance process and the results should be enhanced and performed based on the standards level [41].

Challenges of pharmacovigilance

Below are a few challenges to pharmacovigilance

a) Globalization.

b) Web-based sales and information.

c) Broader safety concerns.

d) Monitoring of established products.

e) Orthodox bias in drug research.

f) Larger gaps between guidelines and laws.

g) Poor knowledge of medical professionals in drug Administration.

h) Lacking experienced resources in Pharmacovigilance.

CONCLUSION

In India pharmacovigilance system has increased awareness in people regarding ADR reporting. The issues of under-reporting are resolving due to available reporting facilities like toll free dial number, message, mail and adverse drug reaction form in vernacular languages. Various multinational companies have started the outsourcing of pharmacovigilance activity in India which is creating the good pharmacovigilance culture. Various universities have incorporated pharmacovigilance courses in their curriculum as compulsory or elective subject. Still government needs to focus on the awareness and enhancement of pharmacists' knowledge and providing them facilities and power to conduct pharmacovigilance activity. Every hospital should have the special pharmacovigilance cell to monitor and report the adverse drug reaction. Considering the Indian population, talent and interest of HCPs and current development in pharmacovigilance sector, India will be the hub and outsourcing centre for global pharmacovigilance activity in near future. Pharmacovigilance gives information to assess the safety profile of a pharmacovigilance is largely dependent on the participation of professionals of health care countrywide to report ADRs/AEs, Current progress in Pharmacovigilance is marked by increase in use of databases to make the process more proactive and organized. It must be in everyone's interest to develop safe and effective medicines to patients.

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