The Need to Streamline Adverse Event Reporting for Clinical Trials

PEER REVIEWED

Given limitations in study size, duration and increasingly earlier approvals, pharmaceutical companies must garner as much relevant, accurate and timely data as possible to understand the true efficacy and safety profile of products during the development process. Consistent, high quality standardised and complete data is a foundation of successful clinical trials and drug development.

Capturing and managing serious adverse events (SAEs) and adverse events of special interest (AESIs) represents a fundamental component of clinical trials. Due to complex and often 'paper-based' data collection methods, poor resources, lack of communication amongst reporters and patients, time-lags, and variable adherence or compliance, traditional adverse event collection in clinical trials has often generated poor-quality, or missing data. Adverse events have resulted in events being reported incompletely, forgotten or missed[1]. It is a significant challenge for pharmaceutical companies to obtain patient safety data during clinical trials that is accurate, comprehensive and on a scale that is large enough to paint a complete picture and inform drug development.

Electronic data capture (EDC) systems used in clinical trials do not address the requirements of the SAE process nor of the actors in the safety organisation, with SAE reporting remaining a separate, often manually managed component. There are various reasons for poor integration with EDC when collecting and processing SAEs and SUSARs (suspected unexpected serious adverse reactions). The nature of information required and the timelines for assessment and regulatory reporting necessitate very different workflows from the standard time and events approach to clinical data, and firms are often highly reluctant to integrate and change their incumbent systems[2].

The industry needs a new way of dealing with SAE processing in clinical trials. Patients, clinicians and all other parties involved in the clinical trial process need to be better equipped with more direct and streamlined adverse event reporting resources. Making these tools more accurate and simpler to understand and use will make the process more efficient, transforming drug safety.

Diagnosing the Problem

The scale of the problem of adverse event reporting is increasingly acknowledged in the pharmacovigilance space, and appetite for change is growing.

At the end of 2017, the American Society of Clinical Oncology (ASCO) found that following a random audit of expedited adverse events reports submitted to the US Food and Drug Administration (FDA), only 14% of 160 adverse events reported to them were helpful in assessing patient safety[3]. ASCO found that the data obtained and reported through set processes, was often either incomplete, missing or of inadequate quality to make any sound judgements about the benefit or harm of the trialled drug.

Previous reports have painted a similar, ongoing picture. Nearly 15 years ago the Institute of Medicine's publication of *Patient Safety*[4] found an industry-wide lack of standardisation in data collection mechanisms was preventing reuse of clinical data to meet the broad range of patient safety and quality reporting requirements. It also found that there was a severe insufficiency in the intake of adverse event reporting in clinical trials, and that inadequate and dated methods were being used across clinical trials.

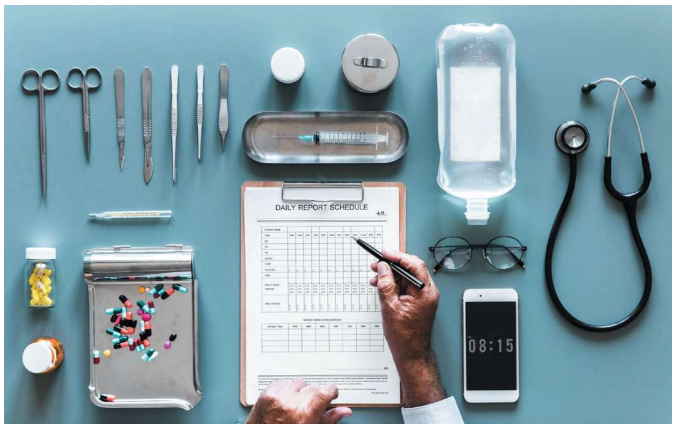
More recently, a study of the quality of severe adverse event (SAE) reporting in clinical studies, conducted at CHU de Limoges, France and published in 2016, found that the accuracy and completeness of reports was "poor" and concluded that the current levels of patient safety in clinical trials was compromised by data quality[5].

Poor data collection and quality in the monitoring of adverse events is clearly a concern for patient safety and drug development. Ultimately, it leads to incomplete or erroneous judgements on the perceived benefit-to-harm profile of an intervention. At the same time, it imposes a substantial resource toll on resources across pharma company medical teams, regulators and clinical professionals. So far, efforts that have been made to integrate technology to simplify the management of adverse events (AEs) in clinical trials, through the use of sponsor-specific electronic portals, have often fallen short of generating change in the industry. In fact, ASCO found that 60% of site investigators and staff respondents indicated that they spend more than ten hours each month processing safety reports – not always to any successful effect[6].

Rhetoric to Reality

The key to understanding how to tackle the issue of incomplete, missing and poor-quality data relies on understanding what is going wrong. The root of the problem is twofold. On one hand there is a lack of precision and consistency in the process of collecting data, and on the other the various systems and methods used across clinical trial reporting are disparate, leading to insufficient, and often confusing means of collating and understanding the data.

A significant barrier to accurate reporting and good quality data in clinical trials is the disconnect between the moment an adverse event occurs, to the reporting of that information.



Standard procedures in clinical trials indicate that the sponsor team, and in particular the medical monitor, must be made aware of a serious adverse event (SAE) within 24 hours of an investigator site first becoming aware of that event. In reality it can often be several weeks from the occurrence of the serious adverse event, to when it is actually notified to an investigator. SAEs are simply identified at the next routine clinical visit and then reported to the sponsor within 24 hours. The spirit of clinical trial regulation is that sponsors are made aware of SAEs and AESIs in real time, thus enabling them to continually reassess the safety of participants within the trial programmes.

This time-lag is problematic for data quality, and thus patient safety. It erodes the accuracy and precision of the data collected. Every time a new step is introduced to the reporting process, the quality of that data is greatly reduced. Recipients of a drug cannot be expected to accurately recall all details of issues they encountered a long time after occurrence, as much as they will be unlikely to be able to precisely describe, for instance, a car accident that they witnessed four weeks previously. As data quality is so vital to successful clinical trials, and as the speed at which adverse events are reported is critical to good quality data, a clear solution to better data lies in accelerating the reporting process.

Another critical issue reducing the quality and flow of data collection for serious adverse events in clinical trials is the disparate nature of the data collection processes themselves. Such processes often differ across the pharma companies and the CROs running the trials, with inconsistency of the tools and routes for notifications of SAEs.

This issue is made significantly more complex with the addition of multiple geographic locations for the trial of a drug, where understanding of the English language, the default for global trials, may vary between sites and create additional variations in reporting. For example, clinical research coordinators, pharmacists and administrative assistants, all immersed in the process, may not maintain the same levels of fluency. Language barriers therefore often result in miscommunication and misunderstanding of information and data. This also stretches timelines and personnel resources, as the time taken to process and translate reports is increased.

Fast-tracking of Clinical Trials

This problem is made even more pertinent when looking at current developments. Ageing populations, segmentation of diseases through scientific discovery and increased patient demand have all led to a rapid increase in demand for better accessibility to new medicines. Whilst clinical trial processes can take up to fifteen years in some instances, recent developments are moving towards a faster process for drug approval.

Since 1992, the FDA has created four groundbreaking 'fast-track' mechanisms for accelerating drug approval; Priority Review, Breakthrough Therapy, Accelerated Approval, and Fast Track[7], all aiming to speed up the process to provide greater accessibility to drugs. Whilst these fast-tracking initiatives are most popular in the US, with much higher drug approval rates, this trend is also evident on the other side of the Atlantic. The European Medicines Agency (EMA) followed suit in 2016 with their "Prime" scheme, aiming to cut assessment times by nearly a third[8]. Just this year in the UK, the NHS introduced a new scheme to fast-track clinical trials in the hope of improving access for patients and reduce bureaucracy costs[9].

Many of these fast-tracked reviews, whilst working towards solving a critical issue in the industry, raise serious questions about speed at the expense of safety, leading to key questions about pharmacovigilance.

Seventy-two of the FDA's fast-tracked systems use single-arm trials as opposed to more rigorous and larger randomised controlled trials (RCT). In the single-arm trials, which are 'not generally used as confirmation of efficacy', objective response rate is used as an endpoint, limiting the data used from these trials (10). Drugs, in effect, are reaching the market based on data from a few hundred patients, as opposed to the thousands that there would be in a standard clinical trial. This is particularly true for drugs aimed at rare disorders or those with poor outcomes, for instance aggressive cancers.

This makes the issue of data collection and analysis much more pressing. Ultimately, the rule of thumb is that the more data obtained, the more it can be cross-checked and the more reliable it becomes. In the case of fast-tracked drug approval, there are significantly fewer data points. Consequently, inaccurate or poor quality data on a smaller data set will have a much greater confounding effect on the results than in larger, more data-intensive RCTs.

It is no surprise, therefore, that much of the opposition to fast-tracked drug approval schemes highlights the safety risks attached to them – greater drug accessibility at the expense of patient safety. With the sustained rise in these types of trials, there has never been a greater need to improve the data collection procedures for adverse events.

Moving Forward

Firstly, we need to be able to simplify and speed up the process between the occurrence of an adverse event, and the time it takes to be reported. As critical gaps in information cannot be corrected post-processing, relevant and accurate information must be collected at source to provide meaningful insights to improve drug development and overall patient safety. As the First Law of Information Theory states, "every relay doubles the noise and cuts the message in half"[11]. It would follow therefore that data collected with the absence of intermediaries and time-lags is of a significantly superior quality to that extracted from the traditional patient-investigator relationships.

Additionally, we need to structure the intake of data. Patients and investigators must have the resources to be able provide information in a consistent and reliable way, where they are prompted to provide information that is relevant. With the high volumes of data being captured, processes need to be in place to collect, structure and collate data across all sources in a standardised and intelligent way.

Rewriting the Script

Technological innovation can provide the solution that clinical trials urgently need. Pharmaceutical companies and drug administrators are increasingly harnessing technology as a means of transforming the data collection processes in clinical trials – putting the safety of the drug at the heart of its development. Tech is now coming to the forefront in providing the answer to the issue of poor quality, disparate data affecting the value of adverse event reporting.

Portable, cloud-based applications are working to improve data quality in clinical trials, whilst simplifying the process and reducing task-times. Both investigators and patients need to be provided with the tools to enable them to capture the key data at the required time and in cases of serious adverse events (SAEs) at the unexpected time points. Direct reporting through portable, cloud-based multi-platform solutions enables the capture of adverse event data at source, meaning the occurrence of gaps or missing data is dramatically reduced, and the most accurate, reliable data can be collected from clinical trials.

Direct, streamlined reporting mechanisms are also empowering patients in the clinical trial process, improving the quality of the data. Since 2005, both the EMA and the FDA have called for greater patient autonomy in adverse event reporting[12,13]. Patients themselves know best how the medicines are affecting them, and through portable cloud-based solutions they can convey that information more quickly and accurately than ever before.

Empowering patients to record their own safety information in clinical trials is far more effective at generating responses and improving the quality of data. A recent study found that in oncology trials, participants were more willing to report their own symptomatic adverse events than when the responsibility lay with investigators. The occurrence of missing data was reduced by a significant amount with overall satisfaction as 'high'[14]. Such technology can complement patient empowerment, which in turn improves the quality of data in clinical trials.

Another clear benefit of cloud-based platforms is in clinical trials they can enable the data to be encrypted in rest and in flight, meaning it cannot be lost or importantly, tampered with. In the first 10 years of reports from The Office of Research Integrity, the body that directs Public Health Service (PHS) research integrity in the US, there were 136 findings of scientific misconduct in data collection, with 26% of these found in clinical trials or other clinical research[15]. Similarly, in China, an investigation of data for 1622 submissions to China's State Food and Drug Administration (CFDA) for registration said that 1307 of the applications should be withdrawn due to fabricated, flawed or inadequate data from clinical trials[16]. By preventing human error, or deliberate deception, from corrupting the data and ensuring it is secure and safe, those at the receiving end are supplied with a more reliable and consistent flow of data than there would be with classic manual processing.

Importantly, cloud-based, portable technological solutions, such as Reportum[17] – a product that is already in use by six of the top 30 pharma companies globally – also work to structure and standardise the data at source and export via E2B direct to client safety databases. Data can be collected in English for global programmes or in local languages for late-phase studies. By virtue of the SaaS model, updates to SAE forms or associated targeted questions can be made simultaneously across the entire trial landscape thereby ensuring consistency and compliance. Hosting data capture in one secure, standardised platform provides a validated data stream direct to the safety team and ensures traceability. Quality of data content is therefore optimised with a focus on 'right first time' capture, whilst simultaneously streamlining the end-to-end process of serious adverse event collection.

The issue of poor-quality, unstructured and disparate data in clinical trials will remain unless the industry takes a more focused approach to collecting clinical trial safety data through appropriate digital tools. Putting data integrity at the heart of clinical trials will transform drug development, and protect patients from the growing risks and harms that testing new drugs entails. Pharmaceutical companies and drug administrators are already beginning to harness the power of technology, adopting direct, digital and structured mechanisms and end-to-end processing tools to manage their clinical trials. A digital strategy focused on the specific requirements of 'clinical safety' and the 'safety organisations' is the way forward.

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Andrew, founder and CEO of MyMeds&Me, is a pharmacovigilance expert and has set up Reportum, a leading pharmacovigilance platform currently in use by six of the top 30 pharma companies. Andrew has deep expertise in pharmacovigilance, as well as the emerging challenges of data privacy. He is a trained physician who has held senior roles spanning drug discovery and development within GSK and has worked across three continents.