



# Final FDA Guidance on Investigator Responsibilities

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# About the Speaker

- Clinical research consultant based in Burnsville, MN since 2003
- Project management, field monitoring, auditing and training for pharmaceutical and medical device clients
- CCRA since 2001 and ACRP Credentialed Trainer since 2008
- Started clinical research career as a study coordinator
- Instructor for St. Cloud State University's new Master's Program in Clinical Research
- Current President of MN ACRP - former President in 2004 and longtime Communications Committee Chair



# Disclaimer

- I have NO financial interest/arrangement or affiliation with any organizations that could be perceived as a real or apparent conflict of interest in the context of this presentation subject
  - This presentation will NOT include any discussion of unapproved or “off-label” usage of a commercial product or device
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# Learning Objectives

- Describe the general purpose of the FDA's Investigator Responsibilities Guidance for Industry
- Discuss the history of the development of the guidance
- Define what the FDA considers to be adequate supervision of study staff and other third parties
- Explain what the FDA considers to be the appropriate delegation and adequate training of study-related tasks
- Examine investigator responsibilities outlined in the guidance for protecting study subjects



# Investigator Responsibilities Guidance

## **Guidance for Industry Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects**

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)

Procedural  
October 2009

- Final version issued in October 2009
- Initial draft issued May 2007
- Applicable to clinical trials of drugs, biologics, and medical devices



# Guidance Purpose

To clarify for investigators and sponsors the FDA's expectations concerning investigator responsibilities:

- To supervise a clinical study in which some study tasks are delegated to employees or colleagues of the investigator or other third parties
- To protect the rights, safety, and welfare of study subjects





# About Guidance Documents

- Represents FDA's “current thinking” on ways to comply with the regulations
- Not legally binding
- Can use an alternative approach if it satisfies the regulations
- The use of the word “should” means something is suggested or recommended but not required
- Non-compliance should not be cited in a FDA Form 483 (“Notice of Inspectional Observations” or written list of discrepancies noted during an FDA inspection)

## Regulatory Information

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### Guidances

FDA Guidance Documents:  
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Documents](#)

Combination Products  
Guidance Documents

Import and Export Guidance  
Documents

International Conference on  
Harmonization (ICH) Guidance  
Documents

Veterinary International  
Conference on Harmonization  
(VICH) Guidance Documents

## Clinical Trials Guidance Documents

We have recently redesigned the FDA Web site. As a result, some Web links (URLs) embedded within guidance documents are no longer valid. If you find a link that does not work, please try searching for the document using the document title. For more assistance, go to [Contact FDA](#).

### Guidance Documents:

- [01/2010 IRB Continuing Review After Clinical Investigation Approval - Draft Guidance \(PDF - 125KB\)](#)
- [07/2009 Frequently Asked Questions - IRB Registration \(PDF - 48KB\)](#)
- [09/2005 Collection of Race and Ethnicity Data in Clinical Trials](#)
- [01/1988 Monitoring Clinical Investigations](#)
- [04/1999 Computerized Systems Used in Clinical Trials](#)
- [01/2006 Significant Risk and Nonsignificant Risk Medical Device Studies - Information Sheet \(PDF - 121KB\)](#)
- [01/1998 Institutional Review Boards Frequently Asked Questions - Information Sheet](#)
- [01/1998 Cooperative Research - Information Sheet](#)
- [01/1998 Non-local IRB Review - Information Sheet](#)
- [01/1998 Continuing Review After Study Approval - Information Sheet](#)
- [01/1998 Sponsor - Investigator - IRB Interrelationship - Information Sheet](#)
- [01/1998 Acceptance of Foreign Clinical Studies - Information Sheet](#)
- [01/1998 Charging for Investigational Products - Information Sheet](#)



# Investigator Responsibilities Guidance History






# Guidance History

FDA Guidance – Guideline for the Monitoring of Clinical Investigations (January 1988)

*“The monitor should visit the investigator at the site of the investigation frequently enough to assure that ... the investigator is carrying out the agreed-upon activities and has not delegated them to other previously unspecified staff.”*





# Guidance History

FDA Guidance – A Guide to Informed Consent – Information Sheet  
(January 1998)

*“The clinical investigator is responsible for ensuring that informed consent is obtained from each research subject before that subject participates in the research study. FDA does not require the investigator to personally conduct the consent interview. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research.”*



# Guidance History

## FDA Guidance – ICH Guidelines for Good Clinical Practice (May 1997)

- *“The investigator should maintain a list of appropriately qualified persons to who the investigator has delegated significant trial-related duties”* (Section 4.1.5)
- *“The investigator should ensure that all persons assisting with the trial are adequately informed of the protocol, the investigational product(s), and their trial-related duties and functions”* (Section 4.2.4)



# Guidance History

Specific tasks indicated in ICH GCP that can be delegated:

- Trial-related medical decisions (4.3.1)
- Documenting and explaining protocol deviations (4.5.3)
- Investigational product accountability (4.6.2)
- Explain correct use of investigational product and check that subject is following instructions properly (4.6.6)
- Obtain informed consent (4.8.5, 4.8.7)
- CRF corrections (4.9.3)



# Recent Warning Letter

## Warning Letter to Dov Linzer, MD (06/12/09)

“According to the trial staff list for Protocol X, your clinical research coordinators ... were delegated responsibilities, including but not limited to, affirmation of inclusion and exclusion criteria and assessment of adverse events, serious adverse events, and study endpoints. You had informed the FDA investigator that as you were inexperienced in conducting clinical trials, you mainly relied on your clinical research coordinators to conduct the study and complete the study’s paperwork. In FDA’s review of the resumes of Mr. X and Ms. X, ... these individuals did not appear to be qualified, certified, or significantly medically trained and licensed to be independently making judgments related to determination of eligibility of subjects for enrollment into the study and/or making the determination as to whether or not adverse events were related to the use of the investigational drug.”



# Recent Warning Letter

## Warning Letter to Thomas Gazda, MD (11/24/09)

“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 RN degree; if the person did not have one of these degrees, then this person must have been approved by X 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 MD, PhD, or RN, as required by the protocol.”

“For Subjects 1001-1007, X was not administered by the principal investigator or a sub-investigator, as required by the protocol. Instead, the X was administered by a study coordinator, contrary to the criteria specified in the protocol.”



# Recent Warning Letter

## Warning Letter to Charles McKay, MD (10/23/09)

“In a written affidavit signed by you during the FDA inspection, you noted that you thought the training provided by the monitors to you and your study coordinators was sufficient, and that if there were problems, the monitors would let you know. You further asserted that you did not know that you had to supervise the study and ensure that the study coordinators were correctly doing such things as completing source records and case report forms, filling out adverse event and hospitalization forms, and notifying the IRB and sponsor on time.”



# Recent Warning Letter

## Warning Letter to Christopher Chappel, MD (02/02/09)

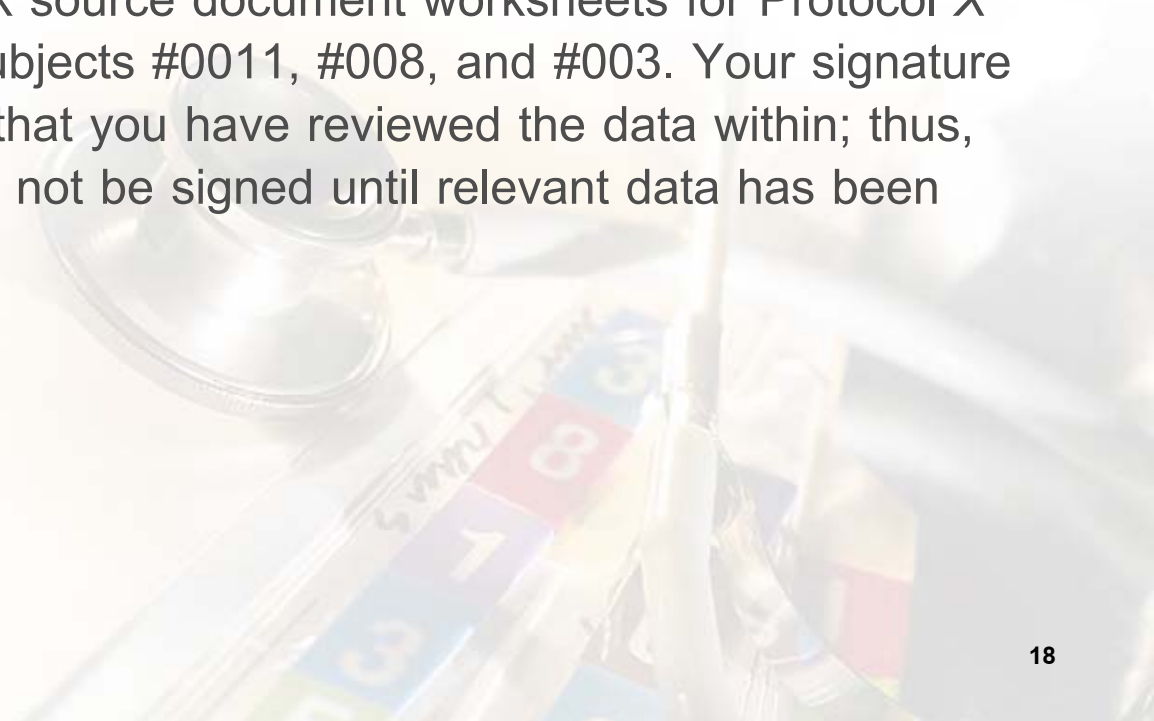
“We note that Ms. X served as the primary study coordinator ... and was terminated from your site as of December 4, 2006. We wish to emphasize, however, that as the clinical investigator, it was your ultimate responsibility to ensure that the studies were conducted properly and in compliance with FDA regulations to protect the rights, safety, and welfare of study subjects. We note that the monitors from two different studies notified you on multiple occasions that Ms. X was failing to follow the protocols and/or incorrectly completing certain study-related tasks. Among the tasks identified by the monitors were those for which she had not been delegated authority. The fact that you permitted her to continue as study coordinator despite these repeated notices indicates your failure to conduct the study in accordance with the investigational plans and the lack of adequate supervision on your part.”



# Recent Warning Letter

## Warning Letter to Anthony Dallas Jr, MD (11/09/09)

“Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that clinical trials were conducted according to the signed investigator statement ... Specifically, multiple blank source document worksheets for Protocol X were signed by you for subjects #0011, #008, and #003. Your signature on a document indicates that you have reviewed the data within; thus, source documents should not be signed until relevant data has been added and reviewed.”





# Supervision of the Study





# Supervision of the Study

- Drugs/Biologics (21 CFR Part 312): Investigators commit themselves to personally conduct or supervise the investigation
- Medical Devices (21 CFR Part 812): Investigators commit themselves to supervise all testing involving human subjects



# Supervision of the Study

- Common practice for investigators to delegate certain study-related tasks to employees, colleagues or other third parties (entities not under direct supervision of the investigator)
- When tasks are delegated, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated
- The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study



# Adequacy of Supervision

FDA focuses on four major areas to assess “adequacy”:

- Are individuals who are delegated tasks qualified to perform such tasks?
- Did the study staff receive adequate training on how to conduct the delegated tasks and were provided with an adequate understanding of the study?
- Is there adequate supervision and involvement by the investigator in the ongoing conduct of the study?
- Is there adequate supervision or oversight of any third parties involved in the conduct of the study?



# Appropriate Delegation

- Individuals delegated tasks should be qualified by education, training, and experience (and state licensure where relevant) to perform the delegated tasks
- Primarily an issue for tasks considered clinical or medical in nature such as:
  - Evaluating study subjects to assess clinical response to an investigational therapy (global assessment scales)
  - Providing medical care to subjects during the course of the study



# Appropriate Delegation

- Most clinical/medical tasks require formal medical training and may also have licensing or certification requirements (may vary by jurisdiction such as states or countries)
- Licensing requirements should be taken into account when delegating specific tasks
- In all cases, qualified physician (or dentist, when appropriate) should be responsible for all trial-related medical (or dental) decisions and care (ICH GCP section 4.3.1)



# Minnesota Statutes

- **Physicians:** Practice of medicine includes prescription and administration of drugs; prevention or treatment by any means of any illness, pain, wound, fracture, infirmity or deformity; surgical or invasive procedures; hypnosis (MN Statute 147.081)
- **Physician Assistants:** MN Statute 147A.09
- **Advanced Practice & Registered Nurses:** MN Statute 148.171
- Minnesota statutes at <https://www.revisor.mn.gov/statutes/>





# Appropriate Delegation

During inspections of sites, FDA has identified the following tasks that have been inappropriately delegated:

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



# Appropriate Delegation

- The protocol may specify the qualifications of individuals to perform certain protocol-required tasks
- The protocol must be followed even if state law permits individuals with different qualifications to perform the task
- For example, if the state allows nurse practitioners or physician assistants to perform physical examinations under supervision of a physician, but the protocol specifies that physical examinations must be done by a physician, a physician must perform such exams



# Appropriate Delegation

- Investigators should maintain a list of appropriately qualified persons to whom significant trial-related duties have been delegated (ICH GCP section 4.1.5)
- The list should also include:
  - Description of the delegated tasks
  - Identification of the training that individuals have received that qualifies them to perform the delegated tasks (can refer to an individual's CV on file)
  - Identification of dates on involvement in the study
- Separate lists should be maintained for each study conducted



# Appropriate Training

- Investigator should ensure there is adequate training for all staff participating in the study including new staff hired after the study has begun to meet unanticipated workload or replace staff
- Staff should be:
  - Familiar with purpose of the study and protocol
  - Have adequate understanding of the specific details of the protocol and investigational product needed to perform assigned task
  - Aware of regulatory requirements and acceptable standards for conduct of clinical trials and human subjects protection
  - Competent to perform or trained to perform delegated tasks
  - Informed of pertinent changes during conduct of trial



# Appropriate Training

- If the sponsor provides training, the investigator should ensure that their staff receive the sponsor's training or receive the training materials from that training that is pertinent to the staff's role in the study





# Supervision of Study Conduct

- Each study site should have a distinct individual identified as the investigator who has supervisory responsibilities
- Sub-investigators should report directly to the investigator. Investigator should have authority to terminate the sub-investigator's involvement in the study
- Sub-investigators should not be delegated the primary supervisory responsibility for the site
- Investigators should have sufficient time to conduct and supervise the study (ICH GCP section 4.2.2)



# Supervision of Study Conduct

The following factors may affect the ability of the investigator to adequately supervise the study:

- Inexperienced staff
- Demanding workload for staff
- Complex trials
- Large number of subjects enrolled at the site
- Seriously ill subject population
- Conducting multiple concurrent studies
- Conducting study from a remote location or at multiple sites



# Supervision Plan

The investigator should develop a plan for supervision that might include the following elements:

- Routine meetings with staff to review trial progress, adverse events, and protocol amendments
- Routine meetings with sponsor's monitors
- Procedure for the timely correction and documentation of problems identified
- Procedure for documenting or reviewing performance of delegated tasks in a satisfactory and timely manner (e.g., observation of the performance of selected assessments or independent verification by repeating selected assessments)



# Supervision Plan

- Procedure for ensuring that the consent process is conducted per 21 CFR part 50
- Procedure for ensuring that information in source documentation is accurately captured on CRFs
- Procedure for dealing with data queries and discrepancies identified by the sponsor monitor
- Procedure for ensuring study staff comply with the protocol, adverse event assessment and reporting requirements
- Procedure for addressing medical and ethical issues that arise during the course of the study in a timely manner



# Supervision of Third Parties

- Investigators should take steps to ensure that staff not under their direct employ (e.g., site management organization [SMO] employees) are qualified and have received adequate training
- Investigators should be “particularly cautious” when SMOs complete source documents, CRFs, investigational product accountability records and IRB correspondence)
- A sponsor who retains an SMO shares responsibility for the quality of work performed by the SMO



# Supervision of Third Parties

- If outside staff performance of study-related tasks is not adequate and cannot be made satisfactory, the investigator should document the deficiencies in writing to the staff member's supervisor and inform the sponsor





# Supervision of Third Parties

- Many critical study functions are performed by parties not involved in direct patient care or under direct control of the investigator such as lab testing, radiologic assessments, ECGs
- When these services are retained by the sponsor, the sponsor is responsible for ensuring that these parties are competent and are fulfilling their study responsibilities
- When an investigator retains outside services for testing with special equipment or expertise not available at the site, the investigator should take steps to ensure that the facility is adequate (e.g., has required certifications or licenses)



# Supervision of Third Parties

- The investigator may also institute procedures to ensure that records coming from outside facilities are authentic and accurate particularly if the assessments are crucial to the evaluation of efficacy, safety of an invention, or decision to include or exclude subjects
- Investigators should carefully review external reports for results that are inconsistent with clinical presentation
- If investigators detect possible errors or that results from a central laboratory or testing facility may be questionable, they should contact the sponsor immediately



# Medical Device Considerations

- Field clinical engineers (device sponsor employees) should be supervised by the investigator because they have the potential to bias the outcome of the study, affect the quality of research data, and/or compromise the rights and welfare of the human subjects
- The field clinical engineer's activities should be described in the protocol
- If the field clinical engineer has face-to-face contact with subjects or conducts activities directly affecting the subject, those activities should be described in the informed consent



# Protecting Study Subjects





# Primary Physician Notification

- The investigator should inform the subject's primary physician about the subject's participation in the trial (if they have a primary physician and agree to the disclosure)
- ICH GCP section 4.3.3 previously only "recommended" the above



# Study Related Medical Care

- During the subject's participation, the investigator or designated sub-investigator should ensure that reasonable medical care is provided to the subject for any adverse event, including clinically significant laboratory values, related to trial participation (ICH GCP section 4.3.2)
- Subjects should receive appropriate medical evaluation and treatment until resolution of any emergent condition related to the study intervention even if the follow-up period extends beyond the end of the study



# Non-Study Related Medical Care

- The investigator should inform the subject when medical care is needed for conditions or illnesses unrelated to the study intervention or the disease under study (ICH GCP section 4.3.2)
- The subject should also be advised to seek appropriate care from the physician who was treating the illness prior to the study or assist the subject in obtaining needed medical care



# Investigator Availability

- Investigators should be available to subjects during the study for medical care related to study participation
- “Particularly important” when the study drug has a significant toxicity or abuse potential
- For study drugs with potentially fatal toxicity, the investigator should be readily available by phone or other electronic communication 24 hours a day and in reasonably close proximity to study subjects (not in another state or on prolonged travel)



# Investigator Availability

- Subjects should be clearly educated on the possible need for investigator contact and provided all contact information (phone numbers, email addresses) in writing
- Prior to undertaking a study, prospective investigators should consider their availability to the extent needed given the nature of the trial
- During any period of unavailability, the investigator should delegate responsibility for medical care to a specific qualified physician who will be readily available to subjects during that time



# Protocol Violations and Subject Risk

- Failure to comply with the protocol sometimes exposes subjects to unreasonable risks
- For example, enrolling subjects who violate certain study inclusion/exclusion criteria or failing to perform safety assessment intended to detect drug toxicity are considered failures to protect the rights, safety and welfare of human subjects
- Investigators should minimize these risks by closely adhering to the study protocol



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