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Significance of Pharmacovigilance Program in Context of Adverse Drug Reactions (ADRs)

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Abstract

This paper will discuss about the need for safe usage of drugs and monitoring in the perspective of Adverse Drug Reactions (ADR). The Pharmacovigilance program will emphasize on patient safety improvement by early detection and future avoidance of any negative consequences from the use of the drug. Hence, the discussion will be around the implementation of an effective regulatory system, clinical practices, and public health programs. Moreover, it will also will also evaluate the necessity of collecting sufficient data before marketing any drug, country wise evidence of adverse reactions, and the advantages of including the consumers in ADR reporting to attain the highest standard of health. The paper will also concentrate on limitations, like the challenges of recognizing the adverse events, underreporting, and quality report submission on the basis of population exposure, for emphasizing the necessity of reducing the adverse effects on the patients and improving their quality of life.

Introduction

The Pharmacovigilance is now considered as an important program in the healthcare industry for avoiding the adverse drug reactions (ADR) globally. The pharmaceutical companies are now understood the need for drug safety and monitoring before marketing any drug to ensure the rationalize prescription of the drugs as well as accomplishing the ultimate objective of improving the overall healthcare system (Rivkin, 2007). The spontaneous reporting of adverse drug reactions and adverse events are recognized as one of the major health care problems for causing the patient morbidity and mortality. It has been observed that even in normal therapeutic use, the drug or medicine can potentiate an adverse reaction. Even the normal doses of prescribed medications for the prophylaxis, diagnosis, treatment or modification of physiological function can cause noxious and unintended drug reactions (Bord&Rachl, 2006). Hence the constant need for increasing the awareness regarding the Pharmacovigilance program is presumed to create an environment that will foster the rational and safe use of medicines.

The management and control of diseases are now changed a lot due to the modern medicines. In spite of attaining a lot of benefits, the evidences of adverse reactions to medicines also exist which are often accountable for illness, disability or even death (Brawn &Castleden, 1990).

Apart from exhibiting intrinsic dangers associated with these products, the individual sensitiveness to products also observe to in a particular and unpredictable way.

The recommendation of more than one medicine can also be associated with a risk of negative interactions (Bhosale et al., 2013). As such, it can be stated that the adverse reactions of the drugs can only be preventable by the skilled practitioners if they ensure prescribing of best and safest use of medicines out of many available choices. Further, the ADRs can also be preventable if approval of medicines is granted after accumulating substantial evidence of case reports, both scientific and legal, to facilitate the Pharmacovigilance surveillance procedure for drugs. Moreover, the necessity of an advanced Pharmacovigilance system has been emerged in the context of forceful marketing of new drugs by the pharmaceutical companies to ensure the transparency in the global assessment system of drug safety (Bord&Rachl, 2006). Besides pharmacist can adopt a proficient attitude in informing the regulatory authority about the suspected cases. Although in a number of countries the significant role of the pharmacists have been acknowledged, yet in some countries, specifically the Nordic countries, their reporting is not accepted by the registration authorities. Hence, the requirement of a universal assessment system has been emerged to review the existing and potential drug risks, significance of availability of adequate data, and the potentially at-risk scenario where the drugs, with no pre-approval, are used (Rivkin, 2007).

Literature Review

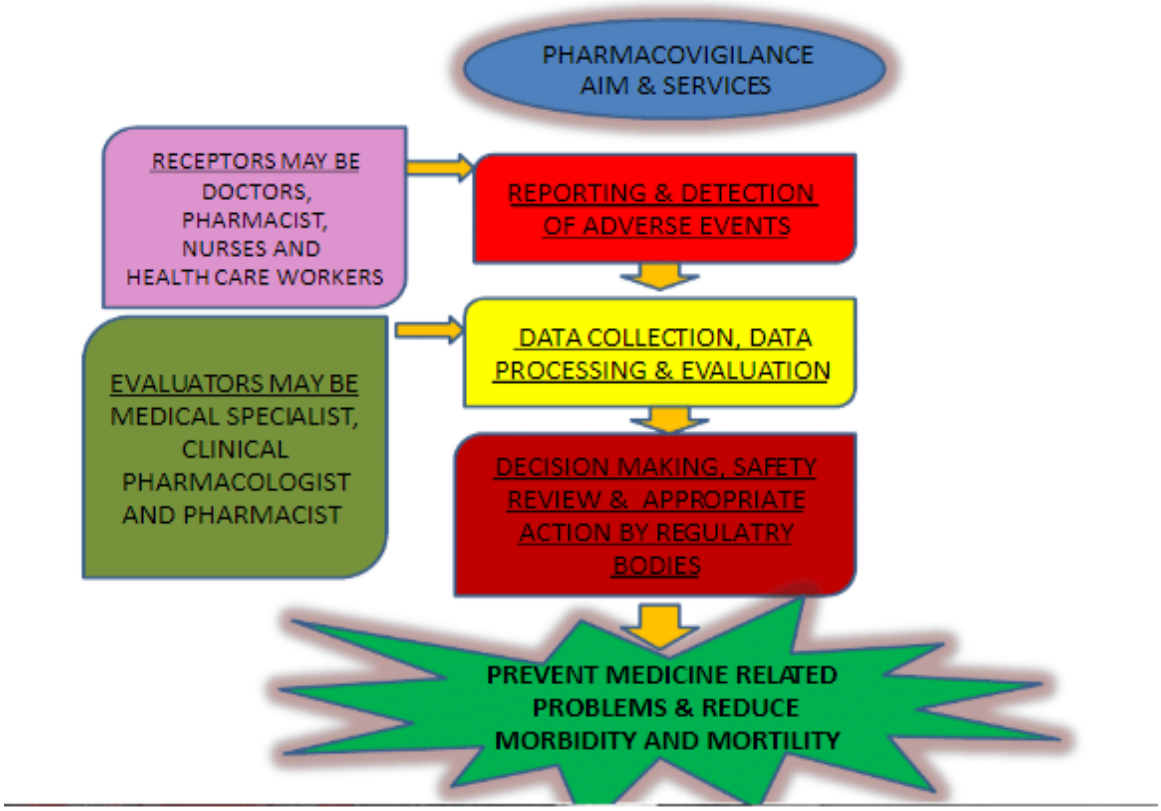
The branch of ‘Pharmacovigilance’ is connected with the scientific activities for identifying, evaluating, and preventing the adverse reactions of medications after acquiring full know-how. Throughout the world the ‘Adverse Drug Reactions’ (ADR)will continue to sustain as a leading threat to public health as long as drugs are used for treating various ailments. In spite of a lot of research before releasing any medicine in the market, they still include the possibility of lack of efficacy and it may result from overdose, misuse or abuse of a medicine (Bhosale et al., 2013). The medicines, once released in the market, are used on patients, who may have different diseases, and as such by using with several other drugs as well as other factors affect the way they react to the medicine. As different medicines use different ingredients and their way of production is also dissimilar, therefore their reactions also vary from patient to patient. Hence, to minimize the adverse drug reactions each country should monitor every aspect, including probability of poisonings associated with traditional and herbal remedies (Brawn & Castleden, 1990). Further, strict regulations should be imposed by each country with effective support from the health professionals, to prevent the unnecessary sufferings and decrease the financial burden of the patients from misuse of medicines.

In recent times the healthcare segment is concerned with the issue of drug safety as adverse drug reactions (ADRs) do not only pose a risk to the patient’s safety, but also in affecting the quality of public life adversely with significantly increasing the healthcare cost. Due to the priority of the drug safety issue, the pharmaceutical companies also need to address this issue properly before launching any drug on the market (Rivkin, 2007). The requirement of Pharmacovigilance has

been emerged in the context of the thalidomide tragedy in the 1960's which significantly highlighted the issue of limitation of clinical trials as it's unable to generate sufficient information for safeguarding the public health. Hence, the Pharmacovigilance program in recent times is covering the following aspects-

- Drug safety after authorization for marketing and (Brawn &Castleden, 1990)
- Provision of continuously monitoring the drug safety as part of the regulatory requirements (Rivkin, 2007)

Therefore, the following layout will give a brief overview of the aim and services of the Pharmacovigilance program-



Source: https://www.researchgate.net/publication/265988270_Pharmacovigilance_An_Overview

Figure 1.Structure of Pharmacovigilance Program

The World Health Organization (WHO) has distinctly emphasized the need of the Pharmacovigilance program as the ultimate aim of this program is to ensure the safe and rational use of medicines with preventing the negative consequences of pharmacotherapy (Carbonin et al., 1991). Hence, to ensure the drug safety and prevent the adverse reactions, the countries should strictly adhere to the principal aims of this Pharmacovigilance program, which are as follows-

- In context of patient safety, initiatives should be undertaken to promote the awareness of the significance, detriment, efficiency, and hazard of medicines (Rivkin, 2007)

- Effective communication should be managed with the health professionals and community in respect of awareness on adverse drug reactions (ADRs), including encouraging edification, education, and clinical training in Pharmacovigilance (Carbonin et al., 1991)
- Promoting rational and safe usage of drugs, including ensuring the cost-effective aspect to assist the public in avoiding the financial losses (Rivkin, 2007)

On the basis of the above analysis, it can be stated that a well-structured program should be built up for effective monitoring of adverse drug reactions (ADRs). The main objective of this program is to data organization for appropriate analysis and recommending properly to the regulatory authority for implementing suitable risk management. However, in recent times the significance of Pharmacovigilance has been increased to the healthcare professionals and scientists due to thereporting of drug recalls increases (Brawn &Castleden, 1990). Besides, the high-probability of drug-related complications in the Intensive Care Units (ICUs) is quite obvious as so many technologies are needed to support medical care for the patients with special needs. It can also be stated that ICU patients may have high-risk exposure to ADR mostly due tomulti-organ dysfunction and altered pharmacokinetics parameters (Edwards, 2000).Further, from the research studies on adverse drug reactions in developed countries, it can be stated that an estimated 5% of hospitalized patients are admitted due to ADR and 6-10% of in-patients will suffer from serious ADR consequences during their stay in the hospital. However, all these statistical figures are unable to present a comprehensive picture of the ADR consequences as the research studies generally exclude the overdose, drug abuse and therapeutic failures.

So, the Pharmacovigilance program should include the healthcare professionals for spontaneous reporting of the ADRs as it is regarded a cornerstone of this program. It has been observed that a well-structured Pharmacovigilance program should include all drugs, including those which exist for many years. This program must be aligned with the drug regulators and other stakeholders, to remain consistently vigilant to drug safety issues (Edwards, 2000). This ongoing process of continuous monitoring is aimed for detecting previously unknown adverse reactions, identifying risk factors that pre-dispose to drug toxicity, and analyzing the rate of causality due to the ADRs. However, the benefit risk ratio is closely related to evaluating the drugs as on the basis of all these information the drug regulators can take appropriate decision for restricting or withdrawing any drug (Brawn & Castleden, 1990). So, in the next section discussion will be around the ADRs, drug safety, and the Pharmacovigilance program to strengthen the whole system as well as avoiding the major negative impact on the public health.

Adrs, Drug Safety, and Pharmacovigilance Program

The adverse drug reactions (ADRs) can be related to an unintended and noxious effect of a medicine, even if prescribed in the normal dosage, which generally occur due to lack of proper product data at the time of the clinical trials. So the life cycle of the drug should be well-connected to clinical fundamentals wellbeing and post-exhibiting Pharmacovigilance (aka post advancing investigations) to reduce the recent withdrawals of the high number of noticeable

drugs (Graf et al., 2005). Hence, the pharmaceutical business throughout the globe should strictly adhere to the following activities for avoidance of the adverse drug reactions-

- Spontaneous reporting system
- Establishment of national Pharmacovigilance centers (Brawn &Castleden, 1990)
- Every country should collect and accumulate sufficient safety data by using other effective methods(Graf et al., 2005)
- Abide by the WHO program for international drug monitoring (Carbonin et al., 1991)

Therefore, it can be stated that the frequency of ADRs generally depends on the age, sex, and duration of hospitalization. As such the ADRs can generally be segregated into Type A and Type B. In case of Type A reaction, it is predictable and associated with the pharmacological actions of the drug. Whereas Type B is contrary to Type A and thereby defined as idiosyncratic reaction. However, Type A reaction is more prevalent than the Type B and both of them are significantly accountable for mortality and morbidity(Graf et al., 2005). According to recent assessment it has been found that in the USA the adverse drug reactions (ADRs) are considered as fourth to sixth major cause of death. Moreover, from research studies, it has been found that hospitalization due to ADRs is considerably higher in some countries, whereas in-patients suffering from ADRs during their hospital stay is another significant aspect of this problem (Kharkar&Bowalekar, 2012). Hence, it has been suggested that appropriate monitoring of ADRs should be managed to safeguard the patients and also at the same time for preventing the ADRs.

On the basis of above analyses the issue of drug safety and Pharmacovigilance can be correlated as it is the best way to attain the quality health right. The Pharmacovigilance program should ensure transparency in each and every phase for rationalizing the prescribed drugs as well as regulation procedure (Kharkar & Bowalekar, 2012). Due to lack of sufficient data and major limitations of animal testing the clinical trials are unable to accurately predict the safety of their products on human. Further, the limited human subjects and time frame, during the clinical trials, are also liable for the ADRs. Therefore, to enhance the drug safety it can be suggested that the Pharmacovigilance program should include the following criteria within the whole process-

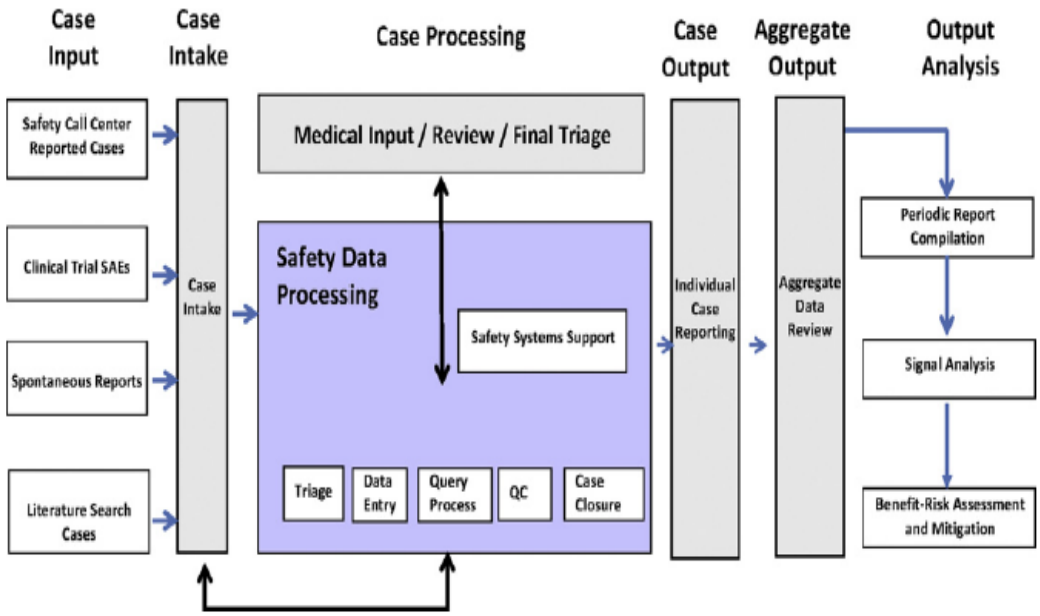
- The pharmaceutical companies should conduct post-marketing surveillance (Bowman, Carlstedt, & Black, 1994)
- Systematic monitoring should be managed for effective identification of safety related issues throughout the life cycle of any drug (Kharkar & Bowalekar, 2012)

However, it has been observed that the consumers can play a key role in ensuring drug safety as the direct reporting is considered as an essential factor in improving as well as managing their own health. Hence, in this complex nature of vital relationships between the different stakeholders, the Pharmacovigilance program should establish an integrated support group, including the health professionals, administrators, public, and policy officials, to assure the quality public life as well as their safety.

New Work Comparison Analysis

However, the critical issues of adverse drug reactions (ADRs) and drug safety should be managed significantly as they are necessary for managing public health risk. Hence, to build an effective Pharmacovigilance program safety information should be accumulated from a variety of sources, including trials statistics, reporting, medical journals, electronic health records databases, and other significant ones (Gould, 2007). Thereby to reduce the ADRs in recent time, researchers have emphasized on exploring the alternative ADR signal discovery approaches, like mining structured and unstructured data in electronic medical record (EMR) systems. In observational research process, the institutional EMRs are now considered as a distinctive method in detailing the patient information as well as for containing the copious longitudinal clinical data (Wang et al., 2009).

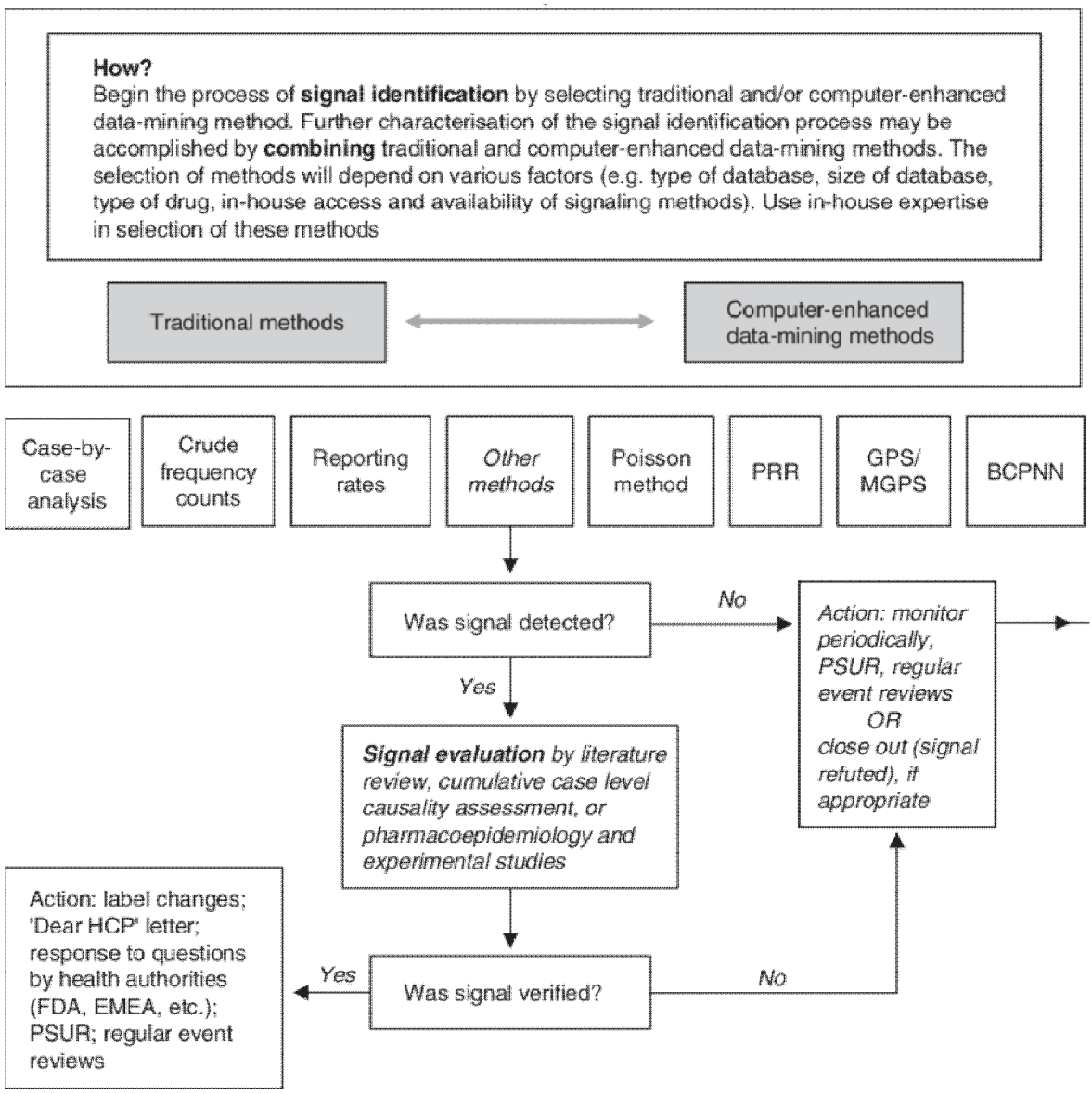
However, in the past the risk/benefit assessment of medicines was treated as therapeutic tools in the clinical pharmacology. The pharmacology perspective of the drugs can be viewed as the balance between the expected benefits (investigated before granting approval for launching in the market) and possible risks (adverse effects) (Hauben, 2004). Moreover, only a distinctive time period can present a clear picture after marketing the drug. As such the aggregate data should be systematically analyzed for safety issues and benefit versus risk outcomes to submit the periodic safety update reports (PSURs) to the regulatory authorities (Wang et al., 2009). The following layout will give an overview of the major activities of the Pharmacovigilance process and risk mitigation planning-



Source: https://www.researchgate.net/publication/233539123_Comparative_analysis_of_pharmacovigilance_methods_in_ the_detection_of_adverse_drug_reactions_using_electronic_medical_records

Figure 2.Risk Mitigation in Pharmacovigilance Program

During the drug development phases several statistical measures, under data mining techniques, are widely applied for accumulating databases to make a significant distinction between the ADR signals and retrospective EMR data. While in some cases the ADR signals may report major adverse reactions, the EMR-derived laboratory data may assist in overcoming the errors caused by biased reporting before marketing the drugs (Hauben, 2004). As such the post-marketing surveillance generally includes the bio-statistical and data mining algorithms. The drug discovery is not the ultimate step in ensuring the drug safety and as such it must be combined with the data mining method to ensure long-term drug safety by exploiting the large chemical as well as biological databases. The straightforward Pharmacovigilance methods in spontaneous reporting systems (SRSs) should include the frequentist metrics calculation (Hauben, 2004). With the help of these methods it is possible to evaluate whether a drug-ADR pair is biased or not. Further, some more complex algorithms are considered, like GPS, MGPS, and EBGMs, all of which are based on Bayesian statistics. The Bayesian logic also helps in identifying the false discovery rate (FDR) and addressing the limitations of the arbitrary thresholds. Data mining algorithms are extremely helpful in analyzing drug-ADR associations from spontaneous reporting. Many research studies also help in identifying drug-drug interactions (DDIs) from adverse event reports by analyzing the latent signals as the indirect evidence of the ADRs can be obtained from this analysis (Gould, 2007). Although little work has been done to explore the large EMR databases for analyzing the ADR signals involving the drug-laboratory test interactions, yet by mapping the EMR data a more reliable outcome can be achieved. Hence it can be stated that by using the data mining techniques, clinical pharmacology has been able to accomplish a new height with proper identification of new effects of drugs and appropriateness in drug usage (Wang et al., 2009). By using this methodology, data management, a part of data mining techniques, can be done effectively as the statistical methodologies are appeared to be helpful in finding the possible associations between the drug and effect. As DMAs often provide high-level accurate outcomes in terms of timely prediction of risk, therefore such information can be used for proper planning and implementation of effective strategies in respect of drug safety issues. As such the modern Pharmacovigilance program will be benefitted a lot by adopting all these data mining techniques (Hauben, 2004). The following layout will give an overview of the whole process to recommend the integration of newly emergedstatistical and traditional methods-



Source: https://www.researchgate.net/figure/Integrating-computer-enhanced-data-mining-methods-and-traditional-pharm acovigilance_fig1_7534434

Figure 3.Data Mining Techniques in Pharmacovigilance Program

Conclusion

From the above analyses it can be understood that adverse drug reactions (ADRs) are a serious issue for the healthcare segment as it not only affects the well-being of patients, but also the society at large due to the limitations of the clinical trials in ensuring the drug safety. Although some common ADRs can be detected during the clinical trials, yet some rare form of ADRs remains undetected for lack of adequate data during the trial process. In spite of all these drawbacks, the Pharmacovigilance program should assure the drug safety by proper drug monitoring and management of ADRs. In this regard the support of all relevant stakeholders, such as health professionals, public, health administrators, and policy officials, is very much necessary in effectively conducting the drug monitoring, ADR management, as well as in

furnishing stimulated and systematic on-line reporting of adverse events. Apart from using the data mining algorithms (DMAs) as an effective statistical tool to analyze the drug-drug interactions (DDIs) and drug-related syndrome, the same should be applied for proper planning and implementation of advanced strategies in respect of drug safety issues. Hence, the Pharmacovigilance program in recent time has changed a lot by embracing the new technologies and specific coverage of the WHO program for international drug monitoring. Specifically, it can be stated that the healthcare professionals have greater obligations for the ADRs as high-percentage of under-reporting throughout the world has posed major challenges for the scientists during the clinical trials. Further the limitations of spontaneous reporting systems (SRSs) are also liable for not generating the desired signal for uncommon type of adverse reactions. As such, it can be stated that the healthcare professionals must be ethically obliged in making the Pharmacovigilance program more functional. In the conclusion it can be recommended that the above criteria should be well-integrated to ensure the safe use of the drug throughout the world and at the same time reducing the mortality as well as morbidity of the populations at-risk to a large extent.

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