A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers

Guidance for Industry

DRAFT GUIDANCE

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A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance on risk-based approaches to monitoring investigational studies of human drug and biological products, medical devices, and combinations thereof. This guidance contains recommendations on planning a monitoring approach, developing the content of a monitoring plan, and addressing and communicating monitoring results. This guidance expands on the guidance for industry *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013) (the RBM guidance)[2] by providing additional guidance to facilitate sponsors' implementation of risk-based monitoring.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Sponsors of clinical investigations involving human drugs, biological products, medical devices, and combinations thereof are required to provide oversight to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality of the data submitted to FDA.[3]

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, the Office of Good Clinical Practice, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).

FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations.[4,5,6] The regulations are not specific about how sponsors are to conduct such monitoring; therefore, a range of approaches to monitoring are compatible with the regulations.

The RBM guidance discusses the importance of identifying critical data and processes necessary for human subject protection and integrity of the investigation, conducting a risk assessment, and developing a monitoring plan specific to the investigation. The RBM guidance also encourages sponsors to tailor monitoring plans to the needs of the investigation, describes factors to consider in developing a monitoring plan, and provides examples of monitoring methods and techniques.

FDA believes risk-based monitoring is an important tool to allow sponsors to identify and address issues during the conduct of clinical investigations. FDA's experience since finalizing the RBM guidance in 2013 suggests that additional guidance would be beneficial regarding FDA's recommendations for planning a monitoring approach, developing the content of monitoring plans, and addressing and communicating monitoring results. The following questions and answers are intended to assist sponsors in planning and conducting risk-based approaches to monitoring.

III. QUESTIONS AND ANSWERS

A. Monitoring Approach

Q1. What is the purpose of the risk assessment and should sponsors document their methodologies and activities for assessing risk?

Consistent with the RBM guidance, sponsors should identify and perform a risk assessment on those critical data and processes that are necessary for human subject protection and integrity of the investigation.

The risk assessment serves to identify and understand the nature, sources, likelihood of detection, and potential causes of risks that could affect the collection of critical data or performance of critical processes. The risk assessment informs the development of a monitoring plan and may also support efforts to manage risks across a clinical investigation (for example, through modifying the protocol design or implementation) or across a product's development program. Therefore, sponsors should document their risk assessment, including methodologies used for the

[4] 21 CFR 312.50 requires a sponsor to, among other things, ensure "proper monitoring of the investigation(s)" and "that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND." 21 CFR 812.40 states that sponsors are responsible for, among other things, "ensuring proper monitoring of the investigation, …"

[5] See also 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

[6] For the purposes of this guidance, the terms investigation, trial, and study are used interchangeably to refer to a clinical investigation, consistent with how these terms are used in the 2013 RBM guidance, *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring.*

risk assessment, conclusions from the risk assessment, and how the assessment was used to make decisions on the management of the risks identified. Any such document should be available for review.

The monitoring plan should include information regarding the identified risks and how the monitoring methods will address those risks. (See Q6 for further details.) The inclusion of these components in the monitoring plan will enhance the utility of the plan by providing a clear explanation of the identified risks and how they will be monitored, managed, and mitigated.

Q2. Should sponsors monitor only risks that are important and likely to occur?

A risk-based approach to monitoring should focus sponsor oversight activities on preventing or mitigating important and likely risks to investigation quality, including risks to human subject protection and data integrity. Sponsors also should consider monitoring risks that are less likely to occur but could have a significant impact on the investigation quality. Sponsors should determine the types and intensity of monitoring activities best suited to address the identified risks. In addition, monitoring plans should permit monitoring activities to evolve based on additional issues and risks that may be identified during the conduct of an investigation.

Q3. What factors should sponsors consider when determining the timing, types, frequency, and extent of monitoring activities?

As described in detail in the RBM guidance, factors sponsors should consider include the following:

- Complexity of the study design
- Types of study endpoints
- Clinical complexity of the study population (for example, study populations that are seriously ill, have multiple co-morbidities, or are more vulnerable and may require more intensive monitoring and consideration of on-site monitoring visits to be sure appropriate protection is being provided)
- Geographic location of clinical investigator (CI) sites where there may be differences in standards of medical practice or less established clinical trial infrastructure
- Relative experience of the CI and of the sponsor with the CI
- Electronic data capture to be utilized[7]
- Relative safety of the investigational product

[7] See the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013).

- Stage of the study (progress of the study)

- Quantity of data

FDA also recommends that sponsors consider the following additional factors:

- Workload at the CI site

- Turnover of personnel at the CI site or among monitoring staff

  – Similar to workload, high personnel turnover may cause unintended disruptions to conduct of the investigation and sponsor oversight.

- Location where subjects will be seen and whether they will be seen at more than one location to complete investigation procedures (for example, data collection at the imaging center, at a local physician's office, or at the subject's home)

  – When designing the monitoring plan, sponsors should take into consideration where and how the data are going to be collected in the investigation relative to where the sponsor oversight activities will be conducted (for example, to confirm that appropriate controls, instructions, and training tools are in place).

- Benefit of an early monitoring visit or other early monitoring activities

  – By scheduling an early monitoring visit (for example, soon after the first trial subject(s) enrolls in the investigation) or by carrying out other early monitoring activities (for example, through remote processes), sponsors can help ensure early in the investigation that procedures are being performed correctly at CI sites. Alternatively, if early monitoring identifies issues, corrective action(s) can be implemented sooner.

- Experience and qualifications of the research coordinator

  – The research coordinator serves an important role in ensuring the quality of the execution of the investigation at the investigation site (for example, the research coordinator often recruits subjects, collects and evaluates study data, and maintains study records.)

- Safety profile of the investigational product

  – When developing a monitoring plan, sponsors should consider the known safety profile, including the available human and non-clinical safety information for the product and the class, and the mechanism of action.

- Characteristics of data to be collected

  – When developing a monitoring plan, sponsors should consider the amount and complexity of the data collected.

Q4. How can a risk-based approach to monitoring that includes centralized monitoring help minimize missing data, protocol violations, or protocol deviations?

There may be situations in which poor trial conduct or adherence to the investigational plan causes or contributes to incomplete data collection. Therefore, by reviewing important investigation activities, in real-time across CI sites, sponsors may be able to identify the reasons for missing data, protocol violations, or protocol deviations and take corrective actions to minimize the likelihood of these occurring during the remainder of the clinical investigation.

Q5. Should the risk-based monitoring approach include processes to ensure that appropriate blinding is maintained?

Yes. As identified in the RBM guidance, for investigations in which blinding will be used for interventions and/or outcome assessments, ensuring that the investigation blind is maintained is a critical process that sponsors should consider in their risk assessment.

Specific risks to the maintenance of the blind that are identified during the risk assessment should be mitigated in advance of investigation initiation, when feasible. In addition, identifying and tracking deviations during investigation conduct that could result in unintentional unblinding of treatment assignment should be considered as a part of the monitoring plan to ensure that appropriate blinding is maintained at CI sites and by the sponsor. For example, in a blinded investigation that requires a site staff member to be unblinded to administer the test article, the site processes for maintaining the blind for the remainder of the site staff and the sponsor should be monitored.

FDA recognizes that Data Monitoring Committees (DMC) may access unblinded data as described in the DMC Charter. (For additional information about DMC, see the guidance for clinical trial sponsors *Establishment & Operation of Clinical Trial Data Monitoring Committees* (March 2006.)

B. Monitoring Plan Content

Q6. What elements should sponsors include in monitoring plans?

The following elements (discussed in detail in section IV.D of the RBM guidance) are summarized here to assist sponsors in developing monitoring plans:

- A synopsis of the study

- Study objectives

- Identification of critical data and study procedures
- Trial-specific risks to be addressed by monitoring
- Monitoring methods and rationale for use of the monitoring methods, including how the methods address identified risks
- Criteria for determining the timing, types, frequency, and extent of monitoring activities
- Specific activities necessary for each monitoring method used
- Definitions of events or results that would trigger changes in monitoring activities (for example, how protocol deviations may be monitored as events that would trigger changes in monitoring activities)
- Identification of protocol deviations and failures that, if occurred, would affect study integrity, and how they will be recorded, tracked, and reported
- Format, content, timing, and archiving requirements for documentation of monitoring activities
- Processes for communicating routine monitoring results to appropriate parties
- Processes for immediate reporting of significant monitoring issues to appropriate parties
- Processes for appropriate communication from study management and other stakeholders to monitors
- Processes to address unresolved or significant issues identified by monitoring
- Processes to ensure that root cause analyses are conducted where important deviations are discovered and that corrective and preventative actions are implemented
- Other quality management practices applicable to the clinical investigation (for example, reference to other documents describing appropriate actions regarding non-compliance)
- Training for personnel who carry out monitoring activities
- Planned audits of monitoring activities
- Process for updating monitoring plans

In addition, FDA recommends that monitoring plans also include the following items, which will help explain how the sponsor intends to address the risks that could affect the clinical investigation.

- A description of the investigation design and the blinding and randomization procedures, if applicable

- Processes for confirming that randomization is performed according to the protocol and investigational plan when randomization is identified as a risk to be addressed by monitoring

- Sampling plan(s) that will be used to identify the specific records and data that will be monitored, including the rationale for how the sampling plan provides a representative picture of the overall information, and how the sampling plan will be implemented

- A description of the types of significant issues identified through monitoring that would trigger immediate issue escalation

- An approach for determining if issues identified at a site also exist at other CI sites and an approach for correcting these issues

The monitoring plan should describe each of these items in sufficient detail. Sponsors also should reference related documents, when appropriate. Sponsors are encouraged to develop monitoring plans that emphasize critical risks that have the greatest potential to adversely affect investigation quality, including the rights, safety, and welfare of investigation subjects, and the collection or analysis of clinical data such as investigation safety and efficacy endpoints.

C. Follow-Up and Communication of Monitoring Results

Q7. How should sponsors follow up on significant issues identified through monitoring, including communication of such issues?

Significant issues identified through monitoring (for example, significant non-compliance with the protocol) should be thoroughly evaluated in a timely manner at the appropriate level (for example, sponsor, CI site(s)) as described in the monitoring plan. Appropriate corrective and preventative actions should be taken. Deviations from the investigational plan should be documented, tracked, and escalated to relevant personnel, as appropriate. Related systemic issues should be identified and resolved promptly to ensure that investigation quality, including the rights, safety, and welfare of investigation subjects and data integrity, is maintained.

Although not an exhaustive list, some examples of corrective and preventive actions that may be needed include retraining CI and site staff; clarifying protocol requirements through protocol amendment(s); or revision(s) to informed consent documents or procedures.

Significant issues identified through monitoring and the actions to be taken should be documented and communicated to the appropriate parties, which may include, but are not limited to, the following: (1) sponsor management, (2) sponsor teams, (3) CI sites, (4) institutional review board(s), (5) other relevant parties (for example, DMCs and relevant contract research organizations), and (6) FDA, when appropriate.

(See Q6 for a description of elements that sponsors should include in monitoring plans regarding follow up and communication of significant issues.)

Q8. How should centralized monitoring activities and the results of these activities be documented and shared with those involved in the investigation?

As described in the RBM guidance, documentation of monitoring activities should generally include the following: (1) the date of the activity; (2) the individual(s) conducting and participating in the activity; (3) a summary of the data or activities reviewed; (4) a description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified; and (5) a description of any actions taken, to be taken, or recommended (see section V of the RBM guidance for details). Such documentation should include the results of centralized monitoring activities in sufficient detail to allow verification of adherence to the monitoring plan describing those activities.

Reports of centralized monitoring activities should be provided to appropriate management, including sponsor staff responsible for investigation and site oversight, in a timely manner for review and follow up. In addition, sponsors should inform a CI of monitoring findings from centralized monitoring activities that are relevant to the CI's activities.