The ever-increasing regulatory requirements for safety reporting have been well-documented in recent months. And now pharmacovigilance (PV) professionals are facing their biggest challenge yet, with the FDA recommending that clinical trial results are made public and that access to Serious Adverse Event (SAE) reporting is broadened to new audiences for review. This move will not only put the PV industry in the spotlight, but will also scrutinise the efficiencies or otherwise of SAE reporting.

Historically, it has been the remit for PV professionals to drive the safety reporting process in order to meet the needs of the regulatory bodies. This has led to a number of new procedures which – with paper systems – are cumbersome and time-consuming for the practitioner.

In addition, the PV practitioner currently operates independently of the clinical trials process. This dissociation can lead to a number of inconsistencies in how data are managed and reported – as a result, adding both time and money to the process. The adoption of Electronic Data Capture (EDC) is now providing a means by which inconsistencies in adverse events reported in clinical trials can be filtered and processed rapidly. However, a lack of access to EDC by PV practitioners, and their separate operational approach to the clinical trials process, means that the industry needs to re-think how to integrate the technology available to create greater time- and cost-efficiencies.

INTEGRATING SAE REPORTING
Currently, separate SAE forms and cumbersome faxing procedures are designed to ensure direct receipt by the pharmacovigilance operation. This would be the first point of notification to the company of a reportable event. Traditional reporting of safety information on paper clinical report forms (CRFs), and submission of these forms to a data management operation, rarely impacts on the order in which company representatives become aware of an event; however, EDC is turning this whole assumption on its head.

Clinical trials utilising EDC or electronic diary technology offer the potential for an entirely paperless instant warning mechanism for SAEs. However, new supporting technology is only ever as good as the process and resource in place to manage it. At present, we typically observe PV practitioners relying on rapid alert systems, such as automatically triggered email. There is no appropriate access provided to PV professionals, and there is currently little interest being expressed for increasing this.

Traditionally, the PV practice would be the first port of call for any SAE reporting, with that department taking direct responsibility for the notification of the rest of the company. The PV operation has generally acted independently of the clinical trial team; however, EDC provides a means through which these two teams can be integrated. An SAE entered directly into the EDC system can generate an immediate alert to the safety department in the form of a text or an email. This will prompt a check to determine whether this adverse event has already been reported directly to them. In this instance, the serious adverse event is stored in both the EDC system and the PV safety database.

BRIDGING THE DATABASE GAP
Another challenge for the successful adoption of EDC is the current level of inconsistency between the data gathered for safety databases and the data gathered in
clinical trial databases. In order to ensure consistency for safety-reporting, the EDC technology must be able to bridge this gap.

Current cumbersome reconciliation techniques are not commonly undertaken until long after the first submission of an SAE. In fact, for the vast majority of cases, this occurs just prior to locking a study database for analysis and reporting. Furthermore, each sponsor of a study tends to develop independent procedures to facilitate comparisons between the different systems. This process is neither time- nor cost-efficient and yet the industry still perpetuates this ‘dual interest’ approach.

One might believe that the industry’s interest in adopting standards would be of benefit in reconciliation. However, the ICH standard for ICSRs (Individual Case Safety Reports) is E2B, and the field content and labels for this standard differ significantly from those adopted by the Clinical Data Interchange Standards Consortium (CDISC) in the Submissions Data Tabulations Model (SDTM). Examples of different labels are: `<reactionmeddra>` is equivalent to `<AEDECOD>` and `<seriousnesslifethreatening>` is equivalent to `<AESLIFE>`.

Consequently, one is forced into a mapping exercise to facilitate comparison.

Nevertheless, the advent of the E2B standard for ICSRs (1) has provided an opportunity. Any EDC database able to generate an E2B file, albeit with gaps, provides the opportunity to perform a direct file comparison between two E2B files for the same SAE.

One observation of note is that E2B files are typically submitted electronically as XML (extensible markup language) files to regulatory agencies in Europe, while the FDA prefers to receive SGML (standard generalised markup language) files. By contrast, the FDA is considering accepting electronically submitted SDS (submissions data standard) files as XML files, although currently expressing a preference to receive SAS (statistical analysis system) Transport files. However, the FDA is constantly reviewing its submissions procedure to account for the technology changes facing the market. The PV industry must anticipate these changes and be ready to adapt.

**SINGLE SOURCE DATA MANAGEMENT**

A more inclusive approach to SAE management is to gather data on a ‘single source’ basis. Building a framework that supports both clinical trial information and the additional data associated with reporting is not beyond the realms of possibility for EDC technology.

Pharmacovigilance groups can be given direct read-access or edit rights to the SAE data and actually manage the data acquisition process. Tailored pop-up screens can be provided for the additional data associated with a reportable event that is not required by the clinical research department.

Alternatively, direct export of data into the safety database can be established, but the process adopted must avoid subsequent data editing in one database independent of the content of the other. Connectivity between an EDC system and the safety database should entail one-way transfer of data from EDC to the safety database, supported by bi-directional query management.

Can ‘single source’ ICSR data from clinical trials be considered the ultimate solution? Actually, one can take this combined approach a step further and adopt single storage of data. Here, both data management and pharmacovigilance personnel would access a shared database, and establish responsibilities and privilege levels that serve their mutual interest. There is no technical reason why this cannot be done today. It is merely organisational structures and protected responsibilities that currently obstruct its implementation.

One area where divergence can occur is in the coding policy for each database. Typically pharmacovigilance will use a current (or near-current) version of the commonly used dictionaries – MedDRA and WHO_DRL (2). However, some data management operations will persist with coding in a particular dictionary version for the duration of a study. Different policies may need to be accommodated. Furthermore, in certain organisations, the coding is performed by different people/groups – which leads to another potential inconsistency. The worst-case scenario is that the same SAE finds itself with a different Preferred Term, or ultimately placed in a different System Organ Group.

**Figure 1: Interfaces Between Safety, EDC and CDM Environments**
CONNECTIVITY WITHIN THE REPORTING PROCESS

Abnormal laboratory results will also uncover adverse events. These results may come from a local laboratory and be supplied to the investigator directly. However, the majority of studies will have laboratory data generated by central laboratories, with results imported directly into a clinical database. These sources may also provide tabulations compliant with CDISC, in the form of LAB files (consistent with the LAB model). The true clinical significance of an abnormal result must be assessed, and an SAE may be identified. In fact, the MedDRA dictionary accommodates the coding of laboratory data, and the EMEA has requested that such events be submitted in coded form, electronically.

In EDC studies, the most effective reporting process is to import laboratory results into the electronic study database, which automatically runs consistency checks with associated patient data and subsequently generates queries. This means that investigators and clinical researchers can access the results through their laptops in real time. Furthermore, the system generates automatic issue alerts making prompt identification of SAEs possible. Such a workflow means that all the SAE information resides within the EDC database, and the EMEA has requested that these ICSRs could then be assessed by the regulatory agencies within a short time-frame of the event. By contrast, summaries of SAEs, together with the CRF data, are evaluated during the review of a submission months and perhaps years later. This results in delays and creates the inevitable difficulties associated with reviewing an historical event instead of in real time.

However, times are changing. Since 1st May 2004, the EMEA EudraVigilance database has a new ‘CT-module’ for the collection of Suspected Unexpected Serious Adverse Reactions (SUSARs). This database is not only available to those engaged in pharmacovigilance, but also to evaluators throughout the 25 EU national competent authorities. The identification of issues in an evaluation will automatically lead reviewers to access SUSARs information from the database, and also to examine periodic reports submitted by the sponsor. The result is that inconsistencies are more likely to be uncovered with the reviewers having good reason to question data validity. Sponsors will clearly wish to avoid this uncertainty developing in reviewers’ minds.

A similar facility exists at the FDA with their Adverse Event Reporting System (AERS) database, receiving not only all Serious Adverse Drug Reactions (SADRs) electronically but also unexpected non-serious events from clinical trials. This database is available for interrogation by FDA reviewers.

As this information has traditionally been supplied from different sources, the potential for conflict will remain. By building EDC into the process, such inconsistencies can be removed via a system that connects with the safety database and can provide robust data for review.

The advent of regulator demands to make all trial data public is creating an increasing need to ensure that SAE procedures are seen as transparent, compliant and time- and cost-efficient. EDC technology meets this need and provides a process which avoids repetition of work flow, integrates the whole process and standardises the differing terms and coding for SAE reporting. The PV industry has previously been shy of addressing the limitations of the current systems for fear of highlighting flaws and inefficiencies in safety reporting. However, broad adoption of EDC within this area of practice will actually support the PV professional in improving SAE reporting processes.

If the PV practitioner embraces a technology that can facilitate change to the fundamentals of its practice, then certain questions surrounding the efficiencies of its work will be answered. Furthermore, integrating trial data capture and safety reporting processes produces a cohesive and transparent flow of information for any company or organisation seeking efficiencies in its business.

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References

2. a) MedDRA www.medramss.com,
   and b) WHO_DRL www.who.int