Deriving meaningful insights from clinical trial and postmarketing safety data: Perspectives from India

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INTRODUCTION

The practice of pharmacovigilance, the science and activities relating to detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem is growing rapidly in India. Appropriate safety data collection and analysis can help derive meaningful insights from the reported safety data and aid in the early detection of hitherto unknown adverse reactions and interactions, detection of increased frequency of known adverse reactions, identification of risk factors and possible mechanisms.

Today, drug safety data collection in India is both manual and electronic with reporting of potential overlapping and duplicate data, which is likely incomplete for further review and analysis. Furthermore, standardized data collection and timelines are not aligned with international standards. Complete coverage of safety data from all sources throughout the life of the drug cannot be ensured. There is no requirement to submit periodic safety data in clinical trials to regulatory authority. There is clearly a lack of emphasis on deriving meaningful safety data insights for ensuring patient safety. Efforts toward the early detection of drug safety issues are minimal. There is no mandate to publicly disclose drug safety findings. Benefit-risk evaluation of investigational and marketed products cannot be assured merely through annual status reports and periodic safety update reports, respectively. Focused initiatives involving stakeholders from regulatory, health-care, and pharmaceutical industries are required to change the current situation and enable derivation of meaningful insights from safety data. Equal emphasis on assessing real-time safety of the drugs and protection of patients’ rights, safety, and well-being is required. Periodic safety data reporting in clinical trials, pro-active safety data collection related to potential safety concerns, electronic medical records, electronic expedited reporting, collection of targeted data from stakeholders, and standardized and harmonized data collection aligned to the International Council for Harmonization guidelines are required. The Central Drugs Standard Control Organization should implement requirements to submit Development Safety Update Reports, Periodic Benefit-Risk Evaluation Reports, and Risk Management Plans. Access to clinical trials and postmarketing safety data through central repository would enable researchers to explore the data for application in clinical practice.

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underlying adverse reactions, estimation of quantitative aspects of benefit/risk analysis, and dissemination of information needed to improve drug-prescribing patterns and regulations.[1] This article aims to review the current methods and processes for drug safety data collation and analysis in India in both the clinical development and postmarketing settings and further suggests a road map for the future of pharmacovigilance in India.

COLLECTION OF SAFETY DATA

There is a mix of manual and electronic safety data collation methods followed for different purposes in clinical trials and postmarketing settings. Clinical trial sponsors collect safety data using the electronic case record forms (eCRFs). The Central Drugs Standard Control Organization (CDSCO) collects the safety data in clinical trials in paper-based forms (physical format). Most of the source data verification and collection of safety data at the investigator sites is done manually and in physical format due to nonavailability of electronic medical records and record linkage systems in both government and private sector health-care systems. The mode of data collection for the purpose of expedited reporting of serious adverse events (SAE) in clinical trials is also done manually and in physical format as investigators and sponsors are expected to complete prescreening checklist for the submission of SAE and submit SAE using paper form to the regulatory authority. In addition, investigators are expected to affix wet ink signature on the expedited SAE reports.[2] Majority of multinational companies and leading Contract Research Organization (CROs) are collating the safety data required for analysis in clinical trials in electronic format using eCRFs and are possibly adapting scan, declare, and destroy approach.[3] However, some sponsors continue to collect data in clinical trials using paper CRFs. Even in the recently established Pharmacovigilance Programme of India (PvPI), the postmarketing data collection at adverse reaction monitoring centers is manual, further the data are transferred electronically to the World Health Organization Vigiflow database. There are no electronic reporting forms for health-care professionals (HCPs) and industries such as MedWatch in the USA.[4]

There is duplication of efforts in the process of safety data collection in clinical trials. For example, the data expedited to the CDSCO from investigator sites and sponsor are nearly same except for sponsors causality and injury assessment as both these stakeholders are expected to submit expedited SAE reports in Appendix XI format of the Schedule Y of Drugs and Cosmetics Act along with the completed checklist.[2][3] Collection of postmarketing spontaneous safety reports associated with marketed products is done by both PvPI and pharmaceutical industry. The adverse drug reactions (ADRs) are reported by HCPs to both pharmaceutical industry and PvPI. In addition, at the regulatory authority level, there is duplicate collection as pharmaceutical industry is expected to report ADRs to both the CDSCO and PvPI. The duplication of efforts decreases efficiency and increases efforts involved in reporting and review of safety data.

Sponsors, investigators, and Ethics Committees are well focused on the collection of safety data to ensure safety and well-being of trial participants and protect the rights of the patients. On the other hand, the CDSCO is primarily focused to a large extent on protection of the rights of the patients through ensuring payment of appropriate compensation and for medical care for trial participants. However, there is minimal focus on the overall assessment of safety data obtained from clinical trials by regulatory authority. So far, the focus of postmarketing safety data collection in India was to impart reporting culture among HCPs, especially to ease the reporting process. In this process, the ultimate purpose of data collection is diluted to some extent. The format for safety data collection in clinical trials is standardized through the use of Appendix XI format. The PvPI postmarketing ADR reporting form is not aligned with Appendix XI leading to differences in data collection. In addition, both Appendix XI and PvPI ADR reporting forms are not harmonized with the International Council for Harmonization (ICH) guidelines such as E2A, E2B, and E2D, particularly data elements and standards to expedite the reports to authority.[2]

In the recent past, the CDSCO shortened the timelines for expedited reporting of SAE from 14 days to 10 days and later, it was reversed back to 14 days.[6] Further, this 14-day regulatory timeline starts from the date of occurrence of SAE rather than the date of awareness. Additional regulatory reporting timelines such as reporting from investigators to authority within 24 h followed by 14-day follow-up report timelines are possibly unique to India. The SAE reporting timelines are not harmonized with the international standards.[8] Timelines for reporting are defined for postmarketed safety reports from industry to authority. However, there are no defined timelines for reporting by HCPs to pharmaceutical industry or PvPI. Furthermore, timelines for reporting periodic safety update reports (PSURs) are not harmonized with the international standards defined in the ICH (postdata lock point, +30 days in India versus +60 days globally).

Currently, there is no requirement for periodic safety data collection and reporting in clinical trials such as Development Safety Update Report (DSUR). The current regulations do not assure 100% coverage of interventional clinical studies for safety monitoring throughout the life of the medicinal product as the current regulations are limited to new drugs.
at large. In most of the instances of safety concerns with marketed products observed in the recent past, there was reactive data collection to safety concerns identified. There is no repository like the US Food and Drug Administration Adverse Event Reporting System and Eudravigilance database to allow researchers to use the collected data. In addition, there is very less collaboration between central laboratories and PvPI/CDSCO to collect and disseminate safety information associated with product quality complaints, lack of therapeutic efficacy reports, and product security complaints such as counterfeits and spurious medications. Lot of efforts have been made by PvPI in the recent past to expand its network to cover countrywide population. However, the program is yet to go a long way to achieve 100% coverage of drug safety information from all sources. Regulatory authority is yet to achieve 100% coverage from all types of safety information such as special situations, special population, overdose, abuse, off-label use, misuse, medication error, occupational exposure, and all sources of information such as all possible solicited and unsolicited sources of information, literature, digital and social media, noninterventional studies, compassionate use, and named patient use. 

**GAINING MEANINGFUL UNDERSTANDINGS**

The sponsors and CROs can derive meaningful insights to protect rights, safety, and well-being of clinical trial participants. However, the focus to derive meaningful insights from the collected data at regulatory authority level is more to protect rights and well-being of the patients, considering compensations and medical care that need to be offered to the patients than on insights related to patient safety.

Nearly all the time, a safety concern in a global clinical trial is identified elsewhere, particularly by health authorities in developed countries, which is subsequently applied to Global Clinical Trials in India. Efforts directed at early detection of safety concerns in clinical trials are minimal from all stakeholders. Specific safety concerns in local population are not completely derived from the collected safety data considering inter- and intra-national differences in patients related to many aspects. These concerns are often reviewed during the scrutiny of marketing authorization application.

Majority of population in India still resides in regions beyond tier 1 and tier 2 cities. Yet, majority of clinical trials are conducted on patients from major cities. Hence, generalizability of safety findings from clinical trials poses challenges. Currently, India does not have a mandate to publicly disclose the clinical trial safety findings and placing them on a repository for use by HCPs, patients, and general public. This further hinders the ability to derive meaningful insights from clinical trial data. Periodic analysis of safety information is crucial for the ongoing assessment of risk to trial patients. It is important to know the evolving safety profile of an investigational drug. The current Indian regulations mandate only submission of annual status reports for clinical trials. In the absence of high-quality, comprehensive report such as DSURs, there is no periodic evaluation of the safety profile of the investigational product.

The signal detection to identify and manage new ADR in postmarketing setup is not a single-step process. It involves a series of activities basically divided into three components: Signal generation, signal strengthening, and signal follow-up. The strength of a signal increases with time as we move from signal generation to follow-up and further action. PvPI has incorporated a signal review panel and efforts are made toward signal generation. However, still lot needs to be done related to signal strengthening, follow-up, and action. In addition, approach to signal detection needs to consider late introduction of new drugs and large number of matured marketed products in India compared to developed countries.

Due to lack of data collection related to benefit-risk aspects of drugs such as periodic benefit-risk evaluation reports (PBRERs) and risk management plans (RMPs), enough meaningful insights are not being drawn to appropriately manage the benefits and risks of marketed products. Legislation and guidelines related to effective communication of safety information to HCPs, patients, and public do not exist. Hence, meaningful insights are not derived to disseminate safety information including but not limited to labeling, prescribing information, direct health professional communications, etc.

Due to lack of deriving meaningful insights, there is minimal application of learning from the collected safety data to actual clinical practice in postmarketing scenario including rational drug use. Although there are isolated publications involving a limited number of health-care facilities, so far meaningful insights have not been drawn on the economic burden of drug safety issues in India, particularly in view of the high out-of-pocket health-care expenses by patients.

**ROAD AHEAD**

**Individual case safety reports**

The purpose of safety data collection at all levels in clinical trials should focus on real-time evaluation of drug safety. The standardized data collection process should be harmonized with international standards. Targeted data need to be collected from specific stakeholders to avoid duplication. Efforts are required from the CDSCO and PvPI to achieve 100% coverage of all types of drug safety information from all sources nationwide. Transformation is required to impart the culture...
of proactive individual case safety report (ICSR) collection at the CDSCO and PvPI based on early identification of safety concerns. Collaboration between central laboratories and PvPI/CDSCO is required to collect, analyze, and disseminate safety information associated with ICSR comprising product quality complaints, lack of therapeutic efficacy reports, and product security complaints such as counterfeits and spurious medications.

There is a need to develop electronic medical records in both government and private sectors at hospital and general practitioner levels. Such systems should be standardized and linked to form record linkage systems which will help uniformity in electronic data collection and ease data retrieval. Electronic expedited reporting of ICSR in clinical trials to authority will enhance efficiency at all stakeholder levels. Similarly, electronic expedited reporting of ICSR in postmarketing settings to CDSCO and PvPI will help improve efficiency of pharmaceutical industry and HCPs. A bottom-up approach in assigning universal identification number for ICSR in postmarketing scenario would help minimize duplication of data collection at central level. Drawing meaningful insights from ICSR should be equally focused on assessing real-time safety of the drug and protecting rights and well-being of trial participants.

**Periodic safety update reports**

Safety evaluation should be an ongoing process throughout the clinical trials to detect any safety concern at an early stage. Immediate transition is required from annual status reports submission requirement to the CDSCO in clinical trials to periodic DSUR submission which will be helpful to derive ongoing meaningful insights related to the safety of investigational drugs. Periodic safety data collection should continue throughout the lifecycle of the product but not limited to clinical trial duration or initial postmarketing period. The focus of data collection needs to change to enable assessment of real time safety of the investigational drugs and marketed products. There is a need to move away from requirement to submit postmarketing PSUR and enforce PBRER. The CDSCO should mandate submission of PBRER during manufacturing/import license renewal. Review of PBRER and DSUR by the CDSCO should identify new safety issues that could have an impact on patients, examine whether the information obtained by the pharmaceutical company during the reporting period is in accordance with the previous knowledge of the drug’s safety, and recommend appropriate management strategies for potential and identified risks.

**Generalizability and public disclosure of safety finding**

Emphasis on deriving meaningful insights should be directed toward applying the learning from the collected data to actual clinical practice to rationalize medication use. Generalizability of safety findings from clinical trials needs enhancement through appropriate representation of countrywide population, particularly from the rural India. The trial designs need to focus on specific safety concerns in local population at least in late phases of clinical trials such as Phase IIIB and IV studies. Prompt reporting and public disclosure of interventional clinical trial results is the need of the hour to enhance visibility of safety data from clinical trials and to empower HCPs and public for deriving meaningful insights. Legislation and guidelines are required for good pharmacovigilance communication practice. Possibly, the European Medicines Agency Good Pharmacovigilance Practices Module XV should lead the way forward. The CDSCO needs to implement a central repository for drug information for HCPs and patients similar to the Electronic Medicines Compendium (eMC) in the UK.

**Signal and risk management**

It is highly unlikely that collected Indian safety data will detect altogether an unknown association with a new drug as nearly all drugs are introduced late in India compared to developed countries. Hence, the approach to signal detection needs to change considering matured products in the market. In addition, the current focus in signal detection needs move past “signal generation” in the direction of appropriate signal selection, strengthening, assessment, follow-up, and action. Risk evaluation mitigation strategies (REMS) and RMP are postmarketing commitments by pharmaceutical industry in the US and Europe, respectively. The CDSCO should emphasize drug safety risk assessment and mitigation through required modifications in Schedule Y of Drugs and Cosmetics Rules to direct REMS/RMP submission by pharmaceutical industry. There is a need to estimate financial burden of drug safety issues on a large scale. Further preventive strategies should be designed and implemented to reduce cost burden associated with drug-related harm.

**CONCLUSION**

In clinical trials, improvements in the mode of safety data collection, timelines, duplication, harmonization, and coverage need to be explored. Emphasis is required toward real-time assessment of investigational drug safety, generalizability of clinical trial findings, public disclosure of results, and periodic drug safety evaluation. In the postmarketing scenario, electronic reporting system, single point of data collection at authority, standardization, harmonization, coverage, and collaboration should be encouraged. Standardized timelines for reporting by HCPs and harmonized timelines for periodic reports from industries, modified approach in signal management in view of matured marketed products, benefit-risk management, good
pharmacovigilance communication practice, emphasis on the application of analyzed data to clinical practice, and estimation of financial burden would overlay the path to achieve the ultimate objectives of pharmacovigilance.

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**Conflicts of interest**

There are no conflicts of interest.

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