Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices

Guidance for Industry

DRAFT GUIDANCE

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Protocol Deviations for Clinical Investigations of Drugs, Biological Products, and Devices
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

This guidance provides recommendations to assist sponsors, clinical investigators, and institutional review boards (IRBs) in defining, identifying, and reporting protocol[2] deviations in clinical investigations. FDA regulations do not include a definition of the term *protocol deviation* or provide a system for classifying the various types of deviations that may occur during the conduct of a clinical investigation. A system that applies consistent classification, reporting, and documentation standards is important to assure the most interpretable and useful information emerges from the reporting of protocol deviations.

To address these considerations, this guidance includes the following:

- Definitions for *protocol deviations* and *important protocol deviations*
- Recommendations on the types of protocol deviations that sponsors should report to FDA in clinical study[3] reports for drugs[4] and devices
- Recommendations on the types of protocol deviations that investigators should report to sponsors and to IRBs
- Recommendations for IRBs in their evaluation of protocol deviations

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Oncology Center of Excellence at the Food and Drug Administration.

[2] In this guidance, the term *protocol* encompasses both written protocols and their related plans and procedures (e.g., monitoring plan, statistical analysis plan).

[3] In this guidance, the terms *clinical investigation*, *trial*, and *study* are interchangeable.

[4] In this guidance, the terms *drugs* or *drug product* include human drugs and biological products unless otherwise specified.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, 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

Protocol deviations are generally unintentional departures from the IRB-approved protocol and are commonly not discovered until after they occur (e.g., an investigator's failure to perform a protocol-required test is discovered by the study monitor during a routine monitoring visit). Protocol deviations may also include an intentional departure from the IRB-approved protocol for a single participant (e.g., investigator seeks and receives sponsor and IRB approval to enroll a participant above the maximum age criteria); such intentional departures should be rare because the protocol should include appropriate flexibility regarding trial conduct (e.g., eligibility criteria, reasonable visit windows). In the conduct of a clinical investigation, however, some deviations from the specifics outlined in the protocol may occur. In 2013, FDA issued the International Council for Harmonisation (ICH) guidance for industry *E3 Structure and Content of Clinical Study Reports: Questions and Answers (R1)*, which includes clarifications for implementing the recommendations in the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996) regarding the structure and content of a clinical study report. To help clarify recommendations regarding the reporting of protocol deviations as recommended in ICH E3, ICH E3(R1) defines a protocol deviation as "any change, divergence, or departure from the study design or procedures defined in the protocol" and defines important protocol deviations as "a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being."[5] In this guidance, FDA is adopting the ICH E3(R1) definitions of protocol deviation and important protocol deviation.

Since publication of ICH E3(R1), FDA has received feedback from interested parties requesting additional guidance on reporting protocol deviations. Therefore, FDA is issuing this guidance to help clarify sponsor and investigator responsibilities for identifying, mitigating, and reporting protocol deviations and to provide recommendations to IRBs for evaluating protocol deviations.

Clinical investigation protocols document the study design, objectives, population, planned procedures, investigational product management, method(s) of data capture, monitoring and oversight plans, and statistical analysis plans either directly or by reference to associated investigational plans. Protocols are a critical part of a clinical investigation, and it is essential that a complete protocol is available before study initiation.

[5] See Q7 in the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports: Questions and Answers (R1)* (January 2013). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Clinical studies are conducted in accordance with the protocol, good clinical practice (GCP) guidelines,[6] and regulatory requirements governing the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies.[7] Although protocols may directly reference GCP guidelines or requirements, FDA does not consider all potential GCP compliance issues to be protocol deviations. For example, if a monitor discovers that the site delegation log is missing a signature of one of the site study staff, this missing signature should be addressed, but it is not considered a protocol deviation because the protocol likely does not specify this level of detail at the site level. Classifying potential GCP compliance issues as protocol deviations can inflate the number of events submitted to sponsors, FDA, and IRBs. FDA recommends that potential GCP compliance issues that are not deviations from the protocol be managed outside the protocol deviation process outlined in this guidance.

III. DISCUSSION

A. Protocol Deviations

Protocol deviations can be identified in many ways (e.g., by site staff, by study staff, through site monitoring, through centralized monitoring, through audits of study records and procedures, through regulatory inspections). Some deviations have limited likelihood of meaningfully altering study data quality or patient safety, whereas others could increase the risks to trial participants and/or adversely impact data quality. Additionally, deviations may occur at the participant level (e.g., missed scheduled visit, inclusion of a participant not meeting eligibility criteria, failure to conduct a protocol-specified procedure during a visit), at the site level (e.g., storage of investigational products outside of protocol-required temperature range), or at the study level (e.g., premature unblinding of treatment assignments).

Proper identification and documentation of protocol deviations are essential for FDA's review of clinical investigations that support the safety and effectiveness of investigational products.[8] FDA staff may consider the impact of both the number and the types of protocol deviations in considering the overall study data quality and the interpretability of trial results, when assessing the safety and efficacy of medical products, and in making benefit-risk determinations during review of medical product premarket submissions. Deviations such as incorrectly enrolled, monitored, or assessed study participants and/or improperly obtained, missing, or inaccurately recorded data may lead to the conclusion that the study is not adequate and well-controlled, and the data is therefore not verifiable. Additional examples of circumstances of concern for FDA include frequent protocol deviations for safety reporting, missing collection of protocol-specified

[6] See the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

[7] For a summary of FDA regulations relating to GCP, see FDA's web page Regulations: Good Clinical Practice and Clinical Trials, available at https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials.

[8] Identification and documentation of protocol deviations may vary depending on whether the protocol deviation impacts data quality or patient safety.

safety laboratory values, and incorrectly performed efficacy endpoint assessment procedures, among other things.

1. Important Protocol Deviations

As noted above, in this guidance an important protocol deviation is a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. While other terms such as major, critical, and significant have sometimes been used to classify such protocol deviations, FDA recommends using *important* to encompass all these terms.

Thoughtful protocol design can help to minimize important protocol deviations. In general, deviations that are classified as important should be those that could affect critical-to-quality factors[9] for the trial; protocol deviations related to critical-to-quality elements should be identified. The quality by design approach to clinical research involves focusing on these critical-to-quality factors to ensure the protection of the rights, safety, and well-being of study participants; the generation of reliable and meaningful results; and the management of risks to those factors using a risk-proportionate approach.[10] Examples of critical-to-quality factors are procedures and processes that affect the protection of trial participants and/or the efficacy or safety analyses (e.g., accuracy in certain eligibility criteria, accuracy in the assessment of randomization integrity, accurate collection of specific endpoint procedures). These quality factors are critical to the reliability and interpretability of the study data.

It may be helpful for a protocol to define important protocol deviations and provide examples of what constitutes such for the particular study. The following is a non-exhaustive list of protocol deviations considered to be important by FDA due to the impact on the protection of trial participants and the assessment of safety:

- Failure to conduct study procedures designed to assess participant safety or failure to adequately monitor participants; for example, (1) failure to collect important laboratory assessments for monitoring safety issues or (2) failure to administer the study product according to specifications in the protocol

- Administration of concomitant treatment prohibited by the study protocol that may increase risks to participants (e.g., drug-drug interactions) and/or impact interpretation of a device's safety and efficacy

[9] See the ICH guidance for industry *E8(R1) General Considerations for Clinical Studies* (April 2022). Critical-to-quality factors are attributes of a study whose integrity is fundamental to the protection of study participants, the reliability and interpretability of the study results, and the decisions made based on the study results.

[10] Ibid.

- Failure to obtain informed consent or meet other applicable requirements under FDA regulations for the protection of human subjects[11] under 21 CFR part 50

- Failure to protect a participant's identifiable private protected health information

- Failure to withdraw investigational product administration from trial participants who meet withdrawal criteria

- Administration of the wrong treatment or incorrect dose to trial participants or implantation of an incorrect device

- Failure to adhere to the protocol-specified randomization scheme

The following is a non-exhaustive list of protocol deviations considered to be important by FDA that may reduce the reliability of conclusions on effectiveness:

- Enrollment of a trial participant in violation of key eligibility criteria designed to ensure a specific participant population[12]

- Failure to collect data to evaluate important study endpoints (e.g., primary or secondary endpoints)

- Premature unblinding of a trial participant's treatment allocation for reasons other than those specified in the study protocol

2. All Other Protocol Deviations

All other protocol deviations that do not meet the definition of an important protocol deviation may encompass the commonly used terms minor, noncritical, and non-significant deviations. Examples of all other protocol deviations may include small deviations from protocol-specified visit windows; a signed consent with a page missing a participant's initial; or failure to perform a study procedure not relevant for safety monitoring or not related to an important study efficacy endpoint (e.g., primary or secondary endpoints).

B. Roles and Responsibilities in Monitoring, Mitigating, and Reporting Protocol Deviations

1. Role of the Investigator in Monitoring, Mitigating, and Reporting Protocol Deviations

[11] FDA uses the term *subject* here to be consistent with the language used in the Agency's human subjects protection regulations. Throughout this document, FDA will use the terms *subject* and *participant* interchangeably, using *subject* only when referencing these regulations.

[12] See ICH E3(R1).

Investigators are responsible for protecting the rights, safety, and welfare of participants under their care during a clinical investigation (21 CFR 312.60 and 812.100). Failing to comply with aspects of the sponsor- and IRB-approved protocol that are designed to ensure that participants are not exposed to unreasonable risks may be considered a failure to protect the rights, safety, and welfare of participants.[13] When reporting protocol deviations to the sponsor, investigators should identify important deviations.

For drug investigations, investigators should report to the sponsor all protocol deviations of which they are aware, using reporting procedures that highlight important protocol deviations. In the rare instance when an investigator contemplates an intentional departure from the IRB-approved protocol intended for a single participant, the investigator should get prior sponsor approval and must get prior IRB approval (21 CFR 312.66) unless there is an urgent need to eliminate apparent immediate hazards to human subjects; however, such protocol deviations should be extremely rare because sponsors should incorporate the appropriate degrees of flexibility within the protocol (see section III.B.2).[14] The investigator must promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others and not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to participants (21 CFR 312.66).

Similarly, for device investigations, investigators must keep records of each protocol deviation (21 CFR 812.140(a)(4)) and must notify the sponsor and the IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency as soon as possible but no later than 5 working days after the emergency occurred (21 CFR 812.150(a)(4)). Except in such an emergency, investigators must get prior sponsor approval for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human participants, prior FDA and IRB approval is also required (21 CFR 812.150(a)(4)).

2. Role of the Sponsor in Evaluating, Mitigating, and Reporting Protocol Deviations

Sponsors are responsible for monitoring clinical investigations and ensuring the investigations are conducted in accordance with the investigational plan and protocol (21 CFR 312.50, 812.40, and 812.46).[15] Monitoring for protocol deviations during study conduct can help sponsors identify site or study quality issues that can be addressed and improved; assessment of protocol deviations after study completion can help in determining whether the study data are of sufficient quality to be reliable and interpretable. Sponsors should also train investigators on the protocol to facilitate their adherence to the protocol as well as provide training on identifying important protocol deviations. Sponsors should focus planned oversight on critical trial activities to

[13] See the guidance for industry *Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects* (October 2009).

[14] Under applicable Federal regulations, investigators must engage with the Drug Enforcement Administration when amending protocols for research involving Schedule I substances under the Controlled Substances Act by requesting a modification to a site-specific investigator registration (see 21 CFR 1301.18).

[15] See the information sheet guidance for IRBs and clinical investigators *Sponsor - Investigator - IRB Interrelationship* (January 1998).

improve detection of important protocol deviations. Whenever possible, identified important protocol deviations should be promptly remedied or addressed during the conduct of the clinical investigation to minimize risks to participants and to preserve the quality of the clinical investigation.

Sponsors should receive information on all protocol deviations, most likely from site and central monitoring efforts. The protocol should pre-specify which types of protocol deviations will be considered important, although with accumulating data and review, the list of important protocol deviations can be updated over time. Sponsors should inform investigators of the time frame and the manner in which they expect to receive information about protocol deviations (e.g., important protocol deviations should be reported to sponsor expeditiously within x days of occurrence; all other deviations reported when the site monitor visits the trial site).

Sponsors should include a discussion of important protocol deviations in the body of the clinical study reports submitted as part of a new drug application (NDA) or a biologics license application (BLA).[16] In the Patient Data Listing section of the appendix to the clinical study report, sponsors should provide a listing of all trial participants (by unique subject identifier) with important protocol deviations organized by clinical trial site (if the study is a multicenter study).[17] Sponsors should also report all protocol deviations in the Study Data Tabulation Model[18] Protocol Deviation (DV) domain, which will assist FDA in confirming whether protocol deviations had a significant impact on data quality. Sponsors should include a variable in the DV domain that provides the sponsor's determination of whether the protocol deviation was important. For device studies, sponsors should include a description of any deviations from the investigational plan by investigators in their premarket approval application.[19]

In addition to including protocol deviation information in their clinical study reports (see section III.B.1), during the conduct of the clinical investigation, sponsors must report serious and unexpected suspected adverse reactions for drug products under 21 CFR 312.32; serious adverse events under 21 CFR 320.31(d)(3) for IND-exempt bioavailability/bioequivalence studies; and unanticipated adverse device effects under 21 CFR 812.150 (b)(1). Sponsors should note in such mandatory reports when protocol deviations contributed to the occurrence of these events (e.g., a safety laboratory test to monitor for a potential drug safety event was not collected, and the safety event subsequently occurred and was serious).

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[16] For applications submitted to the Center for Drug Evaluation and Research, all protocol deviations should also be provided as described in the most current version of the *Bioresearch Monitoring Technical Conformance Guide*. See the *Bioresearch Monitoring Technical Conformance Guide*, Version 3.1, September 2024, available at https://www.fda.gov/media/85061/download.

[17] See the ICH guidance for industry *E3 Structure and Content of Clinical Study Reports* (July 1996).

[18] See *Study Data Technical Conformance Guide - Technical Specifications Document*, October 2024, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document.

[19] See FDA's web page PMA Clinical Studies, available at https://www.fda.gov/medical-devices/premarket-approval-pma/pma-clinical-studies.

For protocol deviations not classified as important, sponsors should document and evaluate the deviations to determine if the types and numbers of these protocol deviations warrant reclassification; if the sponsor determines that reclassification is warranted, they should then notify the investigator of the reclassification. Sponsors should carefully consider investigators' protocol deviation requests to determine whether a protocol amendment is needed to promote consistent trial conduct by all investigators. Sponsors should incorporate appropriate degrees of flexibility in the protocol so that intentional deviations will not be necessary. Irrespective of sponsor approval of an intentional protocol deviation, investigators must get prior IRB approval (21 CFR 312.66) unless there is an urgent need to eliminate apparent immediate hazards to human subjects.

Sponsors may prevent the occurrence or mitigate the impact of important protocol deviations by using quality by design principles to develop study protocols.[20] Developing protocols that are less complex and provide for greater flexibility in implementation, if appropriate, may decrease the occurrence of protocol deviations. Sponsors can minimize the occurrence of protocol deviations by identifying those aspects of the study that are critical to quality and, when possible, mitigating risks such as by:

- Establishing flexible enrollment criteria when appropriate to give investigators more discretion and removing unnecessary enrollment criteria[21]
- Streamlining the study design
- Using flexible time frames for collection of essential data where feasible
- Conducting certain assessments remotely when possible
- Eliminating nonessential activities
- Reviewing prohibited medications to avoid excluding medications that may be appropriate if only taken for a very brief period and where such drug ingestion would not impact either patient safety or study efficacy assessments

When designing the study, sponsors should seek input from relevant stakeholders, including potential trial participants and clinical investigators and their staff, to help ensure adherence to the planned protocol by developing procedures that are feasible and not unnecessarily burdensome. Before or during protocol development, sponsors should conduct a risk assessment to identify protocol elements (e.g., visit structure, visit procedures, visit windows, enrollment criteria) that can be made more flexible (or even eliminated entirely) to avoid the occurrence of protocol deviations. Sponsors should also identify and document those protocol elements (e.g., enrollment criteria, safety monitoring procedures, procedures related to primary or secondary efficacy endpoints) that are critical to patient safety and data quality.

[20] See ICH E8(R1).

[21] For more information on broadening eligibility criteria, see the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

Sponsors should assess the risks that such critical protocol elements may not be properly conducted (e.g., complicated enrollment criteria, complex procedures), work to mitigate risks associated with these elements, and then develop the study's specific plans (e.g., medical monitoring plan, safety monitoring plan, data management plan, risk-based monitoring plan, independent endpoint adjudication charter) that will be used during the conduct of the trial to further minimize the occurrence and the potential impact of important protocol deviations on data quality or participants' safety.[22,23] Further, investigators, site staff, study monitors, and sponsor staff should be trained to focus on critical elements to ensure they are implemented as specified in the protocol and associated study plans and to avoid important protocol deviations that may impact trial participant safety or data quality. Finally, site monitors and centralized monitoring activities should focus on critical elements for early identification of important protocol deviations at specific sites or that suggest a pattern consistent with a systemic study issue.

If there are recurrent protocol deviations that are similar in nature, the sponsor or clinical investigator should conduct a root-cause analysis to determine what actions may be appropriate to address the noted noncompliance and prevent recurrence of the same or similar deviations. Sponsors should document this determination and whether further action is taken (e.g., development of a corrective and preventive action plan, update to the study risk assessment and mitigation plans, protocol amendment) and consider updating their analysis if the deviations impact critical-to-quality factors. A high number of protocol deviations at a specific site or sites may suggest that additional resources (e.g., staffing, training) may be needed. Sponsors should consider closing a trial site when despite attempts at remediation, the site is unable to maintain GCP standards, comply with the protocol, or implement measures to identify and/or address recurring important protocol deviations.

3. Role of the IRB in Evaluating Protocol Deviations

Under applicable FDA regulations, the IRB is responsible for reviewing and approving the initiation of and conducting periodic review of clinical investigations involving human subjects (21 CFR 56.102(g)). The primary purpose of such review is to assure the protection of the rights and welfare of human subjects (21 CFR 56.102(g)). IRBs must follow written procedures for ensuring prompt reporting to the IRB of changes in research activity and for ensuring that changes in approved research may not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to human subjects (21 CFR 56.108(a)(3) and (4)).

For drugs, the IRB must approve all changes in the research, except where necessary to eliminate apparent immediate hazards to participants (21 CFR 312.66). The IRB is also responsible for approving all changes in the protocol (21 CFR 312.30(b)(2)(i)(b)). A protocol change intended

[22] For more information on the use of risk-based monitoring techniques, see the guidance for industry *Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring* (August 2013); see also the guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations: Questions and Answers* (April 2023).

[23] See ICH E6(R2).

to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c).[24] For device studies, if the changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, the investigator is required to get prior IRB and FDA approval (21 CFR 812.150(a)(4)).

Where possible, FDA recommends that protocol deviations that are classified as important be submitted by the investigator to the IRB when they are identified, and in accordance with the IRB's written procedures. The IRB should review important protocol deviations submitted by investigators as soon as possible to determine any impact on participant safety or study conduct. All other protocol deviations that are not classified as important and do not present an apparent immediate hazard to participants do not need to be immediately reported to the IRB.

C. Protocol Amendments and Changes to an Investigational Plan

Changes in a protocol are typically not implemented before review and approval by the IRB and, in some cases, by FDA. Any modifications to protocol-specified procedures that occur without prior IRB approval and submission to FDA of the protocol amendment implementing the modification are considered protocol deviations. Sponsors and clinical investigators are encouraged to engage with IRBs as early as possible when urgent or emergent changes to the protocol or informed consent are anticipated. However, when changes to the protocol or investigational plan are required to minimize or eliminate immediate hazards (e.g., rapidly managing an evolving situation) or to protect the life and well-being of research participants, they may be implemented without prior IRB approval or before filing an amendment to the IND under 21 CFR 312.30(b)(2)(ii). A change to the protocol or investigational plan that is required to minimize or eliminate immediate hazards is still considered a protocol deviation if it occurs before IRB approval and should be reported as such (for additional information, see section III.B). For devices, certain protocol changes or modifications to the investigational plan can be made without prior FDA approval.[25] For example, a change or modification to the clinical protocol may be reported in a 5-day notice if the changes do not affect (1) the validity of the data or information resulting from the completion of the approved protocol or the relationship of likely patient risk to benefit relied upon to approve the protocol; (2) the scientific soundness of the investigational plan; or (3) the rights, safety, or welfare of the human subjects involved in the investigation. The sponsor is responsible for initially determining if the change meets the statutory criteria.[26]

[24] 21 CFR 312.30(b)(2)(ii).

[25] See 21 CFR 812.35(a)(2) through (4).

[26] See section 520(g)(6)(A)(ii)(I) through (III) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360j(g)(6)(A)(ii)(I) through (III)) and 21 CFR 812.35(a)(3).