

# **Supervisory Responsibilities of Clinical Investigators**

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- FDA Draft Guidance – May 2007
  - Clarifies FDA's expectations, Represents current thinking
    - Supervision of clinical studies where some tasks are delegated
    - Protection of rights, safety, welfare of study subjects
  - Applies to clinical investigation of drugs, devices, biologics
  - Nonbinding
  - Alternative approaches that satisfy the requirements are acceptable

FDA document at <http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0173-gdl0001.pdf>

- Investigator must:
  - Conduct the study according to:
    - the signed investigator statement (FDA 1572 for IND studies);
    - the investigational plan;
    - applicable regulations.
  - Protect the rights, safety, welfare of subjects;
  - Control the test article under investigation

- **Nine Investigator commitments**
  - Conduct study according to the protocol, make changes only after sponsor notification;
  - Personally conduct or supervise the investigation;
  - Inform patients, controls of drug being used for investigational purposes and ensure requirements for informed consent and IRB review and approval are met;
  - Report adverse experiences that occur during the study to the sponsor;

- Confirmation of reading, understanding Investigator's Brochure, including potential risks, side effects of the drug;
- Assurance that those assisting in the trial are informed of their obligations in meeting these commitments;
- **Adequate and accurate records will be maintained** and made available for inspection;

- An IRB in compliance with 21 CFR Part 56 will be responsible for initial, continuing review and approval;
  - Promptly report changes in the research, unanticipated problems involving risk to subjects, others to the IRB;
  - Not make changes in the research without IRB approval except when necessary to eliminate immediate hazards to subjects;
- Comply with all other requirements as defined in 21 CFR Parts 50, 56, 312

- Comply with:
  - 21 CFR 812 (Device regulations)
  - General investigator requirements:
    - Commitment to conduct the study according to the signed agreement with the sponsor, the investigational plan, the regulations as well as conditions of approval by the IRB and FDA
    - Protecting the rights, safety, and welfare of subjects under the investigator's care
    - Supervise all testing of the device involving human subjects, including device control
    - Ensure requirements for obtaining informed consent are met.

- Areas of responsibility include:
    - Maintaining Records
    - Inspections
    - Submitting Reports
    - Investigational Device Distribution and Tracking
    - Comply with all other requirements as defined in 21 CFR Parts 50, 56, 812
- Additional investigator guidance for device trials at <http://www.fda.gov/cdrh/manual/invest.html>

- Drug trials
  - Investigator commits to personally conduct or supervise the investigation
- Device trials
  - Investigator commits to supervise all testing of the device involving human subjects
- Delegation of study-related tasks is common
  - Investigator is responsible for adequate supervision
  - Investigator is accountable for regulatory violations resulting from failure to adequately supervise
- Specific responsibilities are not identical, general responsibilities are the same

- Four areas of focus for FDA:
  - Were individuals qualified;
  - Did study staff receive adequate training;
  - Was there adequate supervision and involvement in the ongoing conduct of the study;
  - Was there adequate supervision or oversight of any third parties involved in the conduct of the study.

- Individuals qualified by education, training and experience
  - Most tasks require formal training, may also require licensing or certification – must be considered
- Protocol defined qualifications
  - May take precedence over state licensing laws
  - More stringent standard applies
- Documentation of delegation
  - Investigator maintains study specific list;
  - Includes description of delegated tasks;
  - Training that qualifies individuals to perform tasks;
  - Dates of involvement



# Sample Delegation Log

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Principal Investigator	Protocol/Study Title	Investigational Product Name/Number	Study Identification Number	Study Site Name/ Site Number

Print Full Name and Title	Signature	Initials	Study Role	Key Delegated Study Tasks (use description code list)	Duration		PI Initials/Date when task was delegated
					From	To	

List individuals to whom significant study-related tasks (ICH GCP 4.1.5) have been delegated. Signatures/Initials for all persons authorized to make entries or corrections to case report forms should be included (ICH GCP 8.3.24). All persons listed on Form FDA 1572 must be included. Other supporting study personnel may need to be listed as well.

Update this form as personnel, roles and/or tasks change.

Study task codes:

- |   |   |
|---|---|
| 1. Obtain informed consent                                    | 7. Ongoing AE/Concomitant Medication Assessment |
| 2. Obtain Medical History                                     | 8. CRF Completion                               |
| 3. Perform Physical Exams                                     | 9. CRF Signature                                |
| 4. Inclusion/Exclusion Criteria Assessment                    | 10. Query Completion                            |
| 5. Drug/Investigational Product Dispensing                    | 11. Query Signature                             |
| 6. Drug/Investigational Product Accountability/Reconciliation | 12. Update/Maintain IRB Documents               |
| 7. Ongoing AE/Concomitant Medication Assessment               | 13. Other _____                                 |
| 8. CRF Completion   | 14. Other _____                                 |

PI Signature (close-out):	Date:
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- FDA inspections - Inappropriate delegation
  - Screening evaluations, eligibility assessments conducted by individuals with inadequate medical training;
  - Physical exams performed by unqualified personnel;
  - Adverse event evaluations by those without appropriate medical training, knowledge of protocol or test article
  - Assessment of primary study endpoints by those without appropriate medical training, knowledge of the protocol
  - Informed consent conducted by those without medical training, knowledge of the protocol or test article

- Investigator ensures all staff:
  - Are familiar with the study protocol;
  - Understand protocol details, test article, tasks that have been delegated;
  - Are aware of regulatory requirements
    - For conduct of clinical trials,
    - Human subject protection;
  - Are competent to perform delegated tasks;
  - Are informed of changes;
    - Education or additional training as appropriate
  - Receive any sponsor specific training materials or information pertinent to their role

- Adequate supervision includes:
  - Routine meetings with staff
    - Review trial progress
    - Provide update of protocol, procedure changes
  - Routine meetings with sponsor's monitors
  - Develop procedure for correcting problems
  - Procedure for documenting performance of delegated tasks
  - Procedure for ensuring informed consent process is in compliance with 21 CFR Part 50
    - That subjects understand procedures, risks, etc.

# UIC What is Adequate Supervision?

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- Adequate Supervision includes:
  - Procedure for ensuring accuracy of CRF entries
  - Procedure for handling data queries and CRF discrepancies
  - Procedure for ensuring compliance with the protocol, adverse event assessment and reporting, medical issues

# UIC Possible Compromising Factors

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- **FDA Observations:**
  - Inexperienced study staff
  - Overburdened study staff
  - Complex clinical trials
  - High study enrollment
  - Very sick patient population
  - Conducting large number of studies concurrently
  - Conducting study from remote location\*
  - Multiple study sites with single investigator oversight\*

\*Consider sub-investigator designation/delegation

- Those not employed by investigator/facility
  - Qualified to perform delegated tasks
  - Adequately trained: delegated tasks, protocol,
  - If performance is inadequate, can not be corrected, **document deficiencies**, consider possibility of voluntary stopping study
- Other parties
  - Investigator responsibility
    - Obtain copies of certification, licenses, ensure integrity of data, review reports for inconsistent results
    - Notify sponsor of errors, questionable central laboratory findings
  - Sponsor responsibility
    - Central laboratory, ECG etc.

- Provide reasonable standard of care for study related/possibly related medical problems
- Follow protocol to minimize unreasonable risks
- Ensure proper care: study related adverse events, clinically significant laboratory values until resolution - **even beyond study completion**
- Intercurrent illness
  - Primary care physician
  - Accessibility
- **DOCUMENT ACTIONS/PLAN**

## Examples of Common Protocol Violations

- Inclusion/Exclusion Criteria
- Failure to perform protocol specified safety assessments

- Preventive Strategies

- Protocol Adherence
- Single Subject Exception

- Post Violation Actions

- Prompt Reporting to Sponsor, IRB as required
- **DOCUMENT ACTIONS/PLAN**

## Aspects of Handling

- Prescribing
- Dispensing
- Recordkeeping
- Storage
- Access
- Disposal/Return
- Additional requirements beyond GCP

- Failure to follow the protocol (35%)\*
  - Violation of inclusion/exclusion criteria
  - Failure to perform required tests
  - Failure to report serious adverse events to the sponsor within 24 hours as specified in the protocol
- Failure to maintain adequate and accurate records (25%)\*
  - Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation
    - **Absence of supporting source documents**
    - **Inaccurate or incomplete source documents**
    - **Time of study drug administration discrepancies**

- **Informed consent (7%)\***
  - Records documenting informed consent incomplete
  - Failure to obtain informed consent prior to any study related procedures
- **Drug accountability (6%)\***
  - Tablet quantity discrepancies
- **IRB Notification (5%)\***
  - Failure to promptly report unanticipated problems involving risk to human subjects or others

To learn of the repercussions of failure to adhere...

**FDA Warning Letters**

<http://www.fda.gov/foi/warning.htm>

- **PI must be aware of Responsibilities**
  - Supervision
  - Appropriate Delegation
  - Adequate Training
  - Safety Monitoring/Reporting
  - Adverse Event Reporting
  - Protocol Adherence
  - Documentation

- **Results of adherence:**
  - Subject rights, safety and welfare protected
  - Data integrity
- **Failure to adhere:**
  - Subjects placed at increased risk
  - Poor data quality
  - Issuance of Form 483
  - Suspension/Termination of Research

- For further information, contact:
  - Dr. Clyde Wheeler at [cwheeler@uic.edu](mailto:cwheeler@uic.edu)
  - Patricia Fischer, RN, CCRP at [pfischer@uic.edu](mailto:pfischer@uic.edu)
  - HSPB policy *OVCR Quality Improvement Program - Monitoring and Auditing* at <http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0866.pdf>