

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors FDA Inspections of Clinical Investigators

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Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors¹ FDA Inspections of Clinical Investigators

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 it 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 provide information about FDA inspections of clinical investigators conducted under FDA's Bioresearch Monitoring (BIMO) Program. This document supersedes FDA's Information Sheet Guidance, "FDA Inspections of Clinical Investigators," dated January 2006. This document has been revised to provide updated information and is being issued in accordance with the agency's regulations on Good Guidance Practices (21 CFR 10.115).

FDA's guidance documents, including this guidance, 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

FDA developed its BIMO Program to help ensure the protection of the rights, safety, and welfare of human research subjects involved in FDA-regulated clinical trials, to verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications, and to assess compliance with statutory requirements and FDA's regulations governing the conduct of clinical trials. Among other activities, the FDA BIMO Program involves site visits to clinical investigators, sponsors, monitors, contract research organizations, Institutional Review Boards (IRBs), nonclinical (animal) laboratories, and bioequivalence analytical laboratories. This document addresses site visits to clinical investigators who conduct clinical investigations that are regulated by FDA under 21 USC 355(i) or 21 USC 360j(g).

¹ This guidance document was developed by the Office of Good Clinical Practice in the Office of the Commissioner (OC) in coordination with the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), the Center for Drug Evaluation and Research (CDER), and the Office of Regulatory Affairs (ORA).

III. WHEN ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

FDA conducts clinical investigator inspections to determine if the clinical investigators are conducting clinical studies in compliance with applicable statutory and regulatory requirements. Clinical investigators who conduct FDA-regulated clinical investigations are required to permit FDA investigators to access, copy, and verify any records or reports made by the clinical investigator with regard to, among other records, the disposition of the investigational product and subjects' case histories. See 21 CFR 312.68 and 812.145. The FDA investigator typically performs this oversight function through on-site inspections designed to document how the study was actually conducted at the clinical investigator's site. For investigational drug studies, clinical investigators must retain study records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified. See 21 CFR 312.62(c). For investigational device studies, clinical investigators must retain study records for a period of two years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol. See 21 CFR 812.140(d).

FDA conducts both announced and unannounced inspections of clinical investigator sites, typically under the following circumstances:

- to verify the accuracy and reliability of data that has been submitted to the agency;
- as a result of a complaint to the agency about the conduct of the study at a particular investigational site;
- in response to sponsor concerns;
- upon termination of the clinical site;
- during ongoing clinical trials to provide real-time assessment of the investigator's conduct of the trial and protection of human subjects;
- at the request of an FDA review division; and
- related to certain classes of investigational products that FDA has identified as products of special interest in its current work plan (i.e., targeted inspections based on current public health concerns).

IV. HOW ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

Upon arrival at the clinical investigator study site, the FDA investigator will display his/her FDA credentials and issue a completed Form FDA 482 (Notice of Inspection) to the clinical investigator or appropriate study staff. FDA is authorized at reasonable times to access, inspect, and copy any required records related to the clinical investigation. See section 704 of the Federal Food, Drug, and Cosmetic Act (21 USC 374), 21 CFR 312.68, and 21 CFR 812.145.

During an inspection at the site of a clinical investigator, the FDA investigator typically verifies compliance with the regulations governing the use of investigational products and human subject

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protections at 21 CFR parts 50, 56, 312, and/or 812, by inspecting records and talking to individuals involved in the conduct of the study to ascertain:

- who performed various aspects of the protocol for the study (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data);
- whether the IRB approved the protocol, informed consent form, and any amendments to the protocol prior to implementation;
- whether the clinical investigator and study staff adhered to the sponsor's protocol and investigational plan and whether protocol deviations were documented and reported appropriately;
- whether informed consent documents were signed by the subject or the subjects' legally-authorized representative prior to entry in the study (i.e., performance of any study-related procedures);
- whether authority to conduct aspects of the study was delegated, and if so, how the conduct of the study was supervised by the clinical investigator²;
- where specific aspects of the investigation were performed;
- how the study data were obtained and where the study data were recorded;
- accountability for the investigational product, including shipping records and disposition of unused investigational product;
- whether the clinical investigator disclosed information regarding his financial interests to the sponsor and/or interests of any subinvestigator(s), spouse(s) and dependent children³;
- the monitor's communications with the clinical investigator;
- the monitor's evaluations of the progress of the investigation; and
- corrective actions in response to previous FDA inspections, if any, and regulatory correspondence or sponsor and/or monitor correspondence.

The FDA investigator also may audit the study data by comparing the data filed with the agency or the sponsor, if available, with records related to the clinical investigation. Such records may include the case report forms and supporting source documentation including signed and dated consent forms and medical records including, for example, progress notes of the physician, the subject's hospital chart(s), and the nurses' notes. These records may be in hard copy and/or an electronic format. For electronic records and/or electronic signatures, the FDA investigator may gather information to determine whether 21 CFR part 11 requirements have been met.⁴

² Clinical investigators either conduct a clinical trial or are the responsible party of a team of investigators. See 21 CFR 312.3 and 812.3(i). The clinical investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's care. See 21 CFR 312.60 and 812.100. For further information, refer to "Guidance for Industry: Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects": <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>.

³ See generally 21 CFR part 54 for requirements related to financial disclosures by clinical investigators and "Guidance for Industry - Financial Disclosure by Clinical Investigators": <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm>.

⁴ For more information concerning electronic records and part 11 requirements, refer to 21 CFR part 11 and "Guidance for Industry: Part 11, Electronic Records, Electronic Signatures – Scope and Application": <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf>. In addition, supplemental guidance on the use of computerized systems in clinical investigations is available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070266.pdf>.

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FDA may also examine subjects' medical records that are part of the clinical investigation and predate the study to verify whether the condition under study was in fact diagnosed, the study eligibility criteria were met, and whether the subject received any potentially interfering medication prohibited by the protocol. The FDA investigator may also review subjects' records covering a period after completion of study-related activities to determine if there was proper follow-up as outlined in the protocol, and if the clinical investigator submitted all reportable adverse events (including all clinical signs and symptoms). See 21 CFR 312.64(b) and 812.150(a). For more information about the procedures FDA uses during inspections of clinical investigator sites, see FDA's Compliance Program Guidance Manual (CPGM), *Bioresearch Monitoring, Clinical Investigators and Sponsor-Investigators*, Program 7348.811.⁵

V. INTERNATIONAL INSPECTIONS

FDA's inspection of clinical investigators is not limited to the United States (U.S.). International inspections are generally conducted when the studies are part of a marketing application submitted to FDA and provide data critical to decision-making on product approval. See FDA's CPGM, Program 7348.811, "Clinical Investigators and Sponsor-Investigators."⁶ Such assignments include studies that are conducted under an FDA investigational new drug application (IND), as well as studies at non-U.S. sites that are not conducted under an IND or under an investigational device exemption (IDE).

Studies Involving Investigational Drugs and Biologics

FDA inspects clinical investigators conducting foreign trials, either under an IND or in support of an IND, a new drug application (NDA) or a biologics license application (BLA). Although sponsors of clinical trials conducted outside the U.S. are not required to file an IND, sponsors submitting foreign clinical studies not conducted under an IND to FDA must comply with requirements in 21 CFR 312.120. If a clinical investigator conducts a study under an IND outside of the U.S., the clinical investigator is subject to FDA regulations, including applicable provisions in 21 CFR parts 50, 56, and 312. FDA validates the authenticity and accuracy of data and confirms compliance during an inspection, which is performed under the circumstances listed above in section III.

When FDA considers whether to accept non-U.S., non-IND clinical studies in support of an IND, NDA, or BLA, an FDA inspection may help in determining whether the study was conducted in accordance with 21 CFR 312.120. Specifically, the inspection will evaluate whether the following criteria are met:

- The study is well-designed and well-conducted.
- The study is conducted in accordance with Good Clinical Practice (GCP), which is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials in a way that provides assurance that

⁵ <http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf>.

⁶ *Ibid.*

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the data and reported results are credible and accurate and that the rights, safety, and well-being of trial subjects are protected.

- The study has been reviewed and approved (or provision of a favorable opinion) by an independent ethics committee (IEC) prior to study initiation, continuing review of an ongoing study by an IEC, and the freely given and documented informed consent of the subject (or the subject's legally authorized representative if the subject is unable to provide consent) prior to any study-specific procedures.

Studies Involving Investigational Devices

FDA's inspection of clinical investigators conducting foreign trials includes device trials in support of a premarket approval application (PMA) or a premarket notification (510(k)) submission.

For device studies conducted outside the U.S., FDA will accept research in support of a PMA, but which has not been conducted under an IDE, if certain conditions are met. An FDA inspection may help in determining whether the study was conducted in accordance with 21 CFR 814.15. Specifically, the inspection will evaluate whether the following criteria are met:

- the data are valid; and
- the studies are conducted in conformance with the "Declaration of Helsinki,"⁷ or the laws and regulations of the country in which the research is conducted, whichever affords greater protection to the human subjects.

FDA validates the authenticity and accuracy of data and confirms compliance during an inspection, which is performed under the circumstances listed above in section III. The FDA investigator may request documentation as to whether the study was conducted under the laws and regulations of the non-U.S. country and/or the Declaration of Helsinki, whichever accords greater protection to human subjects.

VI. WHAT HAPPENS AFTER AN INSPECTION?

At the end of an inspection, the FDA investigator conducts an exit interview with the clinical investigator or his/her representative. At this interview, the FDA investigator who conducted the inspection reviews and discusses the findings from the inspection and, if deficiencies were found, issues a written Form FDA 483 (Inspectional Observations; 483) to the clinical investigator or his/her representative. The 483 describes any inspectional observations that, in the opinion of the FDA investigator conducting the inspection, represent deviations from applicable statutes and regulations.

Some common deficiencies that have been observed by FDA investigators during a clinical investigator inspection include:

⁷ 21 CFR part 814 refers to the Declaration of Helsinki as revised in 1983. There have been subsequent revisions of the Declaration, but FDA has not officially adopted subsequent versions.

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- failure to follow the investigational plan and signed investigator statement/agreement (e.g., failure to conduct or supervise the study in accordance with the relevant, current protocol(s)). See 21 CFR 312.60 and 812.110(b).
- protocol deviations (e.g., failure to appropriately document and report any medically necessary protocol deviations). See 21 CFR 312.66 and 812.150(a)(4).
- inadequate recordkeeping. See 21 CFR 312.62 and 812.140(a).
- inadequate accountability for the investigational product. See 21 CFR 312.62(a) and 812.140(a)(2).
- inadequate subject protection, including informed consent issues. See 21 CFR part 50, 312.60, and 812.100.

The clinical investigator may respond to the 483 observations orally during the exit interview and/or respond in writing after the inspection. If the clinical investigator chooses to respond in writing to the deficiencies listed on the 483, the response should be directed to the FDA District Office listed in the upper left corner of the 483.⁸ (A list of FDA District Offices is also posted on FDA's website (<http://www.fda.gov/ICECI/Inspections/IOM/ucm124008.htm>)).

Following the inspection, the FDA investigator who conducted the inspection prepares a written Establishment Inspection Report (EIR). The EIR, Form FDA 483 (if issued), copies of any materials collected during the inspection, and any clinical investigator response that has been received by the District Office are forwarded to the appropriate FDA Center for further evaluation and final classification of the inspection outcome. After this review, one of the following types of letters is typically sent from the appropriate FDA Center to the clinical investigator:

- (1) A letter that generally states that FDA observed basic compliance with pertinent regulations. Note that a letter is not always sent when FDA observes no significant deviations. See FDA's CPGM, Program 7348.811, "Clinical Investigators and Sponsor-Investigators."⁹
- (2) An *Informational or Untitled Letter* that identifies deviations from statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. Generally, such letters may request a written response from the clinical investigator. See FDA's procedures regarding initiation of Untitled Letter procedures, found in the Regulatory Procedures Manual (RPM) in Chapter 4-2.¹⁰
- (3) A *Warning Letter* that identifies serious deviations from applicable statutes and regulations. A Warning Letter is issued for violations of regulatory significance.

⁸ Generally, FDA will allow 15 business days to provide a response to FDA 483 observations. If FDA receives a response to FDA 483 observations within 15 business days after the FDA 483 was issued, FDA plans to conduct a detailed review of the response before determining whether to issue a warning letter. If FDA receives a response to FDA 483 observations more than 15 business days after the FDA 483 was issued, FDA does not plan to routinely include a response on the apparent adequacy of the corrective actions in the warning letter. See 74 FR 40211 (Aug. 11, 2009): <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480a0583c>.

⁹ <http://www.fda.gov/downloads/ICECI/EnforcementActions/BioresearchMonitoring/ucm133773.pdf>.

¹⁰ <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176871.htm>.

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Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. Warning Letters are issued to achieve voluntary compliance, and include a request for correction and a written response to the agency. See FDA's procedures regarding initiation of disqualification proceedings, found in the RPM in Chapter 4-1.¹¹

- (4) *A Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)*. FDA may initiate a process to disqualify the clinical investigator from receiving investigational new drugs and/or biologics if disqualified under part 312, or investigational devices if disqualified under part 812, if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report. See 21 CFR 312.70 and 812.119. The NIDPOE identifies alleged violations and provides the investigator with an opportunity to explain the matter at an informal conference or in writing. If, in response to the NIDPOE, the investigator provides an explanation that is accepted by the agency and the disqualification is not warranted, alternatives such as a detailed corrective action plan may be considered. If the investigator's explanation is not accepted by the agency, the agency may issue a Notice of Opportunity for Hearing (NOOH) under 21 CFR part 16. For more information, please refer to FDA's Information Sheet Guidance, "Clinical Investigator Administrative Actions - Disqualification."¹² See FDA's procedures regarding initiation of disqualification proceedings, found in the RPM in Chapter 5-9.¹³

To help ensure prompt corrective action by the clinical investigator and to help ensure the protection of research subjects, FDA provides copies of warning letters and NIDPOEs to the study sponsor and reviewing IRB.¹⁴

In addition, following final classification of the inspection by the FDA Center, the inspection results are shared with the FDA division assigned to review the marketing submission. The assigned review division considers the results of the inspection during its review of the sponsor's marketing submission. If the inspection reveals serious violations of FDA's clinical investigation regulations (e.g., failure to follow the investigational plan), the assigned review division may request additional analyses of the study data or may reject the affected data in certain situations where FDA considers the data unreliable.

FDA also posts final clinical investigator inspection classifications¹⁵ as well as warning letters, NIDPOEs, and other information about clinical investigators who have been disqualified or restricted in their ability to receive investigational products on its website:

¹¹ <http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176870.htm>.

¹² <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214008.pdf>.

¹³ <http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074324.pdf>.

¹⁴ FDA's disclosure of this information to the sponsor(s) and supervising IRB(s) does not violate the Privacy Act of 1974. See 63 FR 55873, October 19, 1998.

¹⁵ This information is available for clinical studies involving drugs, <http://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm>, and biologics, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/UCM167052.pdf>.

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<http://www.fda.gov/ICECI/EnforcementActions/DisqualifiedRestrictedAssuranceList/default.htm>

VII. WHO CAN PROVIDE MORE INFORMATION?

If, during or after an FDA inspection, a clinical investigator has any questions that the FDA investigator conducting the inspection has not answered, either the District Office Director or the contact person at the FDA Center that assigned the inspection can be contacted. The FDA investigator who conducted the inspection should be able to provide the name and telephone number of the District Office Director and the specific FDA Center contact person.