CLINICAL INVESTIGATION

Exploring the challenges, impacts and implications of risk-based monitoring

"...everyone – industry, academia and regulatory agencies – is aligned to make risk-based methodologies an essential component for the future of drug development."

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The quality of data collected from clinical trials has received a great deal of attention in recent years. Of central importance is the need to protect the well-being of study participants, and maintain the validity and integrity of final analysis results – so-called good clinical practice (GCP). In order to achieve these goals, guidelines from the International Conference on Harmonization suggest that clinical trial data should be actively monitored or reviewed [1]. For trials in the pharmaceutical industry, traditional approaches to assess data quality, including 100% source data verification (SDV) of case report forms (CRFs) through regular on-site monitoring, have come under increased scrutiny as providing little benefit for the substantial cost [2–4]; for example, TransCelerate BioPharma reports that SDV generated only 2.4% of the queries for critical data from nine sample clinical trials [3]. Similarly, Bakobaki and co-authors state that 95% of the data issues from a large international multicenter trial could have been identified directly from the study database [5]. For activities that are estimated to consume up to a third of a trial's cost, there is certainly room for improvement [6].

In contrast to frequent on-site monitoring, risk-based monitoring (RBM) makes use of central computerized review of clinical trial data and site metrics to determine if sites should receive more extensive quality review or intervention. There are several approaches available for RBM. For example, the TransCelerate position paper and regulatory guidance recommend the prespecification of safety and quality indicators and their corresponding thresholds to identify elevated and unacceptable risk. When sites exceed appropriate risk levels, investigation ensues and an intervention is applied to address the problems [2–4]. Other methodologies are more statistical in their approach, analyzing data to identify values that are too extreme (or in the case of misconduct, too good to be true), patients or trial visits that are too similar or data that exhibit unusual patterns or properties [6–8]. The last set of techniques apply sampling approaches, similar to those used in manufacturing, to select a subset of CRF fields for SDV [9,10]. If an unacceptable level of errors occur in the sampled pages, additional fields are sampled for review.

Whatever techniques are ultimately employed, an emphasis on risk-based approaches forces the sponsor to take a more proactive approach to quality through a well-defined protocol, sufficient training and communication and by highlighting those data most important to patient safety and the integrity of the final study results. Furthermore, identifying problems early provides the opportunity to refine procedures and address shortcomings as the trial is ongoing. Of course, an additional benefit of RBM is the reduction of a significant portion of trial expenses. This point is important, for if costs continue to rise at the current pace, clinical trials to establish efficacy and tolerability will become impossible to conduct. This will make drugs unavailable for areas of unmet need, stifling innovation

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in established treatment areas or placing an extreme price burden on consumers and healthcare systems [6].

But what are the challenges of risk-based approaches?

Responsible parties

Perhaps the biggest challenge is one of ownership. I have been asked my thoughts as to which functional area should be responsible for RBM, but it is hard to imagine an effective implementation that does not utilize the strengths of all parties! Any clinical trial is the result of the efforts of a diverse team – including clinicians, monitors, statisticians, trial and data managers, programmers and regulatory associates. Every team member has a role to play in the review of trial data, and a unique skill set important for defining thresholds for unacceptable risk, identifying problematic data, investigating underperforming sites or applying appropriate interventions to minimize or prevent further issues. It is likely that no individual team member will be involved in every aspect of RBM, but he or she should have a good understanding of the importance of their role to the success of the overall process.

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This cross-functional aspect of RBM is emphasized throughout the TransCelerate position paper [3]. While it is important to utilize the diverse skills that are available, the individual pieces need to form a coherent whole. Consider a relay team. Successful relay teams are those that have perfected the transitions between the individual athletes. The same holds true for the different functional areas of the clinical trial team. Each area can be operating at its peak, but if communication breaks down and the handoffs between individual tasks are bungled, this can cause delays to the study timeline. Imagine for a moment what must occur to perform even a single round of RBM successfully: data are retrieved from multiple sources and integrated, analyses and reports are generated and reviewed and the team meets to discuss their findings, run follow-up analyses and implement the steps necessary to address the identified deficiencies. RBM will test how well the team operates; individuals should strive to have a basic understanding of other roles to identify new opportunities for efficiency in the process. While research is needed into the most appropriate model for managing the RBM process, I expect the team responsible will include members from each functional area, at either the study or program level.

Data, data everywhere

There are numerous data available to assess for quality purposes, each of which allows the sponsor to assess the performance of clinical sites, trial participants or even the sponsor itself! First and foremost, the sponsor needs to identify the various sources of data available, and examine the benefits and disadvantages of including these sources of data into the RBM process. The study database is an obvious source that can supply information on safety in the form of reported adverse events (AEs) or hospitalizations, or data on screen failures, early discontinuations or eligibility violations and protocol deviations as determined by the clinical site. Furthermore, database management systems provide data on the frequency of queries, the number of incomplete CRFs, as well as the site's responsiveness to addressing queries and completing CRF pages. Another possibility includes an interactive voice response system or similar system that can more readily provide data on randomization, screen failures and drug kit dispensation.

While the previous paragraph outlines some obvious data sources that can utilized for RBM, it is by no means complete. In my mind, there are two additional important sources of data available that can be utilized. Depending on sponsor experience and the maturity of available processes, these data may involve more effort to integrate than the previously mentioned data sources. The first set of data contains any findings identified by study monitors during their on-site or remote review. This includes, but is by no means limited to, information on whether study drug was stored or dispensed inappropriately, staff not receiving appropriate training and the frequency of staff turnover, absence of signed informed consent and re-consent documents, absence of principal investigator signature on study documents or unreported AEs or protocol deviations. As much as possible, these data should be captured electronically to minimize travel to investigative sites. Furthermore, the data should be maintained in a manner to easily allow these findings to be incorporated into the RBM process. The second source of data includes eligibility violations and protocol deviations as determined by the biostatistics and programming team based on their analysis of the study database. The biggest downside of these data are there availability; it takes time to program the analyses and results may not be available early in the trial.

These data challenges can be made more complex when multiple contract research organization or other vendors are involved in the conduct of the clinical trial. This may require integrating sources of data with varying or unfamiliar data standards, which can complicate the integration process. Here, it may

be possible to utilize CDISC data standards to build some consistency in how nondatabase data are captured and shared between vendors [11]. Furthermore, if these quality data were submitted in datasets that mimicked CDISC Events or Findings domain classes, this could streamline RBM analyses and communication between vendors and regulatory agencies. Since CDISC data standards will one day be a requirement for regulatory submission, I prefer to develop analyses with the study database in its CDISC format. By doing so, any programs written to analyze the database for data quality purposes can be modified and utilized for analyses for the clinical study report. Along with the CDISC database, these programs can be submitted to regulators as supporting documentation of data quality activities.

I highlighted several sources of data that can be utilized for analysis. Some sources are unique in the information they provide; for example, data on queries can only be obtained from a database management systems. Other data can obtained from multiple places, examples of which include eligibility violations, protocol deviations and randomization and screen failures. In cases where data can be obtained from multiple sources, some important choices will need to be made. Consider interactive voice response system data. Sponsors will need to weigh the benefits of quicker access to enrollment and dispensation data and integrating an additional data source into the RBM process versus relying on the study database for these data with delayed availability. Should sponsors employ data sources with some inherent redundancies, they should build efficiencies by minimizing the overlap between the available sources. For example, monitors need not review inclusion or exclusion criteria that are easily programmable. Whatever data are ultimately used, a robust process should be developed so that these data sources can be integrated easily for analysis, at a frequency appropriate for the needs of the ongoing trials.

Analysis

Once all of the data are identified and integrated, it is time to perform the analysis to identify safety and quality anomalies. While data analysis has been limited to a few functional areas in the past, it is my hope that as we move forward, we change the perception that analysis is solely the responsibility of statisticians or programmers. To this end, the TransCelerate position paper suggests that outliers can be identified using a traffic light scheme to label issues of moderate or severe concern (yellow or red, respectively) [3]. Furthermore, straightforward graphical displays of data such as box plots and histograms can be used to identify safety and quality issues that are numerically extreme, and this may further suggest priorities for intervention at the clinical sites. In addition, plotting risks geographically using risk-colored markers may help uncover any trends in the observed findings that may be due to the environment, local regulations or regional vendors. Keeping a majority of the analysis limited to interpreting straightforward plots and color codes allows a greater number of the trial team to participate and share their expertise in the RBM exercise.

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Of course, more complex analyses are available to help understand the observed results or plan appropriate interventions. For example, Mahalanobis distance is a type of multivariate outlier that can be used to identify extreme clinical sites when considering all risk indicators or important subsets of those indicators (e.g., those related to safety) simultaneously [12]. Cluster analyses can be used to group clinical sites based on the observed risk indicators in order to help develop and implement interventions for sites with similar performance [13]. Statistical models can describe the relationship between risk indicators, with the potential to identify important predictors of poor performance. Ultimately, the development of robust predictive models can provide the clinical team with the opportunity to intervene before safety or quality becomes unacceptable [14]. These methodologies will take some experience and time to implement, but it may add further complications to an intervention strategy. For example, it seems reasonable that the appropriate intervention would be different for a predicted versus actual risk (say a phone call vs a site visit).

Other complicating factors in the analysis involves how to define and analyze risk periodically, particularly since sites become active at different times throughout the trial. For example, risk can be calculated for each risk indicator within a period of time, such as the rate of AEs within monthly or quarterly time intervals. Alternatively, the time between each RBM review may serve as a review period. A question then becomes, what is the appropriate comparator for sites in these instances? Do we measure time based on the calendar and compare the findings for a given month between sites, regardless of how long the sites have been in the clinical trial? Or do we measure time within each clinical site based on when they come online, so that the first month of data for each site is

compared with the first month of data for all other sites (for example)? The former may identify quality issues at a given point of calendar time, but the latter may more accurately compare sites based on their current experience within the trial. Both may be informative for assessing a clinical site's performance at the end of the study.

One size does not fit all

While it may be possible to apply the experience gained in RBM from one trial toward another, it may not be as straightforward as applying the same sets of rules and programs to a new set of data. Some risk factors, such as a missing signed informed consent, would be problematic for any study. But in many instances what constitutes as high risk depends on a number of factors related to the disease, sponsor and site experience and the particular characteristics of the clinical trial. First-in-human studies, or trials involving special patient populations (e.g., pediatrics) or severe disease may have a low tolerance for risk among the safety indicators. By contrast, trials with one or more adaptations, a large number of inexperienced sites or new or unfamiliar equipment may have stricter thresholds for quality metrics. For example, a single instance of a serious adverse event may warrant a phone call for further details in an ophthalmology study, but if I applied the same rule to an oncology study, I might be on the phone all day.

In addition, the frequency of RBM reviews may depend on a host of factors, including those that were listed in the previous paragraph. Review frequency will also vary based on the maturity of the current clinical trial. RBM cycles will initially be sparse until a sufficient number of centers are up and running. Reviews will occur more frequently while enrollment and data cleaning is ongoing; cycles may taper off as a certain comfort level is reached with site performance, or reviews may focus on safety and queries as the trial approaches last-patient last-visit.

If possible, the best approach is to use past trials to help define risk thresholds and review strategies for similar upcoming studies. While cumulative results are useful, it will also be informative to examine how the periodic risk varies within certain time intervals of the trials, such as the rate of AEs within monthly or quarterly intervals. The variability of this periodic risk may suggest that multiple instances of periodic elevated risk may be warranted before applying an intervention, since sites may on occasion exceed acceptable thresholds before returning to normal. Even using the past to inform the present, risk thresholds may need tailoring to prevent too many or too few signals for the current clinical trial.

Conclusion

In short, there are still numerous challenges that lie ahead for RBM. First, individuals will need to get comfortable with risk-based approaches. Training in unfamiliar systems and methodologies is a good first step, but practical experience will help refine procedures and analyses over time. The good news is that everyone – industry, academia and regulatory agencies – is aligned to make risk-based methodologies an essential component for the future of drug development.

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