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

DRAFT GUIDANCE

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Center for Devices and Radiological Health (CDRH)
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Procedural
Guidance for Industry

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

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Guidance for Industry

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

This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic.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 is intended to assist 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. This guidance is intended to make clear that sponsors can use a variety of approaches to fulfill their responsibilities related to monitoring investigator conduct and the progress of investigational new drug (IND) or investigational device exemption (IDE) studies. This 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.

II. BACKGROUND

Sponsors of clinical investigations 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
resulting data submitted to FDA.\textsuperscript{2} In the past two decades, the number and complexity of
clinical trials have grown dramatically. These changes create new challenges in clinical trial
oversight such as increased variability in investigator experience, ethical oversight, site
infrastructure, treatment choices, standards of health care,\textsuperscript{3} and geographic dispersion. In light
of these developments, FDA wishes to encourage more effective monitoring of clinical
investigations, to ensure adequate protection of human subjects and the quality and integrity of
clinical trial data.

The regulations require sponsors of clinical investigations involving human drugs, biological
products, medical devices, and combinations thereof to monitor the conduct and progress of their
clinical investigations.\textsuperscript{4,5} The regulations are not specific about how sponsors are to conduct
monitoring of clinical investigations and, therefore, are compatible with a range of approaches to
monitoring.

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

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

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

\[\textsuperscript{2} \text{21 CFR part 312, subpart D generally (Responsibilities of Sponsors and Investigators) and 21 CFR part 812,}
\text{subpart C generally (Responsibilities of Sponsors).}

\[\textsuperscript{3} \text{Glickman et al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM. 360, 816-823 (2009).}

\[\textsuperscript{4} \text{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, …”}

\[\textsuperscript{5} \text{Also see 21 CFR 312.53(d), 312.56(a), 812.43(d), and 812.46.}\]
study data, and compliance with applicable regulations. The findings should be used to correct
investigator and site practices that could result in inadequate human subject protection and/or
poor data quality.

A. Current Monitoring Practices

A survey conducted through the Clinical Trials Transformation Initiative (CTTI)\(^6\) indicates 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 clinical
investigators (e.g., where centralized monitoring indicates problems at a site); and frequent,
comprehensive on-site visits to all clinical investigator sites by company personnel or
representatives (e.g., clinical monitors or clinical research associates).\(^7\) See definitions of on-site
and centralized monitoring in section IV.A.

Despite this range of monitoring methods, periodic, frequent visits to each clinical investigator
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 four- to eight-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 two or three years to qualify/certify clinical study sites\(^9\) to
ensure they have the resources, training, and safeguards to conduct clinical trials. FDA also
recognizes that data from critical outcome studies (e.g., many National Institutes of Health-
sponsored trials, Medical Research Council-sponsored trials in the United Kingdom,
International Study of Infarct Survival,\(^10\) and GISSI\(^11\)), which had no regular on-site monitoring
and relied largely on centralized and other alternative monitoring methods, have been relied on
by regulators and practitioners.\(^12\) These examples demonstrate that use of alternative
monitoring approaches should be considered by all sponsors, including commercial sponsors, when
developing risk-based monitoring strategies and plans.

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\(^6\) 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. A significant part of CTTI’s mission is to identify monitoring practices that through broad adoption will increase the quality and efficiency of clinical trials.

\(^7\) CTTI Workstream 1 work product (May 2010). Available at: https://www.trialstransformation.org/projects/effective-and-efficient-monitoring/monitoring-project-workstream-1.

\(^8\) PhRMA White Paper on Acceptable Approaches for Clinical Trial Monitoring, March 2009.

\(^9\) Id.


\(^11\) Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico- Italian group for the study of the survival of myocardial infarction.

B. Other FDA Guidance on Monitoring

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

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

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

C. Rationale for Facilitating Risk-Based Monitoring

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

There is a growing consensus that risk-based approaches to monitoring, such as focusing on the most critical data elements, are more likely to ensure subject protection and overall study quality, and will permit sponsors to monitor the conduct of clinical investigations more effectively than...
routine visits to all clinical sites and 100% data verification. 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 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. In addition, source data verification and other activities traditionally performed by on-site monitoring can now often be accomplished remotely, as both trial data and source data typically become part of the central submission. These electronic data capture (EDC) systems are making it possible to implement centralized monitoring methods that can enable decreased reliance on on-site monitoring. This guidance is therefore intended to clarify that risk-based monitoring, including the appropriate use of centralized monitoring and technological advances (e.g., e-mail, webcasts, and online training modules), can meet statutory and regulatory requirements under appropriate circumstances.

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

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

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

prior to the submission of the IDE application may either submit a pre-IDE, or contact CDRH’s Division of Bioresearch Monitoring. 26

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

III. FACTORS THAT INFLUENCE STUDY QUALITY AND INTEGRITY

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

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

26 CDRH regulations (21 CFR 812.25(e)) currently require that written monitoring procedures be submitted as part of the IDE application.
27 FDA is considering the need for additional guidance describing overarching quality risk management approaches to clinical trial oversight.
28 Sponsors are encouraged to consult the appropriate review division within FDA’s medical product centers with questions about quality aspects of clinical trial design.
29 Two studies are on-going as of December 2010 that compare the effectiveness of on-site to alternative (e.g., centralized) monitoring methods (OPTIMON study (https://ssl2.isped.u-bordeaux2.fr/optimon/Default.aspx) and ADAMON study (http://ctj.sagepub.com/content/early/2009/11/06/1740774509347398.full.pdf)).
IV. GENERAL MONITORING RECOMMENDATIONS

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).30

A. Types of Monitoring

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

1. On-Site Monitoring

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

2. Centralized Monitoring

Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., data management personnel, statisticians, or clinical monitors) at a location other than the site(s) 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. Centralized monitoring processes should be used to the extent appropriate and feasible to achieve the following:

30 Sponsors of significant risk device studies are required under 21 CFR 812.25(e) to submit and maintain written procedures for monitoring.
• Replace on-site monitoring for monitoring activities that can be done as well or better remotely (e.g., standard checks of range, consistency, and completeness of data and checks for unusual distribution of data within and between study sites, such as too little variance).  

• Target on-site monitoring by identifying higher risk clinical sites (e.g., sites with data anomalies or a higher frequency of errors, protocol violations, or dropouts relative to other sites).  

• Augment on-site monitoring by performing monitoring activities that can only be accomplished using centralized processes (e.g., statistical analyses to identify data trends not easily detected by on-site monitoring).  

• Monitor data quality through routine review of submitted data in real-time to identify missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic and/or significant errors in data collection and reporting at a site.  

• Verify source data remotely, provided that both source data and CRFs can be accessed remotely.  

• Conduct aggregate statistical analyses of study data to identify sites that are outliers relative to others and to evaluate individual subject data for plausibility and completeness.  

• Conduct analyses of site characteristics, performance metrics (e.g., high screen failure rates, high frequency of eligibility violations, and delays in reporting data), and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance.  

• Complete administrative and regulatory tasks (e.g., collecting and archiving regulatory documents).  

FDA encourages greater reliance on centralized monitoring practices than has been the case historically, with correspondingly less emphasis on on-site monitoring. The extent to which centralized monitoring practices can be employed will depend to some extent on accessibility of electronic records and EDC systems. 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. If a sponsor intends to rely heavily on centralized monitoring practices, it may still be advisable to conduct at least one on-site monitoring visit per site, preferably early in the conduct of the study, to evaluate site processes and controls for provision of data and source documents, particularly for trials intended to support marketing applications.


B. Identify Critical Data and Processes to be Monitored

Sponsors should perform a risk assessment that generally considers the types of data to be collected in a clinical trial, 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. Sponsors should consider the findings of the risk assessment when developing a monitoring plan. There is increasing recognition that some types of errors in a clinical trial are more important than others. 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. In contrast, a small number of errors related to study endpoints (e.g., not following protocol-defined definitions) can profoundly affect study results, as could failure to report rare but important adverse events.

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

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

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

- Conduct and documentation of procedures and assessments related to
  - critical study endpoints,
  - protocol-required safety assessments, and
  - 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.
- Adherence to protocol eligibility criteria intended to include only subjects from the targeted study population for whom the test article is most appropriate
- Conduct and documentation of procedures for ensuring that the study blind is maintained, both at the site level and at the sponsor level, as appropriate
Verification that initial informed consent was obtained appropriately, prior to any study-specific procedures.

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

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

C. Factors to Consider when Developing a Monitoring Plan

A monitoring plan ordinarily should focus on the critical data and processes identified by the risk assessment. The types (e.g., on-site and/or centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and intensity (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 extent on a range of factors, considered during the risk assessment, including the following:

- Complexity of the study design
- Types of study endpoints
- Clinical complexity of the study population
- Geography
- Relative experience of the clinical investigator and of the sponsor with the investigator

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 clinical investigator. 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.

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

Sites in geographic areas where there are differences in standards of medical practice or subject demographics or there is a less established clinical trial infrastructure may require more intensive monitoring, including some level of on-site monitoring.
device use may benefit from more intensive monitoring and early mentoring. In addition, the
relative experience of a sponsor with the clinical investigator 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., 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 (e.g., an on-site monitoring visit).

- 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 to ensure appropriate investigator 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 once procedures are established, less intensive monitoring might suffice. Similarly, a
tapered approach could be used for relatively inexperienced clinical investigators.

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

D. 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 plan should provide
those involved in monitoring with adequate information to effectively carry out their duties. All
sponsor and CRO personnel who may be involved with monitoring, including those who review
and/or determine appropriate action regarding potential issues identified through monitoring,
should review the monitoring plan. The components of a monitoring plan might include the
following:

1. Description of Monitoring Approaches

- A description of each monitoring method to be employed during the study and how it will be
  used to address important risks and ensure the validity of critical data
- Criteria for determining the timing, frequency, and intensity of planned monitoring activities
- Specific activities required for each monitoring method employed during the study, including
  reference to required tools, logs, or templates
- Definitions of events or results that trigger changes in planned monitoring activities for a
  particular clinical investigator.
For example, if it is determined that an investigator deviates significantly from other sites in making safety-related findings or other key safety metrics, the site should be considered for targeted on-site visits. Additional examples of potential triggers include suspected fraud, data outliers (e.g., in rate of enrollment, volume of protocol deviations, or quantity of adverse event/effect reporting), or delays in completing CRFs.33

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

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

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

2. Communication of Monitoring Results

- Format, content, timing, and archiving requirements for reports and other documentation of monitoring activities (see section V)
- Process for appropriate communication
  - of routine monitoring results to management and other stakeholders (e.g., CRO and data management),
  - of immediate reporting of significant monitoring issues to appropriate personnel, and
  - from study management and other stakeholders to monitors.

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

3. Management of Noncompliance

- Process for addressing unresolved or significant issues (e.g., significant non-compliance with the investigational plan) identified by monitoring, whether at a particular site or across study sites
  
  FDA recommends that sponsors develop and include specific processes for addressing, investigating, and reporting suspected and/or confirmed data falsification.34

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

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

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

4. Training and Study-Specific Information

- Description of any specific training required for personnel carrying out monitoring activities, including personnel conducting internal data monitoring, statistical monitoring, or other centralized review activities
- Training should include principles of clinical investigations, critical protocol-specific requirements, the study monitoring plan, applicable standard operating procedures, and appropriate monitoring techniques.
- Planned quality monitoring to ensure that sponsor and CRO staff conduct monitoring activities in accordance with the monitoring plan, applicable regulations, guidance, and sponsor policies, procedures, templates, and other study plans.
- For example, many companies have successfully implemented on-site co-monitoring visits (i.e., monitoring visits performed by both a study monitor and the monitor’s supervisor or another evaluator designated by the sponsor or CRO) to evaluate whether monitors are effectively carrying out visit activities, in compliance with the study monitoring plan. These visits may be conducted either for randomly selected monitors or may be targeted to specific monitors, based upon questions arising from review of monitoring visit documentation.
- 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 and require on-site training

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

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

5. Monitoring Plan Amendments

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

35 Sponsors of significant risk device studies are required under 21 CFR 812.25(e) to submit and maintain written procedures for monitoring.
V. DOCUMENTING MONITORING ACTIVITIES

Documentation of monitoring activities should include the following:

- The date of the activity and the individual(s) conducting it
- A summary of the data or activities reviewed
- A description of any noncompliance, potential noncompliance, data irregularities, or other deficiencies identified
- A description of any actions taken, to be taken, and/or recommended, including the person responsible for completing actions and the anticipated date of completion

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

VI. ADDITIONAL STRATEGIES TO ENSURE STUDY QUALITY

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

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

A. Clinical Investigator Training and Communication

Clinical trial monitors conducting on-site visits have historically played an important role in training the investigator and his/her staff during a study. On-site visits also have served as a primary means of providing feedback to investigators 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), investigators 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:

- On-site visits should include sufficient time for mentoring, feedback, and additional training, if needed, during the conduct of the study.
- It may be necessary to implement alternative training and communication methods (teleconferences, webcasts, or online training modules) 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.

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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. Although sponsors can transfer responsibilities for monitoring to a CRO(s), they retain responsibility for oversight of the work completed by the CRO(s) who assume this responsibility.

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