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Quality Risk Management in Clinical Trials

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Introduction

Successful clinical trial conduct relies on the quality of the operational aspects of the trial, leading to good, reliable data, and the overall protection of the people participating in that trial. Recently, there has been much discussion regarding incorporating elements of Quality by Design (QbD) in clinical trials, which encourages "beginning with the end in mind." This means designing the protocol and case report forms, selecting and training investigators and site personnel, and ensuring effective trial monitoring to deliver quality results. Doing so leads to clinical trials that are conducted with reduced risk of protocol deviations, protocol amendments, and data integrity issues. A strong quality system governing clinical trial activities helps to achieve this objective. A quality system built on risk-based decision-making and sound scientific judgment can help us design quality into study conduct, participant safety, clinical data integrity, and regulatory compliance. In this article, we will introduce a model for a robust quality system and provide a case study on how Upsher-Smith Laboratories, Inc. (USL), a drug development and manufacturing company that sponsors clinical trials, used this model, along with elements of quality risk management (QRM), as defined in the ICH Harmonised Tripartite Guideline: Quality Risk Management Q9 (ICH Q9), to successfully design and implement a clinical quality system.[1]

Quality System

A quality system consists of the elements within an organization that direct and control quality. Within clinical research, the objectives of a quality system are to ensure compliance with ethical and regulatory requirements and to deliver credible and reliable data.

Figure 1. Quality System Model

Figure 1 shows one possible model of a clinical quality system. In this model, the quality system is described as a pyramid. At the foundation of the pyramid are the procedures that describe how clinical trial activities are carried out and the training of personnel involved in clinical trial conduct. Written procedures are critical to the success of a quality system, as they help standardize processes and ensure that activities are consistently performed in the same manner and at the same level of quality. At a minimum, a well-defined procedure should be implemented to describe any activity required to fulfill a regulatory obligation. For example, a study sponsor should have procedures for conducting monitoring visits and developing the informed consent form (ICF), and an investigator site should have procedures for screening potential participants for eligibility criteria and submitting required documentation to the Institutional Review Board (IRB). A well-defined procedure clearly defines the what, when and who of specific activities.

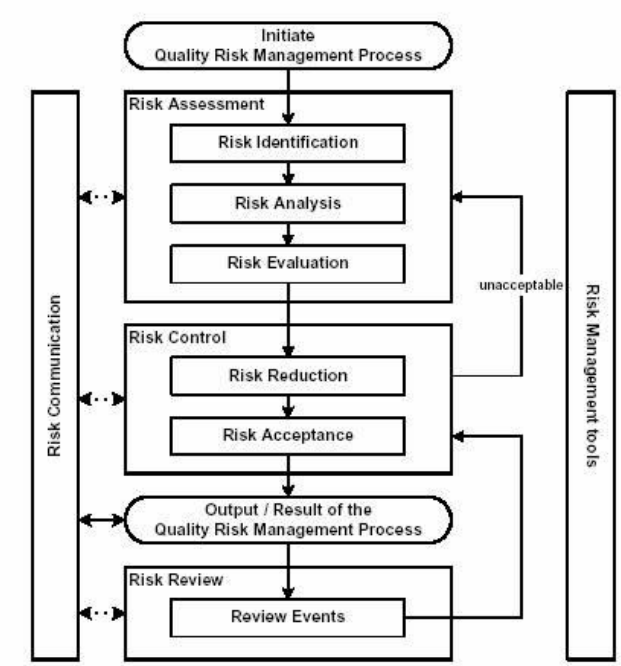
Equally important to the success of a quality system is the training of those involved in clinical trial conduct. Sponsor and investigator site personnel must have appropriate training in Good Clinical Practice and relevant procedures, including those specific to a given trial, to

assure effective implementation of the quality system. Training should be provided, for example, on the protocol, details of completing the case report form, and performing trial-specific assessments.

The second level of a quality system is study conduct. To ensure quality, the study must be conducted in accordance with the procedures at the foundation of the quality system. In addition, the study must be conducted in accordance with the protocol and supporting study plans, e.g., communications plans, monitoring plans, and deviation management plans.

The third level of a quality system is Quality Control (QC), the contemporaneous review and monitoring of study activities throughout the start-up, conduct and conclusion of a clinical trial. Effective QC helps detect errors or problems within the system and then apply corrective actions in a timely manner, as required. Prior to the start of a trial, QC involves a thorough review of ICF documentation and source document templates according to a set of pre-defined standards. During the study, monitoring of study conduct ensures rapid identification of non-conformance to the protocol, study plans, or GCP, and leads to timely resolution to ensure ongoing quality of the study. It includes systematic checks on the reliability of the data through review of source documentation and other study records. At the completion of the trial, common QC activities include checks to ensure appropriate drug accountability and destruction, and review of the clinical study report to defined standards. To ensure overall study quality, the sponsor, the Contract Research Organization (CRO), and the investigator site should all perform QC.

Figure 2. Quality Risk Management Process – ICH Q9



Quality Assurance (QA) sits at the pinnacle of the quality system. QA includes independent assessments of the activities that support the quality system. QA in clinical trials is often supported by audits. Audits of vendors, investigator sites, trial master file (TMF) documentation, and clinical study data and reports provide additional assurance that the procedures, training, protocols, source documents, and QC procedures upon which the quality system is built are leading to quality outputs.

Risk management is inherent in the entire quality system. Risk management tools can be effective in developing a quality system, managing change and process improvement, and conducting clinical trials in a manner that supports the objectives of the quality system.

Quality Risk Management

Quality Risk Management (QRM) is a specific application of risk management defined by the ICH Q9 document as a systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. The guidance document focuses on applying QRM principles to manage risks to the quality of the drug product, and the importance of effective QRM to the overall maintenance of the quality

system. However, the concepts and tools can also be applied to the implementation, maintenance and continuous improvement of a quality system to manage risks to GCP compliance, human subject protection, and data quality in clinical research. Figure 2 shows an overview of the typical QRM process, as described in ICH Q9.

What is Risk?

Risk is most commonly defined as the combination of the likelihood of occurrence of harm and the severity of that harm if it were to occur. The likelihood of a risk can be assessed either qualitatively (e.g., a harm is unlikely to occur) or quantitatively (e.g., a harm may occur in 1 out of 100 participants). The severity of a risk can also be assessed either qualitatively or quantitatively.

The level of effort and formality of the QRM process should be commensurate with the level of risk. It other words, those activities that pose the greatest risk to participant safety and data integrity should be the primary focus of risk management activities.

Quality Risk Management Process – A Case Study

USL has undergone tremendous growth over the past few years. The clinical development program and staff have evolved to support the company's mission to develop safe and effective drugs for patients with central nervous system diseases. This growth has been accompanied by an influx of new employees with varying experiences. Company leadership recognized the need for more robust procedures, training and QA oversight to support clinical trial conduct. The following sections describe how USL designed and implemented a quality system utilizing the principles of QRM.

Initiating the Risk Management Process

To start the project, we identified an internal lead and the initial participants for the project, which included both internal stakeholders and an external consultant.

The first step in the risk management process is to define the problem or risk question. In our case, we sought answers to several questions. First, how well do our current standards and processes meet the needs of a robust quality system? Second, are our current practices in compliance with GCP and internal quality standards? Finally, are there operational gaps in our processes and standards that need to be addressed?

Risk Assessment

The purpose of the risk assessment process is to systematically establish a quantitative or qualitative assessment of all risks relevant to the problem or question at hand. Risk assessment includes the identification of risk, analysis of the potential impact of that risk, and an evaluation of the risk against pre-defined criteria.

Through a thorough gap analysis, we identified the need for new processes and process improvements and qualitatively determined the overall risk to quality. The gap analysis involved interviews with clinical and drug safety personnel across multiple development programs. We asked participants to describe how things were being done, which processes were being followed, and in the case of trials being overseen by a CRO, how sponsor oversight was carried out and documented. The major issue we identified was that some processes were inconsistent across development programs. For each inconsistency, we assigned a ranking of high, medium or low risk in relation to their potential impact on participant safety, clinical data integrity, regulatory compliance, and operational success.

Risk Control

Risk control is a decision-making step in the risk management process whereby process owners must decide, based on the risk assessment, whether to accept specific risks at their current level or to initiate efforts to reduce risks. We prioritized mitigation of high-level risks to allow for better use of resources.

The external consultant and project lead led the risk-mitigation activities. For each process that was to be developed, we assembled a team with representation from all functional areas that were involved in the execution of the process. The team mapped the processes. Process mapping took into consideration the current state, as well as the desired future state. The resulting processes described the activities to be completed, and also assigned responsibility and accountability for each task. Where appropriate, the processes included guidance to ensure proper sponsor oversight of delegated responsibilities and quality oversight.

Risk Review

The final step in the QRM process is risk review. Risk review involves evaluating the outputs of the QRM process to determine its effectiveness and if any residual risk is acceptable. This review is an ongoing process that facilitates continuous improvement of the quality system. After we designed processes to address the high-risk gaps, we reviewed these along with our initial risk assessments to verify that our risk management process was effective.

Outcome

USL implemented a clinical quality system by utilizing QRM principles to identify, assess and manage risks to quality and compliance in the conduct of clinical trials. This systematic approach allowed us to focus our efforts on the areas of greatest risk, and to implement procedures that would support the ongoing compliance of our clinical development program to provide robust and reliable data. We incorporated elements of QRM into established QA procedures, such as vendor qualification audits, investigator site audits, and CAPA (Corrective and Preventative Action) management.

Risk Management in Quality System Activities

As a clinical research sponsor, there are opportunities to continue to support and improve the compliance in conduct of clinical trials through the application of risk management tools and principles. Two hypothetical examples are described in the following paragraphs.

Example 1. Selecting Sites for Audit

Applying a risk-based approach to the selection of investigator sites for audit allows a sponsor to focus its resources on the sites that are more likely to have compliance issues that need to be addressed. General risks might include the regulatory inspection history of the site or the sponsor's experience with the site on previous studies. Study-specific risks might include the number of protocol deviations or data queries. In this example (Figure 3), guidance is provided for assigning a high, medium, or low risk to each investigator site for a given category. The investigator sites are assessed against these criteria, and a score is assigned based on the level of risk. In this case, Investigator 2 "earned" the highest risk score, so should be considered for audit. If desired, risks can also be weighted. For example, recent personnel changes at the site might pose a greater risk than the availability of SOPs, this relative importance can be considered by applying a multiplication factor to each of the criterion.

Figure 3. Risk Matrix – Selecting Sites for Audit

Criteria	High Risk (3 pts)	Medium Risk (2 pts)	Low Risk (1 pt)	Site 1	Site 2	Site 3
Regulatory inspection history	Regulatory action indicated	No regulatory inspections on record	No regulatory action indicated	Low	Medium	Medium
SOPs for study conduct	No SOPs at the site	SOPs for major regulatory obligations	SOPs for all study related activities	Medium	High	Medium
Protocol deviations	>3 protocol deviations per subject	2-3 protocol deviations per subject	<2 protocol deviations per subject	High	Medium	Low
Data queries	>2 data queries per subject	1-2 data queries per subject	<1 data query per subject	Medium	Low	Low
Previous audit history	Previously audited by sponsor with one or more critical observations	Previously audited with no critical observations, but one or more major observations or not previously audited	Previously audited with no critical or major observations	Medium	Medium	High
Personnel changes	Turnover of key site personnel (e.g., study coordinator, sub-investigator) since study start	N/A	No turnover of key site personnel	Low	High	Low
Enrollment activities	Enrollment highly exceeds projections for the site	Enrollment moderately exceeds or is behind projections for the site	Enrollment meets projections for the site	High	Low	Medium
Previous experience with the site	No previous history with the investigator	1-2 previous studies with investigator	>2 previous studies with investigator	Medium	Low	Medium
Evidence of investigator oversight	Monitoring reports indicate issues with investigator oversight	N/A	Monitoring reports do not indicate issues with investigator oversight	Low	High	Low
			Total Score	**16**	**18**	**15**

Example 2. Training

QRM can also be useful in determining appropriate training programs for site, CRO and sponsor personnel for a particular study. In Figure 4, three roles are assessed against six criteria in a simple risk matrix. While this assessment is less formal than that described above, it can be useful in developing and performing training programs. Personnel in high-risk roles might need intensive, in-person training in areas related to their responsibilities, while personnel in low-risk roles might need only basic, online training in those areas.

Figure 4. Risk Matrix – Training Requirements

	Investigator	Study Coordinator	Pharmacist
Level of patient interaction	High	High	High
Level of data management/handling	High	High	Low
Evidence of previous/recent GCP training	Medium	Low	Low
Complexity of the protocol	Low	Low	Low
Complexity of protocol required assessments	Low	Low	Low
Experience with the patient population/disease state	Low	High	Medium

Conclusion

Although the ICH Q9 guidance document focuses on managing risks to product quality, QRM principles have applicability to clinical research quality systems. Implementing a systematic approach to identifying, assessing and managing risks to participant safety, data integrity, and overall compliance provides a mechanism for sponsors to build quality into clinical studies.

References

1. ICH Harmonised Tripartite Guideline; Quality Risk Management, Q9, 9 November 2005

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