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REVIEW ARTICLE

# Food and Drug Administration Guidance: Supervisory Responsibilities of Investigators

Carl Anderson,[1] Patti A. Young,[2] and Ann Berenbaum, C.C.R.C.[3]

## Abstract

Conducting clinical trials for diabetes can present researchers with a number of regulatory questions. The Food and Drug Administration (FDA) has increased regulatory enforcement at clinical sites, with an increased emphasis on oversight by principal investigators (PIs; referred to by the FDA as the clinical investigator). The FDA has issued a guidance document, "Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects" (2009), to assist investigators and sponsors. This guidance document breaks new ground regarding the FDA's expectations for investigator oversight of subinvestigators and study staff. The guidance document corresponds with a sharp increase in FDA warning letters to PIs for noncompliance with good clinical practice regulatory requirements. For the first time, an FDA guidance document discusses issues such as the delegation of authority, standard operating procedures, and training of study staff. The FDA provides specific examples with particular emphasis given to appropriate delegation of duties by the PI and ensuring that the clinical staff entrusted to carry out the trial has had adequate training and experience in order to allow them to perform the designated tasks.

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## Introduction

On May 10, 2007, the Food and Drug Administration (FDA) issued a draft guidance document for comment titled "Protecting the Rights, Safety, and Welfare of Study Subjects—Supervisory Responsibilities of Investigators."[1] The document, as with all FDA guidance documents, was labeled "contains nonbinding recommendations." However, the document set the stage for a major increase in FDA compliance actions. For example, in fiscal year (FY) 2005, the Center for Drug Evaluation and Research, which supervises approximately 60% of FDA clinical trials,[2] did not issue a single warning letter, the most common form of FDA enforcement action to a principal investigator (PI) conducting drug studies.[3] Four years later, in FY 2009, that number had risen to 18.[2]

In FY 2009, the FDA continued to emphasize its enforcement of clinical trial regulations at clinical sites. Of the 867 inspections conducted for the FDA's bioresearch

**Author Affiliations:** [1]Carl A. Anderson, LLC, Tacoma, Washington; [2]Kaiser Foundation Research Institute, Oakland, California; and [3]Health Sciences Research Compliance Program, University of California, San Diego, San Diego, California

**Abbreviations:** (CFR) Code of Federal Regulations, (CRO) contract research organization, (CV) curriculum vitae, (FDA) Food and Drug Administration, (FY) fiscal year, (GCP) good clinical practice, (IRB) Institutional Review Board, (PI) principal investigator, (SOP) standard operating procedure

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**Corresponding Author:** Carl Anderson, Carl A. Anderson, LLC, 3320 N. 27th St., Tacoma, WA 98407; email address carl11anderson@yahoo.com

monitoring program, 730 of the 1135 inspections, or 64%,[3] were clinical investigator inspections, resulting in 26 warning letters being issued to PIs for good clinical practice (GCP) noncompliance.[4] **Table 1** breaks down the number and category of bioresearch monitoring inspections conducted during FY 2010. Historically, the most common PI deficiency category has been failure to follow the protocol or investigational plan.[5] **Figure 1** outlines the most common clinical investigator deficiencies found during FY 2010 inspections. Warning letters have included wording discussing the statement of the investigator, form FDA 1572 for drug and biologic trials and investigator's statement for medical device trials.[6] Informed consent violations continue to be the most serious violation cited by the FDA. Failure to maintain adequate records has also been frequently cited in FDA warning letters. Now, determining if an investigator has personally conducted or supervised the study has become a major focus of FDA clinical investigator inspections.

The FDA states that the 1572 has two purposes: to provide the sponsor with information about the PI's qualifications and to inform the PI of her/his regulatory responsibilities. Although much is discussed about what information goes into the sections on page 1 of the form, the regulatory responsibilities are listed on the reverse side, page 2. The first three of those responsibilities are as follows:

1. 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.

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

3. 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 Code of Federal Regulations (CFR) Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

These are the same three issues that are being cited repeatedly by the FDA in warning letters to clinical investigators for drugs, biologics, and medical devices. The guidance document "Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects"[7] gives an overview of investigator responsibilities that emphasizes the responsibilities listed on the 1572 and the medical device investigator's agreement. The FDA guidance document is meant to inform PIs of their regulatory responsibilities to personally conduct or supervise the clinical trial. It does this in four parts: appropriate delegation of duties, adequate training of staff, adequate supervision by the PI, and oversight of other parties. The guidance document also discusses medical responsibilities of the PI as well as discussing investigator responsibilities for significant risk medical device studies.

**Table 1.**
**Number and Category of Bioresearch Monitoring Inspections conducted during Fiscal Year 2010[a]**

| Center | CI | IRB | Spon/ Mon | GLP | Total |
|---|---|---|---|---|---|
| CBER | 75 | 25 | 14 | 11 | 125 |
| CDER[b] | 387 | 97 | 60 | 33 | 577 |
| CDRH | 218 | 81 | 80 | 7 | 386 |
| CFSAN[c] | 0 | 0 | 0 | 0 | 0 |
| CVM | 45 | N/A | 1 | 26 | 72 |
| All Centers | 725 | 203 | 155 | 77 | 1160 |

[a] CI, clinical investigators; Spon/Mon, sponsor/monitors; GLP, good laboratory practice; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drug Evaluation and Research; CDRH, Center for Drug Evaluation and Research; CFSAN, Center for Food Safety and Applied Nutrition; CVM, Center for Veterinary Medicine; BEQ, bioequivalence; BIMO, bioresearch monitoring program.
[b] + 182 BEQ inspections (CDER specific): Total = 1342
[c] CFSAN's BIMO Program is under reorganization

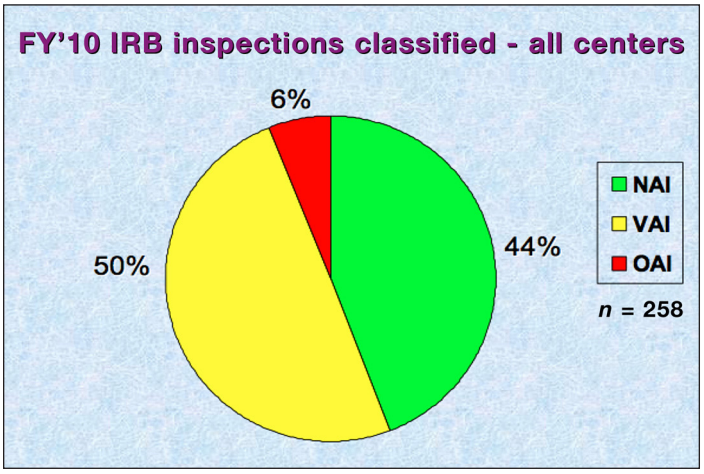


**Figure 1.** The most common clinical investigator deficiencies found during fiscal year 2010 inspections. Inspections were classified in FY 2010 no matter when inspection occurred during the year. NAI, no action indicated; VAI, voluntary action indicated; OAI, official action indicated.

## Appropriate Delegation of Trial-Related Tasks

The guidance document points out a number of circumstances where the FDA has concerns regarding the inappropriate delegation of study responsibilities. They include

- Screening evaluations, obtaining medical histories, and assessment of inclusion/exclusion criteria;
- Physical examinations;
- Evaluation of adverse events;
- Assessments of primary study endpoints; and
- Obtaining informed consent.

This last point has become a point of contention between PIs and the sponsors and contract research organizations (CROs) that monitor clinical trials, including diabetes trials. It is common for a PI to delegate obtaining informed consent to a registered diabetes educator who may be a registered nurse or dietician. There is nothing in the regulations on documenting informed consent that requires the PI to conduct the informed consent process or sign the informed consent form.[8] However, many sponsors and CROs insist that the PI sign the informed consent form to prove that they are personally conducting a study. However, there is no FDA requirement that the PI actually sign an informed consent form. Obtaining informed consent is a duty that is appropriate to delegate to qualified staff.

## Form FDA 1572, Statement of the Investigator

Another important guidance document that discusses investigator responsibilities for biopharmaceutical (drugs and biologics) clinical trials is the final version of their Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs.[9]

Up until the release of this document, the FDA had not given specific guidance on who should be listed as a subinvestigator on the Form FDA 1572. Many clinical sites would only list medical doctors who would perform duties of a PI. Now, the FDA has clearly indicated that research coordinators (study coordinators) should also be included in Section 6. The statement is as follows:

Generally, a research coordinator has a greater role in performing critical study functions and making direct and significant contributions to the study data. For example, a research coordinator often recruits subjects, collects and evaluates study data, and maintains study records. Therefore, the research coordinator should usually be listed in Section #6 of the 1572.

The Division of Scientific Investigations in the Center for Drug Evaluation and Research has emphasized this point. In a warning letter dated October 1, 2008, the FDA cited a PI for the following:

Study coordinators who administered the informed consent, determined subject eligibility, and dispensed study drug were not listed on the Form FDA 1572, Statement of Investigator, for protocols (b)(4) and (b)(4). By performing these significant study activities, the study coordinators should have been listed on the Form FDA 1572s as subinvestigators.[10]

## Site Responsibility Log

Although not a regulatory requirement, the FDA investigator responsibilities guidance document states that an investigator should maintain a list of appropriately qualified persons to whom significant trial-related duties have been delegated. This is also a recommendation of the International Conference on Harmonization "E6 Good Clinical Practice: Consolidated Guidance."[11] The site signature log has become an industry standard and should be part of the documents for any clinical trial. Many PIs utilize the form provided by the sponsor or CRO. This form should be evaluated by the PI to determine that it meets the needs of their clinical site. Although the sponsor may create this for the site, it is the *responsibility* of the PI. Each page should be authorized by the PI with a dated signature.

The FDA guidance recommends that the list identify the training that study staff have received that qualifies them to perform delegated tasks. For a diabetes study, this would fall into two categories: the clinical training a person receives that qualifies them to assist in the treatment of a patient's diabetes and the protocol-specific training for the specific clinical trial.

## Food and Drug Administration Warning Letter on Sufficient Training

The FDA has issued warning letters to investigators who do not use qualified staff. One recent warning letter stated the following:

The protocol specified that the person obtaining informed consent must be sufficiently trained on medical issues, so that questions could be adequately addressed. The protocol specifically required that this person have an M.D., Ph.D., or R.N. degree; if the person did not have one of these degrees, then this person must have been approved by (b)(4) to obtain informed consent. For all subjects enrolled into this study (Subjects 1001–1008 and 1010–1013), the informed consent document and the assent form for children 10–17 years of age were not obtained by an M.D., Ph.D., or R.N., as required by the protocol. In addition, you did not obtain (b)(4) approval for these persons to obtain informed consent and assent of the study subjects.[12]

## Documenting Training of Study Staff

The PI should carefully document that study staff are trained adequately. Not only must study staff be trained on the specific protocol and, for some staff, such as subinvestigators, the investigator brochure, they must also be trained adequately in pertinent clinical skills and in the regulatory requirements for conducting a study using GCP.

A current curriculum vitae (CV) explaining the study staff's previous training and qualifications is not officially required but is almost always necessary. It is important to note that, once qualifications are established, updating the CV, including the PI's CV, is not a requirement. Updating the CV is only important if there are specific relevant skills that need to be included that pertain to the protocol and the delegation of responsibility to the staff member. Beyond the CV, there should be documented training of the study protocol, both as an overview and in specific aspects where it applies to the scope of work of the particular study staff. Documentation should also exist for training that is required per protocol but is not specified in the staff CV. There should be some kind of documented verification that the staff exhibited competence in the task after being trained.

Additionally, once the study is started, the PI is responsible for ensuring that all staff are informed and trained in any changes to the protocol as it applies to them.

Even if tasks are delegated appropriately, the supervision of the PI is documented in subject charts and meeting minutes, CVs reflect the staff qualifications, and there is documented evidence of adequate training for the staff, there are still additional items the PI must take into consideration.

Deliberate thought and consideration should be given to the level of illness of the study population, whether the clinic is staffed by an adequate number of workers, how many studies are under one PI's supervision at any one time, and whether the PI is physically on site where the study is being conducted.

Not all investigator responsibilities are listed on the FDA 1572 or investigator's agreement. The PI has the ultimate responsibility to protect the rights, safety and welfare of study subjects and is always held accountable for any regulatory violations that occur if they fail to adequately supervise the study.

## Adequate Supervision of a Clinical Trial

An area that has drawn close FDA scrutiny is the adequate supervision of study staff by the PI. A unique feature of the FDA guidance document is a discussion of specific steps the PI can take when supervising study personnel. These steps include development of procedures to conduct the study. Although the guidance does not specify that the procedures should be written in the form of a standard operating procedure (SOP), it clearly recommends that some form of procedure should be in place. Investigators should note that the only regulatory requirement for written procedures is for a medical device monitor plan.[13] However, FDA warning letters have cited SOPs used at clinical sites:

We note that these SOPs provide no requirement for the investigator to review the documents to ensure the accuracy and adequacy of the information in the source records. In addition, per the SOP, the only quality assurance performed at your site to ensure adequate and accurate case histories is limited to only the first sets of completed [case report forms].[14]

This indicates that having written procedures is not enough. The FDA will review the SOPs to determine if they are adequate for regulatory compliance. It should also be noted that quality assurance is not a regulatory requirement; it is a recommendation for sponsors, not investigators.[15]

## Oversight of Other Parties

The FDA guidance discusses the problems encountered with site management organizations. These are organizations that contract with investigators and supply many of the staff for conducting the study. The guidance document is clear that, even though the PI may contract with a

third party such as a site management organization, the regulatory responsibility to personally conduct and supervise the study *remains with the investigator.*

The guidance document also discusses the many tasks that are not under the control of the investigator, including electrocardiogram core laboratories and central clinical laboratories. The guidance notes that these services are crucial for the study and are retained by the sponsor and that the sponsor is responsible for ensuring these facilities are performing their responsibilities.

## Medical Devices

One noteworthy section of this new guidance document is Section 4.c, "Special Consideration for Medical Device Studies."

A significant difference between test article and medical device studies is the technical support medical device sponsors may occasionally provide to the device investigator by having a field engineer available on site during the actual conduct of the device study. The field engineer is available to answer questions and provide further explanation of the functionality of the test device at the time of the device placement. As noted in the guidance document, we see this occurring in several specialty areas such as diabetes, cardiology, and ophthalmology. Having these field engineers present can be a great benefit to both the study staff and the subject if the investigator and the field engineer clearly understand the investigator is responsible for the direct supervision of the conduct of the device study, including the activities of the field engineer while they are on site.

The guidance further identifies the potential of bias to the outcome of the quality of the data and/or may compromise the rights and welfare of the human subject. In many cases, the protocol does not define the activities of the field engineer and, more importantly, the informed consent does not notify the human subject of the potential of a field engineer coming into direct contact with the subject. The investigator can ensure the welfare and safety of the subject during medical device studies by paying close attention to this issue in the both the protocol and the informed consent.

During the protocol and informed consent review process for medical device studies, the investigator will want to do the following:

1. Confirm the sponsor outlines any activities of sponsor representatives during the conduct of the study. If the protocol does not define any field engineer activities, the investigator will need to ask if they plan to have field engineers present during the conduct of the trial, and if they verbally make the request, language must be added to the protocol outlining the specific activities of the field engineers during the conduct of the study.

2. Do the field engineer activities include any interaction with the human subject? If yes, confirm these activities are included in the informed consent so the human subject understands the potential of sponsor contact. If the information has not been included in the informed consent, request the addition of the language prior to IRB approval.

A field engineer should never be present during the completion of any subject questionnaires the sponsor requires to avoid any bias in the patient-reported outcome measures. Early assessment of the sponsor's intention on field engineer presence in advance will facilitate a clear understanding of how the investigator will supervise this activity.

## Medical Responsibilities

The medical responsibility of the PI is the concluding section of the guidance document. This includes reasonable access to medical care for participants in a study where the investigational product has a significant toxicity or potential for abuse. The guidance states that study subjects should be fully informed of the possible need to have contact with the PI or study staff regarding medical issues and should be provided with contact information.

Finally, the document discusses protocol violations that present unreasonable risks to clinical trial participants. The FDA specifically discusses failure to adhere to inclusion/exclusion criteria that are specifically intended to exclude subjects for whom the study drug or device poses unreasonable risks. This has been included in a number of FDA warning letters. In a warning letter issued in February of 2010, the FDA states

Eligibility criteria are designed specifically for each clinical investigation by the sponsor to optimize the interpretability of the data to the disease process under study and to minimize foreseeable harm of enrolled subjects due to co-morbidities and possible interactions with concomitant medications. Three of the six subjects randomized in this clinical investigation did not meet eligibility criteria of having Bipolar I Disorder and as such were placed at risk of injury from participation in the study.[15]

## Conclusion

The FDA has increased its regulatory oversight of investigators conducting clinical trials. The responsibility of PIs to personally conduct or supervise a clinical trial is one of the areas of FDA concern. The guidance document on investigator responsibilities and FDA warning letters to investigators indicate a new enforcement environment as well as specific steps that PIs can take to ensure compliance with GCP.

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