Technology is advancing at an extraordinary rate, yet the pharmaceutical industry has been slow in adopting new tools to minimise risks in clinical trials, leading to longer development timelines.

Over the last 10 years, unprecedented advances in technology have revolutionised how people communicate, collaborate, and transact business, whether paying for groceries, video conferencing with colleagues from around the world, collaborating on editing and sharing documents, or analysing data – all from the palm of a hand. For context on how exponential these advances have been, a smartphone from 2014 is able to process information 100 million times faster than the supercomputers that NASA used to guide the Apollo missions to the moon.

Other industries – even those that are heavily regulated, like the financial sector – have integrated technology into their business models to automate processes and are using predictive modelling for better decision making. However, why not the pharmaceutical industry, especially now, when clinical trial performance benchmarks reveal an industry that is performing worse overall than a decade ago. So why is pharma slow in adopting new technologies to reverse these trends?

A Broken Model

Between 2005-2015 the number of countries involved in Phase 3 clinical trials has doubled, and the number of investigative sites has increased by 63%. Simultaneously, the mean number of patients declined by 18%, adding complexity to study startup processes (1). For example, site selection and initiation now takes an average of nearly eight months – longer than it did a decade ago – as more research-naïve sites are being used. 28% of sites engaged represent new relationships with the sponsor or CRO, which adds 9.9 weeks to site initiation timelines compared to when the sponsor or CRO has a pre-existing relationship with the site (2).

In addition to the increased cycle times for site initiation, 48% of sites that do get activated fail to meet enrolment targets, and 11% of sites fail to enrol a single patient, constituting over 50% of sites not meeting expectations (3). As a result, enrolment periods get extended, which prolongs overall timelines – currently affecting over 90% of trials – leading to a near-universal inability to meet study timelines and milestones.

While it must be acknowledged that trial sponsors and CROs are challenged with exponential growth in the average number of sites, countries, data capture systems, and endpoints required per trial, some of the factors driving these trends are self-created.

Risk-Based Monitoring and Beyond

Since 2013, regulatory agencies and industry consortiums have been encouraging the use of risk-based monitoring (RBM) and Quality by Design processes for planning, monitoring, and managing of clinical trials. These efforts are intended to shift the industry paradigm from reactive to proactive, focussing on the critical data required for the protocol and using upfront standardised risk assessments to identify the most critical data elements for quality oversight.

So far, the industry response has been limited to reducing source data verification and piloting components of risk management processes. Phase 2 and 3 trials are now global endeavours, making the traditional oversight model of monitors visiting each research site every four to six weeks the most capital-intensive aspect of trial execution, comprising 30% of the entire clinical trial budget. While RBM has been cited as a more proactive way to reduce risk and improve data quality, many organisations still equate RBM to reduced source data verification, which may save time on-site, but still requires monitors to physically visit every site at some time interval. The Clinical Trials Transformation Initiative determined that this approach is not only inefficient, pulling resources away from more trial-critical activities, it has no quantifiable impact on data quality.

A 2017 study by the Avoca Group revealed that, among organisations who have implemented risk-based approaches, consistent and standardised risk assessment processes were rarely followed. The culture change within cross-functional study teams – shifting from identifying issues that have already occurred to using analytics for identifying and mitigating risks before they occur.
become issues – has been the largest hurdle to adoption (4).

Unfortunately, there are not many easy-to-use technology solutions available today to address these challenges, as first-generation risk-monitoring tools lack the transparency and real-time integration capabilities required to operationalise these systems into sponsors and CROs’ codified standard operating procedures. As a result, many become disconnected silos of information that leave users questioning the findings and create misalignment among the stakeholders using site- and study-level key risk indicators to identify the risks outlined in the risk assessment plan. Most importantly, it has been found that, without implementing standardised processes for upfront risk assessment, using cross-functional representatives and stakeholders and integrating findings into related functional plans, the impact of risk identification and the true potential of RBM is limited and too ambiguous to be quantified.

The ICH E6 R2 Addendum

The ICH E6 (R2) Addendum to Good Clinical Practice, which went into effect two years ago, takes the concept of RBM one step further. It encourages the adoption of a systematic Quality by Design risk management process to be applied from protocol design through trial execution. Companies are expected to document and defend their risk-planning, oversight, and mitigation strategies to achieve compliance (4).

ICH specifically designed the addendum to help sponsors reduce various complexities that put patient safety, data quality, and trial integrity at risk, calling for sponsors to develop process and technology systems that support a more proactive risk-based study oversight approach.

While today’s clinical trials collect an ever-increasing volume of data from more disparate sources than ever, making it more challenging for sponsors and CROs to proactively identify and manage risk, the ICH addendum aims to rein in some of this complexity by calling for sponsors to “identify those processes and data that are critical to assure human subject protection and the reliability of study results.” This is a true paradigm shift from collecting as much data as possible, and it creates an opportunity for sponsors and CROs to rethink their risk...
management culture as a way to improve data quality and achieve significant time and cost savings – a competitive advantage any organisation would sign up for.

However, CROs and sponsors have been slow to embrace this change, in part because they are not sure where to begin. In 2017, the Avoca Group study found a third of sponsors said they still lack good understanding about best practices for risk-based approaches (5).

Transitoning to Quality Management

Taking a risk-based approach to trial oversight and management and focussing on Quality by Design throughout the clinical trial really translates into risk-based quality management (RBQM). RBQM promises to dramatically reduce site and data issues, as well as the most common causes for extended timelines and missed milestones: faulty patient enrolment projections and poor performing sites. From designing more focussed protocols and using data analytics to predict site performance, and by automatically triggering alerts that centralised monitoring teams can act on in real time, organisations will ultimately be able to build on their experience and use benchmarking data to model resource allocation and adjust thresholds based on their specific risks, such as working with a new site, in a new country, or a new indication.

However, this calls for a significant shift from today’s resource-driven and reactionary mindset to a proactive and data-driven mindset. While easier said than done, having the right technology in place can be the catalyst for an organisation to make this change. An effective RBQM strategy has to integrate data from multiple sources into an easy-to-access platform for real-time decision-making. With a technology platform that centralises data, information, and related action items, trial stakeholders from both the sponsor and CRO can access the data they need to carry out risk management activities with confidence and transparency.

Regulators on Board

For years, leading industry voices have been pushing for changes to investigator oversight processes that better ensure patient safety and data integrity. In 2013, the FDA released a guidance titled Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring. While the primary focus was on monitoring, the guidance stated the “FDA considers monitoring to be just one component of a multi-factor approach to ensuring the quality of clinical investigations” (6). Industry consortiums, such as TransCelerate BioPharma, have led the way in creating a standard framework and publishing tools for companies to integrate risk assessment and measurement into their oversight processes. The ICH Addendum’s focus on sponsor obligations has moved the discussion from 'if' to 'how soon companies will begin implementing these changes.

Common Hurdles

Although five years ago, organisations may have cited a lack of technology as their primary obstacle to adopting RBQM, this is no longer the case. In fact, the most common hurdle is that sponsors and CROs have to fundamentally change their approach to risk and how their partnership arrangements are defined. Moving toward a true RBQM environment will require a more collaborative approach where sponsors and CROs work together as a team to jointly redefine the risk management process with a focus on safety, quality, data integrity, and process efficiency. For example, jointly defining the processes, training, and technology requirements (including sponsor access to data) and the roles and responsibilities for oversight activities are critical for success.

The Time Has Come

While taking the necessary steps to comply with the ICH addendum may be causing some anxiety in the industry, these best practices provide both sponsors and CROs with the potential to achieve significant cost savings and study performance improvements. When implemented effectively, this approach can help mitigate risks before they become costly problems and ensure the best quality data is captured consistently throughout the trial lifecycle.

In an industry where organisations invest millions of dollars over many years to get their products to market, hitting clinical development milestones can be the difference between success and failure in being first to market. With growing consolidation and increased competition in almost every therapeutic indication, companies cannot afford to wait on making the move and embracing RBQM as their ‘new normal’.

References


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