

# Guidance for Industry Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

## *DRAFT GUIDANCE*

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Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Devices and Radiological Health (CDRH)  
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Procedural**

# Guidance for Industry

## Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

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1                                    **Guidance for Industry<sup>1</sup>**  
2                                    **Oversight of Clinical Investigations — A Risk-Based**  
3                                    **Approach to Monitoring**  
4  
5

6  
7 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current  
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to  
9 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of  
10 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA  
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call  
12 the appropriate number listed on the title page of this guidance.  
13

14  
15  
16 **I. INTRODUCTION**  
17

18 This guidance is intended to assist sponsors of clinical investigations in developing risk-based  
19 monitoring strategies and plans for investigational studies of medical products, including human  
20 drug and biological products, medical devices, and combinations thereof. The overarching goal  
21 of this guidance is to enhance human subject protection and the quality of clinical trial data. This  
22 guidance is intended to make clear that sponsors can use a variety of approaches to fulfill their  
23 responsibilities related to monitoring investigator conduct and the progress of investigational  
24 new drug (IND) or investigational device exemption (IDE) studies. This guidance describes  
25 strategies for monitoring activities that reflect a modern, risk-based approach that focuses on  
26 critical study parameters and relies on a combination of monitoring activities to oversee a study  
27 effectively. For example, the guidance specifically encourages greater use of centralized  
28 monitoring methods where appropriate.  
29

30 FDA's guidance documents, including this guidance, do not establish legally enforceable  
31 responsibilities. Rather, guidances describe the Agency's current thinking on a topic and should  
32 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
33 cited. The use of the word *should* in Agency guidances means that something is suggested or  
34 recommended, but not required.  
35

36 **II. BACKGROUND**  
37

38 Sponsors of clinical investigations are required to provide oversight to ensure adequate  
39 protection of the rights, welfare, and safety of human subjects and the quality and integrity of the

<sup>1</sup> This guidance has been prepared by the following components of the Food and Drug Administration: CDER's Division of Scientific Investigations in the Office of Compliance, CBER's Office of Compliance and Biologics Quality, CDRH's Office of Compliance, and CDER's Office of Medical Policy. FDA guidance documents are available on the FDA web site at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. FDA guidances are updated periodically; we recommend you check to make sure you have the most up-to-date version.

40 resulting data submitted to FDA.<sup>2</sup> In the past two decades, the number and complexity of  
41 clinical trials have grown dramatically. These changes create new challenges in clinical trial  
42 oversight such as increased variability in investigator experience, ethical oversight, site  
43 infrastructure, treatment choices, standards of health care,<sup>3</sup> and geographic dispersion. In light  
44 of these developments, FDA wishes to encourage more effective monitoring of clinical  
45 investigations, to ensure adequate protection of human subjects and the quality and integrity of  
46 clinical trial data.

47  
48 The regulations require sponsors of clinical investigations involving human drugs, biological  
49 products, medical devices, and combinations thereof to monitor the conduct and progress of their  
50 clinical investigations.<sup>4,5</sup> The regulations are not specific about how sponsors are to conduct  
51 monitoring of clinical investigations and, therefore, are compatible with a range of approaches to  
52 monitoring.

53  
54 FDA conducts on-site inspections of clinical investigators, sponsors, contract research  
55 organizations (CRO), and institutional review boards (IRB) to assess the protection and safety of  
56 subjects and to validate data submitted in new drug applications (NDAs), biologics license  
57 applications (BLAs), and device premarket approval (PMA) applications. However, it is not  
58 possible for FDA to conduct on-site assessments of every clinical investigator conducting studies  
59 involving FDA-regulated products, and most inspections take place after the study is complete.  
60 Thus, effective monitoring by sponsors is critical to the protection of human subjects and the  
61 conduct of high-quality studies. FDA is considering the need for additional guidance describing  
62 overarching quality risk management approaches to clinical trial oversight. Quality is a systems  
63 property that must be built into an enterprise and cannot be achieved by oversight or monitoring  
64 alone.

65  
66 We are aware that the term *monitoring* is used in different ways in the clinical trial context. It  
67 can refer to the assessment of clinical investigator conduct, oversight, and reporting of findings  
68 of a clinical trial; the ongoing evaluation of safety data and the emerging risk-benefit profile of  
69 an investigational product by a medical monitor; and the monitoring of internal sponsor and  
70 CRO processes and systems integral to proposing, designing, performing, recording, supervising,  
71 reviewing, or reporting clinical investigations.

72  
73 For purposes of this guidance, *monitoring* generally refers to the methods used by sponsors of  
74 investigational studies, or CROs delegated responsibilities for the conduct of such studies, to  
75 oversee the conduct of and reporting of data from clinical investigations, including appropriate  
76 investigator supervision of study site staff and third party contractors. The primary focus should  
77 be on the processes that are critical to protecting human subjects, maintaining the integrity of

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<sup>2</sup> 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).

<sup>3</sup> Glickman et al. *Ethical and Scientific Implications of the Globalization of Clinical Research*. NEJM. 360, 816-823 (2009).

<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> Also see 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.

78 study data, and compliance with applicable regulations. The findings should be used to correct  
79 investigator and site practices that could result in inadequate human subject protection and/or  
80 poor data quality.

81  
82 **A. Current Monitoring Practices**

83  
84 A survey conducted through the Clinical Trials Transformation Initiative (CTTI)<sup>6</sup> indicates that a  
85 range of practices has been used to monitor the conduct of clinical trials. These practices vary in  
86 intensity, focus, and methodology, and include centralized monitoring of clinical data by  
87 statistical and data management personnel; targeted on-site visits to higher risk clinical  
88 investigators (e.g., where centralized monitoring indicates problems at a site); and frequent,  
89 comprehensive on-site visits to all clinical investigator sites by company personnel or  
90 representatives (e.g., clinical monitors or clinical research associates).<sup>7</sup> See definitions of on-site  
91 and centralized monitoring in section IV.A.

92  
93 Despite this range of monitoring methods, periodic, frequent visits to each clinical investigator  
94 site to evaluate study conduct and review data for each enrolled subject remain the predominant  
95 mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the  
96 progress of clinical investigations. For major efficacy trials, companies typically conduct on-site  
97 monitoring visits at approximately four- to eight-week intervals,<sup>8</sup> at least partly because of the  
98 perception that the frequent on-site monitoring visit model, with 100% verification of all data, is  
99 FDA's preferred way for sponsors to meet their monitoring obligations. In contrast, academic  
100 coordinating centers, cooperative groups, and government organizations use on-site monitoring  
101 less extensively. For example, some government agencies and oncology cooperative groups  
102 typically visit sites only once every two or three years to qualify/certify clinical study sites<sup>9</sup> to  
103 ensure they have the resources, training, and safeguards to conduct clinical trials. FDA also  
104 recognizes that data from critical outcome studies (e.g., many National Institutes of Health-  
105 sponsored trials, Medical Research Council-sponsored trials in the United Kingdom,  
106 International Study of Infarct Survival,<sup>10</sup> and GISSI<sup>11</sup>), which had no regular on-site monitoring  
107 and relied largely on centralized and other alternative monitoring methods, have been relied on  
108 by regulators and practitioners.<sup>12</sup> These examples demonstrate that use of alternative  
109 monitoring approaches should be considered by all sponsors, including commercial sponsors,  
110 when developing risk-based monitoring strategies and plans.

111  
112

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<sup>6</sup> CTTI is a public-private partnership involving FDA, academia, industry representatives, patient and consumer representatives, professional societies, investigator groups, and other government agencies, initiated in 2008. A significant part of CTTI's mission is to identify monitoring practices that through broad adoption will increase the quality and efficiency of clinical trials.

<sup>7</sup> CTTI Workstream 1 work product (May 2010). Available at:

<https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/monitoring-project-workstream-1>.

<sup>8</sup> PhRMA White Paper on Acceptable Approaches for Clinical Trial Monitoring, March 2009.

<sup>9</sup> *Id.*

<sup>10</sup> Califf et al. *Developing Systems for Cost-Effective Auditing of Clinical Trials*. *Controlled Clinical Trials* 18, 651-660 (1997).

<sup>11</sup> Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico- Italian group for the study of the survival of myocardial infarction.

<sup>12</sup> Temple, R. *Policy developments in regulatory approval*. *Statistics in Medicine* 21: 2939-2948 (2002).

113 **B. Other FDA Guidance on Monitoring**  
114

115 FDA provided guidance on monitoring of clinical investigations in 1988.<sup>13</sup> That guidance,  
116 which was recently withdrawn, stated that the “most effective way” to monitor an investigation  
117 was to “maintain personal contact between the monitor and the investigator throughout the  
118 clinical investigation.”<sup>14</sup> At the time the guidance was issued, sponsors had only limited ways to  
119 effect meaningful communication with investigators other than through on-site visits.  
120

121 The 1996 International Conference on Harmonisation (ICH) guidance on good clinical practice  
122 (ICH E6) addressed monitoring more recently. ICH E6 provides for flexibility in how trials are  
123 monitored, advising sponsors to consider “the objective, purpose, design, complexity, blinding,  
124 size, and endpoints of a trial” in determining the extent and nature of monitoring for a given  
125 trial.<sup>15</sup> Although the ICH guidance specifically provides for the possibility of reduced, or even  
126 no, on-site monitoring, it also makes clear that it would be appropriate only in exceptional  
127 circumstances to rely entirely on centralized monitoring.  
128

129 FDA’s 1998 guidance on Providing Clinical Evidence of Effectiveness for Drug and Biological  
130 Products, although not focused on monitoring, also suggests more flexibility in discussing what  
131 would be considered acceptable monitoring in the context of data standards for published studies  
132 that had little or no on-site monitoring. For example, the 1998 guidance states that FDA will  
133 “accept different levels of documentation of data quality as long as the adequacy of the scientific  
134 evidence can be assured.”<sup>16</sup> Section III.B of that guidance describes criteria (e.g. prospective  
135 plan to assure data quality) for reliance on data from studies that had alternative approaches to  
136 quality control and less intensive on-site monitoring. Additionally, the guidance specifically  
137 acknowledges that there are many credible and valuable studies conducted by government or  
138 independent groups that had very little on-site monitoring, but have addressed data quality in  
139 other ways (e.g., close control of and review of documentation and extensive guidance and  
140 planning efforts with investigators).  
141

142 **C. Rationale for Facilitating Risk-Based Monitoring**  
143

144 Many sponsors have understood these guidances as contributing to the notion that FDA expects  
145 sponsors to conduct frequent on-site monitoring and 100% data verification for all trials,  
146 regardless of their design and complexity. Because existing and recently withdrawn guidance  
147 may not clearly reflect FDA’s current recommendations regarding monitoring practices,  
148 we recognize that we must clearly articulate our recognition of the value of alternative  
149 approaches to facilitate change in industry’s monitoring practices.  
150

151 There is a growing consensus that risk-based approaches to monitoring, such as focusing on the  
152 most critical data elements, are more likely to ensure subject protection and overall study quality,  
153 and will permit sponsors to monitor the conduct of clinical investigations more effectively than

---

<sup>13</sup> Guidance for industry: *Guideline for the Monitoring of Clinical Investigations*, January 1988.

<sup>14</sup> *Id.*

<sup>15</sup> Guidance for industry, *E6 Good Clinical Practice: Consolidated Guidance*, 1996, section 5.18.3.

<sup>16</sup> Guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (1998), see section III.

154 routine visits to all clinical sites and 100% data verification.<sup>17,18,19,20</sup> For example, incorporation  
155 of centralized monitoring practices, where appropriate, should improve a sponsor's ability to  
156 ensure the quality and integrity of clinical trial data. Several publications suggest that data  
157 anomalies (e.g., fraud, including fabrication of data, and other non-random data distributions)  
158 may be more readily detected by centralized monitoring techniques than by on-site monitoring.<sup>21,</sup>  
159<sup>22,23</sup> In addition, source data verification and other activities traditionally performed by on-site  
160 monitoring can now often be accomplished remotely, as both trial data and source data typically  
161 become part of the central submission. These electronic data capture (EDC) systems are making  
162 it possible to implement centralized monitoring methods that can enable decreased reliance on  
163 on-site monitoring. This guidance is therefore intended to clarify that risk-based monitoring,  
164 including the appropriate use of centralized monitoring and technological advances (e.g., e-mail,  
165 webcasts, and online training modules), can meet statutory and regulatory requirements under  
166 appropriate circumstances.

#### 167 **D. Steps FDA is Taking to Facilitate Wider Use of Alternative Monitoring Approaches**

170 The Agency also is initiating operational measures to ensure that its review, compliance, and  
171 other functions reflect this view of monitoring. Specifically, FDA:

- 173 • Has withdrawn the 1988 guidance on monitoring of clinical investigations
- 174 • Is issuing this draft guidance encouraging risk-based monitoring approaches, including  
175 adoption of alternative monitoring methods
- 176 • Will ensure that the bioresearch monitoring compliance program guidance manuals (CPGMs)  
177 for sponsors, CROs, and monitors (CPGM 7348.810)<sup>24</sup> and for clinical investigators and  
178 sponsor-investigators (CPGM 7348.811)<sup>25</sup> are compatible with the approaches described in  
179 this guidance
- 180 • Will ensure that all affected program areas within FDA are aware of the goals and purposes  
181 of this guidance and its compatibility with current CPGMs
- 182 • Will consider establishing processes within CDER for sponsors to voluntarily and  
183 prospectively submit and receive feedback on proposed monitoring plans (see section  
184 IV.D.4). Sponsors of IDE studies wishing to solicit feedback on their monitoring procedures

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<sup>17</sup> PhRMA White Paper on Acceptable Approaches for Clinical Trial Monitoring, March 2009.

<sup>18</sup> FDA, Concept Paper: Quality in FDA-Regulated Clinical Research; Background to HSP/BIMO Workshop 5/10-5/11/07, (4/26/07).

<sup>19</sup> Brosteanu et al. *Risk analysis and risk adapted on-site monitoring in noncommercial clinical trials*. Clin Trials. 6, 585-595 (2009).

<sup>20</sup> Tantsyura et al. *Risk-based Source Data Verification Approaches: Pros and Cons*. DIA J. 44, 745-756 (2010).

<sup>21</sup> PhRMA White Paper on Acceptable Approaches for Clinical Trial Monitoring, March 2009.

<sup>22</sup> Baigent et al. *Ensuring trial validity by data quality assurance and diversification of monitoring methods*. Clin Trials. 5, 49-55 (2008).

<sup>23</sup> Buyse et al. *The Role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials*. Statistics in Medicine. 18, 3435-51 (1999).

<sup>24</sup> CPGM 7348.810: Sponsors, Contract Research Organizations and Monitors (March 22, 2011), available at: <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm>.

<sup>25</sup> CPGM 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008), available at: <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm>.



185 prior to the submission of the IDE application may either submit a pre-IDE, or contact  
186 CDRH's Division of Bioresearch Monitoring.<sup>26</sup>

187  
188 This draft guidance strongly encourages sponsors to tailor monitoring plans to the needs of the  
189 trial (see section IV). FDA recognizes that this draft guidance places greater emphasis on  
190 centralized monitoring than was envisioned at the time ICH E6 was finalized. However, FDA  
191 considers the approach to monitoring described in this draft guidance as consistent with ICH E6.  
192 FDA believes it is reasonable to conclude that the flexibility described in ICH E6 was intended  
193 to permit innovative new approaches to improve the effectiveness of monitoring: notably, the  
194 advancement in EDC systems enabling centralized access to both trial and source data and the  
195 growing appreciation of the ability of statistical assessments to identify clinical sites that require  
196 additional training and/or monitoring. We expect that the pharmaceutical and device industries  
197 will, for the foreseeable future, continue to use some amount of on-site monitoring. Therefore,  
198 as per ICH E6, the complete absence of on-site monitoring will likely continue to be unusual.  
199

### 200 **III. FACTORS THAT INFLUENCE STUDY QUALITY AND INTEGRITY**

201  
202 Although the focus of this guidance is on monitoring the oversight and conduct of, and reporting  
203 of data from, clinical investigations, FDA considers monitoring to be just one component of a  
204 multi-factor approach to ensuring the quality and integrity of clinical investigations.<sup>27</sup> Many  
205 other factors contribute to the quality and integrity of a clinical investigation. The most  
206 important tool for ensuring human subject protection and high-quality data is a well-designed  
207 and articulated protocol.<sup>28</sup> A poorly designed or ambiguous protocol or case report form (CRF)  
208 may introduce systemic errors that can render a clinical investigation unreliable despite rigorous  
209 monitoring. Study-specific training of investigators, other site staff, and monitors also  
210 contributes significantly to study quality (see sections IV.D.4. and VI.A).  
211

212 The following sections reflect FDA's current thinking on monitoring and include  
213 recommendations on how to devise and implement a study-specific monitoring plan as well as  
214 how to document monitoring activities. FDA acknowledges that there are limited empirical data  
215 to support the utility of the various methods employed to monitor clinical investigations (e.g.,  
216 superiority of one method versus another), including data to support on-site monitoring.<sup>29</sup> As a  
217 result, the recommendations are based, in part, on FDA's experience from the review of  
218 protocols during the IND/IDE phase, data submitted in pre-approval applications, results of  
219 inspections conducted to ensure human subject protection and data integrity, and information  
220 obtained from public outreach efforts conducted under the auspices of the CTTI.  
221

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<sup>26</sup> CDRH regulations (21 CFR 812.25(e)) currently require that written monitoring procedures be submitted as part of the IDE application.

<sup>27</sup> FDA is considering the need for additional guidance describing overarching quality risk management approaches to clinical trial oversight.

<sup>28</sup> Sponsors are encouraged to consult the appropriate review division within FDA's medical product centers with questions about quality aspects of clinical trial design.

<sup>29</sup> Two studies are on-going as of December 2010 that compare the effectiveness of on-site to alternative (e.g., centralized) monitoring methods (OPTIMON study (<https://ssl2.isped.u-bordeaux2.fr/optimon/Default.aspx>) and ADAMON study (<http://ctj.sagepub.com/content/early/2009/11/06/1740774509347398.full.pdf>)).

222 **IV. GENERAL MONITORING RECOMMENDATIONS**

223  
224 No single approach to monitoring is appropriate or necessary for every clinical trial. FDA  
225 recommends that each sponsor design a monitoring plan that is tailored to the specific human  
226 subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would  
227 include a mix of centralized and on-site monitoring practices. The monitoring plan should  
228 identify the various methods intended to be used and the rationale for their use (see section IV.D  
229 for recommendations on the components of a monitoring plan).<sup>30</sup>

230  
231 **A. Types of Monitoring**

232  
233 This section is intended to assist sponsors in identifying and designing monitoring practices  
234 appropriate to a given clinical trial. It describes some of the capabilities and limitations of on-  
235 site and centralized monitoring processes and factors to consider in determining which  
236 monitoring practices may be appropriate for a given clinical trial.

237  
238 *1. On-Site Monitoring*

239  
240 *On-site monitoring* is an in-person evaluation carried out by sponsor personnel or  
241 representative(s) at the site(s) at which the clinical investigation is being conducted. On-site  
242 monitoring can identify data entry errors (e.g., discrepancies between source records and CRFs)  
243 and missing data in source records or CRFs; provide assurance that study documentation exists;  
244 assess the familiarity of the site's study staff with the protocol and required procedures; and  
245 assess compliance with the protocol and investigational product accountability. On-site  
246 monitoring can also provide a sense of the quality of the overall conduct of the trial at a site (e.g.,  
247 attention to detail, thoroughness of study documentation, appropriate delegation of study tasks,  
248 and appropriate investigator supervision of site staff performing critical study functions).  
249 Therefore, on-site monitoring ordinarily should be devoted to assessing the critical study data  
250 and processes and evaluating significant risks and potential site non-compliance identified  
251 through other sponsor oversight activities. On-site monitoring is particularly critical early in a  
252 study, especially if the protocol is complex, and includes novel procedures with which  
253 investigators may be unfamiliar. Findings at the site may lead to training efforts both at the site  
254 visited and elsewhere (see section VI.A).

255  
256 *2. Centralized Monitoring*

257  
258 *Centralized monitoring* is a remote evaluation carried out by sponsor personnel or  
259 representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location  
260 other than the site(s) at which the clinical investigation is being conducted. Centralized  
261 monitoring processes can provide many of the capabilities of on-site monitoring as well as  
262 additional capabilities. Centralized monitoring processes should be used to the extent  
263 appropriate and feasible to achieve the following:

---

<sup>30</sup> Sponsors of significant risk device studies are required under 21 CFR 812.25(e) to submit and maintain written procedures for monitoring.

- 265 • Replace on-site monitoring for monitoring activities that can be done as well or better  
266 remotely (e.g., standard checks of range, consistency, and completeness of data and checks  
267 for unusual distribution of data within and between study sites, such as too little variance)<sup>31</sup>
- 268 • Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data  
269 anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other  
270 sites)
- 271 • Augment on-site monitoring by performing monitoring activities that can only be  
272 accomplished using centralized processes (e.g., statistical analyses to identify data trends not  
273 easily detected by on-site monitoring)
- 274 • Monitor data quality through routine review of submitted data in real-time to identify missing  
275 data, inconsistent data, data outliers, and potential protocol deviations that may be indicative  
276 of systemic and/or significant errors in data collection and reporting at a site
- 277 • Verify source data remotely, provided that both source data and CRFs can be accessed  
278 remotely
- 279 • Conduct aggregate statistical analyses of study data to identify sites that are outliers relative  
280 to others and to evaluate individual subject data for plausibility and completeness
- 281 • Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates,  
282 high frequency of eligibility violations, and delays in reporting data), and clinical data to  
283 identify trial sites with characteristics correlated with poor performance or noncompliance
- 284 • Complete administrative and regulatory tasks (e.g., collecting and archiving regulatory  
285 documents).

286 FDA encourages greater reliance on centralized monitoring practices than has been the case  
287 historically, with correspondingly less emphasis on on-site monitoring. The extent to which  
288 centralized monitoring practices can be employed will depend to some extent on accessibility of  
289 electronic records and EDC systems. Sponsors who plan to rely on centralized monitoring  
290 processes should ensure that the processes and expectations for site record keeping, data entry,  
291 and reporting are well-defined and ensure timely access to clinical trial data and supporting  
292 documentation.<sup>32</sup> If a sponsor intends to rely heavily on centralized monitoring practices, it may  
293 still be advisable to conduct at least one on-site monitoring visit per site, preferably early in the  
294 conduct of the study, to evaluate site processes and controls for provision of data and source  
295 documents, particularly for trials intended to support marketing applications.  
296

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<sup>31</sup> Collins, Rory. (2010, October) *Quality Design of Clinical Trials*. Presentation at CTTI work stream 3 expert meeting. Available at: <https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/developing-effective-quality-systems-in-clinical-trials-an-enlightened-approach>.

<sup>32</sup> See FDA guidance documents regarding electronic records and signatures subject to 21 CFR part 11 (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126953.pdf>) and the use of computerized systems in clinical investigations. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>).

297 **B. Identify Critical Data and Processes to be Monitored**

298  
299 Sponsors should perform a risk assessment that generally considers the types of data to be  
300 collected in a clinical trial, the specific activities required to collect these data, and the range of  
301 potential safety and other human subject protection concerns that are inherent to the clinical  
302 investigation. Sponsors should consider the findings of the risk assessment when developing a  
303 monitoring plan. There is increasing recognition that some types of errors in a clinical trial are  
304 more important than others. For example, a low, but non-zero rate of errors in capturing certain  
305 baseline characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant  
306 illness) will not, in general, have a significant effect on study results. In contrast, a small number  
307 of errors related to study endpoints (e.g., not following protocol-specified definitions) can  
308 profoundly affect study results, as could failure to report rare but important adverse events.

309  
310 A study protocol should clearly identify those procedures and data that are critical to the  
311 reliability of the study findings. These generally should include:

- 312
- 313 • Data that are critical to the reliability of the study findings, specifically those data that  
314 support primary and secondary endpoints
  - 315 • Other data that are critical to subject safety, such as serious adverse events and events leading  
316 to discontinuation of treatment
  - 317 • Processes that underpin subject safety and ethical treatment, such as seeking appropriate  
318 medical consultation or scheduling extra visits in the event of specified clinical or laboratory  
319 findings
  - 320 • Processes that underpin the integrity of these data, such as blinding or referring specified  
321 events for adjudication

322 A sponsor's monitoring activities should focus on these critical measurements and on preventing  
323 important and likely sources of error in their collection and reporting. When devising an  
324 appropriate monitoring plan, the sponsor's risk assessment should consider the impact and  
325 likelihood of error and the extent to which error would be detectable for identified data and  
326 processes. The following types of data and processes should ordinarily be subject to more  
327 intensive (e.g., higher frequency and more comprehensive) monitoring:

- 328
- 329 • Conduct and documentation of procedures and assessments related to
    - 330 – critical study endpoints,
    - 331 – protocol-required safety assessments, and
    - 332 – evaluating, documenting, and reporting serious adverse events and unanticipated adverse  
333 device effects, subject deaths, and withdrawals, especially when a withdrawal may be  
334 related to an adverse event.
  - 335 • Adherence to protocol eligibility criteria intended to include only subjects from the targeted  
336 study population for whom the test article is most appropriate
  - 337 • Conduct and documentation of procedures for ensuring that the study blind is maintained,  
338 both at the site level and at the sponsor level, as appropriate

339 • Verification that initial informed consent was obtained appropriately, prior to any study-  
340 specific procedures

341 • Procedures for documenting appropriate accountability and administration of the  
342 investigational product (e.g., ensuring the integrity of randomization at the site level, where  
343 appropriate)

344  
345 Other types of data (e.g., covariate) and processes often may be monitored less intensively and  
346 frequently.

347

### 348 **C. Factors to Consider when Developing a Monitoring Plan**

349

350 A monitoring plan ordinarily should focus on the critical data and processes identified by the risk  
351 assessment. The types (e.g., on-site and/or centralized), frequency (e.g., early, for initial  
352 assessment and training versus throughout the study), and intensity (e.g., comprehensive (100%  
353 data verification) versus targeted or random review of certain data (less than 100% data  
354 verification)) of monitoring activities will depend to some extent on a range of factors,  
355 considered during the risk assessment, including the following:

356

357 • Complexity of the study design

358 More intensive monitoring approaches (e.g., increased frequency of review regardless of the type  
359 of monitoring approach selected and/or use of multiple monitoring approaches) may be  
360 necessary as study design complexity increases. Examples may include studies with adaptive  
361 designs, stratified designs, complex dose titrations, or multiple device placement or unblinded  
362 studies.

363 • Types of study endpoints

364 Endpoints that are more interpretative or subjective may require on-site visits to assess the  
365 totality of subject records and to review application of protocol definitions with the clinical  
366 investigator. More objective endpoints (e.g., death, hospitalization, or clinical laboratory values  
367 and standard measurements) may be more amenable to remote verification. Endpoints for which  
368 inappropriate subject withdrawal or lack of follow-up may impede study evaluation are likely to  
369 need more intensive monitoring to determine whether follow-up can be improved and to identify  
370 the reason(s) subjects are withdrawing.

371 • Clinical complexity of the study population

372 A study that involves a population that is seriously ill and/or vulnerable may require more  
373 intensive on-site monitoring to be sure appropriate protection is being provided.

374 • Geography

375 Sites in geographic areas where there are differences in standards of medical practice or subject  
376 demographics or there is a less established clinical trial infrastructure may require more intensive  
377 monitoring, including some level of on-site monitoring.

378 • Relative experience of the clinical investigator and of the sponsor with the investigator

379 Investigators who lack significant experience in conducting and overseeing investigations, using  
380 a novel or innovative medical device, or with the surgical procedure associated with medical

381 device use may benefit from more intensive monitoring and early mentoring. In addition, the  
382 relative experience of a sponsor with the clinical investigator may be a factor in determining an  
383 appropriate monitoring plan.

- 384 • Electronic data capture

385 Use of EDC systems with the capability to assess quality metrics (e.g., data error rates and  
386 protocol violations) in real-time could help identify potentially higher risk sites for the purpose  
387 of targeting sites in need of more intensive monitoring (e.g., an on-site monitoring visit).

- 388 • Relative safety of the investigational product

389 A study of a product that has significant safety concerns or for which there is no prior experience  
390 in human clinical trials (e.g., a phase 1 pharmaceutical investigation or a device feasibility study)  
391 may require more intensive monitoring to ensure appropriate investigator oversight of subject  
392 safety.

- 393 • Stage of the study

394 A tapered approach to monitoring may be used where appropriate, with more intensive  
395 monitoring at initiation and during early stages of a trial. For example, a tapered approach could  
396 be used for a complex study where more intensive and on-site monitoring might be required  
397 early, but once procedures are established, less intensive monitoring might suffice. Similarly, a  
398 tapered approach could be used for relatively inexperienced clinical investigators.

- 399 • Quantity of data

400 Some centralized monitoring tools may be more useful as the quantity of data collected  
401 increases.

402

## 403 **D. Monitoring Plan**

404

405 For each clinical trial, the sponsor should develop a monitoring plan that describes the  
406 monitoring methods, responsibilities, and requirements for the trial. The plan should provide  
407 those involved in monitoring with adequate information to effectively carry out their duties. All  
408 sponsor and CRO personnel who may be involved with monitoring, including those who review  
409 and/or determine appropriate action regarding potential issues identified through monitoring,  
410 should review the monitoring plan. The components of a monitoring plan might include the  
411 following:

412

### 413 *1. Description of Monitoring Approaches*

414

- 415 • A description of each monitoring method to be employed during the study and how it will be  
416 used to address important risks and ensure the validity of critical data
- 417 • Criteria for determining the timing, frequency, and intensity of planned monitoring activities
- 418 • Specific activities required for each monitoring method employed during the study, including  
419 reference to required tools, logs, or templates
- 420 • Definitions of events or results that trigger changes in planned monitoring activities for a  
421 particular clinical investigator.

422 For example, if it is determined that an investigator deviates significantly from other sites in  
423 making safety-related findings or other key safety metrics, the site should be considered for  
424 targeted on-site visits. Additional examples of potential triggers include suspected fraud,  
425 data outliers (e.g., in rate of enrollment, volume of protocol deviations, or quantity of adverse  
426 event/effect reporting), or delays in completing CRFs.<sup>33</sup>

- 427 • Identification of possible deviations or failures that would be critical to study integrity and  
428 how these are to be recorded and reported

429 For example, sponsors may wish to establish a specific mechanism for tracking and notifying  
430 key study personnel of deviations related to collection or reporting of data necessary to  
431 interpret the primary endpoint, regardless of which monitoring method identified a concern.  
432

433 The study monitoring plan should also describe how various monitoring activities will be  
434 documented, regardless of whether conducted on-site or centralized.  
435

## 436 2. *Communication of Monitoring Results*

- 437 • Format, content, timing, and archiving requirements for reports and other documentation of  
438 monitoring activities (see section V)
- 439 • Process for appropriate communication

  - 440 – of routine monitoring results to management and other stakeholders (e.g., CRO and data  
441 management),
  - 442 – of immediate reporting of significant monitoring issues to appropriate personnel, and
  - 443 – from study management and other stakeholders to monitors.  
444

445 For example, data management personnel may provide monitors with routine reports of  
446 outstanding CRFs or of common data queries at or across sites that may enable effective  
447 targeting of monitoring activities.  
448

## 449 3. *Management of Noncompliance*

- 450 • Process for addressing unresolved or significant issues (e.g., significant non-compliance with  
451 the investigational plan) identified by monitoring, whether at a particular site or across study  
452 sites  
453

454 FDA recommends that sponsors develop and include specific processes for addressing,  
455 investigating, and reporting suspected and/or confirmed data falsification.<sup>34</sup>

- 456 • Processes to ensure that root cause analyses are conducted where important deviations are  
457 discovered and that appropriate corrective and preventive actions are implemented to address  
458 issues identified by monitoring

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<sup>33</sup> CTTI Workstream 1 work product (May 2010) Available at:  
<https://www.trialtransformation.org/projects/effective-and-efficient-monitoring/monitoring-project-workstream-1>.

<sup>34</sup> See FDA's proposed rule on data falsification at: <http://edocket.access.gpo.gov/2010/pdf/2010-3123.pdf>.

- 459 • Other quality management practices applicable to the clinical investigation (e.g., reference to  
460 any other written documents describing appropriate actions regarding non-compliance)

461

462 4. *Training and Study-Specific Information*

463

- 464 • Description of any specific training required for personnel carrying out monitoring activities,  
465 including personnel conducting internal data monitoring, statistical monitoring, or other  
466 centralized review activities

467 Training should include principles of clinical investigations, critical protocol-specific  
468 requirements, the study monitoring plan, applicable standard operating procedures, and  
469 appropriate monitoring techniques.

- 470 • Planned quality monitoring to ensure that sponsor and CRO staff conduct monitoring  
471 activities in accordance with the monitoring plan, applicable regulations, guidance, and  
472 sponsor policies, procedures, templates, and other study plans.

473 For example, many companies have successfully implemented on-site co-monitoring visits  
474 (i.e., monitoring visits performed by both a study monitor and the monitor's supervisor or  
475 another evaluator designated by the sponsor or CRO) to evaluate whether monitors are  
476 effectively carrying out visit activities, in compliance with the study monitoring plan. These  
477 visits may be conducted either for randomly selected monitors or may be targeted to specific  
478 monitors, based upon questions arising from review of monitoring visit documentation.

- 479 • A brief description of the study, its objectives, and the critical data and study procedures,  
480 with particular attention to data and procedures that are unusual and require on-site training

481

482 A monitoring plan may reference existing policies and procedures (e.g., a standard operating  
483 procedure describing issue investigation and resolution). In this case, the sponsor should take  
484 appropriate steps to ensure that monitors, whether sponsor or CRO employees, are aware of and  
485 are trained on these policies and procedures as well as on the monitoring plan.

486

487 CDER intends to evaluate potential processes through which sponsors could voluntarily submit  
488 their monitoring plans to the appropriate review division and request feedback from the clinical  
489 trial oversight component for the Center.<sup>35</sup>

490

491 5. *Monitoring Plan Amendments*

492

493 Sponsors should consider what events may require review and revision of the monitoring plan  
494 and establish processes to permit timely updates where necessary. For example, a protocol  
495 amendment, change in the definition of significant protocol deviations, or identification of new  
496 risks to study integrity, could result in a change to the monitoring plan.

497

498

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<sup>35</sup> Sponsors of significant risk device studies are required under 21 CFR 812.25(e) to submit and maintain written procedures for monitoring.



499 **V. DOCUMENTING MONITORING ACTIVITIES**

500

501 Documentation of monitoring activities should include the following:

502

503 • The date of the activity and the individual(s) conducting it

504 • A summary of the data or activities reviewed

505 • A description of any noncompliance, potential noncompliance, data irregularities, or other  
506 deficiencies identified

507 • A description of any actions taken, to be taken, and/or recommended, including the person  
508 responsible for completing actions and the anticipated date of completion

509

510 Monitoring documentation should be provided to appropriate management in a timely manner  
511 for review or, as necessary, follow-up.

512

513 **VI. ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY**

514

515 A number of additional steps can be taken to ensure appropriate human subject protection and  
516 high data quality.

517

518 A fundamental component of ensuring quality monitoring is a sponsor's compliance with written  
519 monitoring plans and any accompanying procedures.

520

521 **A. Clinical Investigator Training and Communication**

522

523 Clinical trial monitors conducting on-site visits have historically played an important role in  
524 training the investigator and his/her staff during a study. On-site visits also have served as a  
525 primary means of providing feedback to investigators and study personnel on study conduct.  
526 Without meaningful training prior to the conduct of a study and of appropriate instruction during  
527 the study (e.g., when changes are made to the protocol), investigators and their staff may have  
528 difficulty carrying out a trial correctly.<sup>36</sup> Sponsors who plan less frequent or limited on-site  
529 monitoring should consider the following:

530

531 • On-site visits should include sufficient time for mentoring, feedback, and additional training,  
532 if needed, during the conduct of the study.

533 • It may be necessary to implement alternative training and communication methods  
534 (teleconferences, webcasts, or online training modules) for providing and documenting  
535 ongoing, timely training and feedback, as well as to provide notification of significant  
536 changes to study conduct or other important information.

537

538

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<sup>36</sup> Guidance for industry, *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*, October 2009, provides an overview of clinical investigators' responsibilities.

539 **B. Delegation of Monitoring Responsibilities to a CRO**

540  
541 If a sponsor of an IND study delegates the responsibility for ensuring proper monitoring to a  
542 CRO, FDA regulations (21 CFR 312.52) require the written transfer of any obligations from a  
543 sponsor to a CRO and require the CRO to comply with the regulations.<sup>37</sup> Although sponsors can  
544 transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the  
545 work completed by the CRO(s) who assume this responsibility.

546  
547

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<sup>37</sup> The regulations for investigational device exemptions (21 CFR 812) do not contain a provision for delegation to a contract research organization.