Safety Data Management for Clinical Trials

Capture and management of safety data are critical components of the clinical trial (CT) process. In addition to ensuring safety of CT participants, systematic capture and analysis of safety data from CTS is important for developing the safety profile of the drug and contributing to its benefit-risk assessment, which is a key consideration in the approval decision. During the pre-approval CTS (Phase I – III) the safety profile of the drug is largely unknown. The objectives of collecting safety data from CTS are early detection of important safety signals, protecting patients from unnecessary risks, and developing a safety profile of the drug, contributing to its benefit-risk assessment. Safety data from ongoing CTS influences the clinical care of patients enrolled in these and other trials. The ultimate goal is to evolve medically useful safety label information, and to ensure that safety data generated during clinical development can be seamlessly merged with post-marketing data to develop a comprehensive safety profile for the product over a reasonable timeframe.

What Constitutes Safety Data in CTS?
Safety data from CTS covers all safety-related information, including serious and non-serious adverse events, vital signs, laboratory parameters including the ECG, medical history, concomitant medications and demographic details. Some issues specific to collecting safety data from CTS are when to start collecting adverse events (AEs), and what data other than AEs is important for safety assessment. As per the ICH GCP, all AEs reported after the written informed consent is obtained from the patient, must be collected. Concomitant illnesses which existed prior to entry into the clinical study, and abnormal laboratory values (with some exceptions) are not recorded as AEs. If an abnormal laboratory value/vital sign/ECG is associated with a clinical sign or a symptom, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign/ECG is considered additional information. Morbidity and mortality endpoints (disease progression or death due to disease) are treated as protocol-specific issues and not safety events.

CT Safety Reporting Requirements
Safety data from CTS is reported from investigators to sponsors or their representatives, and from sponsors to regulators and data safety monitoring boards (DSMBs). This involves expedited reporting of serious, unexpected suspected adverse reactions (SUSARs) within seven (fatal and life-threatening) to 15 (other serious) days, and periodic

"Operating in the world’s Clinical Trial hotspots, we ensure consistent and reliable time definite and temperature critical services."
reporting of all aggregate safety data in the form of Developmental Safety Update Reports (DSUR – ICH E2F) in the EU, or IND Annual Safety Reports in the US.

The regulatory landscape for safety monitoring of healthcare products has changed considerably in recent years. The new safety regulations require all stakeholders to be more proactive in processing safety information, detecting new risks early and putting in place adequate risk management/mitigation measures throughout the product life cycle. The US FDA published a final rule amending the safety reporting requirements under 21 CFR Part 312 (IND studies) and 21 CFR Part 320 (BA-BE studies) in September 2010. The US regulations (effective March 2011) and the European Commission’s detailed guidance (‘CT-3’, June 2011) on the collection, verification and presentation of adverse event/reaction reports arising from CTs lays strong emphasis on early reporting of serious events with a reasonable possibility of being associated with the drug, so that safety analysis is not confounded by unnecessary noise and product safety can be assessed more meaningfully.

Under the previous US regulations, the IND sponsors were often reporting to the agency and clinical investigators, in an expedited manner, a substantial number of serious adverse events, irrespective of relationship to the study drug. Under the current regulations, the IND sponsors must report to the agency and the investigators, on an expedited basis, only those events that are serious, unexpected (not listed in the investigator’s brochure) and suspected to be caused by the drug (i.e. there is a reasonable possibility or evidence to suggest that the drug caused it). The events need to be reported preferably in an unblinded manner.

Precautions to ensure patient safety require that clinical investigators must report to the sponsors all serious adverse events on an expedited basis, regardless of whether they are considered drug-related or not. Events which cannot be analysed as single cases need to be assessed on an aggregate basis and reported if there is a difference in the reporting rates between the drug and the control groups. As an additional measure to protect patient safety, the FDA also recommends that proceedings of the DSMBs be sent to the institutional review board (IRB) for review.

Under the current European regulations (‘CT-3’, 2011/C 172/01 June 2011) the investigator must report all serious adverse events immediately to the sponsor, except for those that the protocol or investigator’s brochure identifies as not
consolidated during the post-marketing phase. This comprehensive safety profile of the product which gets pre-approval studies can form a solid base for the development of the product. Knowledge of regulatory compliance requirements, and sound clinical judgment is necessary for assessment of safety data. Good quality data from robust systems and processes, and sound clinical judgment is necessary for patient safety, knowledgeable and trained multidisciplinary teams, knowledge of regulatory compliance requirements, robust systems and processes, and sound clinical judgment.

Data Quality & Medical Insight
Collecting good quality data is of paramount importance to draw right conclusions about the safety profile of a product, and the quality process for this needs to begin early. The quality of safety data depends on an appropriately designed study, standardised terms and definitions of anticipated safety issues and an adequately designed CRF that captures relevant safety data at all time points during the study.

The key to good quality data is accuracy, reliability and timeliness with standardised definition of medical concepts, good coding practices, clear patient narratives and filling the data gaps by adequate case follow-up. Over-collection of data is counterproductive in CTs and needs to be avoided. Good medical insight is required in the analysis of safety issues and their impact on the health of individual patients and risk populations. This requires knowledge of mechanism of action specific to the product / class of product and an understanding of the natural history of the target disease.

Safety Data Management in CTs – A Team Effort
Managing CT safety data is a collaborative effort among personnel from study management, the investigator sites, data management and patient safety groups. It requires standardised coding practices, regular data reconciliation between the CT and safety databases, and a timely analysis of individual cases and aggregate data to evaluate potential safety issues. The sponsors/CROs, and DSMBs share the responsibility for scrutinising and evaluating safety data proactively and on an ongoing basis.

CT safety data management requires a high regard for patient safety, knowledgeable and trained multidisciplinary teams, knowledge of regulatory compliance requirements, robust systems and processes, and sound clinical judgment for assessment of safety data. Good quality data from pre-approval studies can form a solid base for the comprehensive safety profile of the product which gets consolidated during the post-marketing phase.

In keeping with the outsourcing trend in pharmacovigilance, safety data from CTs is also often managed by partners. If the study is outsourced to a CRO, the same organisation may enter and analyse safety data from the studies. Alternatively, if the sponsor has a partner for safety data management, the same company may be responsible for managing safety data from CTs in addition to managing post-marketing spontaneous reports. Due to the growing emphasis on collating all available safety data and mining it for trends and signals, sponsors often find it advantageous to use a single partner and a single database to capture all safety data, whether it’s from CTs or from the post-marketing phase. Mandatory electronic reporting in Europe requires registration with the Eudravigilance, and sponsors who may not have the resources and experience may delegate indirect reporting to a partner. When the study is outsourced to a CRO and safety data is managed by another partner, the hand-offs and communication between the investigator, sponsor, CRO and the safety data management partner has to be seamless and timely. Reconciliation of safety data between the CT database and the safety database also involves multiple organisations. Roles and responsibilities of all groups have to be clearly defined and agreed.

Chitra Lele, has a distinguished academic background with a PhD in Statistics from Stanford University, and over 20 years of experience in the healthcare industry. Prior to SciFormix Chitra Lele was with Pfizer for 10 years, where she was Executive Director responsible for India operations of Pfizer Global R&D. Chitra established India’s first Biometrics Center providing services in clinical data management, statistics, programming and medical writing, and successfully grew it to a size of over 400 staff. Chitra’s experience includes work as a biostatistician in cancer epidemiology at Stanford University and University of California, San Francisco and as a faculty member at the School of Statistics at the University of Minnesota and IIT, Mumbai.

Suhasini Sharma, is a physician with over 25 years experience in pharmaceutical medical affairs, clinical research and drug safety. At SciFormix she provides subject matter expertise in the areas of clinical research & post-approval support, regulatory writing and signal detection & risk management.

Darshan Bhatt is a postgraduate in medicine and holds an M.Phil. degree in Hospitals and Health Systems Management. He has clinical experience of more than 20 years and 15 years experience in applied biomedical research. He worked for 10 years with AstraZeneca to provide strategic inputs to drug discovery and development in India and UK. Currently he is the Subject Matter Expert in Patient Safety and Pharmacovigilance at SciFormix Technologies and chairs the Data & Safety Monitoring Board for several clinical studies for other clients.

Suhasini Sharma, Chitra Lele, Darshan Bhatt