

Research Dynamics

## Advanced Topics in Good Clinical Practice

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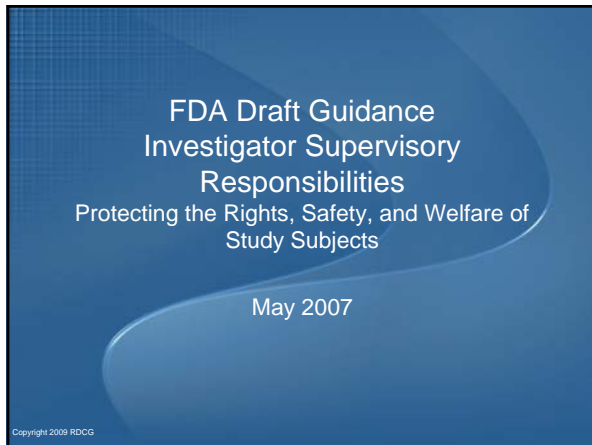
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## FDA Draft Guidance Investigator Supervisory Responsibilities

Protecting the Rights, Safety, and Welfare of  
Study Subjects

May 2007

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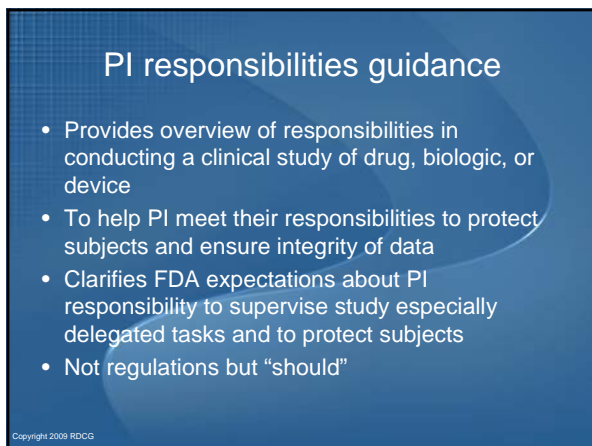
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## PI responsibilities guidance

- Provides overview of responsibilities in conducting a clinical study of drug, biologic, or device
- To help PI meet their responsibilities to protect subjects and ensure integrity of data
- Clarifies FDA expectations about PI responsibility to supervise study especially delegated tasks and to protect subjects
- Not regulations but "should"

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### Investigator Responsibility Overview

For drugs, biologics, and devices

- Ensure study is conducted according to the signed investigator statement or agreement, the investigational plan and regs
- Protect the rights, safety and welfare of subjects
- Control of test materials

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### Drugs and Biologics Part 312 (listed in 1572)

- To follow protocol and make change after Sponsor notification except to protect subjects
- To personally conduct or supervise study
- To inform subjects of investigational nature of product
- To ensure that IC and IRB requirements are met
- To report AE to sponsor
- To read and understand IB and risks and benefits
- To ensure that all staff are informed of obligations
- To maintain adequate and accurate records and allow FDA inspection
- To ensure a compliant IRB conducts initial and ongoing review of study
- To report to IRB all study changes and unanticipated problems
- To not make any changes without IRB approval except to protect subjects
- To comply with all of 312

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### Devices Part 812

A signed agreement between PI and sponsor that includes the following commitments:

- To conduct the investigation in compliance with:
  - Signed agreement with sponsor
  - Investigational plan
  - 21 CFR part 812 and other applicable regulations
  - Any conditions of approval imposed by IRB or FDA
- To supervise all testing
- To ensure ICF meets requirements

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### Devices Part 812 (continued)

Investigator responsibilities part 812

- To permit use of inv. Device only under Inv supervision and to provide it only to authorized persons
- To return to Sponsor remaining supplies of device or dispose as directed by Sponsor
- To maintain accurate and complete records:
  - All correspondence (IRB, INV, Sponsor, monitor, FDA etc)
  - Record of receipt, use and disposition of device
  - Case Hx subject records and device use per subject
  - Protocol and deviations (with dates and reasons)
  - Any other records required by regulation
- To permit FDA to inspect and copy records

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### Devices Part 812 (continued pg 3)

- To prepare and submit to Sponsor (& where required, IRB and monitor)
  - Unanticipated adverse device effects
  - Progress reports
  - Any deviation from inv. Plan
  - Device use without ICF
  - Final report
  - Any additional information required by IRB or FDA
- To protect the rights, safety and welfare of subjects

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### Devices Part 812

- To obtain IRB, FDA and any other approvals before start
- Device regs do not require a specific form for investigator statement
- Parts 50,56 and 812 have other requirements for device trials
- General responsibilities for all products are similar

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**Clarifications to Inv Responsibilities**  
Both drug and device trials

Two primary responsibilities

1. To supervise the conduct of the investigation
2. To protect the rights, safety, and welfare of subjects in drug and medical device trial.

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**Clarifications: Supervision**

- Both 312 and 812 require that inv supervise
- Delegation is common and expected
  - Inv must provide “adequate” supervision
  - Inv. accountable for regulatory violations resulting from failure to “adequately supervise”

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**Clarifications: Supervision**  
Page 2

FDA focuses on 4 major issues of supervision

- Delegated staff were qualified to perform tasks
- Staff received adequate training on how to conduct the delegated tasks and provided an adequate understanding of the study
- Adequate supervision and involvement in ongoing study
- Adequate supervision and oversight of 3<sup>rd</sup> parties as reasonably possible

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**Clarifications: Supervision**  
page 3

Appropriate delegation:

- Person is qualified by education, training and experience.
  - Eg, clinical/medical tasks require formal medical training and may have licensing req.
- Inappropriate delegation
  - Screening evaluations, Med hx, inc/exc criteria, PE, assessments done by staff with inadequate medical training
  - Evaluation of AEs by staff with inappropriate medical training, protocol or product knowledge
  - Assessment of primary study endpoints ( eg tumor response, assessment scales) by staff with inappropriate medical training or protocol knowledge
  - ICF by staff who are not medically trained or knowledgeable of the protocol to describe the risks/benefits of trial

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**Clarifications: Supervision**  
page 4

- Inv. Is responsible for protocol compliance
- If protocol requires and specifies the qualifications of staff to perform protocol tasks, then protocols must be followed:
  - Eg, if state law allows NP to conduct PE under MD supervision and protocol states PE must be done by physician, then Physician must do PE
- Inv should keep list of tasks delegated, persons performing tasks, training completed, and dates of involvement

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**Clarifications: Supervision**  
page 5

Adequate training

- Inv. should ensure adequate training for all staff including replacement staff
- Staff should:
  - General familiarity with study and protocol
  - Have specific understanding of protocol details and inv product relative to their tasks.
  - Know reg. reqs. and acceptable standards for study conduct
  - Be competent to perform the tasks
  - Are kept informed of study changes and provided additional training as appropriate
- If Sponsor provides training materials, the Inv. ensures that staff receives training or information from training.

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### Clarifications: Supervision

page 6

Adequate Supervision

- Inv. Should have a detailed plan for supervision even for highly qualified and experienced staff
- Intensity of supervision appropriate to staff and trial
- Plan elements:
  - Routine meetings with staff to review trial progress and update on changes
  - Routine meetings with monitors
  - Procedure for correcting problems identified by staff, monitors, auditors, etc
  - Procedure for documenting the performance of delegated tasks in a satisfactory manner and verify (eg observation)
  - Procedure for IC in compliance with part 50
  - Procedure for insuring SD info is captured on CRFs accurately
  - Procedure for data queries
  - Procedure for ensuring staff comply with protocol, AE assessment, and other medical issues

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### Clarifications: Supervision

page 7

Adequate Supervision

- FDA .. Following factors compromise Inv ability to provide adequate supervision
  - Inexperienced study staff
  - Over burdened staff
  - Complex trials
  - Lg number of pts
  - Very sick pt pop
  - Conducting lg # of studies at once
  - Remote location or # of sites

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### Clarifications: Supervision

page 8

Inv responsibility for other staff

- Eg. clinical chemistry, ECG assessments, central labs
- Because the Sponsor retains these services, the Sponsor is responsible
- Inv should ensure that results appear reasonable, individually and in the aggregate
- Devices: Field clinical engineers are supervised by Sponsor but Inv should ensure protocol is followed

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### Protecting Subjects

- Inv are responsible for protecting subjects during the trial
- Both drugs (312.60) and devices (812.100)
- Inv should provide reasonable standard of medical care
- Inv should be aware that failure to adhere to the protocol can expose subjects to unreasonable risks

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### Protecting Subjects

page 2

Reasonable medical care

- Inv provide adequate medical care until resolution, even after trial
  - AEs
  - Clinically significant abnormal lab values
  - Intercurrent illnesses
  - Inform primary physician
  - Refer to specialist if necessary

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### Protecting Subjects

page 3

Reasonable access to medical care

- Inv be available to subject
- Provide contact info to subjects
- Educate subjects on need for medical care and how to get it
- If unavailable, delegate to other physician and list as sub on 1572

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### Protecting Subjects

page 4

Protocol violations that present unreasonable risks

- Failure to follow protocol MAY be considered a failure to protect the rights, safety and welfare of subjects
- For example:
  - Failure to comply with inc/exc criteria may enter a subject that the product may cause increased risks and therefore, a failure to protect subjects
  - Failure to perform safety assessments that are to detect toxicity may be a failure to protect subjects
- Compliance with protocol is best way to minimize these risks

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### FDA Draft Guidance Investigator Supervisory Responsibilities

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