Risk Management in Clinical Research: PROCESS DEVELOPMENT & APPLICATION

Introduction

Recently, two key pieces of guidance were released from Food and Drug Administration (FDA) and European Medicines Agency (EMA) regarding risk based approaches to clinical research. These documents include FDA's "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring" and EMA's "Reflection paper on risk based quality management in clinical trials". The focus of the regulators on this concept initiates a discussion of how to introduce, implement, and apply risk management principles to clinical trials. The applicable guidances for good clinical practice (GCP), ICH E6 and ISO14155, state explicitly that the sponsor is responsible for quality assurance and quality control. One aspect of quality involves how risks are approached and managed throughout the course of a clinical trial.

FDA released a final guidance document in August 2013 titled "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring". This final guidance document focused on the implementation of risk based strategies for monitoring within the clinical research field. It explored different monitoring methods and techniques, identification of critical data and processes to be monitored, monitoring plan considerations, and documentation of monitoring activities. In addition, the last section of the guidance includes a chapter titled "Additional Strategies to Ensure Quality." This section focused on other aspects of clinical trial management that if implemented could facilitate greater study quality. The guidance states: "FDA considers monitoring to be just one component of a multi-factor approach to ensuring the quality of clinical investigations." Specific focus areas are protocol and case report form design, clinical investigator training and communication, delegation of monitoring responsibilities to a CRO, and clinical investigator site selection and initiation. While these four aspects are briefly discussed and associated to monitoring a clinical trial, a significant impact to clinical research success can be realized when risk based approaches are applied to all clinical research activities.

EMA released a paper in November 2013 titled "Reflection paper on risk based quality management in clinical trials". The document describes how GCP requirements can become integrated with quality concepts through every aspect of the trial and to encourage and facilitate this integration for a more systematic, prioritized, risk-based approach to the management of clinical trials. The reflection paper describes specific areas of risk within the current clinical research field.

A few of these areas are listed below:

- Cost of clinical development and limitations on available resources
- Globalization of clinical trials, complicating the regulatory, business and scientific/medical environment and target patient population(s) within which they operate
- Over-interpreted or misunderstood regulatory environment, which may result in a failure to achieve its actual intent
- Poor design of studies and study processes, often being much more complicated than necessary to achieve what is required, thus diminishing focus and resource availability to achieve the quality necessary for the more important objectives
- Poor risk identification and poor risk mitigation – a lack of use or understanding of risk-management tools and techniques, is often associated with a reactive, fire-fighting approach to problem management. This results in processes largely based on corrective rather than root-cause preventive action.

Clinical trial risks have evolved as the industry has progressed with globalization and technology, both from a standpoint of trial conduct and the complex nature of the investigational products being examined. Building in quality and inspection readiness from Day 1 of a clinical trial is necessary. Every year, FDA releases the Bioresearch Monitoring (BIMO) inspectional findings for sites, sponsors, and IRBs and these have been virtually identical every year. The EMA Reflection paper stated that the trending of repeated and avoidable quality issues has also been noted by European GCP inspectors. These recently released documents further define the importance of implementing risk management concepts into clinical research. The objective of this whitepaper is to introduce the concept of risk management and discuss methods to apply it to clinical research.

Risk Management Process

Risk management concepts can be extracted from the ISO 14971: Risk Management for Medical Devices and ICH Q9: Quality Risk Management. The first step is to define a procedure for conducting this activity. The basic steps to risk management include: identify and assess risks, mitigate risks, and review risks. Additional steps that are required throughout the process include communication of risks and documentation activities. Overall, these steps are general enough to be applied to any stakeholder in the clinical research process; however, the most effective way to ensure successful risk management is to design a program that integrates into the existing infrastructure of each individual organization.

For risk management, defining the process is critical because of the structured approach, feedback loops, and documentation requirements. This procedure should be a quality document that outlines the process to follow. A detailed flow chart is recommended; a general flow chart is shown in Figure 1 to include the basic steps outlined in the paragraph above.

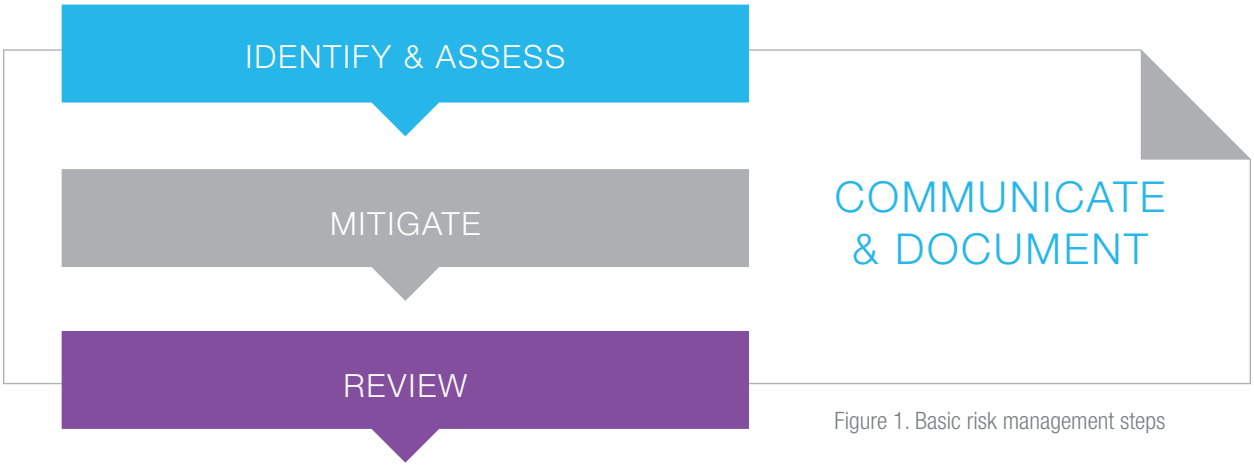

Figure 1. Basic risk management steps

There are many factors to consider when defining the risk management procedure. One of the first decisions is who will participate in the activity. It is important to define a multidisciplinary team; having multiple departments or sub-groups within the risk management team will allow for the greatest benefit of the process. A few communication and documentation considerations include: How will risks be disseminated to the team? Will meeting minutes be taken for each risk management meeting? Who maintains the documentation? How information is captured through documentation and how that documentation is maintained, communicated, and retained throughout the entire process is required to ensure continuous improvement. The basic steps of the risk management process are described below; the approach is general and intended to provide an overview of the process.

IDENTIFY & ASSESS

To begin the risk assessment process, the identification and assessment of risks is the first task. The identification and assessment of risks focus on questions from ICH Q9 such as:

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the chances we will discover (detectability) the issue?
- What are the consequences (severity)?

The process to identify risks is based on information from individuals, historical data, previous analyses, and concerned parties. This information is assessed using a predefined scale. This approach can either be quantitative or qualitative. The quantitative approach would use a numbered scale or calculated probability of an event occurring. The qualitative approach would use a categorization of events to define severity. Because these designations can be subjective, objectivity has to be a top consideration when examining risks.

MITIGATE

The next step in the process is to evaluate whether or not a risk is within an acceptable level or whether it can be reduced or eliminated. Some risks are accepted based on this premise and some may be mitigated through specific actions. The mitigation of risks focus on questions from ICH Q9 such as:

- What is the acceptable level of risk for the clinical study?
- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- Are new risks introduced as a result of the identified risks being controlled?

The process to identify risks is based on information from individuals, historical data, previous analyses, and concerned parties. This information is assessed using a predefined scale. This approach can either be quantitative or qualitative. The quantitative approach would use a numbered scale or calculated probability of an event occurring. The qualitative approach would use a categorization of events to define severity. Because these designations can be subjective, objectivity has to be a top consideration when examining risks.

REVIEW

Review of risks is a continual process throughout the project life cycle. This portion of the process will depend on the type of project that is being examined and its parameters. This step involves the review of risks, mitigation actions, and subsequent results; this step examines whether or not the identified risk was controlled appropriately and the result. This step may also result in new risks being identified; these risks would then follow the assessment and mitigation steps.

COMMUNICATE & DOCUMENT RISKS

Throughout the entire risk management process, steps for risk communication and documentation of activities have to be incorporated. The method of risk communication will vary depending on the organization and could be done using a standard method of communication or could even be accomplished through the use of a computer program. Documentation of activities and this process is required. The saying “If it was not documented, it was not done” applies in this situation.

CONTINUOUS EVALUATION OF RISKS

The risk management process requires continuous evaluation. The listed steps are repeated regularly throughout the entire project; this schedule is defined at the beginning of the project and will ensure a continuous evaluation of risks is achieved. However, it is also important to note that an event may occur that initiates the evaluation process outside of a regularly scheduled risk session. The mitigation strategy may take place immediately and the subsequent review and documentation of the risk would follow. These unexpected risks are part of the risk management approach and should be treated in the same manner as expected risks. The constant nature of risk evaluation is important to understand so a project is appropriately managed and issues are addressed prior to escalation.

Application to Clinical Research Studies

As ISO14971 explores the application of risk throughout an investigational product's lifecycle, these concepts can also be applied to the clinical trial lifecycle. The concept of risk management for clinical studies can be related to the similar process of a medical device or pharmaceutical design lifecycle. Each clinical trial has three primary phases that encompass a variety of tasks. The three phases to a clinical trial are planning, execution, and closure. Planning a trial encompasses the protocol development, general project planning, and development of supporting monitoring, data, or quality plans. Project execution is the actual conduct of the trial and includes all activities required by the protocol and data collection. When the trial is in the closure phase, data management and analysis occur and regulatory applications are prepared.

Clinical research is familiar with the use of standard operating procedures. For risk management, this would require development of a procedure focused only on this topic. This document would be specific to the stakeholder conducting risk management activities, appropriately following internal document structure, formatting, and approval requirements.

After a procedure has been developed for risk management, the identification of risks begins with examining risks to subject safety and data integrity. This is the recommended starting point for identification, prompted by reviewing the annual BIMO findings posted by the FDA or other regulatory agencies for clinical sponsors, sites, and IRBs. This list can assist in creating discussions of topics that would apply to a specific trial. It is important to brainstorm all risks and then move toward classification and mitigation.

Some key questions to ask may include:

- How complex is the study design? Is it an adaptive design trial?
- Does the study have any interpretive or subjective data endpoints?
- Does the study population include a vulnerable population or subset?
- Are sites located in a region of the world there are differences in the standards of medical practice and/or infrastructure of clinical research practice?
- What is the experience of the clinical investigator? What is the sponsor's experience working with the clinical investigator?
- Is the site using electronic data capture (EDC) systems?
- Does the investigational product have any safety concerns?
- What is the stage of the study? Is the study in the enrollment stage or the follow-up stage?

After asking and answering the questions above, risks are identified. These risks may be expected and may not rise to the level of requiring mitigation. The evaluation of risks is dependent on the type of quantitative or qualitative scale being used. This scale should be applied uniformly to each identified risk. If the defined threshold is not met, then risk acceptance is documented. If the defined threshold is met, mitigation strategies are applied. In clinical research, studies are dependent on so many factors and subsequently the control tactics for each risk are going to be project, sponsor, and site dependent. The following examples illustrate how risk management can be applied to issues commonly observed within clinical trials for each phase of the clinical project.

EXAMPLE 1

Clinical Study with Non-standard of Care Testing

The first risk management example explores a clinical study that includes a primary endpoint that is a non-standard of care test. While this non-standard of care test can be collected in a typical core laboratory or central laboratory facility, conduct of this test and collection of the results is not a normal pattern for the type of patient enrolled in this clinical study.

IDENTIFY & ASSESS

There is a potential for missed tests because the site is not used to collecting these tests and/or results for this type of patient. Overall, each site in the study has a different process to collect these tests; some sites have an internal core facility that can conduct the test and some sites have to package and send out their samples to a central facility for testing. Also, personnel may be involved in the testing and results gathering that may not be trained study personnel. The primary risk is of non-standard tests being missed because the test is not ordered initially because it is non-standard, the laboratory skips the test because it is non-standard, or the proper communication is not initiated between the site and the core or central laboratory personnel regarding the required testing.

MITIGATE

To mitigate this risk, the traditional approach is to ensure personnel involved are educated and trained appropriately. Study personnel will be trained on the protocol; however, the extended personnel of the core laboratory or central laboratory will also have to be trained. Another option would be to conduct early on-site monitoring visits that incorporate a specific focus on the non-standard testing; these visits would ensure the proper process steps were being followed to collect this data. The sponsor could also initiate remote monitoring for either all sites or specific sites for the non-standard laboratory tests. A threshold could be created regarding the number of data issues that would initiate additional quality assurance activities. For instance, if a site has a certain number of missed tests with no effective corrective and preventive action plan, then an independent site audit could be conducted. Other visits could involve a more formal review of any central laboratories and this could include a vendor review process if more than one site is going to utilize the laboratory.

REVIEW

For this study, the risk of missed tests has to be evaluated throughout the duration of the study for each site. As the study progresses, some sites may not have any issues and some sites may require additional actions, such as retraining, additional on-site monitoring visits, or even a site audit. A basic tracking spreadsheet could document each site's progress as the study is conducted. This would allow the sponsor to also easily and quickly compare the sites and evaluate where more resources may need to be allocated. The importance of documenting the history and activities associated with these non-standard tests cannot be overstated; this is especially true if the study spans multiple years.

EXAMPLE 2

Training of Clinical Research Sites with Varying Experience

The second risk management example examines a multi-year clinical study that has two sites with specific patient populations of interest. The monitoring plan will follow a risk based monitoring strategy that involves both on-site monitoring visits and remote monitoring of clinical data between the on-site visits. In the first year of the study, it is noted that Site A has little experience with clinical studies and Site B has many years of experience conducting clinical studies.

IDENTIFY & ASSESS

Site A is at risk from an overall clinical study management perspective. The site may make mistakes regarding various aspects of good clinical practice that may include inappropriate management of regulatory documents, inadequate source documentation, or incorrect safety reporting. The inexperience of this site could create challenges from Day 1 of the study. Site B has been conducting clinical research for many years and has a seasoned research coordinator and therefore no significant risk for this site is noted at this time.

MITIGATE

Throughout the study, both sites will be remotely monitored for data discrepancies and trends. For Site A, additional and extensive training is planned to ensure they have proper instruction on how to conduct study tasks and have a greater comfort level with clinical research. Early and frequent on-site monitoring visits can also occur. Investing time into choosing an experienced monitor will also contribute to this site's success. Possibly explore the development of standard operating procedures (SOPs) for the site to follow during the study. Site A should also have a continuous evaluation conducted by the monitor and the project manager to identify if retraining on any topic might also be required.

REVIEW

Upon reviewing the risks for each site, Site A is doing well upon entering the second year of the study. The initial risk for this site has decreased significantly and now Site A is a leading site in managing study conduct, data, and documentation. No further mitigation strategies are needed at this time.

In the second year of the study, some anomalies were discovered through remote monitoring at Site B.

It was discovered that the experienced research coordinator was recently promoted and as a new research coordinator is being trained, data issues are surfacing. This changes the site's risk status and requires the identical approach of identification and assessment, mitigation, and review.

IDENTIFY & ASSESS

Site B's new research coordinator has created the potential for mistakes to be made with clinical study conduct and data issues have already been noted. The first on-site monitoring visit already showed unorganized regulatory documents and some missing source documentation. Site B is at risk for additional mistakes in their conduct of this clinical study.

MITIGATE

The first step will be to conduct extensive, detailed training on the study, protocol, and good clinical practice for the new research coordinator. In addition, adding more frequent on-site monitoring visits with a senior monitor would assist the site in getting back on track.

REVIEW

Site B should be evaluated continuously by the monitor and the study manager, similarly to how Site A was during the first year of the study. As Site B addresses issues and improves on the previously noted data discrepancies, it can be determined if additional training may be necessary or if fewer on-site monitoring visits can be conducted.

Next Steps

Because the sponsor of the study has a responsibility to ensure patient safety and data integrity is maintained throughout the clinical trial, this will require a continuous and diligent approach to evaluate what will happen as the study enters year three.

These two examples provided illustrate two different situations with risks in clinical studies. These examples show how risks may apply to a specific clinical site, may be based on the protocol and apply across the entire study, and may evolve and even shift from one site to another based on circumstances.

Conclusion

Risk management strategies can be applied to the clinical research industry. FDA and EMA have released guidance documents that discuss and reference the incorporation of these principles into the clinical trial development, execution, and closure. The advantage of incorporation of these quality principles is an investment into the overall success of the clinical trial. This investment will save time, resources, and likely eliminate, prevent, and/or minimize subject safety and data integrity risks.

The expectation has been set by the regulatory authorities for the implementation of quality principles and risk-based decision making. It is the responsibility of the industry to incorporate these concepts into existing quality procedures and apply risk management techniques into the clinical research process.

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