Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based 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.

I. INTRODUCTION

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.

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).

II. BACKGROUND

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

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

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

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[2] 21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812, subpart C generally (Responsibilities of Sponsors).

[3] 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, …"

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

[5] Glickman et al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM. 360: 816-823 (2009).

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

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

A. Current Monitoring Practices and FDA Guidance

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

Although a range of monitoring methods was apparent, periodic, frequent visits to each CI site to evaluate study conduct and review data for each enrolled subject remain the predominant mechanism by which pharmaceutical, biotechnology, and medical device companies monitor the progress of clinical investigations. For major efficacy trials, companies typically conduct on-site monitoring visits at approximately 4- to 8-week intervals,[8] at least partly because of the perception that the frequent on-site monitoring visit model, with 100% verification of all data, is FDA's preferred way for sponsors to meet their monitoring obligations. In contrast, academic coordinating centers, cooperative groups, and government organizations use on-site monitoring less extensively. For example, some government agencies and oncology cooperative groups typically visit sites only once every 2 or 3 years to qualify or certify clinical study sites[9] to ensure they have the resources, training, and safeguards to conduct clinical trials. FDA also recognizes that regulators and practitioners have relied on data from critical outcome studies (e.g., many National Institutes of Health-sponsored trials, Medical Research Council-sponsored trials in the

[6] 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. CTTI's mission is to identify practices that will increase the quality and efficiency of clinical trials.

[7] Morrison et al. Monitoring the Quality of Conduct of Clinical Trials: A Survey of Current Practices. Clin Trials. 8: 342-349 (2011).

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

[9] *Id.*

United Kingdom, ISIS (International Study of Infarct Survival) trials,[10] and GISSI[11]), which had no regular on-site monitoring and relied largely on centralized and other alternative monitoring methods.[12] These examples suggest that use of alternative monitoring approaches should be considered by all sponsors, including commercial sponsors, when developing risk-based monitoring strategies and plans.

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

B. FDA's Rationale for Risk-Based Monitoring

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

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

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

[11] Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Italian group for the study of the survival of myocardial infarction.

[12] Temple, R. Policy Developments in Regulatory Approval. Statistics in Medicine. 21: 2939-2948 (2002).

[13] Guidance for industry, E6 Good Clinical Practice: Consolidated Guidance, 1996, section 5.18.3.

[14] ISO 14155:2011, Clinical investigation of medical devices for human subjects – Good clinical practice, sections 5.7 and 6.3.

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

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

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

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

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

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

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

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

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

[21] 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).

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

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

287348.810)[24] and for CIs and sponsor-investigators (CPGM 7348.811)[25] compatible with the 288approaches described in this guidance. For example, CPGM 7348.810 informs FDA field staff 289that the regulations do not prescribe a specific monitoring technique. While CPGM 7348.810 290refers to site visits and does not discuss centralized monitoring, the focus is on the review of 291monitoring activities through documentation and whether these activities were carried out in 292accordance with the sponsor's (or CRO's) monitoring procedures.
293
294The following sections reflect FDA's current thinking on monitoring and include 295recommendations on how to develop and implement a study-specific monitoring plan as well as 296how to document monitoring activities. FDA acknowledges that there are limited empirical data 297to support the utility of the various methods employed to monitor clinical investigations (e.g., 298superiority of one method versus another), including data to support on-site monitoring.[26] As a 299result, the recommendations are based, in part, on FDA's experience from the review of 300protocols during the IND or IDE phase, data submitted in pre-approval applications, results of 301inspections conducted to ensure human subject protection and data integrity, and information 302obtained from public outreach efforts conducted under the auspices of the CTTI.
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304
305**III. OVERVIEW OF MONITORING METHODS**
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307B. **On-Site and Centralized Monitoring**
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309This section is intended to assist sponsors in identifying and designing monitoring practices 310appropriate to a given clinical trial. It describes some of the capabilities and limitations of on-311site and centralized monitoring processes and factors to consider in determining which 312monitoring practices may be appropriate for a given clinical trial. See section IV.C for a 313discussion of factors to consider when determining the types, frequency, and extent of 314monitoring activities and section IV.D.1 for examples of events or results that would trigger a 315change in planned monitoring activities.
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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 321at the sites at which the clinical investigation is being conducted. On-site monitoring can 322identify 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 324documentation exists; assess the familiarity of the site's study staff with the protocol and 325required procedures; and assess compliance with the protocol and investigational product 326accountability. On-site monitoring can also provide a sense of the quality of the overall conduct

66[24] CPGM 7348.810: Sponsors, Contract Research Organizations and Monitors (March 11, 2011), available at:
67http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133777.htm.
68[25] CPGM 7348.811: Clinical Investigators and Sponsor-Investigators (December 8, 2008), available at:
69http://www.fda.gov/ICECI/EnforcementActions/BioresearchMonitoring/ucm133562.htm.
70[26] Two studies are on-going as of June 2012 that compare the effectiveness of on-site to alternative (e.g., centralized)
71monitoring methods (OPTIMON study (https://ssl2.isped.u-bordeaux2.fr/optimon/Default.aspx) and ADAMON
72study (http://ctj.sagepub.com/content/6/6/585.full.pdf+html)).

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

2. Centralized Monitoring

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

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

A. Examples of Alternative Monitoring Techniques

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

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

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

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

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 variance[28]

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
403The following sections provide additional descriptions of alternative monitoring techniques.
404
405 1. Communication with Study Site Staff
406
407Communication between the monitor and the study site staff is an essential component of
408monitoring. Various modes of communication (e.g., teleconferences, videoconferencing, email)

80[28] Collins, Rory. (2010, October) Quality Design of Clinical Trials. Presentation at CTTI work stream 3 expert
81meeting. Available at: https://www.ctti-clinicaltrials.org/website-administration/documents/COLLINS%20FDA
82%20trial%20quality%200811%20FINAL_no%20animation.pdf/view.

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

2. Review of Site's Processes, Procedures, and Records

a. Informed Consent

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

b. Site's Records

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

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

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

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

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

3. Source Data Verification and Corroboration

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

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

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

B. RISK-BASED MONITORING

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

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

A. Identify Critical Data and Processes to be Monitored

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

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

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

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

B. Risk Assessment

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

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

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

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

[32] Guidance for industry, Q9 Quality Risk Management, June 2006.

[33] ISO 31010:2009 Risk Management – Risk Assessment Techniques.

The identified risks should be assessed and prioritized by considering:

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

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

C. Factors to Consider when Developing a Monitoring Plan

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

- Complexity of the study design

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

- Types of study endpoints

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

- Clinical complexity of the study population

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

- Geography

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

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

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

- Electronic data capture

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

- Relative safety of the investigational product

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

- Stage of the study

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

- Quantity of data

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

C. Monitoring Plan

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

644Sponsors of device studies wishing to solicit feedback on their monitoring procedures prior to the
645submission of the application may either submit a pre-IDE, or contact CDRH's Division of
646Bioresearch Monitoring.[34]
647
648Sponsors of drug studies may include specific questions about a monitoring plan in a request for
649a formal meeting with FDA (e.g., end of phase 2 meeting).
650
651The 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
676The study monitoring plan should also describe how various monitoring activities will be
677documented, 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

108[34] IDE regulations (21 CFR 812.25(e)) require that written monitoring procedures be submitted as part of the IDE
109application.

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.

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

112[35] Audits are not required by the regulations. See ICH E6, section 5.19 and ISO 14155:2011, section 6.11 for
113additional information on audits.

724 *5. Monitoring Plan Amendments*
725
726Sponsors should consider what events would indicate a need for review and revision of the
727monitoring plan and establish processes to permit timely updates where necessary. For example,
728a protocol amendment, change in the definition of significant protocol deviations, or
729identification of new risks to study integrity could result in a change to the monitoring plan.

730V. DOCUMENTING MONITORING ACTIVITIES

731
732Documentation 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

740Documentation of monitoring should include sufficient detail to allow verification that the
741monitoring plan was followed.
742
743Monitoring documentation should be provided to appropriate management in a timely manner
744for review and follow-up, as indicated.
745
746

747VI. ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY

748
749Although the focus of this guidance is on monitoring the oversight and conduct of, and reporting
750of data from, clinical investigations, FDA considers monitoring to be just one component of a
751multi-factor approach to ensuring the quality and integrity of clinical investigations. Many other
752factors contribute to the quality and integrity of a clinical investigation. This section highlights
753additional areas that complement monitoring and can affect study quality.
754
755A fundamental component of ensuring quality monitoring is a sponsor's compliance with
756monitoring plans and any accompanying procedures.
757

758A. Protocol and Case Report Form Design

759
760The most important tool for ensuring human subject protection and high-quality data is a well-
761designed and articulated protocol. A poorly designed or ambiguous protocol may introduce
762systemic errors that can render a clinical investigation unreliable despite rigorous monitoring.
763Additionally, the complexity of the trial design and the type and amount of data collected may
764influence data quality.[36] The CRF, which captures the data required by the protocol, is another
765critical tool for which design directly affects the quality of trial data. Care should be taken to

116[36] Sponsors are encouraged to consult the appropriate review division within FDA's medical product centers with
117questions about quality aspects of clinical trial design.

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

B. Clinical Investigator Training and Communication

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

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

B. Delegation of Monitoring Responsibilities to a CRO

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

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

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

D. Clinical Investigator and Site Selection and Initiation

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

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

VII. PAPERWORK REDUCTION ACT OF 1995

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

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

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

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).

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