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Review Article

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## Pharmacovigilance Methods: A Review

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### ABSTRACT

Pharmacovigilance is “defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, principally long term and short term adverse effects of medicines. It is an important and integral part of clinical research. India is the world’s second most billion potential drug consumers. Although, India is participating in the UMC program, its contribution to the UMC database is very little. This problem is essentially due to the absence of a robust ADR monitoring system & also the lack of awareness of reporting concept among Indian HCP. The specific aims of Pharmacovigilance are to advance patient care and safety in relation to the use of medicines and all medical and paramedical interventions contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, promising their safe, rational and more effective use, promote indulgent, education, and clinical training in Pharmacovigilance and its effective communication to the public. Pharmacovigilance methods must also be capable to designate which patients are at risk of developing an ADR. A suitably working Pharmacovigilance system is important if medicines are to be used cautiously. It will be advantageous for healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It aids pharmaceutical companies to monitor their medicines for risk.

**Keywords:** Adverse drug reaction; India; Pharmacovigilance, Uppsala monitoring center

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## 1. Introduction

It has been known that world health organization (WHO) has initiated the program of reporting all adverse reactions possessed by the drugs. The further awareness about the adverse drug reactions resulted in the emergence of the practice and science of Pharmacovigilance [1]. It is defined as the pharmacological science relating to the recognition, assessment, understanding and prevention of adverse effects, particularly long term and short term adverse effects of medicines. [2, 3] After discovery & pre-clinical phase the drug typically undergoes trials in human volunteer. Clinical trials are very well regulated & are no longer an overlooked practice by the pharmaceutical manufacturer. Trails are closely monitored by the investigator & the manufacturing, industrial company and it is a mandatory regulatory requirement to report all the adverse events in a clinical trial setting in a given time frame. At least in the clinical trial setting GCP has moved the Pharmacovigilance word from a reactive to a proactive approach.

A robust, well-defined Pharmacovigilance system for monitoring adverse events is in a place for evaluating the safety of the investigational new drug.[4] Moreover, its concerns have been widened to include the herbal drug products; traditional and complementary medicines; blood products; Biologicals; medical devices; and vaccines. In addition, Pharmacovigilance possess various roles like, identification, quantification and documentation of drug-related problems which are responsible for drug-related injuries. [5,6] An adverse event is any untoward medical occurrence in a patient administered a medicinal product & which doesn't necessarily have a drug reactions are noxious & unintended responses to a medicinal product. A reaction, in contrast to an event, is characterized by the fact that a causal relationship b/w the drug & the occurrence is supposed. India is the world's second most potential populated drug consumers. Although, India is participating in the UMC program, its contribution to the UMC database is very little. This problem is essentially due to the absence of a robust ADR monitoring system & also the lack of awareness of reporting concept among Indian HCP. With over 1 billion US worth of clinical trials conducted in India, it is very important to focus on the attention of the medical community on the importance of adverse drug reporting to ensure max. Benefits for public health and safety. For regulatory reporting purposes, if an event is instinctively reported, even if the relationship is mysterious or unstated, it meets the definition of an adverse drug reaction. [7, 8]. A serious AE (SAE) is any untoward medical manifestation, that at any dose:

- Results in death. Is life-threatening (well-defined as an event in which the subject was at risk of death at the time of the event)
- Requires in-patient hospitalization or causes prolongation of existing hospitalization. Results in persistent or significant disability / incapacity
- It is a congenital anomaly/birth defect. Is an important medical event (defined as an medical event(s) that may not be immediately life-

threatening or result in death or hospitalization but, based upon suitable medical & scientific judgment, may require intervention to prevent one of the serious outcomes as listed above).[9, 10]

### The definite aims of Pharmacovigilance are too:

- Advancing patient care and safety in relation to the use of medicines and all medical and paramedical interventions
- Advance public health and safety in relation to the use of medicines
- Contribute to the valuation of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective use
- Promote understanding, education and clinical training in Pharmacovigilance and its effective communication to the public. [11]

Under reporting occurs when the medicinal product hits the market after going through all the required authorization processes. Many adverse reactions can be noticed only after the medicinal product has been prescribed for, & used by, a large no. of patients world-wide as this environment, with multiple potential new co-factors of real life, cannot be replicated in clinical trials.

### Clinical trials have its own limitations:

- Conducted in a limited patient population
- Restricted population in terms of age, sex and ethnicity
- Restricted co-medication
- Restricted conditions of use
- Limited co-morbidity as the trial has strict inclusion and exclusion criteria
- Reasonably short duration of exposure and follow-up
- Statistical problems accompanying with looking multiple outcomes
- Knowledge concerning the safety profile of any drug is also limited & cannot be considered complete and accurate.

The introduction of a new medicinal product into the market, therefore always carries unknown and unidentified risks, so monitoring very closely at least during five years of post-marketing years. Once a product is marketed, new information related to the safety of the product will be produced, which can have an impact on the benefits or risks of the product. Assessment of this information should be a continuous process, in consultation with regulatory authorities. The Indian pharmacopoeia commission was shown in figure 1. Program communications was shown in figure 2 and ADR monitoring centers was shown in figure 3. The functions of ADR monitoring center were shown in figure 4. Regional resources for training in India were shown in figure 5. The process of collection, analysis and evaluation of ADRs were briefed in figure 6.

## 2. Pharmacovigilance Methods

### I. Passive Surveillance

#### a) Spontaneous reports:

A spontaneous report is a voluntary communication by healthcare professionals or consumers to a company, regulatory authority or other organization that defines one

or more adverse drug reactions (ADRs) in a patient who was given one or more medicinal products and that does not originate from a study or any structured data collection scheme.<sup>[12]</sup> It plays a key role in the identification of safety signals once a medicine is marketed. In various occurrences, spontaneous reports can vigilant a company to rare adverse events that were not noticed in earlier clinical trials or other pre-marketing studies. It can also deliver important information on at-risk groups, risk factors and clinical features of known serious ADRs.<sup>[13-16]</sup> Newly, systematic methods for the recognition of safety signals from spontaneous reports have begun to be used. Several of these methods are static in development and their utility for identifying safety signals is being assessed. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection.<sup>[17-19]</sup> Data mining techniques have also been used to examine medicine-medicine interactions<sup>[20]</sup>, but these techniques should always be used in conjunction with and not in place of, analyses of single case-reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals that merit further evaluation. However, this tool does not quantify the magnitude of risk and caution should be exercised when comparing medicines. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence reporting of spontaneous adverse events are not removed from data mining. The results of data mining should thus be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and more specifically, the large differences in the ADR reporting rate for different medicines and the many potential biases inherent in spontaneous reporting. All signals should be evaluated while recognizing the possibility of false-positives. In addition, the absence of a signal does not mean that a problem does not exist.

#### **b) Case series:**

A series of case-reports can deliver sign of an association between a medicine and an adverse event, but they are normally more valuable for producing theories than for confirming a relationship between medicine exposure and outcome.<sup>[21, 22]</sup>

#### **C) Stimulated reporting:**

A number of methods have been used to reassure and simplify reporting by health professionals in definite circumstances for new products or for partial time periods.<sup>[23]</sup> Such systems comprise on-line reporting of adverse events and methodical motivation of reporting of adverse events based on a pre-designed method. While these methods have been shown to advance reporting, they are not invulnerable to the confines of passive surveillance, particularly discriminating reporting and imperfect information. This should be considered as a procedure of spontaneous event reporting and thus data acquired from stimulated reporting cannot be used to make precise incidence rates, but reporting rates can be projected.

## **II) Active Surveillance**

Active surveillance, in contrast to passive surveillance, pursues to determine the particular number of adverse events through a constant pre-organized process.<sup>[24]</sup> In common, it is more achievable to acquire wide-ranging data on discrete adverse event reports through an active surveillance system than through a passive reporting system.

#### **a) Sentinel sites:**

Active surveillance can be attained by revising medical records or questioning patients and/or physicians in a section of sentinel sites to guarantee that comprehensive and precise data on reported adverse events are collected from these sites. The selected sites can deliver information, such as data from specific patient subgroups, which would not be accessible in a passive spontaneous reporting system.<sup>[25]</sup> The major weaknesses of sentinel sites comprise difficulties with selection bias, small numbers of patients and augmented costs. Active surveillance with sentinel sites is most effective for those medicines used primarily in institutional settings such as hospitals, nursing homes and haemodialysis centers. Institutional settings may use certain medicinal products more commonly and can deliver an arrangement for enthusiastic reporting. Intensive monitoring of sentinel sites can also be supportive in recognizing risks among patients taking orphan medicines.

#### **b) Medicine event monitoring:**

It is a process of active Pharmacovigilance surveillance. Studies using this process are cohort-based and prospective and observational. For medication event monitoring, patients can be acknowledged from electronic or automated health insurance claims. A single prescription or a series might be composed over the period of monitoring. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to acquire outcome data. Requests for data on patient demographics, indication for treatment, duration of therapy, dosage, clinical events, reasons for termination and applicable past history can be involved in the questionnaires. The restrictions of medicine event monitoring can comprise the poor physician and patient reply rates.<sup>[31, 32]</sup>

**c) Registries:** A registry is a list of patients presenting with the identical representative(s). This representative can be a disease (disease registry) or a specific exposure (medicine registry). Both types of registrations, which vary only by the type of patient data of interest, can gather a cordless of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help to gather data on medicine exposure and other factors related to a clinical condition. A disease registry might also be used as a veil for a case control study associating the medicine exposure of cases recognized from the registry with controls selected either from patients with another condition within the registry, or from patients outside the registry. Exposure (medicine) registries address populations exposed to the medicines of interest to govern if a medicine has a distinct influence on this group of patients. Some exposure (medicine) registries address drug exposures in specific populations, such as

pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can quantify incidence, but, without a comparison group, cannot deliver proof of association. This type of registry can be very valuable when examining the safety of an orphan medicine indicated for a specific condition. Customary epidemiological methods are a key constituent in the evaluation of adverse events. There are numerous of observational study designs that are valuable in validating signals from spontaneous reports, case series or medicine event monitoring. The most imperative of these designs is cross-sectional studies, case-control studies and cohort studies.<sup>[33, 34]</sup>

**d) Cross-sectional study (survey):**

Data collected on inhabitants of patients during a specified interval of time, regardless of exposure or disease status constitute a cross-sectional study. These types of study are principally used to collect data for surveys or for ecological analyses. The major disadvantage of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be straight addressed. These studies are paramount used to scrutinize the prevalence of a disease at one time point or to inspect trends over time, when data for serial time points can be captured. These studies can also be used to observe the crude relationship between exposure and outcome in ecological analyses. Cross-sectional studies are utmost valuable when exposures do not change over time.

**e) Case-control study:**

In a case-control study, cases of disease (or events) are recognized. Controls, or patients in whom the disease or event of interest has not happened, are then carefully chosen from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls exemplifies the prevalence of exposure in the source population. The exposure status of the two groups is then paralleled using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be acknowledged from an existing database or using data collected unambiguously for the purpose of the study. If safety data is sought for special populations, the cases and controls can be stratified according to the population of interest. For rare adverse events, prevailing large population-based databases are a useful and efficient means of providing the necessary data on medicine exposure and medical outcome relatively quickly. Case-control studies are predominantly useful when the goal is to examine whether there is a relationship between a medicine (or medicines) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions, such as renal and hepatic dysfunction, which might modify the relationship between the medicine exposure and the adverse event. Under particular conditions, a case-control study can deliver the complete incidence rate of the event.

**f) Cohort study:**

In a cohort study, a population at risk for the disease (or event) is monitored over time to record the occurrence of the disease (or event). Information on exposure status is

accessible during the follow-up period for each patient. A patient might be exposed to a medicine at one time during follow-up, but not exposed at another time. Meanwhile the population exposure during follow-up is acknowledged, incidence rates can be calculated. In many cohort studies concerning medicine exposure, appraisal cohorts of interest are selected on the basis of medicine use and monitored over time. Cohort studies are useful when there is a requisite to know the incidence rates of adverse events in addition to the relative risks. Multiple adverse events can also be scrutinized using the similar data source in a cohort study. Conversely, it can be problematic to recruit adequate numbers of patients who are exposed to the medicine of interest or to study very rare outcomes. Similar to case-control studies, patients in cohort studies can be recognized from large automated databases or from data collected precisely for the study at hand. In addition, cohort studies can be used to scrutinize safety issues in special populations through oversampling of these patients or by stratifying the cohort if adequate numbers of patients are included. There are numerous automated databases obtainable for pharmacoepidemiological studies.<sup>[35, 36, 37]</sup> They consist of databases that contain automated medical records or automated accounting/billing systems. Databases that are fashioned from accounting/billing systems might be connected to pharmacy claims and medical claims databases. These datasets may contain millions of patients. Subsequently, they are fashioned for administrative or billing purposes; they might not have all the detailed and precise information needed for some research, such as authenticated diagnostic information or laboratory data. Even though medical records can be used to establish and authenticate test results and medical diagnoses, one should know about the privacy and privacy regulations that apply to patient medical records.

**g) Targeted clinical investigations:**

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called in to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamics and pharmacokinetic studies might be conducted to define whether a particular dosing instruction can put patients at an increased risk of adverse events. Moreover, based on the pharmacological properties and the predictable use of the medicine in general practice, conducting specific studies to scrutinize potential medicine-medicine interactions and food-medicine interactions might be entitled to. These studies can comprise population pharmacokinetics studies and medicine concentration monitoring in patients and normal volunteers. One drawback of this method is that the outcome measure might be too shortened and this might have an influence on the quality and eventual usefulness of the results of the trial. Large, simplified trials are similarly resource-intensive.

### 3. Descriptive Studies

Descriptive studies are a vital component of Pharmacovigilance, even though not for the recognition or authentication of adverse events related to medicine exposures. These studies are principally used to acquire the

circumstantial rate of outcome events and/or to inaugurate the prevalence of the use of medicines in specified populations.

#### Natural history of disease

The discipline of epidemiology initially concentrated on the natural history of disease, including the features of diseased patients and the dissemination of disease, in particular populations, as well as appraising the incidence and prevalence of possible outcomes of interest. These outcomes of interest currently comprise a narrative of disease treatment outlines and adverse events. Studies that scrutinize precise facts of adverse events, such as the contextual incidence rate of, or risk factors for, the adverse event of interest, can assist in placing spontaneous reports into viewpoint. [38]

#### Medicine utilization study

Medicine utilization studies (DUS) define how a medicine is marketed, prescribed and used in a population and how these factors affect outcomes (including clinical, social and economic outcomes).<sup>[39]</sup> These studies deliver data on definite populations, such as the elderly, children, or patients with hepatic or renal dysfunction, habitually stratified by age, sex, concomitant medication and other characteristics. It can be used to define if a product is being used in these populations. It has been used to define the effect of regulatory actions and media courtesy on the use of medicines, as well as to improve evaluations of the economic burden of the cost of medicines. It can also be used to scrutinize the relationship between optional and definite clinical practice. These studies can help to govern whether a medicine has the probable for abuse by inspecting whether patients are taking mounting doses or whether there is an indication of incorrect duplication prescribing. The main limitations of these studies can comprise an absence of clinical outcome data or information on the indication for use of a product. Many novel drugs are being acquainted with in the country, so there is a huge requirement to increase the Pharmacovigilance system to safeguard the Indian population from possible harm that may be produced by some of the new drugs.

#### 4. Conclusion

Pharmacovigilance system proficient to distinguish new ADRs and compelling regulatory actions desirable to safeguard public health. Diminutive prominence has been put into engendering information that can assist a healthcare professional or a patient in the decision-making process. The collecting and communiqué of this data is a chief goal of Pharmacovigilance. Pharmacovigilance methods must also be capable to designate which patients are at risk of developing an ADR. As a source of the data, Pharmacovigilance method would be reliable with the emergent patient involvement in drug safety. A suitably working Pharmacovigilance system is important if medicines are to be used cautiously. It will be advantageous for healthcare professionals, regulatory authorities, pharmaceutical companies and the consumers. It aids pharmaceutical companies to monitor their medicines for risk. The purpose of the Pharmacovigilance is to obtain the International Journal of Chemistry and Pharmaceutical Sciences

information, documentation of the work and knowledge accessible, while giving precedence to the novel and significant safety concerns.

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