Ensuring safety and efficacy of pharmaceuticals and biotechnology products is one of the top challenges in the healthcare industry today. Drug withdrawals have further heightened the focus on drug safety with consumers and other stakeholders across the healthcare ecosystem demanding more oversight. Regulators across the globe are responding to these pressures by increasing their scrutiny and compliance requirements from the industry. Post-launch product withdrawals pose numerous risks to patient safety, besides being detrimental to business in terms of loss of revenue and credibility. A robust safety management approach during clinical development would help detect safety issues earlier in the product lifecycle and avoid subsequent debacles.

Safety monitoring in clinical trials is integral to the conduct of clinical research to ensure both patient safety and integrity of study data. Clinical trial safety management involves: collection, assessment and submission of expedited reports of serious, unexpected, suspected adverse reactions (SUSARs) to the regulators and all other stakeholders (investigators, ethics committees and Data and Safety Monitoring Board (DSMB)) in a timely manner; collection and periodic analysis of all safety data, including non-serious adverse events and laboratory data of trial patients; preparation and submission of annual safety update reports (Developmental Safety Update Reports in the EU, Investigation New Drug (IND) Annual reports in the US); signal detection and risk management activities, including preparation of risk management plans etc.

The activities are mandatory and requirements are numerous and varied. The regulatory landscape for clinical trial safety reporting has changed in recent years with the introduction of the final rule (Vol. 75, No. 188; September 29, 2010) under 21 CFR part 312 for IND studies and 21 CFR part 320 for BA-BE studies in the US, and ‘CT 3’ (2011/C 172/01) of Eudralex Vol. 10, Clinical Trial Guidelines in the EU. In addition, there are country-specific regulations, local institutional review boards (IRBs)/ethics committees (ECs) requirements and sponsor/policies/standard operating procedures (SOPs).

The requirements of clinical trial safety management are myriad in terms of specialised technology and processes, number and skill sets of resources and drug safety expertise. As in the other areas, many companies look for cost-effective outsourced solutions for management of clinical trial safety rather than invest huge financial resources on building in-house infrastructure, systems and manpower. This allows them to focus on their core objectives.

Most clinical trials today are outsourced to clinical research organisations (CROs) who partner with pharmaceutical sponsors for trial conduct, monitoring and data management activities. Safety management is usually the responsibility of the sponsor company. Though large multinational CROs may have safety capabilities, smaller regional or niche therapeutic area (TA)-focused CROs who garner a significant proportion of outsourced clinical trials may not have internal expertise and resources to carry out specialised drug safety activities. Hence, companies turn to providers specialising in safety services.

The companies that would look for outsourcing clinical trial safety services could be small, primarily discovery/development companies with only a few products in their developmental pipeline; or large pharmaceutical, biotechnology and medical device companies with a stream of products under development. For smaller companies, the main driver is to have a single efficient drug safety organisation to ensure strict regulatory compliance for the real-time safety reporting, plus ongoing safety monitoring and signal detection for the in-development molecules with evolving safety profiles.

For larger companies (with big molecule pipelines plus high case volumes) – additional factors come into play such as access to cost-effective, flexible sourcing solutions, advanced technological tools for improved productivity and the ability to provide integrated safety services across the globe.

Hence, while the smaller sponsors look for service providers with a high level of functional expertise in drug safety and end-to-end safety service capabilities (including access to a compliant safety database), larger companies look for a team of trained resources to work on specific safety tasks, to their processes and standards, while they focus on their core activities. For both, in addition to cost advantage, access to specialised expertise and industry best practices, better quality and productivity of outputs, speed of response, and flexibility to handle volume fluctuations are some of the benefits of outsourcing safety.

What can be outsourced?
A safety service provider may either provide end-to-end safety services or undertake individual tasks, such as collection and initial processing of clinical trial serious adverse events (SAEs), providing medical review support, conducting safety and literature reviews, or authoring annual safety reports (DSURs, IND annual reports) and risk management plans (RMPs) for regulatory submission. The primary goal for the service provider should be to deliver compliance-based, high quality safety data management which helps in detecting safety signals early, and establishing the safety profile of the investigational product while fulfilling compliance requirements. To this end, the service provider must have:

- Knowledgeable and trained resources, including safety scientists, safety physicians, subject matter experts and EU qualified persons for pharmacovigilance (QPPV)
- A regulatory-compliant safety database for hosting safety data with appropriate, built-in signal detection tools
- Knowledge of global and regional regulations for clinical trial safety reporting
- SOPs for clinical trial safety data management, including those for unblinding, expedited and periodic safety reporting, safety surveillance, signal detection and evaluation, and risk management
Mechanisms to ensure audit-readiness and compliance
Appropriate tracking and monitoring systems and performance metrics for each task/activity/piece of work
Robust project management and governance systems

Key drivers
Outsourcing of pharmacovigilance activities is a fairly recent phenomenon. Though many companies now look at this option in the post-marketing phase, there is still considerable reservation and apprehension in giving clinical trial safety to outside players. Some of the key drivers for doing so are:

Work volume uncertainty: Since safety profile of the drug under clinical development is still largely unknown, it is difficult to foresee or estimate work volumes; for example, the number of adverse events that may be reported or number/nature of safety signals that would need to be assessed. This is one of the primary reasons why sponsors may prefer to outsource clinical trial safety rather than investing in building in-house resources. Partnering with a safety service provider offers sponsors scalable resource solutions and flexible employment options.

Multiple reporting requirements: With clinical trials simultaneously ongoing in multiple countries around the world, it is a major effort to ensure that safety reports are processed and submitted to multiple regulators in required timeframes and appropriate formats.

Resources, experience and expertise: Often companies lack the manpower, infrastructure and expertise to manage the complex clinical trial safety requirements on their own. An experienced clinical safety outsourcing partner will give access to all these at a fraction of the cost.

Compliance: By partnering with a knowledgeable and experienced clinical safety outsourcing company, the client can meet regulatory timelines for safety submissions (both expedited and periodic) with optimal quality.

Potential challenges and mitigation measures
Outsourcing clinical trial safety has its own challenges. Some of these are crunched timelines for reporting and unclear accountabilities. Many sponsors would want to review and assess safety reports before regulatory submission, further crunching the timelines available for reporting. This is especially true for expedited reports involving fatalities. Hence, speed and flexibility on the part of the service provider is very important for achieving regulatory compliance. Another major challenge of outsourced safety is clearly delineating, between the sponsor and the vendor, who is responsible for what. Clinical trial safety management involves multiple activities that require clear definition and assigning of responsibility and accountability. In the absence of such clarity, sponsors and providers may just point fingers at each other when noncompliance occurs.

Most of the pitfalls of outsourcing are likely to arise due to selection of an outsourcing partner who is not able to provide services in line with applicable regulatory demands and sponsor requirements. Other factors leading to poor outsourcing partnerships would be treatment of the service provider as a ‘vendor’ rather than a partner, unreasonable demands in excess of projected scope of work, unrealistic forecasts, and resistance to outsourcing within sponsor teams, etc.

On the other hand, vendor behaviours that may lead to failure of the relationship could include treating the engagement as a one-time commercial venture and not investing enough energy and resources in building an internal knowledge base, regulatory understanding and talent pool to meet current and future client expectations and scalability requirements. Choosing the ‘right’ clinical safety outsourcing partner with a proven track record, mature operating models, trained talent pool with strong domain expertise and knowhow in clinical trial safety management is certainly key to successful outsourcing.

Further, clearly defining expectations, regular interactions, measuring and monitoring metrics, timely identification, escalation and joint management of other potential challenges/risks having an impact on the outsourcing partnership through implementation of a structured governance model (three-tier: functional, operational and executive) would help maintain the health of the sponsor-provider partnership.

Outsourcing clinical trial safety data management is a complex process. It requires specialist knowledge and expertise in various aspects of drug safety, which is more likely to reside with a functional safety service provider than a traditional CRO. Selection of the right partner and close working between the sponsor and the service provider is the key to the success of the outsourcing engagement.

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