

# How to Use Risk-Based Monitoring and Clinical CAPA to Ensure Compliance

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## Introduction

It's estimated that the average cost of developing a new drug has increased from \$1 billion in 2010 to \$1.1 billion in 2012<sup>1</sup>. A big part of the cost can be attributed to clinical research, which typically lasts at least eight-and-a-half years.

Given the enormous cost, time, and effort involved in clinical research, sponsors and CROs need to mitigate risks and ensure compliance during this phase to be able to launch their products in a timely manner and avoid unnecessary delays and additional costs.

Regulatory bodies are likewise emphasizing the need to mitigate clinical-trial risks as reflected by guidances and requirements pertaining to risk-based monitoring and quality-by-design (QbD) approach in clinical trials. This is in addition to the requirement that sponsors and CROs integrate CAPA (corrective action and preventative action) as a tool for ensuring patient safety and data integrity throughout the clinical trial.

If your company is a sponsor or a CRO that conducts clinical research for a sponsor, how effective are your risk management and clinical CAPA processes? Are you using a risk-based approach to monitoring and CAPA to mitigate the risks during clinical research and ensure compliance?

## Risk-Based Monitoring and QbD

This white paper will discuss the importance of risk-based monitoring and CAPA in clinical research within the context of the following initiatives by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA):

- **2011 Draft Guidance;** The release of a document titled "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" signaled the agency's intention to maximize its oversight of clinical trials. The guidance encourages the industry to use risk-based approach in monitoring clinical trials, as well as wider use of alternative monitoring approaches, such as the use of centralized monitoring (e.g., remote monitoring conducted by statisticians and data management personnel) instead of putting too much emphasis on on-site monitoring. The FDA recognizes the dramatic increase in the number of clinical trials and greater complexity of those trials. Since it's impossible for the agency to inspect every clinical trial, the guidance is meant to ensure appropriate oversight through effective monitoring<sup>2</sup>.
- **Clinical Trial Transformation Initiative (CTTI);** This program is designed to identify practices that would improve the quality and efficiency of clinical trials. It was initiated based on a partnership created in 2007 by the FDA and Duke University. The CTTI has identified QbD, a risk management approach from the pharmaceutical manufacturing sector, as a strategy that could increase data integrity and improve the quality of clinical trials. The CTTI has been conducting QbD workshops for clinical research stakeholders, including sponsors, regulators, clinical investigators, patient advocates, and academics<sup>3</sup>. Quality by design, as promulgated by quality expert Joseph M. Juran, is a systematic approach to close quality gaps, resolve quality issues, and prevent quality failures from the get-go. He advocated quality planning, quality control, and quality improvement. In a nutshell, Juran believed that if you plan and integrate quality from the earliest phase—design and planning stage—you will be able to avoid or at least minimize quality problems later on<sup>4</sup>.

- **EMA's Reflection Paper on Risk-Based Quality Management in Clinical Trials;** The EMA, which serves as a hub for regulatory agencies in European Union member states, released the reflection paper in 2011 to facilitate the development of a more systematic risk-based approach to quality management of clinical trials and to promote Good Clinical Practice principles and standards. The document identified current problems such as increasing globalization of clinical trials, which complicates the regulatory and business environment for these clinical trials. It proposed approaches that should commence at the earliest stage of a study. Without mentioning the term QbD, this document encourages the identification of risks as part of the basic design of the clinical research (for every protocol throughout the life of a clinical trial), which is essentially QbD's goal<sup>5</sup>.

## Clinical CAPA

The FDA's Good Clinical Practice (GCP) regulations and the International Conference on Harmonization (ICH) E6 GCP Consolidated Guidance, which the FDA has adopted, require that when quality issues arise, there should be a CAPA plan and implementation—including investigation of how widespread the problems are, correction of the problems, and corresponding efforts to help prevent their reoccurrence. The ICH GCP guidelines state that clinical trial deviations should be documented and a corrective action taken. In addition, the ICH E6 consolidated guidance states that the implementation and maintenance of quality assurance and quality control systems—both of which call for CAPA—are part of the sponsor's responsibilities.

**CAPA as a Quality Tool:** While companies must comply with CAPA requirements, sponsors and CROs can also use CAPA as a powerful tool to ensure quality throughout the life of a clinical trial. For example, through the CAPA process, sponsors and CROs can identify existing risks and define what needs to be done to prevent them from happening—the "preventative action" (PA) aspect of CAPA. They can track and trend CAPAs to see how widespread and how persistent the problems are. If the problems turn out to be pervasive, a CAPA will be implemented throughout the study (all clinical trial sites) and the PA component of the CAPA can be integrated with a company's overall risk management efforts.

**CAPA as a Supplement to Risk-Based Monitoring:** Using the analogy of a restaurant, one could say that finding hair in the food is a risk that every restaurant faces. Let's say that a customer finds hair in his food and complains to the restaurant manager about it and also reports the incident to the local health agency responsible for inspecting restaurants. If the restaurant has the equivalent of a CAPA process, this hair-in-the-food scenario would require a CAPA to resolve the issue and prevent it from happening again.

Let's say that the CAPA action required all kitchen employees to wear hairnets. But the restaurant is proactive and it has a risk management process in place, so it also implemented risk-based monitoring as part of its effort to mitigate risks. In addition to requiring kitchen employees to wear hairnets at all times (per CAPA implementation), the restaurant also assigns one of its waiters to act as the "monitor." The monitor's job is to look at every plate that comes out of the kitchen before it's served to the customer to make sure there's no hair in the food. Ideally, the restaurant should have implemented the hairnet policy from the start as part of its risk management strategy; such policy would have prevented the issue in the first place. But in this example, the restaurant resolved the quality issue with the help of both CAPA and risk-based monitoring. It improved the quality of its

service (no more complaints about this particular problem), ensured compliance with health agency regulations, and perhaps avoided an inspection triggered by customer complaints.

### Risk-Based Monitoring Vis-à-vis Clinical CAPA

Most companies have a risk management process in place but not a clinical CAPA process. Others have both processes, but they are not leveraging the CAPA process to strengthen their risk management process and vice versa. How can you effectively use risk management and clinical CAPA processes in a way that they supplement each other? Consider the following strategies.

**Use QbD Principles:** When you apply QbD principles, your goal is to minimize, if not prevent, deviations by incorporating risk management, CAPA, and other GCP principles in your clinical research. QbD calls for careful examination of the study's key processes (e.g. randomization), which will help identify risks. These risks can be addressed early on by tailoring the clinical trial design so as to set tolerance limits and develop risk-mitigation processes. If your organization still uses a paper-based or hybrid system, switching to an electronic clinical quality management system (CQMS) will greatly facilitate data entry of trial information and real-time reporting of clinical trial status, both of which are critical to GCP compliance.

FDA, EMA, and other regulations require the establishment and maintenance of a CQMS for regulatory compliance and to ensure product quality and safety. A CQMS encompasses the Trial Master File and other required documentation, as well as quality processes such as deviation, CAPA, and audit. An electronic CQMS streamlines clinical research by automating and managing all tasks, processes, training, relationships, and audits throughout the life of a clinical trial. It facilitates regulatory submissions and inspections by ensuring that all critical processes are properly documented and managed.

**Use the PDCA Approach:** The Plan-Do-Check-Act approach, also known as the Deming Cycle, provides a continuous loop of feedback, which is essential to continuous improvement<sup>6</sup>. As applied to clinical trials, "plan" refers to identifying critical quality objects during the trial and defining metrics for real-time measurement of quality performance. "Do" refers to implementing risk management plans during the trial. "Check" refers to monitoring quality performance using the metrics defined early on. "Act" refers to concrete steps for quality implementation such as CAPA and risk-based monitoring throughout the life of a clinical trial.

**Ensure that the TMF is Complete:** Regulatory bodies evaluate the conduct of a clinical trial by reviewing and/or inspecting essential documents that constitute the Trial Master File (TMF). Both at the sponsor and at the clinical trial sites, all stakeholders (clinical research associates, clinical investigators, clinical trial support staff) must be vigilant in tracking the location and status of TMF files. Generating essential documents is very important, but maintaining quality—the documents' accuracy, consistency, and reliability—is equally critical. An electronic CQMS will make TMF management easier on a daily basis. It will make searching, tracking, and retrieving documents easier, and therefore it will also be easier to see if the TMF is complete. Choose a solution that provides a robust monitoring visit checklist for all of your clinical trial sites regardless of location. So if your trial is global, you can standardize your checklist—and ensure consistent high quality—in all your trial sites throughout the world.

**Leverage the Flexibility of Monitoring Visit Reports:** The FDA is shifting gears from the old model that relied heavily on on-site monitoring to a more modern and flexible approach that encourages the industry to

use risk-based approach in monitoring clinical trials, including wider use of alternative approaches and electronic tools. Sponsors and CROs should take advantage of the FDA's new thinking by utilizing an electronic CQMS with robust tools such as monitoring visit reports.

Choose a system that allows customization of visit report checklists to help clinical monitors focus on areas of increased risk for each study.

**Integrate Training with CAPA to Boost Risk Management:** Both the CAPA and risk management processes cannot exist in a vacuum. Most CAPAs require re-training and when they do, both CAPA and training become critical to risk management. Choose an electronic CQMS that connects CAPA, training, risk management, and all other critical clinical processes seamlessly.

**Establish CAPA and Risk Management as Part of CQMS:** If your organization is still using paper-based or hybrid processes, you should take advantage of the latest technology and switch to an electronic CQMS that will serve as the centerpiece of your compliance efforts. Choose a solution that provides tools such as CAPA matrix, analytics and reporting tools, best-practice forms for collecting and tracking data for risk assessment, and monitoring visit checklists.

### Conclusion

Now more than ever, regulatory bodies are open to using alternative approaches to on-site monitoring, which is ultimately more expensive and time consuming. Regulators also encourage incorporating risk management strategies from the earliest phase of a clinical study, hence the increasing popularity of QbD in clinical research.

Most sponsors and CROs already have risk-based monitoring and clinical CAPA processes, or at least they are familiar with the concept. But their existing processes are not as effective and efficient. If your organization happens to be in this situation, take advantage of the latest CQMS technology that would allow you to have both processes integrated into your quality management system. A robust CQMS will help you mitigate risks, maintain high quality data and information across your trial sites, and ensure compliance throughout the life of your clinical research.

### References

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deline/2011/08/WC500110059.pdf. The EMA evaluates marketing authorization applications for human and veterinary drugs that fall under the scope of its centralized procedures. It provides a single marketing authorization that's valid throughout the EU.

6. In the 1950s, W. Edwards Deming advocated that business processes should be analyzed and measured to identify sources of deviations. He created the PDCA cycle to illustrate the continuous process. From "The Deming Cycle," by Paul Arveson, Balanced Scorecard Institute, viewed on July 1, 2013 at: <http://balancedscorecard.org/?TabId=112>

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