

IMPLEMENTING A PROACTIVE APPROACH TO RISK MANAGEMENT

How to align your trials with the latest guidance in ICH GCP E6(R2)

Sponsors running clinical research studies confront enormous pressures today. From complex study designs, industry cost constraints, new geographical locations and significant technological advancements, there are many challenges to face. The International Council for Harmonisation (ICH) efficacy guideline on Good Clinical Practice (GCP) aims to help sponsors keep up with these major shifts and implement improved practices in the industry.

This article discusses how the ICH has changed with the recently approved Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2) and outlines some of the major areas where sponsors can develop more efficient approaches in the design and conduct of their clinical trials.

An increased focus on risk management methodologies

As a set of internationally recognized ethical and scientific standards, the ICH GCP outlines the best practices for the design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials.

Revision E6(R2), which was finalized in November 2016, encourages the adoption of quality-by-design and quality risk management methodologies in clinical trials. This revision states the need for well-established processes to align GCP with advances in clinical trial monitoring. It also suggests an enhanced quality management where the sponsor implements and maintains systems for risk management and oversight.

While changes to the guidelines have been anticipated as the revision has developed, many regulatory bodies have proactively written position papers outlining requirements for quality risk management, risk-based monitoring and quality by design approaches for conducting and overseeing clinical trials.

A three-tiered strategy to address ICH GCP E6(R2)

At Covance, we continually monitor the evolving clinical research environment and have heavily invested in developing clinical trial risk review processes in anticipation of ICH GCP E6(R2). Our innovative processes include detailed assessments of site, patient and data flows through the life of a study, approaches that help visualize challenges in conducting clinical trials. These processes also help develop high-level delivery quality, risk mitigation and contingency strategies in all Covance studies.

Sponsors partnering with us can leverage our multilayered strategy to address ICH GCP E6(R2) compliance, which includes:

- ▶ Ensuring robust SOPs (standard operating procedures) and tools are set to meet expectations of the revised guideline, as set up by the Covance ICH GCP E6(R2) initiative led by our regulatory compliance team
- ▶ Enhancing planning, communication and risk management through mandatory study specific journey maps, such as process maps
- ▶ Creating refinements to the risk management processes and developing tools to cover end-to-end study execution, such as Covance Risk-Based Monitoring (RBM) through the Xcellerate® Monitoring system and the Xcellerate® Insights portal and study summary reporting

More details about how sponsors can benefit from each strategy are discussed below.

Addressing regulatory change with a regulatory compliance-led organizational initiative

To ensure that we help sponsors achieve the requirements outlined in ICH GCP E6(R2), a pan-Covance assessment team worked to proactively identify affected areas of the business and adjust SOPs as necessary. A multi-functional team has provided gap analysis responses for the 26 addendum items and the organization has initiated the activity of adjusting our SOPs.

In an effort to internally support the change to the regulation, we then launched a drug development services change management campaign to ensure all operational staff understand the regulation and how their roles and responsibilities have been enhanced. The initiative includes an education campaign for our clinical research associates to conduct outreach to investigators to ensure they're aware of the upcoming addendum and that investigators have access to publically available material about E6(R2).

Implementing successful risk planning on clinical trials with study mapping

Keeping up with today's complex clinical trial requires a more comprehensive risk management effort. At Covance, we mapped the key sequence of activities expected of patients, sites, CROs and other collaborators. This "study mapping" serves as a basis for a variety of multi-disciplinary discussions and provides a "walk-through" between key stakeholders in the study to drive systematic risk assessment. Proactive mitigation and decision making processes are enacted to ensure that the identified risk areas are minimized.

These maps can also facilitate the project review process by senior management. As a result, sponsors and their CRO partner can expect much more informed oversight discussion during the clinical trial management office project governance review process.

Promoting risk-appropriate approaches to trial execution

When sponsors outsource services by partnering with Covance, they can rely on newly established SOPs that define how Covance conducts risk management activities, from the time of receiving a trial award through the actual trial. Clinical study quality risk management is a cross-functional, collaborative process that involves all relevant, functional study team roles.

The goal of using a risk management approach is to address areas of clinical trial risk in a proactive manner. Sponsors can expect proactive planning and prevention of negative risk, as well as maximizing the value of pre-identified activities for improvement of trial objectives and/or deliverables.

Leveraging the Covance risk-based monitoring solution: Xcellerate® Monitoring

As an early adopter of RBM approaches, Covance initiated an effort to address the draft RBM guidance from the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2011. Since then, the Covance RBM team has worked to implement several innovative approaches and technologies into sponsors' trials such as:

- ▶ Xcellerate® Monitoring organizational structures and new roles like RBM leads and central monitors
- ▶ RBM and central monitoring processes and SOPs
- ▶ Tools for study risk assessment, such as Risk Review and Medical Review

To complement those current tools, many other components are in pilot phases. The Risk Assessment Categorization Tool (RACT) helps sponsors identify and assess study risk while Statistical Review oversees integrity of data by systematic review of non-random anomalies in distributions of clinical site data. Other enhancements include the Risk and Issue Management System as a central location to track, review, categorize and prioritize all levels of project risks – from site level to compound development issues and risks. Data Management Review has been shown to improve data integrity by real-time monitoring of site data through an analytical tool that identifies missing, erroneous or inconsistent data across multiple data streams.

These tools were initially conceptualized to support studies with risk-based monitoring strategies but now have been recognized as value-added assets for the whole Covance portfolio. Over the course of 2017 and beyond, these tools will be deployed on studies to enhance the oversight of our core quality principles of subject rights, well-being, data integrity, scientific validity, regulatory compliance and clinical trial execution.

Enabling oversight with Xcellerate® Insights and study summary reporting

The ICH GCP E6(R2) amendment also addresses sponsor oversight. The Covance Xcellerate® Insights portal and study reporting tools provide a collaboration area for teams to work with full transparency. In particular, study reporting offers near-real-time study level metrics for

sponsors to have access to study start-up, subject recruitment, protocol deviations and data management metrics. This integrated workspace keeps sponsors up to date on the latest reports and helps drive collaboration between study teams.

Holistic management of risk across projects

By combining an enhanced approach with innovative tools, sponsors can expect a more consistent underlying view of any individual project. This approach also allows Covance senior leadership, regulatory compliance and quality assurance and the clinical trial management office teams to review projects both therapeutically and by protocol design to further evaluate any patterns of deficiency.

Quality governance bodies can look across Corrective and Preventive Action (CAPA) investigations and aggregates of study performance measure that can guide additional ongoing systematic process improvements. Understanding the issues that arise out of incidents and CAPA investigations is valuable. Covance can apply those lessons into the assessment and mitigation strategies to develop best practices for future studies.

An ongoing process of continual improvement

Long before the ICH GCP E6(R2) guideline revisions took effect, Covance started exploring multifaceted tools, processes and systems to execute clinical trials through proactive risk management. With the text now agreed upon for the E6(R2) addendum, we are excited to help sponsors achieve the underlying principles established to ensure human subject protection and reliability of trial results. As the health authorities across the world implement regulations to support the guidance, we will continue to improve upon our approaches that help sponsors plan, conduct and oversee successful clinical research trials.

Learn more about our drug development solutions at www.covance.com

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