Risk-based Quality Management: Improving Trials Data through Minimalism

PEER REVIEWED

There is no doubt about the importance of maintaining quality standards throughout clinical research processes, but in recent years the regulatory bodies have begun to question the industry's approach to quality management. This has led to an addendum to the good clinical practice (GCP) guidelines that advocates rethinking of current quality management practice during clinical trials. While any perceived change in regulations is likely to throw the industry into turmoil, the latest guidance intends to help drug companies to streamline their research through risk-based approaches to quality management. This article considers the new way of thinking, which promises to allow more focused and cost-effective trials that could reduce considerably the enormous time and cost burdens of current quality management practices.

Over the past twenty years, regulatory requirements have become more stringent throughout all stages of the pharmaceutical research and development pipeline. For clinical trials in particular, pharmacovigilance expectations have increased dramatically, requiring thousands of additional patients for every Phase III study and, typically, resulting in several billion dollars of additional work for every potential blockbuster drug. For many drugs produced today, the clinical phases account for the majority of the drug's total development costs (around 75 per cent), far outweighing the investment required for all other steps, including discovery, preclinical development and manufacturing. Furthermore, approximately half of these inflated clinical costs are spent on oversight – especially source data verification (SDV), the labour-intensive checking and verification of all clinical data in order to demonstrate that quality standards are being upheld. Many pharmaceutical companies have adopted 100 % SDV within their quality management processes, and routinely spend millions or even billions of dollars per trial checking that every single data point in the trial CRF matches the original data source information. However, it has recently become apparent that this costly approach does not necessarily meet the data quality requirements for the industry.

According to the European Medicines Agency (EMA), every clinical trial must be conducted to acceptable quality. Crucially, acceptable quality means the data collected must be of sufficient quality to support good decision-making – i.e., fitness for purpose. All trials are likely to contain some data errors and it would be unrealistic to set a specific tolerance level for errors within the good clinical practice guidelines[1]. The important point here is that the data must be good enough for the authorities to make the right decision when reviewing a trial report. In other words, the decision made following the study would be the same decision if the data were perfect.

The Need for Change

The guidance clearly does not require 100 % SDV, but many sponsors insist on including full SDV within their trials and are perhaps reassured by generating large volumes of checked data. In reality, quantity does not guarantee quality and such reliance on SDV can leave sponsors oblivious to two worrying truths. Firstly, verifying that all original source data match the trial's CRF data does not prove that the original source data were inputted correctly in the first place. As a result, the trial data could contain major systematic errors that severely impact the quality and trial outcomes, but these errors would not be detected through SDV. Secondly, conducting 100 % SDV typically requires huge use of resources that can preclude any other type of error-checking from taking place during the trial, again meaning that systematic errors are not detected early on, resulting in poor quality data collection. In 2014, TransCelerate Biopharma assessed the value of SDV through a literature review and retrospective multi-study analysis of clinical trial data[2]. The analysis found that SDV has a negligible impact on data quality, and across 1168 studies, only 3.7 % eCRF data was corrected by any method after initial data entry by site personnel; only 1.1 % was corrected by SDV methods[2]. Incredibly, 96.3 % of the data collected in the studies was never corrected.

The regulatory authorities have recognised the growing problem with current approaches to quality management. In 2011, the EMA produced a draft reflection paper that was adopted by the GCP Inspectors Working Group in 2013. The paper identified the shortcomings of current practice, in particular the disproportionate costs and time-consuming nature of oversight, and the lack of prioritisation, risk identification and risk mitigation within trial designs[3]. It recommended that sponsors move towards a more proportionate, systematic and risk-based approach in quality management, facilitating new thinking in trial design that would focus on the most important issues and priorities. Risk-based approaches have similarly been recommended by the FDA[4] and MHRA[5]; elsewhere, TransCelerate Biopharma has been working to find ways for pharmaceutical companies to accommodate this industry shift in a simplified fashion[6].

Becoming Minimalistic

Risk-based quality management (RBQM) represents a significant change in mentality compared to traditional quality processes. The aim is to focus on the reliability of the trial results, and the wellbeing and safety of trial subjects, by identifying the trial priorities and ways to mitigate significant and serious risks[3]. RBQM is a systematic way of thinking that must be applied right from the start of a study, because it dictates the trial

design and influences numerous fundamental decisions, such as which parameters to include, how and when to collect data, and how frequently to check the data. Risk mitigation can then be built into the protocol design and monitoring plan. For example, rather than reactively checking all the data points collected during a trial, RBQM should ensure that inputs can only be entered correctly in the first place. By rethinking quality management in this manner, sponsors will not only improve the quality of their clinical trials, but also be able to streamline trial designs, thereby saving vast amounts of time and expense.

RBQM involves conducting a risk assessment for every trial to consider what might go wrong, how and where, so that ways can be identified to prevent problems arising in the first place. The risk assessment considers risks to trial patients, risks to the data (impacting decisions made based on the trial outcomes and, therefore, affecting future patients), risks to the trial provider and even risks to the sponsor. It forces sponsors to ask themselves what level of risk is acceptable and set their own quality control processes to ensure these limits are in place. Ultimately, by considering these risks, companies are encouraged to focus on the most relevant and important points for their quality management. By doing so, they can minimise the introduction of systematic errors into the study, resulting overall in better quality data, without having to check every data point in the CRF.

Traditional SDV-focused approaches to data quality management focus primarily on on-site monitoring. In contrast, implementation of RBQM should involve a combination of both on-site and centralised data monitoring methods. On-site monitoring does not have to involve frequent site visits and SDV, but should focus on compliance of the protocol and documentation of collected data and processes, ensuring any systematic errors are spotted and dealt with early in the trial. Centralised monitoring includes checking for data anomalies, higher frequency of errors and protocol violations[4]. Standard checks might include data range, consistency and completeness, and checking for unusual distribution of data between sites.

With today's EDC and eCRF technologies, centralised monitoring can easily be carried out remotely at the sponsor or CRO's facilities. It focuses on review and assessment of reported data, including checking the quality of real-time data entry, statistical analyses of data across different sites to identify outliers, analysis of site characteristics and performance metrics, and detection of data trends that would not be spotted through on-site monitoring. The combination of on-site and centralised monitoring is expected to ensure that patient integrity and safety are upheld, and that the data collected are trustworthy.

Empowering Sponsors

RBQM clearly offers important advantages for the pharma industry as well as for patients. Accordingly, the GCP guidelines have been updated with requirements for a risk-based approach that includes a risk assessment to be made prior to the trial, with SOPs and appropriate plans in place to support risk control and risk reporting, as well as centralised and on-site monitoring[7]. The shift towards RBQM will require sponsors to demonstrate that they have applied the principles correctly in order to establish and prioritise the risks, while meeting GCP objectives. When assessing trial reports, the regulatory authorities will then need to be able to understand those thought processes underlying the trial design.

On the face of it, drug developers may feel that the introduction of yet more guidelines and documentation can only increase their burden of quality management, and set back timelines for new trials. Arguably, however, the principles of RBQM were included in the 1996 GCP guidelines[1]: *"The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial"* (§5.18.3). The recent addendum to GCP simply places more emphasis on empowering the sponsors to decide on a suitable quality management system for their specific trial.

Some pharma companies may not like being forced into a new way of thinking. The pharma industry is renowned for being highly regulated, but it is becoming apparent that some of the perceived constraints and administrative burdens are practices that sponsors have themselves instigated through over-interpretation of the guidelines. For example, there is no GCP requirement to perform on-site monitoring at a specific frequency, but simply "before, during and after the trial". This contrasts with current popular belief that on-site monitoring should be conducted at regular and very frequent time intervals.

The principles of RBQM clearly require fresh thinking for each trial, so sponsors cannot expect to receive template risk assessment forms to complete and directions on which quality control methods to include in their trial design. GCP guidelines also specify that the responsibility of the risk assessment, plans and documentation lies with the sponsor. When partnering with a CRO, therefore, it will be essential that the sponsor and CRO have full and joint understanding of the risk assessment, trial design and RBQM underpinning the trial. Sponsors will benefit from working with a proactive and up-to-date CRO that has fully embraced the concept of RBQM. At our company, for example, we are accustomed to working in a transparent, well documented and collaborative manner with the sponsor. Furthermore, our senior advisory team includes experienced GCP inspectors and offers a wealth of expertise to guide RBQM, trial design and conduct. By focusing only on essential trial activities, with assessment and QC methods that are proportionate to the risk, we can help our partners to design efficient and simple, yet high quality studies, in line with the latest regulatory requirements.

Conclusions and Future Directions

RBQM is a simple principle that directs pharma companies to focus on the most relevant points for a specific trial and spend less time on data and processes that are not so important for the study outcome. This is an important step forwards for the industry, that will help companies to work in smarter, more efficient ways that use fewer resources. However, the success of such an approach relies on being able to empower people with greater responsibility and strip out the layers of duplicated responsibilities that are created by repeated checking of controls. This requires a complete change of mindset in the current industry that may take several years to show results, but the expectation is that everyone will gain in the long term.

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