



Received on 13 March, 2015; received in revised form, 13 May, 2015; accepted, 21 June, 2015; published 01 October, 2015

DRUG SAFETY ASSESSMENT IN CLINICAL TRIALS: CONCEPTS AND ISSUES

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Keywords:

Pharmacovigilance,
Adverse Event, Adverse Drug
Reactions, Clinical Trial, Drug Safety

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ABSTRACT: Ensuring patient safety during and after clinical trials is the sole priority of the drug-development process. In both clinical trials and clinical practice, each patient must be treated according to his or her illness and needs. For this purpose, monitoring of patient safety at all levels of drug-development is given utmost importance. Such monitoring is a dynamic process having motive of protecting trial volunteers and patients from preventable harm during and after clinical trials respectively. For this purpose, knowledge of the basics of drug safety at all levels is essential especially for the healthcare professionals. Many literatures have been published on drug safety and clinical trials but a systemic document focusing strictly on all the dimensions is lacking. In this article, we have discussed upon all aspects of drug safety in clinical trials including the basics of drug safety, patient suitability for safety in trials, regulatory aspects of drug safety, causality, risk assessment and post marketing safety of the drug products.

INTRODUCTION: All medicinal products carry risks in addition to their possible benefits. For developing a new medicine, a decision can only be made if both benefits and risks are addressed. The risk associated with the drug is minimized when medicines of good quality, safety and efficacy are used rationally by an informed health professional and by patients. Pharmacovigilance helps in reducing the risk of harm by ensuring use of good quality medicines appropriately.

Pharmacovigilance has emerged as science to examine the safety and efficacy of drugs and other therapeutic products.

The need of systemic international efforts to address drug safety were realized and initiated in 1961, following the Thalidomide disaster^{1,2}. When Thalidomide was introduced, there were very few or no laws regulating drug development and marketing. Thalidomide use by pregnant mothers resulted in birth of thousands of congenitally deformed infants¹. Following thalidomide disaster, efforts were made to address the drug safety issues by developing a system for detecting previously unknown or poorly understood adverse effects of medicines. Guidelines were developed to monitor drugs, foods and environmental contaminants for adverse reactions and toxicity. In the beginning these guidelines were restricted to local needs. Globalization resulted in recognized need of a system, accepted internationally, to ensure safety of medicinal products.

Clinical trials are prospective biomedical or behavioral research studies on human subjects that

QUICK RESPONSE CODE 	DOI: 10.13040/IJPSR.0975-8232.6(10).4159-67
	Article can be accessed online on: www.ijpsr.com
DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(10).4159-67	

are designed to answer specific questions about biomedical or behavioral interventions, generating safety and efficacy data. A selected group of individuals is given the investigational product and another group is given a reference or comparator. Both groups are carefully watched or monitored. All other things being equal, differences between the groups that are large enough not to be explained by chance are attributed to the investigational product.

Basics of drug safety:

Adverse event (AE) (also referred to as an adverse experience) has to be described above all, while moving in-depth to drug safety. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. For clear and consistent understanding of drug safety, Food and Drug Administration (FDA) introduces terms and definitions³.

Adverse drug reaction:

An AE that has a causal relationship with the medicinal product is termed as an adverse drug reaction (ADR).

Suspected adverse reaction:

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Unexpected:

An adverse event or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Serious:

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent

or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Life-threatening:

An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

New drugs are always marketed on the basis of comparatively limited information. In the United States, about 500 to 2000 patients usually receive a new drug during clinical trials, and at most only a few hundred of them are treated more than three to six months⁴. The safety evaluation during clinical drug development is not expected to characterize all the AEs, for example, those occurring in less than 1 in 1000 patients⁵. Risks that may be missed include a) rare events b) events occurring after long-term use c) events occurring in special populations d) events occurring in association with specific diseases and e) events occurring in association with concomitant therapy.

Common adverse events (cumulative 3-month incidence of about 1%) are generally identified and well characterized in prospective trials whereas infrequent or delayed adverse events need to be characterized depending on their severity and importance to the risk-benefit assessment of the drug and require special techniques (e.g., case-control studies, cohort studies).

Isolated reports can be definitive in associating a drug with an adverse effect if drug administration and the event are temporally related, the event disappears when the drug is stopped (dechallenge) and if the event reappears when the drug is readministered (rechallenge).

AEs can be ascertained by spontaneously reported symptoms or symptoms reported as a result of a probe or both. Spontaneously reported symptoms have advantage of detecting the more severe episodes, truly unexpected adverse events and identifying what's important to the patient.

However, it may lack standardization (e.g. within and across trials). Symptoms reported as a result of a probe allows standardization within and across trials but may miss unexpected adverse events.

AEs can be described on the basis of a) objectivity (e.g. symptoms vs. laboratory tests) b) seriousness (e.g., non-serious vs serious) c) predictability (e.g. expected vs. unexpected) d) attribution to therapy (e.g. ADE vs. ADR) e) intensity (e.g. mild vs. severe) f) incidence (e.g. rare vs. common) and g) latency (e.g., short-term vs. delayed). Objectivity refers to adverse reactions that are measured primarily in numerical or objective terms e.g. clinical laboratory abnormalities detected in biological samples, in the patient and abnormalities detected on physical examination. Just because a scale is numerical doesn't necessarily mean it's an objective scale. It may be pseudo-quantitative e.g. visual analog scale (VAS) for assessment of pain (a subjective endpoint). Also, just because a symptom is subjective doesn't mean that it's not real or important. Adverse reactions may also be described in subjective and/or descriptive terms e.g. pain and nausea.

In these trials, critical efficacy endpoints are identified in advance and sample sizes are estimated for an adequate assessment of effectiveness. In contrast, with few exceptions, phase 2-3 trials are not designed to test specified hypotheses about safety nor to measure or identify adverse reactions with any pre-specified level of sensitivity. The exceptions occur when a particular concern related to the drug or drug class has arisen and when there is a specific safety advantage being studied. In these cases, there will often be safety studies with primary safety endpoints that includes all the features of hypothesis testing, including blinding, control groups, and pre-specified statistical plans⁶.

Knowing if the subject is fit for the trial:

Since safety of the subject is of utmost importance in a clinical trial, it is necessary to determine whether the subject is fit for the trial or not. For this, investigation brochure (IB) findings are applied to the protocol and a prospective subject. The fitness of the subject is decided based on the Inclusion/Exclusion criteria and by examining the

potential for drug accumulation/ toxicities. Inclusion/Exclusion criteria involves medical history, lab values and concomitant medications used by the subject whereas examining the potential for drug accumulation/ toxicities involves PK parameters single versus multiple doses and linearity of exposure with dose escalation.

Safety Concerns:

Pharmacology of the drug or pharmacologically related drugs can be useful in the identification and exploration of major safety concerns. For example, the clearance pathway of a drug can be indicative of certain potential drug-drug interactions or certain effects of decreased renal or hepatic function. Similarly, the pharmacologic class, and prior experience, could lead to focus on particular laboratory or clinical abnormalities (e.g., muscle or liver abnormalities with HMGCoA reductase inhibitors, QT prolongation with fluoroquinolone anti-infectives, gastrointestinal, renal and cardiovascular effects of nonsteroidol anti-inflammatory drugs, liver abnormalities with endothelin receptor antagonists, cognitive impairment with sedating drugs, sexual dysfunction with selective serotonin reuptake inhibitors⁶.

Investigational New Drug (IND) Safety Reporting Requirements:

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA. The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor's initial receipt of the information. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

The sponsor must also report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (e.g., mutagenicity, teratogenicity, arcinogenicity). Any relevant additional information that the sponsor obtains that pertains to a previously submitted IND safety report must be submitted as a Follow-up

IND Safety Report without delay, as soon as the information is available, but should be submitted no later than 15 calendar days after the sponsor receives the information.

The IND annual safety reporting is required of all IND holders and should include most frequent and most serious AEs by body system, list of subjects who died, including cause and list of subjects who dropped out in association with an adverse experience.

FDA believes that Bioavailability (BA) and Bioequivalence (BE) studies that meet the requirements for exemption are generally safe. The occurrence of a serious adverse event is very unusual because the number of subjects enrolled in such a study is small, subjects are usually healthy volunteers, and drug exposure is typically brief. However, FDA occasionally receives safety-related information associated with these types of studies, which could reflect either a problem with the drug product being evaluated or with the study design being used. For these reasons, the occurrence of any serious adverse event, whether or not it is considered drug related, is of interest. Timely review of this safety information is critical to ensuring the safety of study subjects.

The sponsor is required to notify FDA and all participating investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting.

Fifteen-day reports should be sent by email to OGD-PremarketSafetyReports@fda.hhs.gov. Paper reports may be sent to the Clinical Safety Coordinator, Office of Generic Drugs, in the Center for Drug Evaluation and Research at FDA. FDA recommends that 7-day notifications be made by telephone, email, or facsimile transmission. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required³. Forms & submission requirements for investigational new drug include FDA 1571 (Investigational New Drug

Application) and FDA 1572 (Statement of Investigator). Forms & submission requirements for new drug application (NDA) includes FDA-356h (application to market a new drug, biologic, or an antibiotic drug for human use), FDA-3397 (user fee cover sheet) and FDA-3331 (new drug application field report) whereas FDA-356h (application to market a new drug, biologic or an antibiotic drug for human use) is used as application form for abbreviated new drug application (ANDA) for generic drug products. There is no form for orphan drug products (drugs used for rare diseases and disorders), but there is a prescribed format for application for orphan drug status on the 'The Orphan Drug Act and Related Law and Regulations' page of FDA's website⁷.

Causality assessment:

An inherent problem in pharmacovigilance is that most case reports concern suspected adverse drug reactions. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a rechallenge is rarely ethically justified. In practice few adverse reactions are 'certain' or 'unlikely'; most are somewhere in between these extremes, i.e. 'possible' or 'probable'⁸. Statistical analysis can lead to structured and harmonized assessment of causality by decreasing disagreement between assessors, classifying relationship likelihood, marking individual case reports and improvement of scientific evaluation.

It can be particularly useful for evaluation of common adverse events. Causality assessment can be performed simply by categorizing evidence by the quality of its sources and evaluating the evidence of a causal relationship using standard guidelines. The word "quality" incorporates consideration of study design, control groups, randomization, blinding, appropriate patient population, outcome measures, study size, etc.

Various sources for causality assessment can be clinical trials, cohort or case-control studies, time-series studies and case-series. Use of standard guidelines for evaluating the evidence of a causal relationship may include a) temporal relationship b) strength of association, c) dose-response relationship d) replication of findings e) biologic plausibility f) consideration of alternate

explanations g) cessation of exposure h) specificity of the association and i) consistency with other knowledge.

FDA system of managing risks:

FDA approves a product when it judges that the benefits of using a product outweigh the risks for the intended population and use. A major goal of the premarketing review is to ensure that products are truthfully and adequately labeled for the population and use. Labeling is given considerable emphasis because it is the chief tool the Agency uses to communicate risk and benefit to the healthcare community and patients.

Once medical products are on the market, however, ensuring safety is principally the responsibility of

healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis. They are expected to use the labeling information to select and use products wisely, thereby minimizing adverse events. To assist with post marketing risk management, the Agency maintains a system of complex post marketing surveillance and risk assessment programs to identify adverse events that are not identified during medical product development and premarketing review.

FDA monitors suspected adverse events associated with the use of an approved medical product. The Agency uses this information to initiate labeling updates and, on rare occasions, to reevaluate the marketing decision⁹ (Fig. 1).

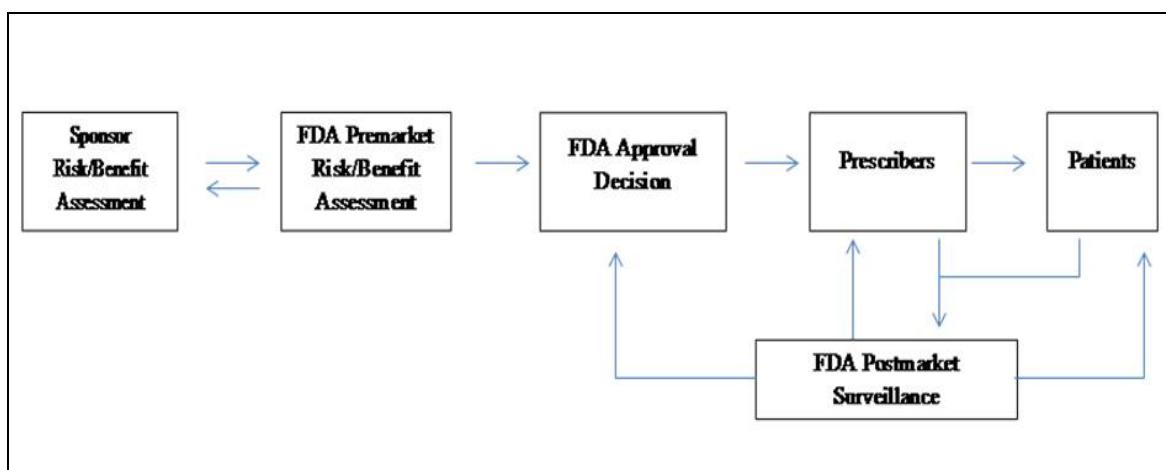


FIG.1: FDA SYSTEM OF MANAGING RISKS

Postmarketing Safety:

Postmarketing surveillance (PMS) is the practice of monitoring the safety of a pharmaceutical drug or medical device after it has been released on the market and is an important part of the drug safety. Since drugs are approved on the basis of clinical trials, which involve relatively small numbers of people who normally do not have other medical conditions which may exist in the general population - postmarketing surveillance can further refine, or confirm or deny, the safety of a drug after it is used in the general population by large numbers of people who have a wide variety of medical conditions.

Postmarketing surveillance uses a number of approaches to monitor the safety of licensed drugs, including spontaneous reporting databases,

prescription event monitoring, electronic health records, patient registries and record linkage between health databases. These data are reviewed to highlight potential safety concerns in a process known as data mining.

For postmarket safety evaluations FDA consider several data sources including the product's pre-approval safety profile, current FDA-approved label, reports made to the FDA Adverse Event Reporting System (FAERS), previously known as AERS, reports made to the Vaccine Adverse Event Reporting System (VAERS), manufacturer-submitted periodic safety reports, medical literature, drug utilization databases and data from post-approval clinical trials and other studies, when applicable.

Postmarketing Reports:

For ensuring drug safety on long term and on a wider population, regulatory authorities ask the marketing authorization holders (MAH) for reporting of AEs and periodic submission of safety reports. For serious and unexpected AEs, FDA recommends reports to be submitted within 15 calendar days either foreign or domestic. A Follow-up to 15-day alert reports should be submitted within 15 calendar days. Safety reports are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the postauthorisation phase. In USA, periodic adverse drug experience reports (PADER) are submitted quarterly within 30 calendar days of the data lock point (day 0) for 3 years from date of approval, then annually within 60 calendar days of the data lock point (day 0).

In Europe, each marketing authorisation holder is responsible for submitting Periodic Safety Update Reports (PSURs) for its own products and should submit PSURs to the European Medicines Agency (EMA) within 70 calendar days of the data lock point (day 0) for PSURs covering intervals up to 12 months (including intervals of exactly 12 months) and within 90 calendar days of the data lock point (day 0) for PSURs covering intervals in excess of 12 months. The timeline for the submission of ad hoc PSURs requested by competent authorities are specified in the request, otherwise the ad hoc PSURs has to be submitted within 90 calendar days of the data lock point¹⁰.

FDA recently adopted the guidance for industry *E2F Development Safety Update Report*, which describes a common standard for periodic reporting on drugs under development among the ICH regions and is intended to meet the IND annual reporting requirements. Questions have arisen about whether the Agency will accept the Development Safety Update Report (DSUR) because of the difference in the party responsible for making the causality judgment (see section III.C of this document). To promote global harmonization, FDA will accept the DSUR, as described in the E2F Development Safety Update Report guidance, to meet the IND annual report

requirements. The Agency does not expect the IND safety reporting requirements to have any impact on the adverse reaction information presented in prescription drug labeling.

Improving risk minimization:

Medical products today are developed and used within a complex system involving a number of key participants: (1) manufacturers who develop and test products and submit applications for their approval to the FDA; (2) the FDA, which has an extensive premarketing review and approval process and uses a series of post marketing surveillance programs to gather data on and assess risks; (3) other participants in the healthcare delivery system, including healthcare practitioners; and (4) patients, who rely on the ability of this complex system to provide them with needed interventions while protecting them from injury.

All participants in the medical product development and delivery system have a role to play in maintaining this benefit-risk balance by making sure that products are developed, tested, manufactured, labeled, prescribed, dispensed, and used in a way that maximizes benefit and minimizes risk.

Medicinal products provide great benefit to the public, but same time they can also be harmful. FDA and the many other participants in healthcare delivery act to maximize the benefits and minimize the risks associated with using medical products, but often the actions of the participants are insufficiently integrated. The common goal of maximizing benefits and minimizing risks could be greatly advanced if the participants in the system work together to gain an understanding of these activities within a systems framework. To achieve such a framework, better understanding of the risks involved and their sources, and clarifications of individual roles can be effective.

Improving Post marketing Risk Assessment and safety:

Regulatory authorities like International Conference on Harmonisation (ICH), FDA and (European Medicines Agency) EMA are working in collaboration to make sure drug safety throughout the lifespan of a drug product. With

their strict regulations and adherence of various MAHs to these regulations can be effective in exploring new dimensions of drug safety. Applying new tools or gathering better data from observational trials and targeted post-approval studies, active surveillance system to query diverse automated healthcare data, drug utilization databases and medication error prevention can be effective tools in improving post marketing risk assessment and safety.

Sources of safety information and Safety evaluation:

For a medicine to be considered safe, its expected benefits should be greater than any associated risks of harmful reactions. All medicines can cause reactions; however, it is important to note that most people take medicines without suffering any serious side effects. The patient information leaflet accompanying a medicine, list all of its known associated side effects.

Various sources of information are used for drug safety e.g. spontaneous adverse drug reaction reporting schemes, clinical and epidemiological studies, worldwide published medical literature, pharmaceutical companies, worldwide regulatory authorities and morbidity, mortality databases, nonclinical data (CMC, in vitro, animals), post marketing experience and safety profile of other drugs in the same class. Other information sources are used to confirm, characterise and assess the frequency of the reported adverse reactions. Information from all of these sources is carefully screened and may identify unexpected side effects; indicate that certain side effects occur more commonly than previously believed, or that some patients are more susceptible to some effects than others. Such findings can lead to changes in the marketing authorisation of the medicine, such as restrictions in use, changes in the specified dose of the medicine and introduction of specific warnings of side-effects in the product information.

As new information related to a marketed drug becomes available, the regulatory agencies review the data and evaluates whether there is a potential drug safety concern. When a potential drug safety concern arises, relevant scientific experts within the agency engage in a prompt review and analysis of

available data. Often, there is a period of uncertainty while agency evaluates the new safety information to determine whether there is an important drug safety issue related to a specific drug or drug class and whether regulatory action is appropriate. During this period, agency also is actively engaged in scientific efforts to gather additional safety information. In case of FDA, The Drug Safety Oversight Board may be consulted and provide recommendations to the Director of the Center for Drug Evaluation and Research regarding the management and communication of an emerging drug safety issue. FDA also may consult an Advisory Committee regarding an emerging drug safety issue¹¹.

Sponsors also evaluate the new safety information and provide the results of their analyses to agency during this time. As additional data relevant to an emerging drug safety issue become available (e.g., data from an ongoing study or data from available clinical databases), such data are considered in the analysis and decision-making process. Upon evaluation of additional data, further regulatory action, such as a revision to product labeling or a Risk Minimization Action Plan (RiskMAP), may be appropriate.

As the agency evaluates a drug safety issue to determine whether regulatory action is warranted, we may communicate further information to the public at appropriate points in the decision making process. Consistent with public health mandate, the regulatory agency may advise the public of an emerging drug safety concern as well as the next steps the agency may take regarding an important drug safety issue.

Pharmacovigilance in India:

India has more than half a million qualified Doctors and 15,000 hospitals having bed strength of 624,000. It is the fourth largest producer of pharmaceuticals in the world¹¹. It is emerging as an important Clinical trial hub in the world. Many new drugs are being introduced in India. Therefore, there is a need for a vibrant pharmacovigilance system in the country to protect the population from the potential harm that may be caused by drugs. Clearly aware of the enormity of task the Central Drugs Standard Control Organization

(CDSCO) has initiated a well structured and highly participative National Pharmacovigilance Program. It is largely based on the recommendations made in the World Health Organization (WHO) document titled “Safety Monitoring of Medicinal Products – Guidelines for Setting up and Running a Pharmacovigilance Centre”

The specific aims of the Pharmacovigilance Programmers are to:

- Contribute to the regulatory assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost effective) use.
- Improve patient care and safety in relation to use of medicines and all medical and paramedical interventions.
- Improve public health and safety in relation to use of medicines.
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public.

The Programme aims to foster the culture of ADR notification in its first year of operation and subsequently aims to generate broad based ADR data on the Indian population and share the information with global health-care community through WHO.

However, despite of these efforts, pharmacovigilance in developing countries like India is lacking focused vision and effective strategy for developing the pharmacovigilance systems. Pharmacovigilance has not picked up well in India and the subject is in its infancy. India rates below 1% in pharmacovigilance as against the world rate of 5%¹².

This is due to ignorance of the subject and also lack of training. A regulation is required to implement the system of reporting adverse events of drugs introduced in the Indian market by pharmaceutical companies.

Improving pre and post marketing risk assessment:

Ongoing safety analyses during trials are critical in ensuring that serious adverse events are discovered as soon as possible. Safety data from ongoing clinical trials influence the clinical care of patients enrolled in those and other trials of a given drug; if the drug is already on the market, these data may affect its clinical use. Safety reports derived from ongoing clinical trials must be meaningful, relevant, and amenable to timely analysis¹³.

Post marketing risk assessment can be effectively improved by applying new tools or gathering better data involving observational trials and targeted post-approval studies. Additionally, active/sentinel event surveillance, use of drug utilization databases and medication error prevention can be of worth in improving post marketing risk assessment.

CONCLUSION: The safety assessment of a medicinal product is an ongoing, dynamic enterprise that never ceases during a product's active life cycle. The probability of detecting all possible relevant AEs of a drug during premarketing development is moderate. However, with systematic and effective pharmacovigilance previously unrecognized, clinically significant ADRs can be frequently detected and corrective measures can be initiated soon after commercialization.

ACKNOWLEDGEMENT: The authors are highly thankful to Fresenius Kabi Oncology Limited for providing the necessary facilities and encouragement in completing this article. Authors also wish to express their thanks to the Fresenius Kabi Global Vigilance team, for excellent support.

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How to cite this article:

Nautiyal N, Rastogi R and Gamperl HJ: Drug Safety Assessment in Clinical Trials: Concepts and Issues. *Int J Pharm Sci Res* 2015; 6(10): 4159-67. doi: 10.13040/IJPSR.0975-8232.6(10).4159-67.

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