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Health Sciences

The Evolution of Risk Management in Clinical Trials

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Introduction

When the concept of risk based monitoring was first introduced, following draft guidance from the FDA, the industry implemented it primarily as a cost saving measure to reduce source data verification and to decrease monitors' travel time and time on site. Over the past five years, that emphasis has shifted from risk based monitoring of data to risk management of all factors that could jeopardize a trial at each clinical site. The concept of addressing trial risk holistically has also been aided by the relatively recent introduction of cloud-based clinical trials. The cloud has made anywhere/anytime, centralized monitoring (adaptive-on-site and off-site) of all risk-related trial factors a seamless reality.

Looking ahead, the cloud can integrate centralized monitoring, risk management measures, and predictive analytics. It can also create risk repositories, to keep trial costs in check and optimize better quality results for life saving therapies.

History and Background

As early as 2007, the Food & Drug Administration (FDA) described Quality By Design Risk Management Approaches to clinical trials. This guidance was initially interpreted to mean monitoring electronic data collection (EDC) for 100 percent (100%) source data verification (SDV)[1]. However, over time, this approach -- conducted almost exclusively by clinical research associates (CRAs) -- not only proved time consuming, costly, and narrow in scope, but also, on the average, it resulted in only a two percent (2%) change in the data entered into the EDC system. The industry took notice. Clinical trial risk had to be addressed. But, it was broader than had been initially interpreted.

In 2012, a group of major pharmaceutical companies formed TransCelerate Biopharma, a non-profit organization created to drive efficient, effective, and high-quality delivery of new life saving medicines to the market. The organization collaborated, not only across participating member companies, but also with regulatory authorities and industry groups. This body developed "an adaptive approach to clinical trial monitoring that directs monitoring focus and activities to the evolving clinical trial's greatest areas of need which have the most potential to impact patient safety and data quality."

This approach was first realized in a 2013 TransCelerate Position Paper on Risk-Based Monitoring Methodology that proposed by "building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely."

The organization coupled this methodology with additional materials including a planning document (Integrated Quality Risk Management Plan Framework (IQRMP)) and a template of 70 questions (Risk Assessment and Categorization Tool (RACT) Template) to be answered for each trial to assess the impact, probability, and detectability of risk that might turn into an issue at a given trial site. Risk was defined as something that *might* happen in the future. An issue was defined as something *that was currently* happening (or had already happened) at a given trial site.

1 Source Data Verification, a procedure that verifies that data recorded within the trial Case Report Form (CRF) matches the primary source data which are contained in the relevant source documents such as the patient medical records.

As each trial tests a specific drug candidate and includes different sites, patients, protocols, personnel, and technologies, different risk factors can be judged important to monitor at any given trial site. TransCelerate's Quality by Design model mandates building quality into the scientific/operational design and conduct of the study. It also advises that researchers identify risks at the program, study, and site level to apply the appropriate amount of data quality control that monitors on-site issues, safety issues, medical issues, and quality control mechanisms. Its RACT set of questions determine the degree of risk for each trial site factor. Many of the TransCelerate concepts and tools can be integrated into clinical trial and data gathering solutions.

Another important aspect of the Quality by Design model for clinical trials mandates a continuous improvement effort. That is, an effort that not only identifies and mitigates/eliminates risks at trial sites, but also one that shares best practice improvements in a knowledgebase for streamlining similar risks in future trials.

For example, specialty contract research organization (CRO), Novella Clinical, needed to address its interactions with site staff. The CRO partnered with a vendor to develop a custom solution that improved operational efficiency, as well as created increased customer-base value. To date, almost 60 percent (60%) of Novella's clinical sites use its "Novella Conduit" for site team information exchange. The CRO has developed a best practices application that is being built into many of its trials for streamlined site communications, data exchange, and site training administration.

In 2015, the Metrics Champion Consortium (MCC) defined some of the benefits that could be derived from these kinds of tools, establishing clear, consistent, performace expectations for internal and external operations.

- Facilitating adoption of best practices across sponsors and services providers.
- Ensuring consistent measures [which] reduce the garbage in/garbage out problem.
- Avoiding the cost of custom programming.
- Supporting comparison of performance across all studies within an organization, including across multiple vendors.
- Decreasing time spent trying to understand what is being measured and focusing on achieving meaningful process improvement.

The Technology

Broadly speaking, when building a risk management capability into a clinical trial, the three major areas of concern are patient/subject safety, data quality, and operational efficiencies. Within these categories – that span a number of systems – there are five major questions that need to be asked in relation to each clinical trial site. These are:

1. What might go wrong?
2. What is the likelihood that it will go wrong?
3. What are the consequences?
4. How easy is it to detect?
5. How can it be resolved?

Different companies in the life sciences are at different stages of maturity in adopting risk management methodology to address these questions. Given that people, processes, and technology risk factors vary within each clinical trial site and for every clinical trial, currently there is no "one size fits all" risk management solution. However, according to a 2016 ISR Report, currently about 40 percent (40%) of Phase II/II studies use risk management, and this use in Phase II/II studies is growing at an average rate of nine percent (9%), year over year. Also, over half of current non-users in a wide variety of therapeutic areas expect to use risk management within the next two years.

Implementation of risk management tools now is seen throughout industry organizations, including emerging biotech, small pharmas, and CROs. These companies are evaluating several different options. They may utilize in-house capabilities. Or, they may take advantage of existing applications through software providers or capabilities provided by CROs.

Large pharma and CRO companies currently utilize in-house, home-grown systems at various levels of maturity. They employ combinations of existing tools and systems -- including various Excel, electronic data collection (EDC), safety, clinical trial management systems (CTMS), interactive response technology (IRT) solutions, and analytics/dashboards -- to maximize their investments and contribute to the overall process. Many have established central monitoring teams to provide initial assessments, review trends/outliers/risk indicators, identify issues, and provide alerts. Using a warehouse approach that combines data from multiple sources, they provide visualization and analytics capabilities and compile risk repositories for knowledge sharing.

Oracle Health Sciences, Data Quality, and Risk Management

Oracle Health Sciences' established and proven, yet also innovative, solutions are well aligned with current thinking and trends in risk management. Understanding the importance of data quality in risk management, the Oracle Health Sciences team endorses industry concepts, tools, and metrics, and has built industry metric tools into its clinical trial solutions. These tools help clinical researchers identify risks and pinpoint trial events that require further tracking or intervention. Oracle continues to focus on holistic risk management processes through investment in cloud technologies that support a holistic risk management process.

For instance, Oracle has moved TransCelerate's* Risk Assessment Categorization Tool (RACT) into Oracle's Siebel Clinical Trial Management System (CTMS). Taking a holistic view of how risk can affect the entire trial lifecycle in any functional area of the study, it helps study planners identify potential study data factors that will require risk management, from trial planning through analytics. Through the data results, Oracle's CTMS solution can identify risk areas for a drug, and adjust for it, based on the results per trial. It can then rollup those results and provide deeper insights on the full trial risk at the program level.

Oracle has also incorporated TransCelerate's Key Risk Indicators into out- of-the-box dashboards in its Oracle Health Sciences Clinical Data Analytics (CDA) solution. With this tool, CDA study teams can set up thresholds to gage the status of each indicator at the study or site level and determine appropriate actions to be taken based on the Key Risk Indicator, as defined in their monitoring or quality plans.

Additionally, Oracle uses its CTMS system for risk-based-monitoring centralized-issue-management- tracking. As risks are identified within a clinical trial through a review of patient or site data in any of the Oracle Health Sciences products (including Oracle Argus Safety, Oracle InForm, Oracle CDA), or by a partner solution (such as CluePoints CSM), the Oracle CTMS solution provides a centralized location to track and record the risk, the mitigation action for the risk, and the result. This data is then available in CDA to provide a consolidated report of risk, actions, and resolutions for submission with the study to regulatory agencies.

Looking Ahead

Central monitoring and predictive analytics are key to the future direction of risk management. Centralized monitoring is also emerging as a critical means of improving overall patient safety and study quality, while reducing trial costs.

In its Technology Considerations to Enable the Risk-Based Monitoring Methodology, TransCelerate singles out predictive analytics, stating that they "offer a new dimension with respect to data quality and the ability to identify trends, patterns, and outliers in trial and site performance. Therefore, future technology solutions need to combine

clinical trial data sources and operational systems (e.g., clinical trial management systems [CTMS]) to supply the necessary data for predictive analytics."

Using Central Monitoring and Advanced Analytics as a Risk Management Watchdog

As an example of the above, a global CRO, has developed a mature, in–house, central monitoring system that employs advanced analytics, predictive analytics, and machine learning to identify and mitigate risk in its clinical trials. In a recent webinar, Achieve Better Outcomes With RBM Tech Enhancements, presented along with Applied Clinical Trials, the CRO provided an overview of how it built a centralized data surveillance platform for holistic monitoring of the people, processes, and technology associated with a given clinical trial. The data platform is focused on key risk indicators (KRIs) and trigger management, subject level data reviews, study specific analytics, and targeted site support – all derived from the site level.

The platform is continually monitoring site data to identify risks based on statistical models. Once the data is collected and verified, the CRO uses advanced analytics to identify site risk, predictive analytics to predict-- within a certain probability-- the likelihood of risk occurrence at site and subject levels, and machine learning to train algorithms for pattern identification. The CRO then applies data from this knowledgebase -- or risk repository -- to many of its trials occurring around the world to identify, mitigate, and sometimes avoid, clinical trial risk.

As far back as 2011, industry information cited in an Applied Clinical Trials article confirmed that SDV was a very labor intensive process, prone to inaccuracies, and often resulted in less than three percent (3%) of critical data queried, on average. This article also estimated that a risk based approach to monitoring would reduce the number of monitoring visits and had the potential to save companies billions of dollars each year.

Another article in ContractPharma.com states, **"**The use of advanced and predictive analytics in risk management is the start of a major change in our industry, helping [to] get ahead of safety issues and operational challenges. Risk management adoption will only increase as data and technology continue to evolve in the coming years. The sooner we begin implementing this technology, the more knowledge we can harness for the good of sponsors, sites, and ultimately, patients."

Oracle Health Sciences has made a commitment to supporting best-of-breed risk management methodology and solutions that support higher quality clinical trials at lower costs and that boost regulatory confidence in the quality, efficacy, and safety of new drugs and therapies.

We look forward to a future in which cloud-based clinical trials throughout the industry seamlessly incorporate the best risk management practices in people, processes, and technology to advance the reliability of trial findings, support government standards, and ensure the protection of study participants.

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