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Guidance for Industry

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

U.S. Department of Health and Human Services
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)
Office of Good Clinical Practice (OGCP)
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Guidance for Industry

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**U.S. Department of Health and Human Services
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**Month 2012
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TABLE OF CONTENTS

78I.	INTRODUCTION.....	1
79II.	BACKGROUND.....	2
80	A. Current Monitoring Practices and FDA Guidance.....	3
81	B. FDA’s Rationale for Risk-Based Monitoring.....	4
82III.	OVERVIEW OF MONITORING METHODS.....	6
83	A. On-Site and Centralized Monitoring.....	6
84	1. On-Site Monitoring.....	6
85	2. Centralized Monitoring.....	7
86	B. Examples of Alternative Monitoring Techniques.....	7
87	1. Communication with Study Site Staff.....	9
88	2. Review of Site’s Processes, Procedures, and Records.....	9
89	3. Source Data Verification and Corroboration.....	10
90IV.	RISK-BASED MONITORING.....	11
91	A. Identify Critical Data and Processes to be Monitored.....	11
92	B. Risk Assessment.....	12
93	C. Factors to Consider when Developing a Monitoring Plan.....	13
94	D. Monitoring Plan.....	14
95	1. Description of Monitoring Approaches.....	15
96	2. Communication of Monitoring Results.....	15
97	3. Management of Noncompliance.....	16
98	4. Ensuring Quality Monitoring.....	16
99	5. Monitoring Plan Amendments.....	16
100V.	DOCUMENTING MONITORING ACTIVITIES.....	17
101VI.	ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY.....	17
102	A. Protocol and Case Report Form Design.....	17
103	B. Clinical Investigator Training and Communication.....	17
104	C. Delegation of Monitoring Responsibilities to a CRO.....	18
105	D. Clinical Investigator and Site Selection and Initiation.....	18
106VII.	PAPERWORK REDUCTION ACT OF 1995.....	19
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Guidance for Industry¹
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Approach to Monitoring

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This guidance represents the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

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123I.

INTRODUCTION

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This guidance assists sponsors of clinical investigations in developing risk-based monitoring strategies and plans for investigational studies of medical products, including human drug and biological products, medical devices, and combinations thereof. The overarching goal of this guidance is to enhance human subject protection and the quality of clinical trial data by focusing sponsor oversight on the most important aspects of study conduct and reporting.

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This guidance makes clear that sponsors can use a variety of approaches to fulfill their responsibilities for monitoring clinical investigator (CI) conduct and performance in investigational new drug (IND) or investigational device exemption (IDE) studies. The guidance describes strategies for monitoring activities that reflect a modern, risk-based approach that focuses on critical study parameters and relies on a combination of monitoring activities to oversee a study effectively. For example, the guidance specifically encourages greater use of centralized monitoring methods where appropriate.

FDA’s guidance documents, including this guidance, do not establish legally enforceable responsibilities. Rather, 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 (CDER) in cooperation with CDER’s Office of Scientific Investigations in the Office of Compliance, CBER’s Office of Compliance and Biologics Quality, CDRH’s Office of Compliance, Office of the Commissioner’s Office of Good Clinical Practice, and the Office of Regulatory Affairs (ORA).

145II. BACKGROUND

146

147Effective monitoring of clinical investigations by sponsors is critical to the protection of human
148subjects and the conduct of high-quality studies. Sponsors of clinical investigations involving
149human drugs, biological products, medical devices, and combinations thereof are required to
150provide oversight to ensure adequate protection of the rights, welfare, and safety of human
151subjects and the quality and integrity of the clinical trial data submitted to FDA.² FDA's
152regulations require sponsors to monitor the conduct and progress of their clinical
153investigations.^{3,4} The regulations are not specific about how sponsors are to conduct such
154monitoring and are therefore compatible with a range of approaches to monitoring (see section
155III) that will vary depending on multiple factors (see section IV.C).

156

157During the past two decades, the number and complexity of clinical trials have grown
158dramatically. These changes create new challenges to clinical trial oversight, particularly
159increased variability in clinical investigator experience, site infrastructure, treatment choices, and
160standards of health care,⁵ as well as challenges related to geographic dispersion. At the same
161time, increasing use of electronic systems and records, as well as improvements in statistical
162assessments, present opportunities for alternative monitoring approaches that can improve the
163quality and efficiency of sponsor oversight of clinical investigations. FDA encourages sponsors
164to develop monitoring plans that manage important risks to human subjects and data integrity
165and address the challenges of oversight in part by taking advantage of the innovations in modern
166clinical trials. A risk-based approach to monitoring does not suggest any less vigilance in
167oversight of clinical investigations. Rather, it focuses sponsor oversight activities on preventing
168or mitigating important and likely risks to data and processes critical to human subject protection
169and trial integrity. Moreover, a risk-based approach is dynamic, more readily facilitating
170continual improvement in trial conduct and oversight. For example, monitoring findings should
171be used to correct CI and site practices that may result in inadequate human subject protection or
172poor data quality. Furthermore, monitoring findings should be evaluated to determine whether
173additional actions (e.g., clarification of protocol requirements) are necessary to ensure human
174subject protection and data integrity across sites.

175

176This guidance focuses on only one aspect – monitoring – of the processes and procedures needed
177to ensure clinical trial quality and subject safety. Monitoring is a quality control tool for
178determining whether study activities are being carried out as planned, so that deficiencies can be
179identified and corrected. Monitoring, or oversight, alone cannot ensure quality. Rather, quality
180is an overarching objective that must be built into the clinical trial enterprise. FDA recommends
181a *quality risk management* approach to clinical trials and is considering the need for additional
182guidance describing this approach.

16² 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812,
17subpart C generally (Responsibilities of Sponsors).

18³ 21 CFR 312.50 requires a sponsor to, among other things, ensure “proper monitoring of the investigation(s)” and
19“that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in
20the IND.” 21 CFR 812.40 states that sponsors are responsible for, among other things, “ensuring proper monitoring
21of the investigation, ...”

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

23⁵ Glickman et al. Ethical and Scientific Implications of the Globalization of Clinical Research. *NEJM*. 360: 816-823
24(2009).

183

184We are aware that the term *monitoring* is used in different ways in the clinical trial context. It
185can refer to the assessment of CI conduct, oversight, and reporting of findings of a clinical trial;
186to the ongoing evaluation of safety data and the emerging risk-benefit profile of an
187investigational product by a medical monitor; and to the monitoring of internal sponsor and
188contract research organization (CRO) processes and systems integral to proposing, designing,
189performing, recording, supervising, reviewing, or reporting clinical investigations.

190

191For purposes of this guidance, *monitoring* refers to the methods used by sponsors of
192investigational studies, or CROs delegated responsibilities for the conduct of IND studies, to
193oversee the conduct of, and reporting of data from, clinical investigations, including appropriate
194CI supervision of study site staff and third party contractors. Monitoring activities include
195communication with the CI and study site staff; review of the study site's processes, procedures,
196and records; and verification or corroboration of the accuracy of data submitted to the sponsor.

197

198A. Current Monitoring Practices and FDA Guidance

199

200A survey conducted through the Clinical Trials Transformation Initiative (CTTI)⁶ indicated that a
201range of practices has been used to monitor the conduct of clinical trials. These practices vary in
202intensity, focus, and methodology and include centralized monitoring of clinical data by
203statistical and data management personnel; targeted on-site visits to higher risk CIs (e.g., where
204centralized monitoring suggests problems at a site); and frequent, comprehensive on-site visits to
205all CI sites by sponsor personnel or representatives (e.g., clinical monitors or clinical research
206associates).⁷ See definitions of on-site and centralized monitoring in section III.A.

207

208Although a range of monitoring methods was apparent, periodic, frequent visits to each CI site to
209evaluate study conduct and review data for each enrolled subject remain the predominant
210mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the
211progress of clinical investigations. For major efficacy trials, companies typically conduct on-site
212monitoring visits at approximately 4- to 8-week intervals,⁸ at least partly because of the
213perception that the frequent on-site monitoring visit model, with 100% verification of all data, is
214FDA's preferred way for sponsors to meet their monitoring obligations. In contrast, academic
215coordinating centers, cooperative groups, and government organizations use on-site monitoring
216less extensively. For example, some government agencies and oncology cooperative groups
217typically visit sites only once every 2 or 3 years to qualify or certify clinical study sites⁹ to ensure
218they have the resources, training, and safeguards to conduct clinical trials. FDA also recognizes
219that regulators and practitioners have relied on data from critical outcome studies (e.g., many
220National Institutes of Health-sponsored trials, Medical Research Council-sponsored trials in the

27⁶ CTTI is a public-private partnership involving FDA, academia, industry representatives, patient and consumer
28representatives, professional societies, investigator groups, and other government agencies, initiated in 2008. CTTI's
29mission is to identify practices that will increase the quality and efficiency of clinical trials.

30⁷ Morrison et al. Monitoring the Quality of Conduct of Clinical Trials: A Survey of Current Practices. Clin Trials. 8:
31342-349 (2011).

32⁸ Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial
33Monitoring. Drug Inf J. 44: 477-483 (2010).

34⁹ *Id.*

221United Kingdom, ISIS (International Study of Infarct Survival) trials,¹⁰ and GISSI¹¹), which had
222no regular on-site monitoring and relied largely on centralized and other alternative monitoring
223methods.¹² These examples suggest that use of alternative monitoring approaches should be
224considered by all sponsors, including commercial sponsors, when developing risk-based
225monitoring strategies and plans.

226

227The 1996 International Conference on Harmonisation of Technical Requirements for
228Registration of Pharmaceuticals for Human Use (ICH) guidance on good clinical practice (ICH
229E6) and the 2011 International Standards Organization (ISO) Clinical investigation of medical
230devices for human subjects – good clinical practice (ISO 14155:2011) address monitoring. Both
231ICH E6 and ISO 14155:2011 specifically provide for flexibility in how trials are monitored. ICH
232E6 and ISO 14155:2011 advise sponsors to consider the objective, design, complexity, size, and
233endpoints of a trial in determining the extent and nature of monitoring for a given trial.^{13,14} The
234ISO standard further states that a sponsor’s assessment of these factors should be used to develop
235a monitoring plan, consistent with FDA’s recommendation for monitoring plan development in
236this guidance. Although the ICH guidance and ISO standard specifically provide for the
237possibility of reduced, or even no, on-site monitoring, they also make clear that it would be
238appropriate to rely entirely on centralized monitoring only in exceptional circumstances.

239

240B. FDA’s Rationale for Risk-Based Monitoring

242FDA is issuing this guidance to provide FDA’s current recommendations regarding monitoring
243practices and to encourage consideration of change in industry’s approach to monitoring. FDA
244believes there is reason to expect that risk-based monitoring could improve sponsor oversight of
245clinical investigations. This guidance is therefore intended to make it clear that risk-based
246monitoring, including the appropriate use of centralized monitoring (see section III.A.2 for
247discussion of centralized monitoring) and reliance on technological advances (e.g., e-mail,
248webcasts, and online training modules), can meet statutory and regulatory requirements under
249appropriate circumstances.

250

251There is a growing consensus that risk-based approaches to monitoring, focused on risks to the
252most critical data elements and processes necessary to achieve study objectives, are more likely
253than routine visits to all clinical sites and 100% data verification to ensure subject protection and

37¹⁰ Califf et al. Developing Systems for Cost-Effective Auditing of Clinical Trials. *Controlled Clinical Trials*. 18: 38651-660 (1997).

39¹¹ Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Italian group for the study of the 40survival of myocardial infarction.

41¹² Temple, R. Policy Developments in Regulatory Approval. *Statistics in Medicine*. 21: 2939-2948 (2002).

42¹³ Guidance for industry, E6 Good Clinical Practice: Consolidated Guidance, 1996, section 5.18.3.

43¹⁴ ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, sections 445.7 and 6.3.

255 overall study quality.^{15,16,17,18} For example, incorporation of centralized monitoring practices,
 256 where appropriate, should improve a sponsor’s ability to ensure the quality and integrity of
 257 clinical trial data. Several publications suggest that certain data anomalies (e.g., fraud, including
 258 fabrication of data, and other non-random data distributions) may be more readily detected by
 259 centralized monitoring techniques than by on-site monitoring.^{19, 20, 21} It has been suggested that a
 260 statistical approach to central monitoring can “help improve the effectiveness of on-site
 261 monitoring by prioritizing site visits and by guiding site visits with central statistical data
 262 checks,” an approach that is supported by illustrative examples using actual trial datasets.²² A
 263 recent review of on-site monitoring findings collected during a multi-center international trial
 264 also suggests that centralized monitoring can identify the vast majority of on-site monitoring
 265 findings. The review determined that centralized monitoring activities could have identified
 266 more than 90% of the findings identified during on-site monitoring visits.²³
 267

268 This guidance strongly encourages sponsors to tailor monitoring plans to the needs of the trial
 269 (see section IV). FDA recognizes that this guidance places greater emphasis on centralized
 270 monitoring than appeared feasible at the time ICH E6 was finalized. However, FDA considers
 271 the approach to monitoring described in this guidance as consistent with ICH E6 and ISO
 272 14155:2011. FDA believes it is reasonable to conclude that the flexibility described in ICH E6
 273 and ISO 14155:2011 was intended to permit innovative approaches to improve the effectiveness
 274 of monitoring. Notably, the advancement in electronic systems and increasing use of electronic
 275 records facilitate remote access to electronic data (i.e., electronic data capture (EDC) systems)
 276 and increasingly to some source data (see section III.B.2.b for further discussion of access to
 277 electronic source data). Additionally, statistical assessments using data submitted on paper CRFs
 278 or via EDC may permit timely identification of clinical sites that require additional training,
 279 monitoring, or both. We expect that the pharmaceutical and device industries will, for the
 280 foreseeable future, continue to use some amount of on-site monitoring, but we anticipate
 281 decreased use of on-site monitoring with evolving monitoring methods and technological
 282 capabilities.

283

284 FDA has communicated the goals of, and recommendations for, risk-based monitoring to FDA
 285 staff in review, inspection, and compliance functions. FDA considers the bioresearch monitoring
 286 compliance program guidance manuals (CPGMs) for sponsors, CROs, and monitors (CPGM

47¹⁵ Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial
 48 Monitoring. *Drug Inf J.* 44: 477-483 (2010).

49¹⁶ FDA, Concept Paper: Quality in FDA-Regulated Clinical Research; Background to HSP/BIMO Workshop 5/10-
 50 505/11/07, (4/26/07).

51¹⁷ Brosteanu et al. Risk Analysis and Risk Adapted On-Site Monitoring in Noncommercial Clinical Trials. *Clin*
 52 *Trials.* 6: 585-595 (2009).

53¹⁸ Tantsyura et al. Risk-Based Source Data Verification Approaches: Pros and Cons. *Drug Inf J.* 44: 745-756 (2010).

54¹⁹ Usher, R. PhRMA BioResearch Monitoring Committee Perspective on Acceptable Approaches for Clinical Trial
 55 Monitoring. *Drug Inf J.* 44: 477-483 (2010).

56²⁰ Baigent et al. Ensuring Trial Validity by Data Quality Assurance and Diversification of Monitoring Methods. *Clin*
 57 *Trials.* 5: 49-55 (2008).

58²¹ Buyse et al. The Role of Biostatistics in the Prevention, Detection and Treatment of Fraud in Clinical Trials.
 59 *Statistics in Medicine.* 18: 3435-51 (1999).

60²² Venet et al. A Statistical Approach to Central Monitoring of Data Quality in Clinical Trials. *Clin Trials.* 0: 1-9
 61 (2012).

62²³ Bakobaki et al. The Potential for Central Monitoring Techniques to Replace On-Site Monitoring: Findings from
 63 an International Multi-Centre Clinical Trial. *Clin Trials.* 9: 257-264 (2012).

2877348.810)²⁴ and for CIs and sponsor-investigators (CPGM 7348.811)²⁵ compatible with the 288 approaches described in this guidance. For example, CPGM 7348.810 informs FDA field staff 289 that the regulations do not prescribe a specific monitoring technique. While CPGM 7348.810 290 refers to site visits and does not discuss centralized monitoring, the focus is on the review of 291 monitoring activities through documentation and whether these activities were carried out in 292 accordance with the sponsor's (or CRO's) monitoring procedures.

293
294 The following sections reflect FDA's current thinking on monitoring and include 295 recommendations on how to develop and implement a study-specific monitoring plan as well as 296 how to document monitoring activities. FDA acknowledges that there are limited empirical data 297 to support the utility of the various methods employed to monitor clinical investigations (e.g., 298 superiority of one method versus another), including data to support on-site monitoring.²⁶ As a 299 result, the recommendations are based, in part, on FDA's experience from the review of 300 protocols during the IND or IDE phase, data submitted in pre-approval applications, results of 301 inspections conducted to ensure human subject protection and data integrity, and information 302 obtained from public outreach efforts conducted under the auspices of the CTTI.

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305 III. OVERVIEW OF MONITORING METHODS

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307 B. On-Site and Centralized Monitoring

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309 This section is intended to assist sponsors in identifying and designing monitoring practices 310 appropriate to a given clinical trial. It describes some of the capabilities and limitations of on- 311 site and centralized monitoring processes and factors to consider in determining which 312 monitoring practices may be appropriate for a given clinical trial. See section IV.C for a 313 discussion of factors to consider when determining the types, frequency, and extent of 314 monitoring activities and section IV.D.1 for examples of events or results that would trigger a 315 change in planned monitoring activities.

316

317

318 1. On-Site Monitoring

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320 *On-site monitoring* is an in-person evaluation carried out by sponsor personnel or representatives 321 at the sites at which the clinical investigation is being conducted. On-site monitoring can 322 identify data entry errors (e.g., discrepancies between source records and case report forms 323 (CRFs)) and missing data in source records or CRFs; provide assurance that study 324 documentation exists; assess the familiarity of the site's study staff with the protocol and 325 required procedures; and assess compliance with the protocol and investigational product 326 accountability. On-site monitoring can also provide a sense of the quality of the overall conduct

66²⁴ CPGM 7348.810: Sponsors, Contract Research Organizations and Monitors (March 11, 2011), available at: 67 <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm>.

68²⁵ CPGM 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008), available at: 69 <http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm>.

70²⁶ Two studies are on-going as of June 2012 that compare the effectiveness of on-site to alternative (e.g., centralized) 71 monitoring methods (OPTIMON study (<https://ssl2.isped.u-bordeaux2.fr/optimon/Default.aspx>) and ADAMON 72 study (<http://ctj.sagepub.com/content/6/6/585.full.pdf+html>)).

327of the trial at a site (e.g., attention to detail, thoroughness of study documentation, appropriate
 328delegation of study tasks, and appropriate CI supervision of site staff performing critical study
 329functions). On-site monitoring can therefore be particularly helpful early in a study, especially if
 330the protocol is complex and includes novel procedures with which CIs may be unfamiliar.
 331Findings at the site may lead to training efforts at both the site visited and elsewhere (see section
 332VI.B).

333

334

2. Centralized Monitoring

335

336*Centralized monitoring* is a remote evaluation carried out by sponsor personnel or
 337representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location
 338other than the sites at which the clinical investigation is being conducted. Centralized
 339monitoring processes can provide many of the capabilities of on-site monitoring as well as
 340additional capabilities.

341

342FDA encourages greater reliance on centralized monitoring practices than has been the case
 343historically, with correspondingly less emphasis on on-site monitoring. The types of monitoring
 344activities and the extent to which centralized monitoring practices can be employed depend on
 345the sponsor's use of electronic systems; the sponsor's access to subjects' electronic records, if
 346applicable; the timeliness of data entry from paper CRF, if applicable; and communication tools
 347available to the sponsor and study site. These may vary by study and by site. Sponsors who plan
 348to rely on centralized monitoring processes should ensure that the processes and expectations for
 349site record keeping, data entry, and reporting are well-defined and ensure timely access to
 350clinical trial data and supporting documentation.²⁷ If sponsors intend to rely heavily on
 351centralized monitoring practices, they should identify, in the monitoring plan, when one or more
 352on-site monitoring visits would be indicated.

353

A. Examples of Alternative Monitoring Techniques

355

356As discussed in section II, monitoring activities broadly include communication with the CI and
 357study site staff; review of the study site's processes, procedures, and records; and verification or
 358corroboration of the accuracy of data submitted to the sponsor. This section highlights areas for
 359which centralized monitoring techniques could be considered. For certain monitoring activities,
 360centralized monitoring techniques can be considered in lieu of, or to complement, traditional
 361monitoring techniques. Specific techniques used should be prospectively included in the
 362monitoring plan and should be informed by the risk assessment (see section IV.B for discussion
 363of risk assessment).

364

365Centralized monitoring techniques should be used to the extent appropriate and feasible to:

366

- 367• Replace or supplement on-site monitoring for monitoring activities that can be done as well
 368 or better remotely or for monitoring activities that can be accomplished only using
 369 centralized processes. Examples include:

²⁷ See guidances for industry: Part 11, Electronic Records; Electronic Signatures – Scope and Application and
 76Computerized Systems Used in Clinical Investigations.

77

- 370 ○ Monitor data quality through routine review of submitted data to identify and
 371 follow-up on missing data, inconsistent data, data outliers, and potential
 372 protocol deviations that may be indicative of systemic or significant errors in
 373 data collection and reporting at a site
- 374 ○ Conduct statistical analyses to identify data trends not easily detected by on-
 375 site monitoring, such as
- 376 ▪ Standard checks of range, consistency, and completeness of data
 - 377 ▪ Checks for unusual distribution of data within and between study sites,
 378 such as too little variance²⁸
- 379 ○ Analyze site characteristics, performance metrics (e.g., high screen failure or
 380 withdrawal rates, high frequency of eligibility violations, delays in reporting
 381 data), and clinical data to identify trial sites with characteristics correlated
 382 with poor performance or noncompliance
- 383 ○ Verify critical source data remotely as described in the monitoring plan, in
 384 cases where such source data are accessible, or where CRF data are, per
 385 protocol, source data
- 386 ○ Complete administrative and regulatory tasks (e.g., verify continuous
 387 institutional review board (IRB) approval by reviewing electronic IRB
 388 correspondence, if available; perform portions of investigational product
 389 accountability such as comparison of randomization and CRF data to
 390 preliminarily assess whether the subject was administered or dispensed the
 391 assigned product and to evaluate consistency between investigational product
 392 receipt, use, and disposition records; verify whether previously requested CRF
 393 corrections were made).
- 394 Centralized techniques, including routine review of submitted data and statistical and other
 395 analyses, may also be used to identify significant concerns (e.g., need for clarification of a
 396 protocol procedure, indications of data fabrication) with non-critical data that may not have
 397 otherwise been a focus of monitoring (e.g., source document verification).
- 398• Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data
 399 anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other
 400 sites), through the activities described above. Such findings, whether related to critical or
 401 non-critical data, may warrant more intensive monitoring.

402

403 The following sections provide additional descriptions of alternative monitoring techniques.

404

405 1. Communication with Study Site Staff

406

407 Communication between the monitor and the study site staff is an essential component of
 408 monitoring. Various modes of communication (e.g., teleconferences, videoconferencing, email)

80²⁸ Collins, Rory. (2010, October) Quality Design of Clinical Trials. Presentation at CTTI work stream 3 expert
 81 meeting. Available at: https://www.ctti-clinicaltrials.org/website-administration/documents/COLLINS%20FDA%20trial%20quality%200811%20FINAL_no%20animation.pdf/view.

409could be considered for specific study time points (e.g., study initiation), activities (e.g., to
410discuss findings of a monitor’s eCRF review), and other circumstances (e.g., training of new site
411staff).

412

413 2. Review of Site’s Processes, Procedures, and Records

414

415 a. Informed Consent

416

417Verification of subjects’ informed consent is a critical activity that should be monitored (see
418section IV.A). Alternatives to the traditional approach (monitors verifying the original signature
419on the consent form for each subject at the site) may be more effective in identifying
420inadequacies in the consent process and may be more efficient. For example, the study site’s
421electronic submission (e.g., faxing, e-mailing) of the signed page(s) of consent forms (partially
422masked, if necessary) to the monitor or the monitor’s remote comparison of dates of study
423procedures and documentation of informed consent on CRFs may facilitate a more timely review
424of the informed consent documentation and process. An internet portal that enables the site staff
425to upload signed consent forms and enables access by designated monitors is a tool that can be
426considered. Use of electronic informed consent may also facilitate sponsor oversight of human
427subject protection. We recognize that sponsors must attend to privacy and confidentiality
428concerns when considering techniques for monitoring informed consent.

429

430 b. Site’s Records

431

432A growing portion of source documents (e.g., laboratory and radiology reports, source
433documents submitted by the CI for other purposes such as health records documenting serious
434adverse events or adjudicated events) are electronic and may be available to the sponsor
435remotely. Furthermore, consistent with ICH E6 and ISO 14155:2011, original observations can
436be entered directly into the eCRF or transmitted to the eCRF from various locations, devices, or
437instruments.²⁹ We recognize that sponsors may not have access to electronic health records
438maintained by hospitals, universities, and other institutions because of data privacy and security
439concerns as well as technological challenges. We encourage all sponsors to consider risk-based
440approaches to monitoring using the format of study information (i.e., electronic or hard copy),
441tools, and other resources available to them.

442

443As discussed in this guidance, a variety of centralized monitoring techniques can be used to
444replace, supplement, and target on-site monitoring activities. The majority of these techniques
445(e.g., checks for completeness of data, sites with a higher frequency of protocol violations
446relative to other sites, sites with high screen failure rates) can be performed regardless of the
447extent of use of electronic records in the study. For example, the majority of these techniques
448can be performed using CRF data collected either using electronic data capture systems or
449entered into a database from a hard copy CRF collected by the sponsor. A recent publication
450discusses statistical techniques for identifying various types of data errors.³⁰ We recognize that
451the statistical techniques described in this guidance may not be routinely used by all sponsors

85²⁹ Section 6.4.9 of ICH E6 provides that the trial design description should include “The identification of any data to
86be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be
87source data.” ISO 14155:2011, section 6.8.2, provides that the clinical investigation plan “shall specify which data
88can be recorded directly in the CRFs.”

452and may not be appropriate for every trial, but they are included in this guidance as examples of
453monitoring techniques that may be considered by sponsors.

454

455Additional monitoring techniques are possible for studies that use electronic CRFs, such as
456routine review of data as they are submitted. Although not specifically a monitoring technique,
457another method of ensuring data quality routinely implemented in eCRFs is the use of electronic
458prompts in the eCRF to minimize errors and omissions at the time of data entry, particularly if
459data are entered directly into the eCRF.

460

461 3. Source Data Verification and Corroboration

462

463The sponsor should consider the quantity and types of source data that need to be verified against
464CRFs or corroborated against other records (e.g., review of medical record to corroborate a
465subject's response of "no hospitalizations" since the previous visit on a CRF) during the
466sponsor's identification of critical data and processes or in the risk assessment, or both. The
467sponsor should include a description of the quantity and types of source records to verify or
468corroborate in the monitoring plan. The sponsor should consider which source records are likely
469to provide the most meaningful information about a subject's participation and the CI's conduct
470and oversight.

471

472For example, for a particular study, there may be minimal benefit in comparing 100% of the
473source data for each subject to the CRFs for each study visit. Rather, it may be sufficient to
474compare the most critical data points for a sample of subjects and study visits as an indicator of
475data accuracy. Similarly, for a particular study, although collection of all concomitant
476medications, body temperature, and body weight are required by the protocol and are
477documented in the medical record and transcribed to a CRF, they may not be identified by the
478sponsor as critical data, because a small error rate in those variables would not affect the
479outcome of the trial. In the absence of information indicating potential concerns with the data
480(e.g., sites with data anomalies, inconsistent data), source document verification or corroboration
481of these non-critical data may not provide significantly useful information to the sponsor.

482

483

91³⁰ Venet et al. A Statistical Approach to Central Monitoring of Data Quality in Clinical Trials. Clin Trials. 0: 1-9
92(2012).

93

484B. RISK-BASED MONITORING

485

486 No single approach to monitoring is appropriate or necessary for every clinical trial. FDA
 487 recommends that each sponsor design a monitoring plan that is tailored to the specific human
 488 subject protection and data integrity risks of the trial. Ordinarily, such a risk-based plan would
 489 include a mix of centralized and on-site monitoring practices. The monitoring plan should
 490 identify the various methods intended to be used and the rationale for their use (see section IV.D
 491 for recommendations on the components of a monitoring plan).

492

493 Monitoring activities should focus on preventing or mitigating important and likely sources of
 494 error in the conduct, collection, and reporting of critical data and processes necessary for human
 495 subject protection and trial integrity. Sponsors should prospectively identify critical data and
 496 processes, then perform a risk assessment to identify and understand the risks that could affect
 497 the collection of critical data or the performance of critical processes, and then develop a
 498 monitoring plan that focuses on the important and likely risks to critical data and processes.

499

500A. Identify Critical Data and Processes to be Monitored

501

502 Sponsors should prospectively identify critical data and processes that if inaccurate, not
 503 performed, or performed incorrectly, would threaten the protection of human subjects or the
 504 integrity of the study results. As examples, the following types of data and processes should
 505 ordinarily be identified as critical:

506

- 507• Verification that informed consent was obtained appropriately
- 508• Adherence to protocol eligibility criteria designed to exclude individuals for whom the
 509 investigational product may be less safe than the protocol intended and to include only
 510 subjects from the targeted study population for whom the test article is most appropriate
- 511• Procedures for documenting appropriate accountability and administration of the
 512 investigational product (e.g., ensuring the integrity of randomization at the site level, where
 513 appropriate)
- 514• Conduct and documentation of procedures and assessments related to
 - 515 – study endpoints
 - 516 – protocol-required safety assessments
 - 517 – evaluating, documenting, and reporting serious adverse events and unanticipated adverse
 518 device effects, subject deaths, and withdrawals, especially when a withdrawal may be
 519 related to an adverse event
- 520• Conduct and documentation of procedures essential to data integrity, such as ensuring the
 521 study blind is maintained, both at the site level and at the sponsor level, as appropriate,
 522 referring specified events for adjudication, and allocation concealment

523 Other types of data (e.g., covariates such as concomitant treatments or demographic
524 characteristics; routine laboratory tests performed as part of patient monitoring that do not
525 address protocol specified safety or efficacy endpoints) and processes (e.g., a hospital
526 pharmacy's storage of an investigational product with no specific critical handling instructions)
527 identified by the sponsor as non-critical often may be monitored less intensively.

528

529 There is increasing recognition that some types of errors in a clinical trial are more important
530 than others.³¹ For example, a low, but non-zero rate of errors in capturing certain baseline
531 characteristics of enrolled subjects (e.g., age, concomitant treatment, or concomitant illness) will
532 not, in general, have a significant effect on study results if the errors are distributed randomly. In
533 contrast, a small number of errors related to study endpoints (e.g., not following protocol-
534 specified definitions) can profoundly affect study results, as could failure to report rare but
535 important adverse events. Based on FDA's inspection and review experience, infrequent errors
536 in non-critical data are unlikely to alter FDA's conclusions about whether a product is safe and
537 effective and whether participants' safety was appropriately monitored.

538

539 **B. Risk Assessment**

540

541 This guidance discusses the risk assessment, a component of risk management, as applied in the
542 context of clinical monitoring. Risk assessment generally involves identifying risks, analyzing
543 risks, and then determining whether risks need to be modified by implementing controls (e.g.,
544 processes, policies, or practices). The risk assessment recommended in this guidance to inform
545 development of a monitoring plan may also support efforts to manage risks across a clinical trial
546 (e.g., through modifying the protocol design or implementation) or development program, and
547 vice versa. This guidance does not provide comprehensive detail on how to perform a risk
548 assessment. There are many risk assessment methodologies and tools from a variety of
549 industries that can be applied to clinical trials.^{32,33}

550

551 Following the identification of critical data and processes (section IV.A), sponsors should
552 perform a risk assessment to identify and understand the nature, sources, and potential causes of
553 risks that could affect the collection of critical data or the performance of critical processes.
554 Risks to critical data and processes most merit consideration during risk assessment, to ensure
555 that monitoring efforts are focused on preventing or mitigating important and likely sources of
556 error in their conduct, collection and reporting.

557

558 Risk identification for monitoring purposes should generally consider the types of data to be
559 collected, the specific activities required to collect these data, and the range of potential safety
560 and other human subject protection concerns that are inherent to the clinical investigation (e.g.,
561 based on trial design or investigational product).

98³¹ Baigent et al. Ensuring Trial Validity by Data Quality Assurance and Diversification of Monitoring Methods. Clin
99 Trials. 5: 49-55 (2008).

100³² Guidance for industry, Q9 Quality Risk Management, June 2006.

101³³ ISO 31010:2009 Risk Management – Risk Assessment Techniques.

562The identified risks should be assessed and prioritized by considering:

- 563• the likelihood of errors occurring,
- 564• the impact of such errors on human subject protection and trial integrity, and
- 565• the extent to which error would be detectable.

566

567Sponsors should use the results of the risk assessment in developing the monitoring plan (e.g.,
568determining which risks may be addressed through monitoring, determining the types and
569intensity of monitoring activities best suited to addressing these risks). Sponsors may also
570determine that some risks are better managed through other activities (e.g., modifying the
571protocol to remove the source of the risk). Sponsors should periodically evaluate emerging risks
572and whether monitoring activities require modification to effectively oversee the risks.

573

574C. **Factors to Consider when Developing a Monitoring Plan**

575

576A monitoring plan ordinarily should focus on preventing or mitigating important and likely risks,
577identified by the risk assessment, to critical data and processes. The types (e.g., on-site,
578centralized), frequency (e.g., early, for initial assessment and training versus throughout the
579study), and extent (e.g., comprehensive (100% data verification) versus targeted or random
580review of certain data (less than 100% data verification)) of monitoring activities will depend to
581some degree on a range of factors, considered during the risk assessment, including the
582following:

- 583• Complexity of the study design

584More intensive monitoring (e.g., increased frequency and extent of review) may be necessary as
585study design complexity increases. Examples may include studies with adaptive designs,
586stratified designs, complex dose titrations, or multiple device placement studies.

- 587• Types of study endpoints

588Endpoints that are more interpretative or subjective may require on-site visits to assess the
589totality of subject records and to review application of protocol definitions with the CI. More
590objective endpoints (e.g., death, hospitalization, or clinical laboratory values and standard
591measurements) may be more amenable to remote verification. Endpoints for which
592inappropriate subject withdrawal or lack of follow-up may impede study evaluation are likely to
593need more intensive monitoring to determine whether follow-up can be improved and to identify
594the reason(s) subjects are withdrawing.

- 595• Clinical complexity of the study population

596A study that involves a population that is seriously ill or vulnerable may require more intensive
597monitoring and consideration of on-site monitoring visits to be sure appropriate protection is
598being provided.

- 599• Geography

600Sites in geographic areas where there are differences in standards of medical practice or subject
601demographics, or where there is a less established clinical trial infrastructure may require more
602intensive monitoring and consideration of on-site monitoring visits.

- 603• Relative experience of the CI and of the sponsor with the CI

604CIs who lack significant experience in conducting and overseeing investigations, using a novel
605or innovative medical device, or with the surgical procedure associated with medical device use
606may benefit from more intensive monitoring and frequent communication to ensure CI
607understanding of responsibilities. In addition, the relative experience of a sponsor with the CI
608may be a factor in determining an appropriate monitoring plan.

609• Electronic data capture

610Use of EDC systems with the capability to assess quality metrics (e.g., missing data, data error
611rates, and protocol violations) in real-time could help identify potentially higher risk sites for the
612purpose of targeting sites in need of more intensive monitoring.

613• Relative safety of the investigational product

614A study of a product that has significant safety concerns or for which there is no prior experience
615in human clinical trials (e.g., a phase 1 pharmaceutical investigation or a device feasibility study)
616may require more intensive monitoring and consideration of on-site monitoring visits to ensure
617appropriate CI oversight of subject safety.

618• Stage of the study

619A tapered approach to monitoring may be used where appropriate, with more intensive
620monitoring at initiation and during early stages of a trial. For example, a tapered approach could
621be used for a complex study where more intensive and on-site monitoring might be required
622early, but where, once procedures are established, less intensive monitoring might suffice.
623Similarly, a tapered approach could be used for relatively inexperienced CIs.

624• Quantity of data

625Some centralized monitoring tools may be more useful as the quantity of data (e.g., size or
626duration of trial, number of sites) collected increases.

627

628C. **Monitoring Plan**

629

630For each clinical trial, the sponsor should develop a monitoring plan that describes the
631monitoring methods, responsibilities, and requirements for the trial. The monitoring plan should
632include a brief description of the study, its objectives, and the critical data and study procedures,
633with particular attention to data and procedures that are unusual in relation to clinical routine and
634require training of study site staff. The plan should also communicate the specific risks to be
635addressed by monitoring and should provide those involved in monitoring with adequate
636information to effectively carry out their duties. A monitoring plan may reference existing
637policies and procedures (e.g., standard operating procedure describing general monitoring
638processes or issue investigation and resolution). All sponsor and CRO personnel involved with
639monitoring, including those who review or determine appropriate action regarding potential
640issues identified through monitoring, should review the monitoring plan and associated
641documents (e.g., standard operating procedures or other documents referenced in the monitoring
642plan).

643

644 Sponsors of device studies wishing to solicit feedback on their monitoring procedures prior to the
 645 submission of the application may either submit a pre-IDE, or contact CDRH's Division of
 646 Bioresearch Monitoring.³⁴

647

648 Sponsors of drug studies may include specific questions about a monitoring plan in a request for
 649 a formal meeting with FDA (e.g., end of phase 2 meeting).

650

651 The components of a monitoring plan might include the following:

652

653 D. *Description of Monitoring Approaches*

654

655 • A description of each monitoring method to be employed during
 656 the study and how it will be used to address important risks and ensure the validity of critical
 657 data

658 • Criteria for determining the timing, frequency, and extent of
 659 planned monitoring activities

660 • Specific activities required for each monitoring method employed
 661 during the study, including reference to required tools, logs, or templates

662 • Definitions of events or results (e.g., findings from central
 663 monitoring activities) that would trigger changes in planned monitoring activities for a
 664 particular CI

665 For example, if it is determined that a CI differs markedly from other CIs in making safety-
 666 related findings or other key safety metrics, in rate of enrollment, in the number of protocol
 667 deviations, or in the rate of missing CRFs, the CI's site should be considered for targeted on-
 668 site visits. The establishment of acceptable variation for particular critical data and processes
 669 would facilitate identification of significant deviations.

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

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

675

676 The study monitoring plan should also describe how various monitoring activities will be
 677 documented, regardless of whether they are conducted on-site or centrally (see section V).

678

679 E. *Communication of Monitoring Results*

680

681 • Format, content, timing, and archiving requirements for reports
 682 and other documentation of monitoring activities (see section V)

683 • Process for appropriate communication

108³⁴ IDE regulations (21 CFR 812.25(e)) require that written monitoring procedures be submitted as part of the IDE
 109 application.

- 684 – of routine monitoring results to management and other stakeholders (e.g., CRO, data
685 management),
- 686 – of immediate reporting of significant monitoring issues to appropriate parties (e.g.,
687 sponsor management, CI and site staff, IRB, FDA), as necessary, and
- 688 – from study management and other stakeholders to monitors.

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

692

693 F. *Management of Noncompliance*

694

695• Processes for addressing unresolved or significant issues (e.g.,
696 significant non-compliance with the investigational plan, suspected or confirmed data
697 falsification) identified by monitoring, whether at a particular site or across study sites

698• Processes to ensure that root cause analyses are conducted where important deviations are
699 discovered and that appropriate corrective and preventive actions (e.g., additional training on
700 a study or site level) are implemented to address issues identified by monitoring

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

703

704 G. *Ensuring Quality Monitoring*

705

706• Description of any specific training required for personnel carrying out monitoring activities,
707 including personnel conducting internal data monitoring, statistical monitoring, or other
708 centralized review activities. Training should include principles of clinical investigations and
709 human subject protection. In addition, study-specific training should include discussion of
710 the trial design, protocol requirements, the study monitoring plan, applicable standard
711 operating procedures, appropriate monitoring techniques, and applicable electronic systems.

712• Planned audits of monitoring to ensure that sponsor and CRO staff conduct monitoring
713 activities in accordance with the monitoring plan, applicable regulations, guidance, and
714 sponsor policies, procedures, templates, and other study plans. Auditing is a quality
715 assurance tool that can be used to evaluate the effectiveness of monitoring to ensure human
716 subject protection and data integrity.³⁵

717• Many sponsors have successfully implemented on-site co-monitoring visits (i.e., monitoring
718 visits performed by both a study monitor and the monitor's supervisor or another evaluator
719 designated by the sponsor or CRO) to evaluate whether monitors are effectively carrying out
720 visit activities, in compliance with the study monitoring plan. These visits may be conducted
721 either for randomly selected monitors or may be targeted to specific monitors, based upon
722 questions arising from review of monitoring visit documentation.

723

112³⁵ Audits are not required by the regulations. See ICH E6, section 5.19 and ISO 14155:2011, section 6.11 for
113 additional information on audits.

724 5. *Monitoring Plan Amendments*

725

726 Sponsors should consider what events would indicate a need for review and revision of the
 727 monitoring plan and establish processes to permit timely updates where necessary. For example,
 728 a protocol amendment, change in the definition of significant protocol deviations, or
 729 identification of new risks to study integrity could result in a change to the monitoring plan.

730 **V. DOCUMENTING MONITORING ACTIVITIES**

731

732 Documentation of monitoring activities should generally include the following:

733

734 • The date of the activity and the individual(s) conducting and participating in it

735 • A summary of the data or activities reviewed

736 • A description of any noncompliance, potential noncompliance, data irregularities, or other
 737 deficiencies identified

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

740 Documentation of monitoring should include sufficient detail to allow verification that the
 741 monitoring plan was followed.

742

743 Monitoring documentation should be provided to appropriate management in a timely manner
 744 for review and follow-up, as indicated.

745

746

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

748

749 Although the focus of this guidance is on monitoring the oversight and conduct of, and reporting
 750 of data from, clinical investigations, FDA considers monitoring to be just one component of a
 751 multi-factor approach to ensuring the quality and integrity of clinical investigations. Many other
 752 factors contribute to the quality and integrity of a clinical investigation. This section highlights
 753 additional areas that complement monitoring and can affect study quality.

754

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

757

758 **A. Protocol and Case Report Form Design**

759

760 The most important tool for ensuring human subject protection and high-quality data is a well-
 761 designed and articulated protocol. A poorly designed or ambiguous protocol may introduce
 762 systemic errors that can render a clinical investigation unreliable despite rigorous monitoring.
 763 Additionally, the complexity of the trial design and the type and amount of data collected may
 764 influence data quality.³⁶ The CRF, which captures the data required by the protocol, is another
 765 critical tool for which design directly affects the quality of trial data. Care should be taken to

116³⁶ Sponsors are encouraged to consult the appropriate review division within FDA's medical product centers with
 117 questions about quality aspects of clinical trial design.

766ensure that the CRF captures data accurately (e.g., as required by the protocol) and that the CRF
767design and instructions facilitate consistent data collection across CI sites.

768

769B. **Clinical Investigator Training and Communication**

770

771Clinical trial monitors conducting on-site visits have historically played an important role in
772training the CI and site staff during a study. On-site visits also have served as a primary means
773of providing feedback to CIs and study personnel on study conduct. Without meaningful
774training prior to the conduct of a study and of appropriate instruction during the study (e.g., when
775changes are made to the protocol), CIs and their staff may have difficulty carrying out a trial
776correctly. Sponsors who plan less frequent or limited on-site monitoring should consider the
777following:

778

- 779• Monitoring activities should include sufficient time for discussion of CI's and site staff's
780 responsibilities, feedback, and additional training, if needed, during the conduct of the study.
- 781• It may be necessary to implement alternative training (e.g., teleconferences, webcasts, online
782 training modules) and communication methods (see section III.B.1) for providing and
783 documenting ongoing, timely training and feedback, as well as to provide notification of
784 significant changes to study conduct or other important information.

785

786B. **Delegation of Monitoring Responsibilities to a CRO**

787

788If a sponsor of an IND study delegates the responsibility for ensuring proper monitoring to a
789CRO, FDA regulations (21 CFR 312.52) require the written transfer of any obligations from a
790sponsor to a CRO and require the CRO to comply with the regulations.³⁷ Although sponsors can
791transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the
792work completed by the CRO(s) that assume this responsibility. Sponsors should evaluate CRO
793compliance with regulatory requirements and contractual obligations in an ongoing manner. For
794example, sponsor oversight of monitoring performed by a CRO may include the sponsor's
795periodic review of monitoring reports and vendor performance or quality metrics and
796documented communication between the sponsor and CRO regarding monitoring progress and
797findings.

798

799Sponsors and CROs should consider additional factors when a sponsor transfers responsibilities
800for monitoring to a CRO. Sponsors and CROs should prospectively establish a clear
801understanding of both parties' responsibilities and of the expectations for the conduct of the
802transferred obligations. Sponsors should share information with a CRO that may inform
803decisions a CRO may make regarding the monitoring practices for a trial (e.g., findings of a risk
804assessment). Sponsors should prospectively evaluate monitoring procedures and monitoring
805plans developed by a CRO to ensure the monitoring approach is consistent with applicable
806aspects of the trial. In addition, sponsors and CROs should have processes in place for timely
807exchange of relevant information (e.g., significant monitoring findings, significant changes in
808risk for a trial).

120³⁷ The regulations for investigational device exemptions (21 CFR 812) do not contain a provision for delegation to a
121contract research organization.

809

810D. Clinical Investigator and Site Selection and Initiation

811

812 In addition to regulatory requirements for CI selection, sponsors should consider factors such as
813 sponsor's previous experience with the CI or site, workload of the CI and study staff, and
814 resource availability at the study site during CI and site selection.

815

816 Site initiation is a critical study activity that often involves sponsor personnel from a range of
817 disciplines, including monitors. Key components of site initiation include ensuring the CIs and
818 site staff understand their responsibilities, including applicable regulatory requirements as well
819 as study processes and procedures, including the sponsor's processes for monitoring the
820 investigation. Communication and documentation tools for monitoring discussed in this
821 guidance can also be used for site selection and initiation activities.

822

823

824VII. PAPERWORK REDUCTION ACT OF 1995

825

826 This guidance contains information collection provisions that are subject to review by the Office of
827 Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-
828 3520).

829

830 The time required to complete this information collection is estimated to average 4 hours per
831 response, including the time to review instructions, search existing data resources, gather the data
832 needed, and complete and review the information collection. Send comments regarding this burden
833 estimate or suggestions for reducing this burden to:

834

835 Food and Drug Administration
836 Center for Drug Evaluation and Research
837 Office of Medical Policy
838 10903 New Hampshire Avenue, Bldg. 51, rm. 6352
839 Silver Spring, MD 20993-0002

840

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information in §§ 312, including certain provisions under subpart D, and 812 have been approved under OMB Control Numbers 0910-0014, and 0910-0078. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The OMB control number for this information collection is XXXX-XXXX (expires XX/XX/XXXX).

841

842Chronology: Monitoring Final Guidance

843

844COMIS # 10555 FRDTS # CDER201214

845

846Working Group Meeting: 3/5/2012

847Working Group Meeting: 4/9/2012

848Drafted: SShapley 5/7/2012

849Working Group Meeting: 5/15/2012

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