BEST PRACTICES GUIDE

COMPLYING WITH THE ICH E6(R2) ADDENDUM

Six steps to ensuring risk-based quality management in clinical trials
EVOLVING REGULATIONS ON RISK-BASED MONITORING

In 2016, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) made a much-heralded change to its international guidelines. The E6(R2) Addendum to Good Clinical Practice\(^1\) introduced 26 new standards for how risk-based monitoring (RBM) and data management are handled in clinical trials, and clarified responsibilities of investigators and sponsors for data management outcomes.

The Addendum—which is the first change the ICH has made to good clinical practice (GCP) in more than two decades—is designed to address many obstacles in the current clinical research environment. It harmonizes existing guidance between the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and others, thus reducing opportunity for misinterpretation of regulatory requirements on a global scale.
The Addendum is designed to increase adoption of quality-by-design and RBM principles and methodologies in clinical development, while driving the use of innovative strategies and technologies for risk monitoring. It encourages a centralized, technology-driven approach to risk monitoring that begins in planning and continues throughout the research lifecycle. In addition, the Addendum further defines the scope of clinical trial oversight responsibilities as well as the sponsor’s responsibility to establish a risk-based quality management (RBQM) strategy, which focuses on quality by design in clinical trials, with a goal of ensuring the tools and methods used are “proportionate to the risks inherent in the trial and the importance of the information collected.”
Progress brings unintended consequences

As it’s becoming increasingly difficult and costly to recruit patients, sponsors have steadily increased the number of endpoints per trial (71% increase over the last five years), seeking to collect as much data as possible from the patients they do enroll. The rising number of endpoints has resulted in more work for research staff and a greater risk of lost or inaccurate data. It may also exacerbate recruiting challenges if data collection requires more frequent site visits and/or invasive tests. Recent studies show actual enrollment timelines now regularly double expectations, more than a third of sites on average under-enroll, and the average dropout rate is 30%.

ICH recognizes the cost, time and quality benefits that come with simplifying the clinical trial process, and they believe taking a centralized approach to RBQM will better protect trial participants while ensuring the reliability and quality of trial results.
THE GOOD, THE BAD AND THE RISKY

The Addendum is designed with obvious good intentions, but also brings some significant implications for trial sponsors.

The good news
Adapting to the E6(R2) Addendum requirements doesn’t just ensure ICH compliance. It can also significantly cut the time and cost of clinical trials, which gives sponsors and contract research organizations (CROs) a competitive advantage in bringing new drugs to market. Additionally, a 2016 report from the Metrics Champion Consortium (MCC) entitled, “An Updated Look at Risk Assessment and Risk-Based Management Practices,” featured new analysis on the use of formal risk assessment as a tool for identifying causes of risk that could affect critical data collection or the performance of critical processes prior to a clinical trial.7

TOP REASONS ORGANIZATIONS IMPLEMENT RBM PROGRAMS
The top reasons organizations implement RBM programs have shifted from reducing monitoring costs to improving quality oversight and data quality.8
**The bad news**

Despite the clear advantages of adapting to a more centralized approach to managing clinical trial risk, most organizations have yet to fully comply with the Addendum, and that may be putting them at risk. In many cases, sponsors still rely on onsite monitors and source data verification (SDV) as their primary quality oversight practices, and often manually compile data from their electronic data capture system (EDC), clinical trial management systems (CTMS) and other data sources to produce reports that are ultimately outdated and can only provide a retrospective view of trial performance. As a result, they are missing opportunities to cut time and costs while improving overall quality across the trial. Worse, they’re potentially opening themselves up to quality and safety risks. Now that ICH has released the E6(R2) Addendum to GCP, sponsors may also be exposing themselves to regulatory compliance issues when this Addendum takes full effect.

<table>
<thead>
<tr>
<th>OPPORTUNITIES</th>
<th>CHALLENGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure ICH compliance</td>
<td>Reliance on onsite monitors and source data verification</td>
</tr>
<tr>
<td>Cut time and cost of clinical trials</td>
<td>Manual compilation of data from multiple sources</td>
</tr>
<tr>
<td>Reduce clinical trial risk</td>
<td>Outdated reports provide view of the past</td>
</tr>
<tr>
<td></td>
<td>Data quality and patient safety</td>
</tr>
<tr>
<td></td>
<td>Exposure to regulatory compliance issues</td>
</tr>
</tbody>
</table>

**CURRENT STATE OF ICH ADHERENCE**
OBSTACLES TO ADOPTION

The Addendum went into effect in December 2016, which means organizations have had more than a year to adapt — yet many sponsors and CROs are still struggling.

**Shifting strategies requires significant change management**

To achieve compliance, CROs and sponsors must implement proactive and collaborative risk management processes and leverage technology to help balance monitoring resources appropriately based on the level of risk identified for the trial or site. This requires an overhaul of their entire study management and oversight culture, including rebuilding data management processes, establishing more collaborative partner relationships and selecting technology solutions that provide both CROs and sponsors with control and visibility over the entire trial management process from planning through execution.
Developing processes that don’t transfer administrative burden

CROs and sponsors must also develop effective programs with processes that don’t add administrative burden to investigative sites. When evolving processes, providers must ensure all stakeholders have access to critical data at all times. Some investigators are concerned about duplication of effort due to interaction among study team members; therefore, CROs and sponsors should consider how the roles of study team members and their relationships with sites may need to change.9

Technology changes affect adoption of RBM strategies

RBQM cannot be achieved using disparate CTMS and EDC technologies. The lack of integration or analytics capabilities between these data systems, and the resulting need to manually enter and re-enter data in each system, inhibits the real-time monitoring capabilities that define RBQM and creates opportunities for lost data and delays in risk response. Organizations must update their technology portfolios to enable an integrated and transparent view of trial risk, including the implementation of a system that can centralize and analyze trial data based on the risk and quality tolerances they’ve identified during their up-front risk assessment planning.
THE COST-CUTTING BENEFITS OF RBM AND RBQM

For years, RBM and RBQM have been touted as catalysts to drive consistent quality management while cutting costs. Both FDA and EMA have issued guidance documents for RBM, opening the pathway to deploying more efficient monitoring strategies while ensuring patient safety is protected and the quality of clinical trial data is maintained in the most efficient manner possible — but these are only guidance documents and lack specificity. Sponsors and CROs are left to determine whether the changes they make will in fact be embraced by regulatory authorities.

Given the lack of clarity that existed prior to the ICH Addendum, adoption of RBM and RBQM strategies stagnated. Those who did employ techniques often limited their strategies to targeted SDV conducted by onsite monitors, who use data from case report forms (CRFs) and other systems without implementing further quality oversight measures such as centralized monitoring, or without undergoing a thorough and comprehensive risk assessment and mitigation process.
RE減ING ONSITE MONITORING COSTS

Traditional onsite monitoring requires Clinical Research Associates (CRAs) to visit every site participating in the study at some frequency interval, usually every 4-6 weeks. While onsite, these CRAs perform 100% SDV, which calls for them to confirm that the data captured on paper case report forms (CRFs) or in health records systems matches what has been entered into the trial’s electronic data capture (EDC) system. Research by an industry consortium, the Clinical Trials Transformation Initiative (CTTI), found that 100% SDV had “...negligible impact on data quality.”10 In addition to being inefficient, traditional 100% SDV is regarded as the most capital-intensive aspect of a trial, comprising up to 25-30% of overall trial costs.11 That price tag has risen steadily in recent years, due in part to high turnover rates12 among site investigators and limited talent pools to replace them, which further affects trial performance.
Implementing a holistic approach that tracks risks from planning through execution — and creates real-time data transparency for CROs and sponsors — can have a huge impact on these costs while potentially mitigating the risk of staff turnover. One survey shows sponsors who use RBM strategies in Phase 3 trials reduce their costs by up to 32%, in part thanks to remote and reduced-frequency monitoring while still achieving high levels of data accuracy and site efficiency.

CURIOUS ABOUT HOW YOUR DATA MEASURES UP TO OTHERS? GET ANSWERS TO THE TOP 3 QUESTIONS SPONSORS TYPICALLY HAVE.
A ROADMAP FOR SUCCESS: SIX STEPS TO COMPLIANCE WITH ICH E6 ADDENDUM

Taking a centralized, proactive approach to risk management delivers clear, measurable benefits to sponsors and CROs. Along with achieving GCP compliance, this new approach to managing risk enables stakeholders to identify and address risks in real-time, cut the cost of onsite monitoring and gain a trial-wide view of performance so they can identify risks and trends across all sites and capture best practices for future trials. In effect, they’re doing more than simply monitoring their trials, they’re managing their trials — and doing so in a more predictive, controlled manner that ensures achievement of milestones and overall study timelines.

1. UNDERSTAND ADDENDUM
2. ASSESS CRO PARTNERS
3. IDENTIFY GAPS
4. EVALUATE SYSTEM
5. PROVE IT WORKS
6. JOIN INDUSTRY DISCUSSIONS
This transformation will require significant culture change—and in many cases technology transformation—that can be difficult to embrace in a highly-regulated marketplace. But if companies want to be ICH compliant while also benefitting from the time and cost savings that come from a centralized, real-time approach to risk management, they need to make the move today.

Here’s how to get started:

1. **Understand the ICH E6(R2) Addendum in its entirety**
   Before making any changes, sponsors and CROs should assemble an in-house working group of GCP experts to study the new Addendum and determine the full implications of the change to their organizations. Having an in-house team of experts ensures companies will make the best decisions about how to adapt their technology and practices to meet the new requirements.
2 Assess CRO partners

Even if a sponsor relies on its CRO for all clinical trial activities, the sponsor is still responsible for the quality, safety and efficacy of its processes and data. To ensure compliance, sponsors should audit their CRO’s technology and quality risk management approaches to determine if they meet ICH requirements and if not, how the CRO plans to move toward compliance. In addition, sponsors should proactively work with their CRO and other technology partners to define and develop a consistent risk assessment process (not limited to CRO performance metrics/scorecards).

3 Identify technology and process gaps

Once the GCP team has defined a future state of compliance, it should review current approaches to monitoring clinical trial risk and determine where current processes and technologies fall short of the new requirements. For example, the team may need to define a more formal risk identification process, create or acquire a library of risk identifiers and industry standards and/or replace manual spreadsheets with a more robust, technology-driven solution for assessing risks. This gap analysis will help define a strategy for change and the steps needed to get there.
**Evaluate current data systems**

Most sponsors and CROs rely on transactional study data drawn from a patchwork of systems that are often siloed, use unique codes and naming conventions, and are captured redundantly across systems (therefore requiring constant reconciliation). This lack of integration limits visibility and makes it difficult to proactively identify and mitigate risks. To overcome these shortcomings, organizations should first identify where silos occur, then look for technology solutions that can integrate these systems and provide a single operational view that supports real-time risk management across the entire trial site network.

**Prove it works**

One of the biggest challenges companies will face in this transformation is the culture change required to redefine the way risks are identified and managed. To ease stakeholders into this change, organizations can roll out pilot projects with clearly-defined metrics to demonstrate value, run blinded studies comparing the results of onsite monitors versus centralized solutions and share case studies of other organizations that have already successfully made the switch. Studies show that a centralized approach cuts the time and cost of monitoring and often uncovers risks that onsite monitors miss: Being able to demonstrate these benefits to stakeholders using real quantitative outcomes is the best way to drive engagement with the change.

**Studies show that centralization uncovers risks that onsite monitors miss**
Participate in industry discussions

The adoption of RBQM has the potential to disrupt the industry, and this transformation has only just begun. To achieve the greatest benefits for patients and their own bottom line, sponsors should look for opportunities to collaborate with industry consortia, including TransCelerate BioPharma and the Clinical Trials Transformation Initiative as they define standards and best practices for leveraging quality risk management strategies.
SAVE TIME AND MONEY – ADAPT TO NEW GUIDANCE NOW

Sponsors and CROs are under constant pressure to cut the time and cost of their trials, while improving quality and safety. Those that have a plan in place to adapt to the new regulation have an opportunity to gain a competitive advantage and will be strongly positioned to generate the greatest time and cost savings during clinical development.

Biopharma executives need to champion the Addendum and work with their clinical research teams and CRO partners to define a roadmap that addresses the necessary people, process and technology changes so they achieve compliance and begin benefitting from the time and cost savings these changes will deliver. Those who implement new technology and process changes can benefit from significant time and cost savings in their near-term trials, potentially enabling them to bring drugs to market faster and more efficiently than their peers.

To get started on the path to success, contact us at info@ert.com
REFERENCES


ABOUT ERT

ERT is a global data and technology company that minimizes uncertainty and risk in clinical trials so that customers can move ahead with confidence. With nearly 50 years of clinical and therapeutic experience, ERT balances knowledge of what works with a vision for what’s next, so we can adapt without compromising standards.

Powered by the company’s EXPERT® technology platform, ERT’s solutions enhance trial oversight, enable site optimization, increase patient engagement and measure the efficacy of new clinical treatments while ensuring patient safety. In 2017, ERT supported 60% of all FDA drug approvals. Pharma companies, biotechs and CROs have relied on ERT solutions in 13,000+ studies spanning more than three million patients to date. By identifying trial risks before they become problems, ERT enables customers to bring clinical treatments to patients quickly — and with confidence.