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

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A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry¹

This guidance represents 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides information on risk-based approaches to monitoring the conduct of clinical investigations² of human drug and biological products, medical devices, and combination products.³ Clinical investigation monitoring is a quality control tool for determining whether investigation activities are being carried out as planned. 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 2013 RBM guidance)⁴ by providing additional information 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.

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 Clinical Policy, the Office of Combination Products, and the Office of Regulatory Affairs at the Food and Drug Administration.

² For FDA's regulatory definitions of *clinical investigation* or *investigation*, see 21 CFR 50.3(c), 56.102(c), 312.3(b) and 812.3(h). For the purposes of this guidance, we use the terms *clinical investigation*, *investigation*, *trial* or *trials*, and *study* or *studies* interchangeably consistent with how these terms are used in the guidance for industry *Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring* (August 2013) (the 2013 RBM guidance).

³ For the definition of *combination product*, see 21 CFR 3.2(e).

⁴ 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>.

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II. BACKGROUND

Sponsors of clinical investigations involving human drugs, biological products, medical devices, and combination products are required to provide oversight, including ensuring proper monitoring of the investigation.⁵ Such oversight helps to ensure adequate protection of the rights, safety, and welfare of participants in the clinical investigation and the integrity of the data submitted to FDA. Therefore, sponsors should implement a system to manage, throughout all stages of the clinical investigation, both risks to participants (e.g., a safety problem) and to data integrity (e.g., incomplete and/or inaccurate data).

This system to manage the quality of the investigation should help ensure data integrity while safeguarding the rights, safety, and welfare of trial participants,⁶ for example, by focusing on the design of efficient clinical trial protocols, tools for identifying and tracking potential risks, and procedures for data collection and processing. This system should include a risk-based approach to monitoring tailored to the potential risks for the specific clinical investigation. Effective implementation of risk-based monitoring, including the prioritization of monitoring and other oversight activities directed at processes and procedures critical for human subject protection and maintaining data integrity, should help maximize the quality of a clinical investigation.

Although FDA's regulations require sponsors to monitor the conduct and progress of their clinical investigations,^{7, 8} FDA regulations are not specific about how sponsors are to conduct monitoring. FDA recommends that sponsors use a risk-based approach to develop their monitoring plans and to revise their monitoring plans, if needed, as the clinical investigation proceeds. This risk-based approach should be informed by the sponsor's overarching quality management activities undertaken in the development of the protocol and associated investigational plans and should be adjusted throughout the conduct of the investigation as needed.

As described in the 2013 RBM guidance, FDA recommends that at the protocol design stage, sponsors identify the critical data and processes necessary for human subject protection and maintaining data integrity for the investigation. Once these are identified, sponsors should perform a risk assessment and determine whether risks to critical data and processes may be

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

⁶ For FDA's regulatory definitions of *human subject* and *subject*, see 21 CFR 50.3(g), 56.102(e), 312.3(b) and 812.3(p). For the purposes of this guidance, the terms *human subject* and *participant* are used interchangeably.

⁷ 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," and 21 CFR 812.46 requires, among other things, that sponsors take certain actions when they discover that an investigator is not complying with the signed agreement, the investigational plan, the requirements of 21 CFR part 812 or other applicable FDA regulations, or any conditions of approval imposed by the reviewing institutional review board or FDA.

⁸ See also 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

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mitigated through revisions to the protocol and investigational plans. When risks cannot be resolved through such revisions, sponsors should determine how remaining critical risks will be identified, tracked, and managed via the sponsors' monitoring plan or related study oversight plans during the conduct of the investigation. Such efforts to build quality into the design and execution of clinical investigations should be informed by representative study team members⁹ involved with conduct, monitoring, and/or reporting of the investigation. Perspectives from patients within the target population to be recruited for a clinical investigation would also be valuable.

Monitoring should be conducted per the pre-established monitoring plan, and important issues identified through monitoring should be addressed as they are identified. Monitoring plans should also include directions for when and to whom important issues identified during monitoring should be escalated. In addition, FDA recommends that monitoring plans provide guidance on when and how to adjust monitoring activities based on observed monitoring findings. For example, when important issues are identified during monitoring of a clinical site, there may be a need to increase the duration or frequency of on-site visits at that site.

Sponsors' risk management processes should continue throughout the conduct of the investigation. FDA also encourages sponsors to use the information gained from each investigation, including the monitoring experience, to inform, as appropriate, the conduct of other ongoing investigations, future clinical investigations, risk assessments, and monitoring plans.

The study-level monitoring plan and associated monitoring activities are among the elements utilized by sponsors in their overall risk-based quality management approach to product development; they are important tools to facilitate sponsors identifying and addressing issues during the conduct of clinical investigations. The 2013 RBM guidance outlines factors that sponsors should consider in developing a monitoring plan and tailoring monitoring plans to the needs of the investigation and provides examples of monitoring methods and techniques. Since finalizing the 2013 RBM guidance, FDA has concluded that additional guidance may be beneficial regarding its 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.

⁹ For example, clinical investigator, research nurse, project managers, study physician/medical monitor, data managers/data scientists, statisticians, monitoring staff, quality assurance personnel, and contracted service providers tasked with critical study functions.

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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?

The purpose of the risk assessment is to optimize the study quality in terms of eliminating or mitigating important risks to both human subject protection and data integrity. Therefore, consistent with the 2013 RBM guidance, during the protocol design phase, sponsors should identify risks, including to protocol-driven processes, that could affect human subject protection and data integrity. The risk assessment should include an evaluation of the potential causes, likelihood of detection, and severity of the consequences of risks to critical data or human subject protections. There are various risk assessment methodologies and tools that can be applied to clinical trials.^{10,11}

The risk assessment should inform the development of the clinical trial protocol and associated investigational plans, including the monitoring plan, and may also support efforts to manage risks during the conduct of a clinical investigation or across a product's development program. Therefore, sponsors should document their risk assessment, including methodologies used for the risk assessment, conclusions from the risk assessment, and how the assessment was used to make decisions on the management of the risks identified. Sponsors should reevaluate their risk assessment and management processes throughout the conduct of the investigation as issues are identified, and monitoring plans (and if necessary, protocol design) should be revised when needed to continue to protect the rights, safety, and welfare of participants in the clinical investigation and the integrity of data generated during the investigation. When new risks are identified, their potential impact across that product development program, as well as on the sponsor's other product development programs, as appropriate, should be considered. If a risk-based monitoring approach is being used, FDA may request, during inspection, documentation of the sponsor's initial risk assessment, and any relevant updated risk assessments.

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 or eliminated.

Q2. Should sponsors monitor only risks that are important and identified during their initial risk assessment as likely to occur?

No. Sponsors should monitor the important and likely risks identified during their initial risk assessment, and they should also monitor for additional risks detected during the conduct of the clinical investigation that were not identified before the investigation began. For example, if an

¹⁰ See the ICH guidance for industry *Q9 Quality Risk Management* (June 2006).

¹¹ IEC 31010:2019 *Risk Management — Risk Assessment Techniques*.

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additional risk is detected during the investigation that was not anticipated and that risk could impact the conduct, collection, or reporting of critical processes, procedures, or data, that risk should be addressed.

Sponsors should also monitor risks that are less likely to occur, but that could have a significant impact on the quality of the investigation including on the rights, safety, and welfare of trial participants.

Monitoring plans should consider important risks and should be sufficiently comprehensive so that risks that arise during the investigation that were not anticipated can be identified and addressed.

Monitoring plans should take into account important risks identified in the initial risk assessment while also enabling sponsors to identify and address risks that arise during the investigation that were not anticipated. Monitoring plans should therefore be revised, as needed, if new information about risks becomes available.

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

As described in detail in the 2013 RBM guidance, during the risk assessment, sponsors should consider a range of factors to inform the development of the monitoring plan. While some factors described below (see bulleted factors) relate to the investigation overall, other factors relate to specific clinical sites; therefore, FDA recommends that the monitoring plan be organized to account for both the overall investigation and site-specific risks, recognizing that some mitigating activities may not be relevant for all sites.

Sponsors should consider:

- How well established the clinical investigation infrastructures are at different clinical sites
- Relative experience of the clinical investigator and of the sponsor with the clinical investigator
- Electronic data capture to be utilized¹²
 - Use of electronic data capture (EDC) systems with the capability to assess quality metrics (e.g., missing data, data error rates, protocol violations) in real time could help identify potentially higher risk sites for the purpose of targeting sites in need of more intensive monitoring.

¹² See the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013) and the revised draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* (March 2023). When final, this guidance will represent FDA's current thinking on this topic.

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- Stage of the study (e.g., for a complex study, more intensive and on-site monitoring might be warranted early, but once procedures are established, less intensive monitoring might suffice)
- Quantity, extent, complexity, and criticality of data to be collected

When developing the monitoring plan, sponsors should determine the types and intensity of monitoring activities best suited to address the identified risks while also facilitating identification of unanticipated risks. When suitable, statistical and analytical methods to monitor critical data in a centralized manner may be particularly advantageous. Monitoring activities should evolve based on additional issues and risks that may be identified during the conduct of the investigation. The types and intensity of monitoring activities also should be proportionate to the risks to participants' rights, safety, and welfare and to data integrity inherent in the investigation.

While source data verification (SDV)¹³ may be a part of a risk-based monitoring approach, the extent to which SDV is used should be guided by the sponsor's risk assessment process and focused on critical study data and processes. Focusing more monitoring activities on risks to the most critical data elements and processes should enable sponsors to achieve the objective of conducting a quality clinical investigation, including human subject protection and data integrity, without necessarily having to conduct frequent routine visits to all clinical sites and extensive SDV.

FDA also recommends that sponsors consider the following additional factors:

- Adequate staffing to support the clinical investigation. Specific considerations include relevant study-specific trainings of site staff, the experience and qualifications of the research coordinator and specialized research professionals working with and under the direction of the clinical investigator, and turnover of personnel at the investigational site or among monitoring staff.
- Location where participants 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 participant's home), including when all activities take place at locations remote from the investigator without the need for a physical clinical site.
 - 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).

¹³ For the purposes of this guidance, SDV refers to the process of confirming that study data included in efficacy/effectiveness and safety analyses reflect source data obtained during the clinical investigation.

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- Benefit of an early monitoring visit or other early monitoring activities
 - By scheduling an early monitoring visit (for example, soon after the first few trial participants enroll in the investigation) or by carrying out other early monitoring activities, sponsors can help ensure early in the investigation that the protocol is being followed and procedures are being performed correctly at clinical sites. Additionally, if early monitoring identifies issues, such as a number of protocol deviations, corrective actions can be implemented sooner. For complex studies, early and more intensive on-site monitoring might be warranted.

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

Centralized monitoring is a systematic analytical evaluation of study conduct across multiple clinical sites, carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians). Centralized monitoring may allow sponsors to (1) review study-wide data for inconsistencies or omissions; (2) perform activities such as data checks, for completeness and consistency; (3) verify source data; (4) ensure that institutional review board and informed consent documents are current; and (5) determine which clinical sites need on-site review.

Depending on how centralized monitoring is used, incorporating centralized monitoring as a part of a risk-based approach to monitoring may help ensure the quality of a clinical investigation by allowing sponsors to aggregate and compare site data and detect potential anomalies more quickly. By reviewing study data and metadata¹⁴ in real time across clinical sites, sponsors may be able to identify quality issues, such as delays in entering data or incomplete entries, earlier than when relying on on-site monitoring alone. Sites with multiple issues detected through centralized monitoring, such as delays in assessments or missing assessments, may also provide an early signal that the sponsor should promptly determine whether there is a need for a site visit and corrective actions to minimize the likelihood of similar issues 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 2013 RBM guidance, for investigations that include blinding of interventions and/or outcome assessments, ensuring that the blinding of the investigation is maintained is a critical process that sponsors should consider in their risk assessment.

Specific risks to the maintenance of the blinding that are identified during the risk assessment should be mitigated in advance of investigation initiation, when feasible. In addition, identifying and tracking deviations during the conduct of the investigation that could result in unintentional

¹⁴ For the purposes of this guidance, metadata is structured information that describes, explains, or otherwise makes it easier to retrieve, use, or manage data. Metadata provides the contextual information required to understand data. See the guidance for industry *Data Integrity and Compliance with Drug CGMP: Questions and Answers* (December 2018).

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unblinding of treatment assignment should be considered as a part of the monitoring plan, to ensure that appropriate blinding is maintained at clinical sites and by the sponsor, organizations such as contract research organizations and other vendors. For example, in a blinded investigation that requires the site staff personnel dispensing the test article to know whether the test article is the investigational product or the placebo, the adequacy of maintaining the blinding for the remainder of the site staff should be monitored.

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

B. Monitoring Plan Content

Q6. What elements should sponsors include in monitoring plans?

Monitoring plans should be developed for each investigation based on the risk assessment for that investigation. Monitoring plans should address both study-specific and site-specific risks. Monitoring plans also should be designed to enable the management of anticipated and unanticipated risks. As stated earlier, sponsors are encouraged to develop risk-based monitoring plans that emphasize critical risks with the greatest potential to adversely affect investigation quality, including (1) the rights, safety, and welfare of participants in a clinical investigation; and (2) the collection or analysis of critical clinical data such as safety and efficacy/effectiveness endpoints. Section IV.D of the 2013 RBM guidance discusses in detail the recommended components of a monitoring plan. Sponsors also may reference in the monitoring plan other clinical trial management plans used for risk management (e.g., a data management plan) that address the components recommended in the 2013 RBM guidance rather than repeat the same information in the monitoring plan.

In addition to the components recommended in the 2013 RBM guidance, FDA recommends that monitoring plans also include the following components, which will help explain how the sponsor intends to address the risks that could affect the clinical investigation:

- A description of the investigation design, including the blinding and randomization procedures, if applicable
- Processes for confirming that randomization is performed according to the protocol and investigational plan or plans
- The sampling plan or plans that will be used to identify the specific records and data that will be monitored, including (1) the rationale for how the sampling plan provides a representative picture of the overall information and (2) how the sampling plan will be implemented
- A description of the types of issues identified through monitoring that would trigger immediate issue escalation

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- An approach for determining whether (1) an important issue that is detected at a clinical site may also be present at other clinical sites; and (2) the finding suggests a systemic problem with the protocol or associated investigational plans that requires remediation

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 should be thoroughly evaluated in a timely manner at the appropriate levels (for example, sponsor, clinical sites) as described in the monitoring plan. A root cause analysis followed by appropriate corrective and preventive actions should be undertaken promptly to reduce the impact of the identified issue on the rights, safety, and welfare of participants in the clinical investigation and/or the integrity of the data. Additionally, the risk assessment and monitoring plan should be reviewed and revised, as needed, to help ensure the risk of recurrence is decreased, or if possible, eliminated. In instances in which corrective actions modify study processes, the protocol and/or associated investigational plans should be amended to reflect changed processes. Related systemic issues should be identified and resolved promptly to help ensure that investigation quality, including the rights, safety, and welfare of investigation participants and data integrity, is maintained.

Examples of preventive and corrective actions that may be warranted include but are not limited to (1) improved training for the clinical investigator and site staff; (2) halting enrollment at a clinical site pending resolution of identified issues; (3) clarifying or revising the protocol and/or other related investigational plans and documents; and/or (4) modifying vendor service agreements to ensure adequate trial support.

Significant issues identified through monitoring and oversight activities and the actions to be taken should be documented and communicated to the appropriate parties, which may include, but are not limited to (1) sponsor management; (2) sponsor teams; (3) clinical sites; (4) institutional review boards; (5) other relevant parties (for example, DMCs and relevant contract research organizations); and (6) applicable regulatory agencies, including FDA, when appropriate.

See the 2013 RBM guidance for additional recommendations regarding follow-up and communication of significant issues identified via monitoring.

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

As described in the 2013 RBM guidance, documentation of monitoring activities should generally include the following: (1) the date of the activity; (2) the individuals 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, and/or other deficiencies identified; and (5) a description of any actions taken, to be taken, or recommended (see section V

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of the 2013 RBM guidance for additional information). Such documentation should include the results of monitoring activities in sufficient detail to allow verification of adherence to the monitoring plan describing those activities. Monitoring activities to be documented should include on-site and remote monitoring of clinical sites and centralized monitoring across clinical sites.

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