Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors

FDA Inspections of Clinical Investigators

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U.S. Department of Health and Human Services
Food and Drug Administration

January 2006

Contains Nonbinding Recommendations

Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors[1] FDA Inspections of Clinical Investigators

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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 another document, "FDA Clinical Investigator Inspections," issued in September 1998, by the former Office of Health Affairs, FDA. 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)[2].

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 ensure the protection of the rights, safety, and welfare of human research subjects and the quality and integrity of data submitted to the Agency. Among

[1] This guidance document was developed by the Good Clinical Practice Program 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).

[2] 65 FR 56477, September 19, 2000.

other things, 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) and 21 USC 360(j) and clinical investigations that support applications for research or marketing permits for products regulated by FDA.

III. WHEN ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

FDA conducts clinical investigator inspections to determine if the clinical investigators are operating in compliance with current FDA regulations and statutory 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 the disposition of the product and subject case histories (21 CFR 312.68 and 812.145). FDA personnel typically perform this oversight function through on-site inspections designed to document how the study was actually conducted at the clinical investigator's site. Clinical investigators are required to retain records for a period of two years following the date a marketing application is approved for the product or, if no application is filed or if the application is not approved, until two years after the investigation is discontinued and FDA is notified. (See 21 CFR 312.62(c) and 812.140.) FDA conducts both announced and unannounced inspections of clinical investigator sites:

- routinely to verify data that has been submitted to the Agency;
- as a result of a complaint to the Agency about the conduct of the study at the site;
- in response to sponsor concerns or termination of the clinical site;
- 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 issues).

IV. HOW ARE CLINICAL INVESTIGATOR INSPECTIONS CONDUCTED?

During an inspection at the site of a clinical investigator, FDA personnel typically verify:

- who performed various aspects of the protocol (e.g., who verified inclusion and exclusion criteria, who obtained informed consent, who collected adverse event data);
- the degree of delegation of authority (e.g., how the clinical investigator supervised the conduct of the investigation);
- where specific aspects of the investigation were performed;
- how and where data were recorded;
- accountability for the investigational product;
- the monitor's communications with the clinical investigator; and
- the monitor's evaluations of the progress of the investigation.

FDA personnel also 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 include the case report forms and supporting data including signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. FDA may also examine medical records about the subjects that predate the study to find out whether the condition under study was in fact diagnosed, the study eligibility criteria were met, and whether the subject received a possibly interfering medication before the investigation began. FDA personnel also review subjects' records covering a reasonable period after completion of the product-related portion of the investigation to determine if there was proper follow-up as outlined in the protocol, and if the clinical investigator reported all signs and symptoms reasonably attributable to the product's use.

V. WHAT HAPPENS AFTER AN INSPECTION?

At the end of an inspection, FDA personnel conduct an exit interview with the clinical investigator or his/her representative. At this interview, FDA personnel who conducted the inspection review and discuss the findings from the inspection and if deficiencies are found, issue 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 personnel conducting the inspection, represent deviations from applicable statutes and regulations. The clinical investigator may respond to the 483 observations verbally 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. (A list of FDA District Offices is also posted on FDA's website (http://www.fda.gov/ora).

Following the inspection, the FDA personnel who conducted the clinical investigator inspection prepare a written Establishment Inspection Report (EIR). The EIR, 483 (if issued), copies of any materials collected during the inspection, and any clinical investigator response are forwarded to the appropriate FDA Center for further evaluation. After this review, one of the following types of letters is typically sent from the Center to the clinical investigator:

(1) A letter that generally states that FDA observed no significant deviations from the regulations. Note that a letter is not always sent when FDA observes no significant deviations.

(2) An *informational or untitled letter* that identifies deviations from statutes and regulations for which voluntary corrective action is sufficient. Occasionally, such letters request a response from the clinical investigator.

(3) A *Warning Letter* that identifies serious deviations from applicable statutes and regulations. A Warning Letter generally requests prompt correction by the clinical investigator and a formal written response to the agency.

Please note that FDA may disclose to sponsors and IRBs records that indicate a violation or potential violation of the law by clinical investigators that have conducted or are conducting studies.[3]

In addition to issuing these letters, FDA can take other administrative action against clinical investigators for non-compliance with applicable statutes and regulations. For example, FDA may initiate a process to disqualify the clinical investigator from receiving investigational products in the future if the investigator has repeatedly or deliberately failed to comply with applicable statutory or regulatory requirements or has submitted false information to the sponsor or FDA in any required report. (See § 312.70, § 812.119.)

VI. WHO CAN PROVIDE MORE INFORMATION?

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

In addition, the FDA Compliance Program Guidance Manual for Clinical Investigator Inspections (Program 7348.811), used by FDA to conduct these inspections, is available on the Internet at http://www.fda.gov/ora/cpgm/default.htm#bimo.

[3] See 63 FR 55873, October 19, 1998.