Guidance for Industry

Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within ___ days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

May 2007

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators

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Guidance for Industry[1] Protecting the Rights, Safety, and Welfare of Study Subjects - Supervisory Responsibilities of Investigators

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 provides an overview of the responsibilities of a person who conducts a clinical investigation of a drug, biologic, or medical device (an investigator as defined in 21 CFR 312.3(b) and 21 CFR 812.3(i)). The intent of this guidance is to help investigators meet their responsibilities with respect to protecting human subjects and ensuring the integrity of the data from clinical investigations. This guidance is also intended to clarify FDA's expectations concerning the investigator's responsibility: (1) to supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties, and (2) to protect the rights, safety, and welfare of study subjects.

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. OVERVIEW OF INVESTIGATOR RESPONSIBILITIES

In conducting clinical investigations of drugs, including biological products, under 21 CFR part 312 and of medical devices under 21 CFR part 812, the investigator is responsible:

- for ensuring that a clinical investigation is conducted according to the signed investigator statement for clinical investigations of drugs, including biological products, or agreement for clinical investigations of medical devices, the investigational plan, and applicable regulations;
- for protecting the rights, safety, and welfare of subjects under the investigator's care; and

[1] This guidance has been prepared by the Investigator Responsibilities Working Group, which includes representatives from the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration.

- for the control of drugs, biological products, and devices under investigation (21 CFR 312.60, 21 CFR 812.100).

A. Clinical Trials of Drugs, Including Biological Products

An investigator's responsibilities in conducting clinical investigations of drugs or biologics under part 312 are stated in the regulations in that part. Many of these responsibilities are included in the required investigator's signed statement, Form FDA-1572 (see Attachment A) (hereinafter referred to as "1572"), in which the investigator makes the following commitments (see 21 CFR 312.53):

- To conduct the study(ies) in accordance with the relevant, current protocol(s) and to only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects;
- To personally conduct or supervise the described investigation(s);
- To inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met;
- To report to the sponsor adverse experiences that occur in the course of the investigations(s) in accordance with 21 CFR 312.64;
- That he/she has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug;
- To ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments;
- To maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available to FDA for inspection in accordance with 21 CFR 312.68;
- That an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation;
- To promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others;
- To not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects:
- To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312.

Note that although the 1572 specifically incorporates most of the requirements directed at investigators in part 312, there are additional requirements that are not listed in the 1572. Investigators and sponsors should refer to 21 CFR Parts 50, 56, and 312 to ensure that they are familiar with all of FDA's requirements for the conduct of drug and biologics studies.

B. Device Trials

An investigator's responsibilities in conducting clinical investigations of a medical device under 21 CFR part 812 are stated in the regulations in that part, including the requirement that there be a signed agreement between the investigator and sponsor that includes a statement in which the investigator makes the following commitments (see 21 CFR 812.43(c)(4) and 812.100):

- To conduct the investigation in accordance with:
  - the signed agreement with the sponsor;
  - the investigational plan;
  - the regulations in 21 CFR part 812 and other applicable regulations; and
  - any conditions of approval imposed by the reviewing IRB or FDA.
- To supervise all testing of the device involving human subjects (§ 812.43(c)(4)(ii))
- To ensure that the requirements for obtaining informed consent are met (§ 812.43(c)(4)(iii) and § 812.100)

In addition to following the signed agreement, the investigator's responsibilities under part 812 are:

- To permit an investigational device to be used only with subjects under the investigator's supervision and to supply an investigational device only to persons authorized to receive it (§ 812.110(c))
- To return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs upon completion or termination of a clinical investigation or the investigator's part of an investigation (§ 812.110(e))
- To maintain accurate, complete, and current records relating to the investigator's participation in an investigation (§ 812.140):
  - All correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA, including required reports;
  - Records of receipt, use or disposition of a device;
  - Records of each subject's case history and exposure to the device;
  - The protocol, with documents showing the dates of and reasons for each deviation from the protocol, and
  - Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- To permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects (§ 812.145):
- To prepare and submit to the sponsor and, when required by regulation, the reviewing IRB and monitor, the following complete, accurate, and timely reports (§ 812.150):
  - Any *unanticipated adverse device effect* occurring during an investigation
  - *Progress reports* on the investigation
  - Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency
  - Any use of the device *without obtaining informed consent*
  - A final report
  - Any further information requested by FDA or the IRB about any aspect of the investigation.

The medical device regulations do not require use of a specific form for an investigator's statement and there are additional requirements that are not listed above (see Attachment B). Investigators and sponsors should refer to 21 CFR Parts 50, 56, and 812 to ensure that they are familiar with all of FDA's requirements for the conduct of device studies.

Although the specific responsibilities for investigators in drug and biologic clinical trials are not identical to the responsibilities for investigators in medical device clinical trials, the general responsibilities are essentially the same. This guidance discusses certain of the general responsibilities that are applicable to clinical trials of drugs, biologics, and medical devices.

Nothing in this guidance is intended to conflict with recommendations for investigators contained in the International Conference on Harmonization Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance (Good Clinical Practice Guidance") (April 1996). http://www.fda.gov/cder/guidance/959fnl.pdf

III. CLARIFICATION OF CERTAIN INVESTIGATOR RESPONSIBILITIES

This section of the guidance is intended to clarify the investigator's responsibility: (1) to supervise the conduct of the clinical investigation and (2) to protect the rights, safety, and welfare of study participants in drug and medical device clinical trials.

A. Supervision of the Conduct of a Clinical Investigation

As stated above, investigators who conduct clinical investigations of drugs, including biological products, under 21 CFR Part 312 commit to personally conduct or supervise the investigation. Investigators who conduct clinical investigations of medical devices, under 21 CFR Part 812 commit to supervise all testing of the device involving human subjects. It is common practice for investigators to delegate certain study-related tasks to employees, colleagues, or other third parties (individuals or entities not under the direct supervision of the investigator). When tasks are delegated by the investigator, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated and the investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

In assessing the adequacy of supervision by an investigator, FDA focuses on four major issues: (1) whether delegated individuals were qualified to perform such tasks, (2) whether study staff received adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study, (3) whether there was adequate supervision and involvement in the ongoing conduct of the study, and (4) whether there was adequate supervision or oversight of any third parties involved in the conduct of a study to the extent such supervision or oversight was reasonably possible.

1. What is Appropriate Delegation of Study-related Tasks?

The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience to perform the delegated task. Appropriate delegation is primarily an issue for tasks that would be considered to be clinical or medical in nature, such as evaluating study subjects to assess clinical response to an investigational therapy (e.g., global assessment scales, vital signs) or providing part of the medical care provided to subjects during the course of the study. Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements. Such licensing requirements will vary from state to state.

Clinical investigators should take such qualifications/licensing requirements into account when considering to whom it would be appropriate to delegate specific tasks.

During inspections, FDA has identified instances in which study tasks have been delegated to individuals lacking appropriate qualifications. Examples of inappropriate delegation include:

- Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with inadequate medical training (e.g., a medical assistant)
- Physical examinations performed by unqualified personnel
- Evaluation of adverse events by individuals lacking appropriate medical training, knowledge of the clinical protocol, and knowledge of the investigational product
- Assessments of primary study endpoints (e.g., tumor response, global assessment scales) by individuals lacking appropriate medical training and knowledge of the protocol
- Informed consent obtained by individuals who lack the medical training, knowledge of the clinical protocol, or familiarity of the investigational product needed to be able to discuss the risks and benefits of a clinical trial with prospective subjects

The investigator is responsible for conducting studies in accordance with the protocol (see 21 CFR 312.60, Form FDA-1572, 21 CFR 812.43 and 812.100). Some protocols specify the qualifications of the individuals who are to perform certain protocol-required tasks, and these protocols must be followed even if state law permits differently qualified people to perform the task. For example, even if the state in which the study site is located permits nurse practitioners to perform physical examinations under the supervision of a physician, if the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams.

The investigator should maintain a list of the appropriately qualified persons to whom significant trial-related duties have been delegated.[2] This list should also describe the delegated tasks, identify the training that individuals have received that qualifies them to perform delegated tasks, and identify the dates of involvement in the study. An investigator should maintain separate lists for each study conducted by the investigator.

2. What is Adequate Training?

The clinical investigator should ensure that there is adequate training for all staff participating in the conduct of the study. The investigator should specifically anticipate the possibility of staff turnover during the conduct of the study (particularly if the study is of long duration) and plan to ensure that there is adequate training of any replacement staff. The investigator should ensure that staff:

- Have a general familiarity with the study and the protocol

[2] See Good Clinical Practice Guidance, section 4.1.5

- Have a specific understanding of the details of the protocol and the investigational product, relevant to the tasks they will be performing
- Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials, both in respect to conduct of the clinical trial and human subject protection
- Are competent to perform the tasks that they are delegated
- Are informed of any pertinent changes during the conduct of the trial and educated or given additional training as appropriate

If the sponsor provides training materials for investigators in the conduct of the study, the investigator should ensure that staff receives the sponsor's training, or information from the training, that is pertinent to their role in the study.

3. What is Adequate Supervision of the Conduct of an Ongoing Clinical Trial?

The investigator should have a detailed plan for the supervision and oversight of a clinical trial. Supervision and oversight should be provided even for individuals who are highly qualified and experienced. A plan might include the following elements, to the extent they apply to a particular trial:

- Routine meetings with staff to review trial progress and update staff on any changes to the protocol or other procedures
- Routine meetings with the sponsor's monitors
- A procedure for correcting problems identified by study personnel, outside monitors or auditors, or other parties involved in the conduct of a study
- A procedure for documenting the performance of delegated tasks in a satisfactory manner and, where appropriate, verifying findings (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)
- A procedure for ensuring that the consent process is being conducted in accordance with 21 CFR Part 50 and that study subjects understand the nature of their participation, risks, etc.
- A procedure for ensuring that information in source documents is accurately captured on the Case Report Forms
- A procedure for dealing with data queries and discrepancies identified by the study monitor
- Procedures for ensuring study staff comply with the protocol, adverse event assessment and reporting, and other medical issues that arise during the course of the study.

The investigator should have sufficient time to properly conduct and supervise the clinical trial. The intensity of the supervision should be appropriate to the staff, the nature of the trial, and the subject population. In FDA's experience, the following factors may compromise the ability of an individual investigator to provide adequate supervision of the conduct of an ongoing clinical trial:

- Inexperienced study staff

- Overburdened study staff
- Complex clinical trials (e.g., many observations, large amounts of data collected)
- Large number of subjects enrolled at a site
- A patient population that is quite sick
- Conducting a large number of studies concurrently
- Conducting a study from a remote (i.e., off-site) location;
- Conducting a study at multiple sites under the oversight of a single investigator, particularly where those sites are not near each other (e.g., sites that are geographically distant, in another city, county, state, or country).

It is preferable for any site with substantial enrollment to have an identified investigator with clear responsibilities, but if that is not arranged, FDA believes there should ordinarily be an individual responsible for the conduct of the clinical trial at each trial site, identified as a subinvestigator. Subinvestigators should report directly to the investigator (i.e., the clinical investigator should have clear responsibility for evaluating the individual's performance and should have the authority to hire/fire the subinvestigator).

4. What are an Investigator's Responsibilities for Oversight of Other Parties Involved in the Conduct of a Clinical Trial?

a. Study staff not in the direct employ of the investigator

The staff involved directly in the conduct of a clinical investigation may include individuals who are not in the direct employ of the clinical investigator. For example, a site management organization (SMO) may hire an investigator to conduct a study and provide the investigator with a study coordinator or nursing staff employed by the SMO. In this situation, the investigator should take steps to assure that the staff not under his/her direct employ are qualified to perform delegated tasks (see section III.A.1) and have received adequate training on carrying out the delegated tasks and on the nature of the study (see section III.A.2), or the investigator should provide such training. The investigator is responsible for supervision of the study tasks performed by this staff, even though they are not in his/her direct employ during the conduct of the study (see section III.A.3) and this responsibility exists, no matter how qualified and experienced these staff members are. In the event that the staff's performance of study-related tasks is not adequate and cannot be made satisfactory by the investigator, the investigator should document the observed deficiencies in writing to the staff's supervisor(s). Depending on the severity of the deficiencies, the clinical trial may need to be voluntarily suspended until personnel can be replaced.

b. Parties other than Study Staff

There are often critical aspects of a study performed by parties not involved directly in patient care or contact, and not under the direct control of the clinical investigator. For example, clinical chemistry testing, radiologic assessments, and electrocardiograms are commonly done by a central independent laboratory retained by the sponsor or the investigator. Under these arrangements, the central

laboratory usually provides the test results directly to the sponsor and to the clinical investigator. Because the activities of these parties are critical to the outcome of the study, and because the sponsor retains the services of the laboratory, the sponsor is responsible for seeing that these parties are fulfilling their responsibilities for the study.

Less frequently, a study may require that clinical investigators arrange to obtain information critical to the study that cannot be obtained at the clinical investigator's facility. For example, if the study protocol requires testing with special equipment or expertise not available at the clinical investigator's facility, the investigator might make arrangements for someone outside the facility to perform the test. In this case, the results are provided directly to the clinical investigator, who then submits the information to the sponsor. Where such assessments are retained by the investigator, the investigator should take steps to ensure that the facility is adequate (e.g., has the required certifications or licenses). The investigator may also institute procedures to ensure the integrity of data and records obtained from the party providing the information (e.g., a process to ensure that records identified as coming from the party are authentic). Procedures are particularly important when assessments are crucial to the evaluation of the efficacy or safety of an intervention or to the decision to exclude subjects who would be exposed to unreasonable risk.

Clinical investigators should carefully review the reports from these external sources for results that are inconsistent with clinical presentation. To the extent feasible, and considering the specifics of study design, the clinical investigator should evaluate whether results appear reasonable, individually and in aggregate. If clinical investigators detect possible errors or suspect that results from a central laboratory might be questionable, the investigator should contact the sponsor immediately.

c. Exception for Certain Device Studies

In some cases, specialized expertise from a device sponsor is needed to perform certain tasks. For example, when there is no one at the clinical site who can program an investigational pacemaker, the expertise may be provided by the sponsor's personnel, such as a field clinical engineer. The field clinical engineer should be supervised by the sponsor and not by the clinical investigator. When a field clinical engineer is designated by the sponsor to perform a specific activity within the investigational plan, this activity should be described in the protocol. The investigator retains responsibility for ensuring that the protocol is followed.

B. Protecting the Rights, Safety, and Welfare of Study Subjects

Clinical investigators are responsible for protecting the rights, safety, and welfare of subjects under their care during a clinical trial (21 CFR 312.60 and 812.100). The clinical investigator should provide a reasonable standard of medical care for study subjects for medical problems arising during participation in the trial that are, or could be related, to the

study intervention. The investigator should be readily available to provide such care during the study or should assure that other identified, qualified individual(s) are available to provide such care. Failure to adhere to the protocol can expose subjects to unreasonable risks.

1. Reasonable Medical Care Necessitated by Participation in a Clinical Trial

During and following a subject's participation in a trial, the investigator should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The investigator should inform a subject when medical care is needed for intercurrent illness(es). The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

If the investigator does not possess the necessary skills to provide adequate medical care for the subject, the investigator should make every effort to obtain appropriate care. For example, if a carotid stent is placed in a subject by an interventional neuroradiologist and the subject suffers a cerebral stroke, the neuroradiologist should assess the clinical status of the subject and transfer the subject to a neurology service. Subjects should receive appropriate medical evaluation and treatment until resolution of any condition related to the study intervention that develops during the course of their participation in a study, even if the follow-up period extends beyond the end of the study at the investigative site.

2. Reasonable Access to Medical Care

To protect subjects from unnecessary risks, clinical investigators should be available to subjects during the conduct of the trial at their site. Availability is particularly important where subjects are receiving a drug that has significant toxicity or abuse potential. For example, if a study drug has potentially fatal toxicity, the investigator should be readily available by phone or other electronic communication, and in reasonably close proximity to study subjects (e.g., not in another state or on prolonged travel). Study subjects should be clearly educated on the possible need for such contact and on precisely how to obtain it, generally by providing pertinent phone numbers, websites, etc., in writing. Prior to undertaking the conduct of a study, prospective investigators should consider whether they can be available to the extent needed given the nature of the trial.

If the investigator is not going to be available for some period during the study, clinical responsibility for study subjects should be delegated to a specific qualified physician who will be readily available to subjects. This delegation should be documented in a 1572 or investigator agreement (the physician should be listed as a subinvestigator) and also submitted to the IRB for review (as a change in the research activity requiring IRB review under 21 CFR 56.108(a)). If the clinical investigator is a non-physician, the investigator should make adequate provision for any necessary medical care that the investigator is not qualified to provide.

3. Protocol Violations that Present Unreasonable Risks

There are occasions when a failure to adhere to the protocol may be considered a failure to protect the rights, safety, and welfare of subjects. For example, failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks (e.g., enrolling a subject with decreased renal function in a trial in which decreased function is exclusionary because the drug may be nephrotoxic) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Similarly, failure to perform safety assessments intended to detect drug toxicity within protocol-specified time frames (e.g., CBC for an oncology therapy that causes neutropenia) may be considered failure to protect the rights, safety, and welfare of the enrolled subject. Investigators should seek to minimize such risks by adhering closely to the study protocol.

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Attachment A

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **STATEMENT OF INVESTIGATOR** ***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)*** (See instructions on reverse side.)	Form Approved: OMB No. 0910-0014. Expiration Date: January 31, 2006. *See OMB Statement on Reverse.* NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES).

6. NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☐ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please **DO NOT RETURN** this application to this address.

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Attachment B

INVESTIGATORS' RESPONSIBILITIES FOR SIGNIFICANT RISK DEVICE INVESTIGATIONS

This document is intended to assist investigators in identifying and complying with their responsibilities in connection with the conduct of clinical investigations involving medical devices. Although this guidance primarily addresses duties imposed upon clinical investigators by regulations of the Food and Drug Administration (FDA), investigators should be cognizant of additional responsibilities that may derive from other sources (such as the study protocol itself, the investigator agreement, any conditions of approval imposed by FDA or the governing Institutional Review Board, as well as institutional policy and state law).

GENERAL RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.100)

1. Ensuring that the investigation is conducted according to the signed agreement, the investigational plan and applicable FDA regulations.

2. Protecting the rights, safety, and welfare of subjects under the investigator's care.

3. Controlling devices under investigation.

4. Ensuring that informed consent is obtained from each subject in accordance with 21 CFR Part 50, and that the study is not commenced until FDA and IRB approvals have been obtained.

SPECIFIC RESPONSIBILITIES OF INVESTIGATORS (21 CFR 812.110)

1. Awaiting IRB approval and any necessary FDA approval before requesting written informed consent or permitting subject participation.

2. Conducting the investigation in accordance with:
   a. the signed agreement with the sponsor;
   b. the investigational plan;
   c. the regulations set forth in 21 CFR Part 812 and all other applicable FDA regulations; and
   d. any conditions of approval imposed by an IRB or FDA.

3. Supervising the use of the investigational device. An investigator shall permit an investigational device to be used only with subjects under the investigator's supervision. An investigator shall not supply an investigational device to any person not authorized under 21 CFR Part 812 to receive it.

4. Disposing of the device properly. Upon completion or termination of a clinical investigation or the investigator's part of an investigation, or at the sponsor's request, an investigator shall return to the sponsor any remaining supply of the device or otherwise dispose of the device as the sponsor directs.

MAINTAINING RECORDS (21 CFR 812.140)

An investigator shall maintain the following accurate, complete, and current records relating to the investigator's participation in an investigation:

1. Correspondence with another investigator, an IRB, the sponsor, a monitor, or FDA.

2. Records of receipt, use or disposition of a device that relate to:
   a. the type and quantity of the device, dates of receipt, and batch numbers or code marks;
   b. names of all persons who received, used, or disposed of each device;
   c. the number of units of the device returned to the sponsor, repaired, or otherwise disposed of, and the reason(s) therefore.

3. Records of each subject's case history and exposure to the device, including:
   a. documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent;
   b. all relevant observations, including records concerning adverse device effects (whether anticipated or not), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests;
   c. a record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.

4. The protocol, with documents showing the dates of and reasons for each deviation from the protocol.

5. Any other records that FDA requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

INSPECTIONS (21 CFR 812.145)

Investigators are required to permit FDA to inspect and copy any records pertaining to the investigation including, in certain situations, those which identify subjects.

SUBMITTING REPORTS (21 CFR 812.150)

An investigator shall prepare and submit the following complete, accurate, and timely reports:

1. To the sponsor and the IRB:
   - -Any *unanticipated adverse device effect* occurring during an investigation. (Due no later than 10 working days after the investigator first learns of the effect.)
   - -*Progress reports* on the investigation. (These reports must be provided at regular intervals, but in no event less often than yearly. If there is a study monitor, a copy of the report should also be sent to the monitor.)
   - -Any *deviation from the investigational plan* made to protect the life or physical well-being of a subject in an emergency. (Report is due as soon as possible but no later than 5 working days after the emergency occurs. Except in emergency situations, a protocol deviation requires prior sponsor approval; and if the deviation may affect the scientific soundness of the plan or the rights, safety, or welfare of subjects, prior FDA and IRB approval are required.)
   - -Any use of the device *without obtaining informed consent*. (Due within 5 working days after such use.)
   - -A *final report.* (Due within 3 months following termination or completion of the investigation or the investigator's part of the investigation. For additional guidance, see the discussion under the section entitled "Annual Progress Reports and Final Reports.")
   - -*Any further information* requested by FDA or the IRB about any aspect of the investigation.

2. To the Sponsor:
   - -*Withdrawal of IRB approval* of the investigator's part of an investigation. (Due within 5 working days of such action).

INVESTIGATIONAL DEVICE DISTRIBUTION AND TRACKING

The IDE regulations prohibit an investigator from providing an investigational device to any person not authorized to receive it (21 CFR 812.110(c)). The best strategy for reducing the risk that an investigational device could be improperly dispensed (whether purposely or inadvertently) is for the sponsor and the investigators to closely monitor the shipping, use, and final disposal of the device(s). Upon completion or termination of a clinical investigation (or the investigator's part of an investigation), or at the sponsor's request, an investigator is required to return to the sponsor any remaining supply of the device or otherwise to dispose of the device as the sponsor directs (21 CFR 812.110(c)). Investigators must also maintain complete, current and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140(a)(2)). Specific recordkeeping requirements are set forth at 21 CFR 812.140(a).

PROHIBITION OF PROMOTION AND OTHER PRACTICES (21 CFR 812.7)

The IDE regulations prohibit the promotion and commercialization of a device that has not been first cleared or approved for marketing by FDA. This prohibition is applicable to sponsors and

investigators (or any person acting on behalf of a sponsor or investigator), and encompasses the following activities:

1. Promotion or test marketing of the investigational device;

2. Charging subjects or investigators for the device a price larger than is necessary to recover the costs of manufacture, research, development, and handling;

3. Prolonging an investigation beyond the point needed to collect data required to determine whether the device is safe and effective; and,

4. Representing that the device is safe or effective for the purposes for which it is being investigated.