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

## *DRAFT GUIDANCE*

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1 **A Risk-Based Approach to Monitoring of Clinical Investigations**  
2 **Questions and Answers**  
3 **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

12  
13  
14  
15 **I. INTRODUCTION**  
16

17 This document provides guidance on risk-based approaches to monitoring investigational studies  
18 of human drug and biological products, medical devices, and combinations thereof. This  
19 guidance contains recommendations on planning a monitoring approach, developing the content  
20 of a monitoring plan, and addressing and communicating monitoring results. This guidance  
21 expands on the guidance for industry *Oversight of Clinical Investigations – A Risk-Based*  
22 *Approach to Monitoring* (August 2013) (the RBM guidance)<sup>2</sup> by providing additional guidance  
23 to facilitate sponsors' implementation of risk-based monitoring.  
24

25 In general, FDA's guidance documents do not establish legally enforceable responsibilities.  
26 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only  
27 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
28 the word *should* in Agency guidances means that something is suggested or recommended, but  
29 not required.  
30

31  
32 **II. BACKGROUND**  
33

34 Sponsors of clinical investigations involving human drugs, biological products, medical devices,  
35 and combinations thereof are required to provide oversight to ensure adequate protection of the  
36 rights, welfare, and safety of human subjects and the quality of the data submitted to FDA.<sup>3</sup>

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<sup>1</sup> 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.

<sup>2</sup> 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>.

<sup>3</sup> 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).

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37 FDA’s regulations require sponsors to monitor the conduct and progress of their clinical  
38 investigations.<sup>4,5,6</sup> The regulations are not specific about how sponsors are to conduct such  
39 monitoring; therefore, a range of approaches to monitoring are compatible with the regulations.  
40

41 The RBM guidance discusses the importance of identifying critical data and processes necessary  
42 for human subject protection and integrity of the investigation, conducting a risk assessment, and  
43 developing a monitoring plan specific to the investigation. The RBM guidance also encourages  
44 sponsors to tailor monitoring plans to the needs of the investigation, describes factors to consider  
45 in developing a monitoring plan, and provides examples of monitoring methods and techniques.  
46

47 FDA believes risk-based monitoring is an important tool to allow sponsors to identify and  
48 address issues during the conduct of clinical investigations. FDA’s experience since finalizing  
49 the RBM guidance in 2013 suggests that additional guidance would be beneficial regarding  
50 FDA’s recommendations for planning a monitoring approach, developing the content of  
51 monitoring plans, and addressing and communicating monitoring results. The following  
52 questions and answers are intended to assist sponsors in planning and conducting risk-based  
53 approaches to monitoring.  
54

55

### **III. QUESTIONS AND ANSWERS**

57

#### **A. Monitoring Approach**

59

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

61

62  
63 Consistent with the RBM guidance, sponsors should identify and perform a risk assessment on  
64 those critical data and processes that are necessary for human subject protection and integrity of the  
65 investigation.  
66

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

---

<sup>4</sup> 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, ...”

<sup>5</sup> See also 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

<sup>6</sup> 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*.

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

76  
77 The monitoring plan should include information regarding the identified risks and how the  
78 monitoring methods will address those risks. (See Q6 for further details.) The inclusion of these  
79 components in the monitoring plan will enhance the utility of the plan by providing a clear  
80 explanation of the identified risks and how they will be monitored, managed, and mitigated.

81  
82 **Q2. Should sponsors monitor only risks that are important and likely to occur?**

83  
84 A risk-based approach to monitoring should focus sponsor oversight activities on preventing or  
85 mitigating important and likely risks to investigation quality, including risks to human subject  
86 protection and data integrity. Sponsors also should consider monitoring risks that are less likely  
87 to occur but could have a significant impact on the investigation quality. Sponsors should  
88 determine the types and intensity of monitoring activities best suited to address the identified  
89 risks. In addition, monitoring plans should permit monitoring activities to evolve based on  
90 additional issues and risks that may be identified during the conduct of an investigation.

91  
92 **Q3. What factors should sponsors consider when determining the timing, types, frequency, and extent of monitoring activities?**

93  
94  
95 As described in detail in the RBM guidance, factors sponsors should consider include the  
96 following:

- 97  
98
- Complexity of the study design
  - 99
  - 100 • Types of study endpoints
  - 101
  - 102 • Clinical complexity of the study population (for example, study populations that are  
103 seriously ill, have multiple co-morbidities, or are more vulnerable and may require more  
104 intensive monitoring and consideration of on-site monitoring visits to be sure appropriate  
105 protection is being provided)
  - 106
  - 107 • Geographic location of clinical investigator (CI) sites where there may be differences in  
108 standards of medical practice or less established clinical trial infrastructure
  - 109
  - 110 • Relative experience of the CI and of the sponsor with the CI
  - 111
  - 112 • Electronic data capture to be utilized<sup>7</sup>
  - 113
  - 114 • Relative safety of the investigational product
  - 115

---

<sup>7</sup> See the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013).

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116 • Stage of the study (progress of the study)

117

118 • Quantity of data

119

120 FDA also recommends that sponsors consider the following additional factors:

121

122 • Workload at the CI site

123

124 • Turnover of personnel at the CI site or among monitoring staff

125

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

128

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

132

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

137

138 • Benefit of an early monitoring visit or other early monitoring activities

139

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

146

147 • Experience and qualifications of the research coordinator

148

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

153

154 • Safety profile of the investigational product

155

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

159

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- 160 • Characteristics of data to be collected
- 161
- 162 – When developing a monitoring plan, sponsors should consider the amount and
- 163 complexity of the data collected.
- 164

### 165 **Q4. How can a risk-based approach to monitoring that includes centralized monitoring**

### 166 **help minimize missing data, protocol violations, or protocol deviations?**

### 167

168 There may be situations in which poor trial conduct or adherence to the investigational plan

169 causes or contributes to incomplete data collection. Therefore, by reviewing important

170 investigation activities, in real-time across CI sites, sponsors may be able to identify the reasons

171 for missing data, protocol violations, or protocol deviations and take corrective actions to

172 minimize the likelihood of these occurring during the remainder of the clinical investigation.

173

### 174 **Q5. Should the risk-based monitoring approach include processes to ensure that**

### 175 **appropriate blinding is maintained?**

### 176

177 Yes. As identified in the RBM guidance, for investigations in which blinding will be used for

178 interventions and/or outcome assessments, ensuring that the investigation blind is maintained is a

179 critical process that sponsors should consider in their risk assessment.

180

181 Specific risks to the maintenance of the blind that are identified during the risk assessment

182 should be mitigated in advance of investigation initiation, when feasible. In addition, identifying

183 and tracking deviations during investigation conduct that could result in unintentional unblinding

184 of treatment assignment should be considered as a part of the monitoring plan to ensure that

185 appropriate blinding is maintained at CI sites and by the sponsor. For example, in a blinded

186 investigation that requires a site staff member to be unblinded to administer the test article, the

187 site processes for maintaining the blind for the remainder of the site staff and the sponsor should

188 be monitored.

189

190 FDA recognizes that Data Monitoring Committees (DMC) may access unblinded data as

191 described in the DMC Charter. (For additional information about DMC, see the guidance for

192 clinical trial sponsors *Establishment & Operation of Clinical Trial Data Monitoring Committees*

193 (March 2006.)

194

## 195 **B. Monitoring Plan Content**

## 196

### 197 **Q6. What elements should sponsors include in monitoring plans?**

### 198

199 The following elements (discussed in detail in section IV.D of the RBM guidance) are

200 summarized here to assist sponsors in developing monitoring plans:

201

- 202 • A synopsis of the study
- 203
- 204 • Study objectives
- 205



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- 206 • Identification of critical data and study procedures
- 207
- 208 • Trial-specific risks to be addressed by monitoring
- 209
- 210 • Monitoring methods and rationale for use of the monitoring methods, including how the
- 211 methods address identified risks
- 212
- 213 • Criteria for determining the timing, types, frequency, and extent of monitoring activities
- 214
- 215 • Specific activities necessary for each monitoring method used
- 216
- 217 • Definitions of events or results that would trigger changes in monitoring activities (for
- 218 example, how protocol deviations may be monitored as events that would trigger changes
- 219 in monitoring activities)
- 220
- 221 • Identification of protocol deviations and failures that, if occurred, would affect study
- 222 integrity, and how they will be recorded, tracked, and reported
- 223
- 224 • Format, content, timing, and archiving requirements for documentation of monitoring
- 225 activities
- 226
- 227 • Processes for communicating routine monitoring results to appropriate parties
- 228
- 229 • Processes for immediate reporting of significant monitoring issues to appropriate parties
- 230
- 231 • Processes for appropriate communication from study management and other stakeholders
- 232 to monitors
- 233
- 234 • Processes to address unresolved or significant issues identified by monitoring
- 235
- 236 • Processes to ensure that root cause analyses are conducted where important deviations are
- 237 discovered and that corrective and preventative actions are implemented
- 238
- 239 • Other quality management practices applicable to the clinical investigation (for example,
- 240 reference to other documents describing appropriate actions regarding non-compliance)
- 241
- 242 • Training for personnel who carry out monitoring activities
- 243
- 244 • Planned audits of monitoring activities
- 245
- 246 • Process for updating monitoring plans
- 247

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

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- 252 • A description of the investigation design and the blinding and randomization procedures,  
253 if applicable
- 254
- 255 • Processes for confirming that randomization is performed according to the protocol and  
256 investigational plan when randomization is identified as a risk to be addressed by  
257 monitoring
- 258
- 259 • Sampling plan(s) that will be used to identify the specific records and data that will be  
260 monitored, including the rationale for how the sampling plan provides a representative  
261 picture of the overall information, and how the sampling plan will be implemented
- 262
- 263 • A description of the types of significant issues identified through monitoring that would  
264 trigger immediate issue escalation
- 265
- 266 • An approach for determining if issues identified at a site also exist at other CI sites and an  
267 approach for correcting these issues
- 268

269 The monitoring plan should describe each of these items in sufficient detail. Sponsors also  
270 should reference related documents, when appropriate. Sponsors are encouraged to develop  
271 monitoring plans that emphasize critical risks that have the greatest potential to adversely affect  
272 investigation quality, including the rights, safety, and welfare of investigation subjects, and the  
273 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?**

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

287

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

291

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

297

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

300

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

303

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

312

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

317