Quality Risk Management Framework: Guidance for Successful Implementation of Risk Management in Clinical Development

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Abstract

Effective quality risk management is fundamental to ensuring the protection of human subjects and reliability of clinical trial results during the conduct of clinical trials. Quality risk management supports effective delivery of clinical development programs and ultimately delivery of treatments to patients. Thus, risk management is a core element of an effective quality management system (QMS) as described in the TransCelerate Clinical Quality Management System (CQMS) conceptual framework. In addition, the landscape of quality risk management in clinical development evolves as regulatory authorities adopt elements of risk management to promote proactive quality management. This paper's goal is to provide a conceptual framework for quality risk management as part of a CQMS. The components of a quality risk management program are explored including foundational elements and quality risk management methods appropriate for clinical development.

Keywords

risk management, ICH E6(R2), quality management system, clinical trial risk assessment, quality risk management.

Quality Risk Management for Clinical Development

Over the past several years, the pharmaceutical industry has focused on the modernization of the clinical development environment by embracing the paradigms of quality and risk management. In 2012, the Clinical Trials Transformation Initiative introduced Quality by Design to the industry.¹ Then, in 2013, the European Medicines Agency (EMA) issued its Reflection Paper on Risk-Based Quality Management in Clinical Trials.² In 2016, TransCelerate's Clinical Quality Management System: From a Vision to a Conceptual Framework provided guidance on a clinical quality management system (CQMS) including risk management.³ The quality and risk management paradigms, combined in the International Council on Harmonisation E6 Guidance Revision 2 (ICH E6[R2]),⁴ describe a quality management system (QMS) that uses a risk-based approach. In addition, other risk-based approaches are emerging from the United States Food and Drug Administration (US FDA), including "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring, August 2013."⁵ While the FDA guidance is specific to risk-based monitoring (RBM) and is not to be confused with a more comprehensive quality risk management program; this indicates an openness by the FDA to risk-based approaches.

Regulators and the industry are moving toward an acceptance of risk management as a best practice for preventing issues and efficiently managing work and resources. In general, risk management identifies potential issues before activities are undertaken and proactively addresses them. In clinical development, value is derived from using risk management in the prevention of issues related to human subject protection and reliability of clinical trial results. In addition, risk management preserves resources that would otherwise be consumed on corrective actions and rework and avoids disruptions to delivering on objectives.

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Because the ICH E6(R2) requirements for quality risk management were recently updated, there is no comprehensive, harmonized guidance or well-understood regulatory expectation for applying the fundamental concepts of quality risk management in clinical development. This leads to disparate implementation within individual companies and inefficiencies in practical application. This paper attempts to consolidate knowledge and provide best practices for an effective quality risk management program in clinical development.

Overview of Quality Risk Management Approaches

A risk management program allows an organization to identify and mitigate risks that threaten the achievement of business objectives and is an integral part of an effective QMS. General guidance on risk management exists from multiple sources. As a discipline, risk management is described in academic settings, in other industries, and through standards. Commonly referenced quality standards such as ICH Q9, International Organization for Standardization (ISO) 31000, and ICH E6(R2) provide different perspectives and scopes in risk management best practices. It is essential for each organization to assimilate these best practices and standards into a fit-for-purpose quality risk management program. In addition, each organization's culture and tolerance for risk are unique and will be reflected in its approach. Of the standards previously mentioned, ICH E6(R2) applies most directly to quality risk management in clinical development. As a result, it is emphasized in this paper.

Defining a Quality Risk Management Program

While there is no single way to manage risks, there are best practices for a successful quality risk management program. A general risk management approach includes the processes for prevention of potential issues with the aim of avoiding unwanted outcomes. A fit-for-purpose application of risk management identifies the most significant risks. Identifying, evaluating, and appropriately controlling these risks focuses an organization's resources on the areas where they are most impactful. Understanding the significance of a given risk to the organization and its risk tolerance defines the actions that will be taken or not taken to address that risk. Risk tolerance refers to the degree of acceptance an organization has for risk and its definition in general terms of when it will act and when it will not. Risk tolerance may be determined in various ways, but it is typically defined by leadership or governance. For risks that are determined to be significant based on that risk tolerance, it may be appropriate to employ one or more available options for controlling risk. For a less significant risk, existing process controls may be sufficient. Risks that are identified as below the risk tolerance may be accepted and require no further action. In addition, instituting a risk management program

requires a structure to support repeatability with sufficient flexibility to adapt to the various situations that may arise.

Moving from general risk management to quality risk management, ICH E6(R2) introduces the concept that "the sponsor should identify risks to critical trial processes and data" and "risk should be considered at both the system level and clinical trial level" within a quality risk management program.⁴ This reference to system-level risks is commensurate with the way TransCelerate has defined a QMS: "an integrated approach through which an organization systematically defines quality objectives taking into account both its strategic objectives and applicable regulatory requirements and develops and implements the infrastructure, including the foundations, organizational structure, processes, and resources, required to achieve these objectives."³ An organization's characteristics, such as size, portfolio type, and organizational structure, may influence how it characterizes system and clinical trial level risks. For instance, system-level risk may include vendor, process, asset, program, and site risks, while clinical trial-level risk focuses on trial-specific risks. ICH E6(R2) also gives us the minimum definition of quality risk as risks to human subject protection and reliability of trial results.⁴ The related field of therapeutic risk/benefit of medicines is covered elsewhere and is typically addressed separately from the more comprehensive approach to quality risk management for clinical development.

In addition to defining risk at the appropriate level, it is important to identify the interdependencies of the quality risk management program with the other aspects of the QMS. For example, issue management, risk management, and knowledge management are interconnected parts of the QMS that interact and work together to make it effective. There is also a relationship between a quality risk management program and a risk-based monitoring (RBM) program. While the scope of each is different, the underlying principles are similar. Risk-based monitoring is an adaptive approach that directs monitoring resources based on risk.⁶ Monitoring is also a method of detecting issues that can support risk control in a quality risk management program. Proactive quality risk management can drive RBM strategy. Alignment on fundamental risk principles, such as risk tolerance, identification of significant risks, and potential controls between these two programs, drives a more efficient and dynamic QMS. Such alignment helps a company avoid misappropriation of resources and the confusion of having different approaches to risk.

The considerations for implementation or improvement of a quality risk management program vary based on the maturity of an organization's existing program. For example, a newly established program faces challenges of sponsorship and infrastructure. An established program is concerned with change management challenges such as understanding and implementing the ICH E6(R2) changes. Each organization must define its tolerance for risk to determine which risks pose significant threats to its objectives, including quality, and implement a quality risk management program that effectively controls the risks that are most significant to its business outcomes.

Components of a Quality Risk Management Program

Based on quality risk management best practices, effective quality risk management programs address the following:

- Leadership commitment and oversight
- A methodology for identifying, evaluating, and controlling risks
- Communication of risks and the approach to quality risk management
- Periodic review of the effectiveness of the quality risk management program
- Reporting of performance of the quality risk management program at the trial level

Leadership Commitment and Oversight

As with any other program or process implemented in an organization, sustained leadership commitment is foundational for effectiveness. Leadership commitment may be exemplified in the following ways:

- Strategic alignment of quality risk management with business objectives:
 - Identification of objectives for quality risk management
 - Definition of the organization's risk tolerance
 - Alignment with the overall QMS
- Incorporation of quality risk management into the organization's processes:
 - Corporate policies, department policies, standard operating procedures (SOPs), and training that reflect the required elements of quality risk management in the context of a QMS
 - Technology to support the identified risks and their controls ranging from spreadsheets for simple applications to custom technology or one of the emerging "off the shelf" technologies for clinical development quality risk management
 - Organizational goals and/or objectives consistent with quality risk management processes
- Commitment to using a proactive, risk-based approach that is evident in communications and actions:
 - Risk-based strategic decision making as a standard approach prior to implementation
 - Expectation that risk is considered before significant action (eg, risk-related plans at the trial level are developed in parallel with the protocol)
 - Communications that reinforce the use and benefits of quality risk management through behavioral examples
- Resourcing for quality risk management:
 - Identification of the needed amount and type(s) of resource(s) including appropriately qualified individuals to support quality risk management activities

- Definition of roles and responsibilities (eg, responsible, accountable, consulted, and informed [RACI]) across functions including assignment of responsibilities required to conduct quality risk management activities
- Oversight to ensure that the quality risk management program meets requirements and functions effectively.
 - Oversight may take the form of cross-functional governance or simply functional line leadership depending on the size and scope of the quality risk management program. Because clinical development typically includes multiple specialized functions (eg, clinical, operations, quality), representation from each of these is recommended.
- Oversight includes monitoring whether the program is delivering as expected and answers questions such as the following:
 - Are the right resources in place to support quality risk management?
 - Are the most important quality risks being identified and controlled?
 - Is the program/organization compliant with current regulatory requirements?
 - How can the process be improved?
 - What do the issue management program, metrics, and analytics reveal about the effectiveness of the risk controls?
- Oversight may also include resolution of escalated risks or issues or approval of quality risk management plans.

Establishing leadership commitment by addressing these topics reinforces an organization's quality culture and builds a more efficient quality risk management program. The company's operational infrastructure should also influence the approach to implementation.

Quality Risk Management Methodology

The methodology used to manage risks should consider an organization's risk tolerance, asset portfolio, company size, and other factors such that the resulting processes are fit-for-purpose. Using a preplanned, collaborative process is essential regardless of the details of the methodology. Many line functions are involved in clinical development; each contributing function should have input into quality risk management plans. All involved functions should be aware of the plan and aligned with the resulting perspective on which risks are most significant and require additional controls. The same quality risk management approach can be applied to manage risks at the system or trial level. In addition, there should be sufficient time for risk management before an activity starts in order to leave time to apply risk controls. For example, quality risk management at the trial level should be initiated early enough to be incorporated into the design of the final approved protocol. For a new activity or a planned change, controls should be in place before the activity associated with the risk occurs so that risks

Figure 1. Minimum requirements for quality risk management methodology based on ICH E6(R2).

are controlled before they are realized. As a result, most trial-level controls will be required before the first subject's first visit.

Before initiating a risk assessment, the objective of the assessment must be understood and documented. In clinical development, the objective is to control for risks that, if realized, would significantly impact the following:

- Human subject protection
- Reliability of trial results
- Other factors (compliance with requirements, etc)

ICH E6(R2) states that “sponsors should focus on trial activities essential to ensuring human subject protection and the reliability of trial results.”⁴ This terminology is used throughout this manuscript as the minimum standard and is intended to be inclusive of subject's rights, safety, and well-being. Organizations may add other factors to their definition of quality. The quality risk management methodology should include at a minimum the areas highlighted in ICH E6(R2) as shown in Figure 1.

An initial risk assessment is often completed before starting the activity being assessed, but these steps can be iteratively applied to identify or update risks from a prior risk assessment. In addition, risk review speaks to the need to check actual performance against expectations after the activity has started and to make adjustments to risk identification, evaluation, and/or control based on actual performance. Updates to risk assessments may also result in additional communication and reporting.

Critical Process and Data Identification

Critical data and processes are those that potentially jeopardize human subject protection or reliability of trial results if not conducted as expected. These data or processes are identified

both at the system and the trial level to satisfy the requirements of ICH E6(R2). At the system level, critical processes can be identified through an approach that systemically reviews processes for their relative contributions to the outcomes of interest. How and whether an organization applies this type of process management will be determined by the level of the QMS at which critical processes and, subsequently, risks are defined. For example, an organization that manages risks across their QMS may define issue management as a critical process for the QMS. In subsequent steps in the quality risk management process, risks related to the issue management process may be identified; such risks include underreporting of issues, which can be evaluated and controlled as needed. Critical processes may also be processes that are common to all or most trials and contribute significantly to human subject protection; such processes include obtaining informed consent and reporting adverse events.

At the trial level, critical processes and data are based on an individual trial's design. As with the system-level risks, trial-level risks are designated as critical because of their impact on human subject protection and/or the reliability of trial results. Examples of trial-level critical processes include those associated with a unique diagnostic, a new vendor, unique rating scales, an informed consent consideration, or introduction of a new technology. Critical data at the trial level are typically in support of a primary endpoint or key conclusion in a submission.

Minimally, the factors considered in determining criticality should include potential impact to human subject protection and reliability of trial results. Discretion can be used for determining criticality based on additional factors that an organization sees as impactful to its objectives, but care should be taken in applying criticality too broadly to maintain focus on and resourcing of the controls that matter most to mitigate the most significant risks.

Table 1. Example of Risk Evaluation Criteria.

Scale	Impact	Likelihood	Detection
10	Definitively negative impact on subject's rights, safety, well-being and/or reliability of trial results	High likelihood (occurs over 50%)	Unlikely to be detected
7	High potential for a negative impact on subject rights, safety, well-being and for reliability of trial results	Occurs frequently (occurs 10%-40%)	Detected more than 25% of the time (detected occasionally)
4	Some potential for a negative impact on subject rights, safety, well-being, and/or reliability of trial results	Occurs infrequently (occurs 1%-10%)	Detected more than 50% of the time (detected by routine processes)
1	Very low potential for a negative impact on subject rights, safety, well-being, and/or reliability of trial results	Occurs rarely (less than 1%)	Will be detected every time it occurs (automated detection and alarm)

Risk Identification

Risk identification defines potentially significant quality risks to be included in subsequent steps in the quality risk management process. Risks may be identified from elements of the QMS or critical processes, based on their relationship to critical data, or newly identified based on a systematic assessment. Identification of risks using a structured, systematic methodology such as a process management-based approach helps ensure that potentially significant risks are recognized and included in subsequent quality risk management activities. A cross-functional approach to risk identification should be applied as needed. For example, if discussing a potential risk related to treatment blinding, whether at the system or trial level, a cross-functional team could be engaged to define the risk more fully in risk identification and to fulfill subsequent steps in the quality risk management process. Quality signals, which may include historical quality events, protocol deviations, SOP deviations, audit/inspection findings, trends in data, etc are also an important input to risk identification.

To improve the risk identification process, establishing and maintaining a list of potential risks or a risk library is recommended. The risk library's purpose is to make frequently used risks and their attributes easy to access. It should not be a list of all risks ever identified; it should only include risks that may have broad applicability. It may be developed from knowledge and process management activities, data analysis, internal assessments (eg, TransCelerate's tool for assessing the QMS [ACQMS]), audits, issue management activities, industry best practices, or a combination of these. Additional sources for the risk library include external information arising from inspection trends, government/regulatory body changes, and stakeholders such as patients. Each team conducting a risk assessment can access the risk library for consideration of common risks; however, it is important to avoid the pitfall of being complacent when using a risk library. The risk identification process needs to preserve space for open thinking about unique or previously unidentified risks. The risk library can also be used later in the risk management process to support risk review.

For each risk identified, documentation of additional attributes is helpful in subsequent steps of the quality risk

management process. These may include a description of the risk, the source and impact of the risk, quality signal(s) supporting the significance of the risk, existing risk controls, and/or risk owner.

Risk Evaluation

After risk identification, risks are evaluated for their relative significance based on an organization's risk tolerance. This step determines which risks will or will not be controlled during subsequent quality risk management activities and carried forward in documentation. Risks are assessed based on 3 characteristics: impact, likelihood of occurrence, and probability of detection. Impact is defined within each company, but minimally includes the impact on human subject protection and reliability of trial results to meet the requirements of ICH E6(R2).

Several approaches may be used to evaluate risks including qualitative analysis, quantitative analysis, or a combination. One method of evaluation is having a cross-functional team or subject matter expert (SME) apply a rating for each characteristic of the identified risks. Rating scales used in this method of characterization can be set to numerical values based on the available data or the assessment of a team or SME. If numerical values are set, then the product of the ratings for each characteristic can be used for relative prioritization of risks. Depending on how the scales are set, the level of risk tolerance can be based on this combined score. Risks that are significant relative to an organization's risk tolerance (eg, above a certain score, the top 10 risks identified, above a certain severity and score, etc) are progressed into risk control activities.

Table 1 shows example criteria that can be applied to each characteristic of a risk when conducting an evaluation. The most significant risks in this example would be ranked as a 10 for impact, a 10 for likelihood, and a 10 for detection. These scores may be used to calculate a numerical value for comparison to other risks.

Each company defines its approach to evaluation and the factors that may contribute to impact based on its risk tolerance and objectives. Once the evaluation of each risk is completed, the risks can be compared to each other and to the organization's risk tolerance. The risks that are significant following the

Figure 2. Example of risk scoring.

evaluation require controls. In the following example, risks have been scored relative to each other (Figure 2) and Risk 2 and Risk 4 require additional controls.

The threshold for requiring risk control is based on the organization's risk tolerance and is not to be confused with quality tolerance limits that are discussed elsewhere.⁷ A risk threshold may be set based on a risk's score, a percentage of total risks, the potential impact, or other method that considers the allocation of resources in risk control.

The evaluation of a given risk may change over time because it is influenced by new or strengthened controls for a system or a trial. System or trial design changes may impact the overall assessment and the relative significance of the risk. Other quality signals, such as enhanced detection through the use of a metric, may alter the understanding of the risk and its impact. Quality signals indicative of risks or emerging risks may include quality events, protocol deviations, SOP deviations, audit/inspection findings, trends in data, etc. Their significance and systemic occurrence determine whether and at what level, system or trial, they should be further managed. For these reasons, risk evaluations should be reviewed and updated periodically (see Risk Review section). Following the evaluation and prioritization of risks, controls can be established for the significant risks.

Risk Control

The purpose of risk control is to mitigate risk by avoiding it, reducing it to an acceptable level, or accepting it as is.

- Risk avoidance is removing the source(s) of the risk or finding another way to achieve the same objective without realizing the risk.
- Risk reduction is decreasing the exposure to the risk, its likelihood of occurring, or the impact resulting from its realization. Risk reduction can also be accomplished by increasing detectability.
- Risk acceptance is choosing not to further control the risk. Risks are accepted based on the current activities in the organization with no additional controls. If accepted

risks are realized, they may or may not become issues. If they do become issues, then they are managed through an issue management process.

Investments in risk control prevent issues, including the negative impacts of realized risks and the need to resource remediation of issues. Any of the 3 methods of risk control can be applied to significant risks, but one may be more effective than another for a given risk.

The fundamental actions and deliverables of risk control may be documented to facilitate implementation and assessment of effectiveness. Documentation may include the following:

- The relative priority of the risk (output of the risk evaluation process)
- Method or source of risk detection (metric, data aggregation, edit check, etc)
- Type of action (avoid, reduce, or accept)
- Description of the action(s) taken
- Owner(s) for any action(s) taken
- Action implementation due dates
- Status of the action implementation

The amount of effort applied to control risk will vary depending on the risk and its relative significance. Simplifying a process to remove a risk may require technology, training, and behavior change in implementation. For example, to control the risk of inclusion criteria not being met, a process-level risk control might include adding real-time automation that does not allow a patient to be enrolled if eligibility criteria are not met. Some trial-level risks may be controlled sufficiently by an existing process control. As a result, at the trial level this same risk may be controlled through checklists, study-related plans, the protocol, or training. A thoughtful approach to risks at both the system- and trial-levels results in more effective use of the resources available to control risks. Risks may need to be controlled at the system and trial levels, only at the system level, or only at the trial level depending on the evaluation of the risk, the organization's risk tolerance, and the required level of control. Regardless, control activities should address the most significant risks identified in risk evaluation and consider the use of the various ways risks can be controlled. For example, during protocol development, teams assessing risk may do the following:

- Avoid: Remove the risk by modifying the protocol or implementing other changes before starting the study.
 - Choosing less invasive or fewer interventions/assessments
- Reduce: Modify the trial design.
 - Reducing the amount of data to be collected
 - Reducing the process steps required to conduct an assessment
 - Adding instructor-led training for the use of rating scales

- Adding edit checks to match the study inclusion/exclusion criteria
- Enhancing monitoring for important data (eg, inclusion/exclusion, primary endpoints)
- Increasing the frequency of monitoring/detection
- Adding a metric to facilitate detection
- Accept: Consider plans of action to respond if realized risks become issues.

There are many other possibilities for avoiding, reducing, or accepting risk to control risk at the system or trial level. Through assessment of current process controls, vendors, protocols, etc, each company can determine where the current process controls are sufficient and where additional controls are required. Clinical development has inherent risks as do other industries and processes. The goal is not to eliminate all risks, because every process has risks associated with it, but to control the most significant ones.

Ownership of the overall risk plan, the individual risks, and implementation of controls are paramount to realizing the benefits of risk management. Documenting and communicating a risk plan is an initial step in establishing ownership and effectively implementing controls. The success of quality risk management efforts hinge on implementation of the controls.

Quality tolerance limits are included in ICH E6(R2) as a method of risk control.⁴ They connect existing controls and their effectiveness. Quality tolerance limits may be based on quality metrics derived from risks to critical data and processes. The quality risk management plan, especially the controls identified, should be revisited if quality tolerance limits are reached. Approaches to risk reporting and quality tolerance limits are covered in detail in TransCelerate's Risk-Based Quality Management: Quality Tolerance Limits and Risk Reporting.⁷

Risk Communication

Once the risks in clinical development are understood, they should be communicated to the relevant stakeholders both at the system and trial levels. Communication supports other elements of the quality risk management process by increasing the probability of successful implementation of controls and, thereby, risk reduction. Communication and reporting mechanisms also support and encourage accountability and ownership of controls. Communication planning may include identification of the important stakeholders of quality risk management processes, development of a communication plan, and execution of the communication plan.

Identification of stakeholders

Because quality risk management processes exist at the system and trial levels, stakeholders should be inclusive of both. Examples of stakeholders include the following:

- Action owners
- Functional lines (clinical, medical, safety, operations, etc)

- Quality assurance
- Subject matter experts (or SMEs; legal, quality, culture)
- Process owners
- Vendor management organization
- Training organization
- Quality governance
- Senior management
- Investigator site staff

Each organization should consider the relevant stakeholders who are responsible or accountable for the conduct of quality risk management processes, require quality risk management information for decision making, or need to be informed of the outcomes of quality risk management processes to do their work. Ideally, many of these stakeholders will be involved in quality risk management activities already, and communication is a confirmation of what has been agreed for those most affected and involved.

Development of the Communication Plan

A communication plan defines the expected process for risk communication across the enterprise QMS. Communication plans typically include the media, content, and frequency of communication with each stakeholder group. Communication activities should support the initial implementation of a quality risk management framework, ensure that quality risk management continues to be part of a proactive culture of quality management, inform stakeholders of changes to risk, outline how risks are escalated to key stakeholders, and define communication expectations for trial-level risks. While there is no requirement to document a formal communication plan, it is helpful to review these elements regardless of whether they are formally documented or informally considered.

Execution of the Communication Plan

Communication should focus on the significant risks identified in the quality risk management process and influence a culture of proactive risk identification. Execution of the communication plan will result in feedback that modifies subsequent versions of the plan. The plan should evolve over time as additional information becomes available and as the quality risk management program matures.

Quality Risk Communication Best Practices

Communicating risks to quality is relevant across the system and trial levels and among other processes in the interest of maturing the quality risk management program and the QMS. Available metrics and analytics regarding the performance of quality risk management processes should be included in periodic discussions with stakeholder groups. Selecting forums for communication that include opportunities for feedback and discussion are also preferred. Lessons learned sessions are one example of this type of communication forum. Communication with some stakeholder groups may require consolidation of risk

information from a variety of sources. As a result, consideration should be given to the sensitivity of the information.

Documentation

As with many things, sharing the outcomes of quality risk management in writing helps ensure agreement, capture outcomes, and give an opportunity for clarification. This includes communicating through the clinical study report (CSR) as described in the Risk Reporting section. In addition, filing trial-level quality risk plans in the trial master file (TMF) is recommended to ensure that documentation of quality risk management plans is maintained.

Periodic Risk Review

Risk review ensures that risk assessments and quality risk management processes are up-to-date and effective. This includes refreshing risk assessments and quality risk management processes periodically based on agreed triggers both at the system and trial levels. The triggers for refreshing a risk assessment may be time, process changes, quality signals, milestones, or other events. As noted in risk identification and evaluation, quality signals indicative of risks may include quality events, protocol deviations, SOP deviations, audit/inspection findings, trends in data, etc.

When a risk assessment is refreshed, changes may include updating the significance of a risk(s), identifying risks that were not previously detected, changing controls based on observed effectiveness, and/or the quality signals above. Review of the effective implementation of risk controls may also be part of the periodic review process for a risk assessment.

Reviewing the quality risk management program keeps it contemporary relative to the current environment, processes, controls, quality signals, portfolio, and other factors relevant to the business. Periodic review of the program should include reviewing the risk library, incorporating lessons learned from issue management, and updating the quality risk management program based on new or revised regulatory guidance, business objectives, input from internal process reviews/audits, QMS assessments (eg, ACQMS), industry inspection experience, and other factors. This periodic review of the program should be cross-functional in nature and leverage available quality data and analytics to support changes. Ideally, effectiveness measures will show if risk identification, evaluation, and control prevented risks from being realized and determine future opportunities for improvement. Quality metrics, quality tolerance limits, and process or compliance metrics may act as surrogates if effectiveness metrics are not available. If using a risk library, it will be updated to reflect changes to these inputs. There is no fixed frequency for review of the elements of the quality risk management program. Each organization needs to define the triggers for review and the appropriate timing for review to keep the quality risk management program and the risk assessments current.

Risk Reporting

Risk reporting as per ICH E6(R2) is specific to reporting quality performance at the trial level. Additional reporting is recommended within an organization and these topics are covered in the section on risk communication. ICH E6(R2) requires a description of the quality management approach for the trial and a summary of important deviations from the predefined quality tolerance limits and remedial actions taken in the CSR.⁴ Approaches to risk reporting and quality tolerance limits are covered in detail in TransCelerate's Risk-Based Quality Management: Quality Tolerance Limits and Risk Reporting.⁷ The important deviations may be a summary of potentially important protocol deviations, quality events, quality metrics, or trial-specific metrics depending on the risk tolerance of the organization and the processes and data important to the trial. The quality tolerance limits may be used across a portfolio of trials or unique to an individual trial.

Conclusion

The quality risk management approaches described in this paper are integral parts of an effective QMS. These concepts can be applied at both the system and trial levels. Quality risk management should be dynamic, iterative, and responsive to change to maintain its effectiveness over time. It should help an organization answer the following questions:

- What are the most significant quality risks?
- To which risks should resources be allocated?
- Are effective controls being applied to the significant risks?

Identifying the most significant risks and allocating resources to control these risks will improve an organization's ability to reach its objectives effectively and with the best interest of patients at the forefront.

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biopharmaceutical R&D community to identify, prioritize, design, and facilitate implementation of solutions designed to drive the efficient, effective, and high-quality delivery of new medicines.

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