Clinical Navigation

With significant developments being continually implemented within pharmacovigilance, sponsors and marketing authorisation holders across the globe must ensure they are up-to-date with the frequently changing environment

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Over the last decade within pharmacovigilance, significant developments and improvements to regulations have been made. With the revision of regulations occurring within multiple countries and regions, the pressure on sponsors/marketing authorisation holders (MAHs) to be knowledgeable of and abide by these is an ongoing challenge. Outsourcing different tasks and responsibilities is one available option. CROs are often able to provide sponsors (and/or MAHs within said sponsors) with greater global reach through coverage in multiple countries and take a proactive approach to remain knowledgeable on the current pharmacovigilance regulations to properly advise sponsors. Furthermore, CROs not only have the ability to advise sponsors, but also the skills, processes, systems, and resources to be able to adhere to this continually changing and costly environment, while still providing a high-quality service and maintaining compliance.

A shift in dynamic has been marked from the typical client-contractor relationship, where sponsors may now see CROs as their collaborative partner and, essentially, an extension of their company. CROs must recognise that each sponsor may have different needs and expectations and therefore appreciate the need to be flexible, while still remaining compliant with all regulations as the ultimate responsibility for pharmacovigilance activities remain with the sponsor. However, the willingness of sponsors to listen to advice from CROs and make informed decisions on best practice means that they remain compliant. This article will explore several instances where CRO support may be required by sponsors.

The ICH E2B (R3) standard outlines the data elements used in the electronic transmission of individual case safety reports (ICSRs) to promote greater consistency and standardisation. The Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) Data Elements and Message Specification aims to "assist reporters and recipients (including pharmaceutical companies, regulatory authorities and non-commercial sponsors) in implementing systems to construct transmittable ICSR messages. The representation of the ICSR follows an international standard that is platform-, application-, and vendor-independent." This will enable pharma companies and regulatory authorities to handle an increased number of ICSRs so that they are processed and exchanged electronically (between regulatory authorities, pharma companies, WHO-collaborating centres for international drug monitoring, etc) in an efficient manner. This supports sponsors and regulatory authorities by providing valuable and complete information on the safety of products, facilitating the authoring of aggregate safety reports (such as development safety update reports, periodic safety update reports in periodic benefit-risk evaluation report format, and periodic adverse drug experience reports); improved risk management/minimisation activities; and signal detection activities ultimately enabling healthcare professionals and consumers to make informed decisions regarding the products they prescribe/use.

CROs often host the safety database on behalf of sponsors. The new ICH E2B (R3) standard requires safety database service providers to update their systems to be compatible with these new specifications. As a result, CROs, on behalf of their sponsors, may be required to upgrade to the latest version of the safety database available by the vendor. This requires extensive planning, testing, and validation (in line with internal procedures) prior to the cut-over of data to secure a seamless transition in ensuring:

- All data is migrated to the upgraded system correctly, through accurate field mapping/configuration between the previous safety database version and new version
- Minimal system downtime during the cut-over, with the cut-over often occurring over a weekend to guarantee end-users can continue to process cases received immediately prior to and following the cut-over
- Minimal post-upgrade issues
- Processes are updated in advance in readiness to be made effective immediately once the cut-over occurs
- End-user updated training/guidance is provided shortly after the cut-over

During this process, CROs may need to collaborate closely with the safety database vendor over extended periods of time to ensure the success of the upgrade's implementation. These efforts also help guarantee no impact to ongoing case processing activities, therefore minimising the possibility of compliance issues.

All sponsors (and investigators) must maintain documentation for every clinical trial they conduct according to applicable local and global regulations. The trial master file (TMF) acts as a collection of content in efforts to demonstrate that the sponsor conducted

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the study in accordance with both the protocol and Good Clinical Practice (GCP). To date, no single comprehensive, standardised model to follow exists across the industry and regulatory guidances (such as ICH E6), only sub-sets of the documents that are commonly contained within the TMF. As a result, each trial sponsor must decide on a particular guidance and develop their unique structure, which is then defined and supported by company-specific operational procedural documents.

With ambiguity usually comes expense, and sponsors and CROs alike have been found to expend a substantial amount of exhausting resources to define (and redefine) TMF content for each clinical trial. This inefficiency results in the inconsistency of terminology and file structure across the industry as well as the use of over-qualified personnel for purposes of tending to a laborious and cumbersome task when their time may be better suited elsewhere (ie, ensuring efficient trial conduct, compliance in data collection/reporting, and overall patient safety). The lack of an industry-standard TMF structure leads to compromised collaboration between CROs and their business partners when exchanging and sharing data is needed (ie, mergers, acquisitions), as well as exhibiting and exacerbating the potential risk for variability during a regulatory inspection of the sponsor and/or CRO.

In recent years, the industry has pushed to develop a more consistent and standardised approach to the organisation of contents within the TMF to ensure a shared level of comprehensiveness as it applies to trial conduct and execution, as well as regulatory inspection readiness. The TMF reference model developed by a working group within the Drug Information Association is an example of a currently available standard. Adoption of such models is usually popular for CROs as a unified approach is found to not only reduce differences, but also cost when performing filing practices for clients. The need for fewer but more comprehensive models will continue to evolve as the industry expands, regulations change, and financial burdens increase.

Recent changes in data protection regulation include the General Data Protection Regulation (GDPR) 2016/679, which becomes effective in May 2018 and replaces the Data Protection Directive 95/46/ec as the primary law regulating how companies protect the privacy and security of individuals' personal data. This was adopted as a regulation (as opposed to the previous 'directive'), meaning it must be adopted uniformly throughout the EU. Within the pharma, biotechnology, and medical device industry, CROs play an important role in supporting sponsor efforts to meet all of the requirements contained within the new GDPR in a timely manner, as companies found to be noncompliant with the new regulation face costly penalties, and CROs assume a certain level of responsibility for the sponsors they perform clinical activities for.

More importantly, companies that are already compliant under the current privacy directive may still be required to make significant changes to their internal infrastructure and processes in regard to the handling of personal data in preparation to comply by May 2018. Such audit readiness initiatives, coupled with lack of a compliance grace period, can quickly become a costly measure for smaller companies. However, within the industry, regulatory compliance most often comes at a high cost and CROs are relied upon to perform such regulatory intelligence activities. In this case, businesses affected by this new law will benefit from avoiding potentially costly penalties due to noncompliance, while, at the same time, improving personal data protection and patient trust.

Some may argue that the increased level of GDPR security regulating the use, collection, processing, and disclosure of personal data by controllers and processors also has the potential to challenge the transparency of pre-authorisation safety data as it applies to safety reporting regulations within clinical trials. As personal privacy regulations carry on evolving, regulators and businesses alike will carry on striving to meet the regulatory, financial, and ethical demands of bringing effective, safe, and affordable products to post-market in efforts to treat the health of the public population. Such efforts often require support by CROs that manage the ever-changing challenge of ensuring the privacy and security of clinical safety patient data while sponsors/MAHs fill their pipelines.

Within day-to-day clinical safety, a strong focus is on investigators recognising and appropriately redacting potential subject identifiers. Particular care needs to be taken with reports such as discharge summaries, death certificates, autopsy reports, laboratory, and diagnostic tests to ensure that a subject is not identifiable. Sponsors and

CROs must be on high alert to check source documents and, where found, redact appropriately while communicating with clinical teams to remind investigators of their obligations.

What Does the Future Hold?

As history usually repeats itself, the R&D phases of clinical safety will continue to be costly, complex, and arduous. CROs will remain challenged to meet the demands inflicted by the industry as well as the sponsors they serve. Regulations and guidances will continue to evolve, particularly as technological advances increase efficiency and address the growing complexity, cost, and scale of clinical trials. This is also particularly pertinent in post-marketing pharmacovigilance, where safety information can be located in a huge array of sources such as social media, blog articles, and visual media. The continued automation of manual processing steps within pharmacovigilance coupled with the evolution of artificial intelligence is likely to lead to further proficiencies and affect the way CROs support sponsors in clinical trial design, oversight, and the recording and reporting of data moving forward. Nonetheless, with these advances, the challenge of safeguarding patient protection and privacy while ensuring reliability and transparency of clinical trial results as well as being compliant with the ever-changing regulations will remain.

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