

Investigator Responsibilities in FDA Regulated Research

Carol Fedor, RN, ND, CCRC

Clinical Research Manager
Center for Clinical Research and Technology
UH Case Medical Center

Steven Strausbaugh, M.D., FCCP

Assistant Professor of Pediatrics and Medicine
Director, Adult Cystic Fibrosis Program
Associate Director Combined Internal Medicine/Pediatrics Residency Program
Division of Pediatric Pulmonology and Division of Pulmonary/Critical Care & Sleep Medicine
Rainbow Babies & Children's Hospital and University Hospitals at Case
Case Western Reserve University

The Bad Apples: Criminal Prosecutions

- 1997: Richard Borisan (Med College of Georgia): performing schizophrenia drug trials, funneling money to private accounts (15 year jail term, fine)
- 1999: Robert Fiddes: falsified drug trial data, “made up” patients (15 months jail, fine)
- 2006: Eric Poehlman (Univ. Vermont): falsified data on 17 grant applications and on 10 papers (1 yr jail, fine)
- 2006: Hwang Woo Suk (So. Korea) falsified data on human cloning, lost faculty position

The Bad Apples

Los Angeles Times
THURSDAY, MARCH 25, 1999
COLUMN ONE
VA Hospital's Ethical Nightmare
U.S. Suspends Research at VA Hospital in L.A.
VA: U.S. Orders Research Halted at L.A. Hospital
By TERENCE MONMONEY
FEDERAL MEDICAL WRITER

VA Hospital in L.A. Reassigns Research Chief
By TERENCE MONMONEY
FEDERAL MEDICAL WRITER
Officials at the troubled West Los Angeles VA Healthcare Center have removed the director of research from his post and started a new inquiry into allegations of possible patients' rights abuses in cardiology research.

THE NATION'S NEWSPAPER
USA TODAY
Monday, July 10, 2000
Clinical trials halted
Feds: Cancer study endangered patients
By Edward T. Pound
USA TODAY
WASHINGTON — In a continuing crackdown on
More trials
The number of clinical trials per new drug has

Denver Rocky Mountain
September 24, 1999 • InsideDenver.com
FRIDAY
Most awards in Colorado for the fourth straight year

Houston Chronicle
Vol. 99 No. 343 Wednesday, Sept. 20, 2000 50 Cents ***
Some research at UTMB frozen
Federal investigation alleges inadequate patient protection
By LEIGH HOPPER
Houston Chronicle Medical Writer

Washington Post
WEDNESDAY, MAY 12, 1999
Halts Research Humans at Duke
City Can't Ensure Safety, Probers Find
research, officials said.
Among the problems cited by

CU medical research halted
Federal agencies cite concerns about safety of patients; university aims to resume clinical trials within a week. 4A

CLINTON VETOES TAX CUT. 2A

Chicago Tribune
Saturday, August 28, 1999
Chicagoland Final 50c NEWSSTAND
UIC suspended from doing most human research
Federal panel says some test subjects not fully informed
Cmdr. Viktor Afanasyev (front) and Jean-Paul Haignere wave goodbye to the much-maligned space station as they and Sergei Avdeyev prepare to undock and return to Earth.

THE SUN
Friday, July 20, 2001
HOWARD COUNTY
Baltimore, Maryland : 50 cents
U.S. halts Hopkins research

Research Misconduct

“Research misconduct does not include honest errors or honest differences of opinion”

- From S. Woollen, Associate Director for Bioresearch Monitoring, FDA, 2003

If FDA has information indicating an investigator has *repeatedly or deliberately failed to comply* with the requirements identified in the Code of Federal Regulations or has submitted false information to FDA or a sponsor s/he may be disqualified and be subject to criminal and civil liability.

Differences between the role of clinician and role of researcher

Clinical Care

- Individualized
- Physician-driven
- Patient welfare
- Established standards

Research

- Rigid, pre-determined
- Protocol driven
- Knowledge, validity
- Protocol elements

You're In Charge: Principal Investigator



Investigator

Investigator means an individual who actually conducts a clinical investigation. In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team.

21 CFR 312.3 (b)

Who is a Principal Investigator (PI)?

- “The” person responsible for the conduct of the clinical trial at a trial site
 - If a trial is conducted by a team, the investigator is the responsible leader of the team and is usually called the principal investigator
- Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decision (e.g. associates, residents, fellow) are, under the regulations, considered sub-investigators, not PIs or Co-investigators

An Investigator is responsible for

- Ensuring that an investigation is conducted according to
 - Signed investigator statement (FDA 1572)
 - Study protocol
 - IRB requirements
 - All applicable federal, state, & institutional regulations
- Control of all drugs/agents/devices under investigation
- For protecting the rights, safety, and welfare of subjects under the investigator's care

Reference: 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, October 2009)
<http://www.fda.gov/downloads/drugs/guidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>

Investigator Responsibilities

- Respond to participants who have an adverse event
- Keep participant fully informed of any new information
- Protect the privacy of participants and maintain confidentiality of data
- Either obtain consent or designate authorized person to obtain consent
- Provide reports as required by the sponsor and the IRB
- Make records available for inspection
- Ensure accountability of investigational drugs, devices or biologics
- Provide contact information on consent form
- Provide a data and safety monitoring plan

Source: UHCMC IRB Policy: Investigator Responsibilities

Qualifications for Investigators

- Qualified by education, training, & experience to assume proper conduct of the trial
- Aware of & comply with GCP
- Familiar with the use of investigational product(s)
- Interested in the scientific aspects of the trial

Qualifications for Investigators

- Adequate time to:
 - Discuss, read & approve protocol
 - Identify & recruit subjects
 - Properly assess & follow subjects
- Adequate personnel & resources to conduct the trial
- Ability to meet the recruitment target
- Conduct the trial in compliance with the protocol without deviation

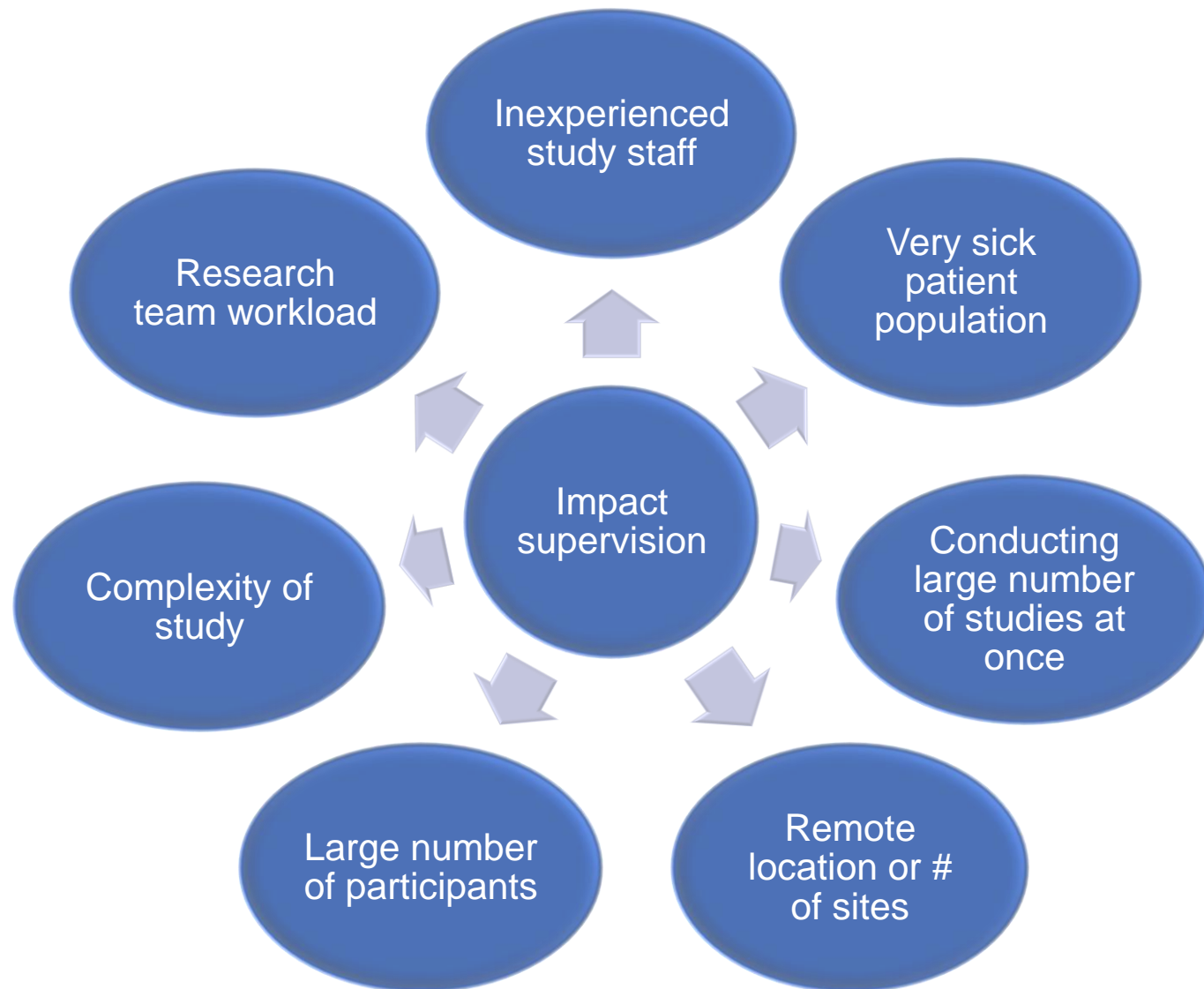
Supervision

- Both CFR 312 and 812 require investigators supervise drug and device investigations
- Delegation is common and expected
 - Investigator must provide “adequate” supervision
 - Investigator is accountable for regulatory violations resulting from failure to “adequately supervise”

Supervision

- FDA focuses on 4 major issues of supervision
 - Delegated staff were qualified to perform tasks
 - Staff received adequate training
 - Adequate supervision and involvement in ongoing study
 - Adequate supervision and oversight of 3rd parties as reasonably possible

Factors that impact Investigator's ability to provide adequate supervision



Form FDA 1572

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.

Form FDA 1572

- Statement signed by the investigator
- Provide information to the sponsor
- Assure the investigator will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic

When is Form FDA 1572 Required?

- Under the regulations, a 1572 is required for studies of investigational drugs or biologics conducted under an Investigational New Drug (IND) application
- A 1572 is not required for studies not conducted under an IND and is not applicable to investigational device studies

When an Investigator Signs the 1572 – What do you commit to?

- To conduct the study in accordance with the protocol
- To inform the subjects of the investigational status of the test article
- To report adverse events to the sponsor
- To read and understand the Investigational Brochure
- To inform all support personnel of the investigation requirements
- To maintain adequate records and make them available for inspection
- To assure that the IRB is in compliance

(continued)

Information Sheet Guidance for Sponsors, Clinical Investigator, and IRBs – Frequently Asked Questions – Statement of Investigator (Form FDA 1572). Final May 2010

When an Investigator Signs the 1572 – What do you commit to?

- To assume responsibility for initial and continuing review by the IRB
- To promptly report study changes and unanticipated risks to the IRB
- Not make changes in the research without IRB approval
- To comply with the requirements regarding the obligations of clinical investigators
- To personally supervise or conduct the investigation

Information Sheet Guidance for Sponsors, Clinical Investigator, and IRBs – Frequently Asked Questions – Statement of Investigator (Form FDA 1572). Final May 2010

What does it mean to personally supervise or conduct the investigation?



Understanding what “Personally Supervise” really means

- Appropriate delegation
- Adequate training
- Adequate supervision

FDA guidance for industry: Investigator responsibilities - protecting the rights, safety and welfare of study subjects - 2009

What is appropriate delegation?

Qualified by:

- Education
- Training
- Experience
- Licensure (when required)

to perform the delegated task

Most clinical/medical tasks require formal medical training/licensing/certification

What is adequate training?

- Familiarity with purpose of the study and protocol
- Understanding of the specific details of the protocol and investigational product to perform assigned tasks
- Knowledge of regulatory requirements and acceptable standards for conducting clinical trials and the protection of participants

What is adequate supervision?

- Level of supervision should be appropriate to staff, nature of the trial and participant population.

Holland Case

Lax Supervision

- Study coordinator enrolled ineligible subjects in oncology trials
- Coordinator altered source records and created fraudulent CRFs to make subjects appear eligible
- Data manipulations should have been apparent to attentive clinician
- Subject who was ineligible due to poor renal and liver function was enrolled, dosed, and died as a result
- Study coordinator sentence to 71 months in prison and debarred from many future involvement in FDA regulated research
- Dr. Holland – 5 years probation, \$500k restitution to defrauded drug companies, disqualified

FDA PI Warning Letter 2/16/11

1. You failed to personally conduct or supervise the clinical investigation [21 CFR 312.60].

When you signed the Statement of Investigator (Form FDA 1572) for the above referenced clinical trial, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trial is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60]. By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trial was conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.

Specifically, you failed to adequately supervise the study staff to whom you delegated tasks. Many, if not all, of the other violations listed in this letter are traceable to your failure to adequately supervise staff and the conduct of the investigation. For example, multiple episodes of chemotherapy misadministration occurred for 3 of 3 subjects enrolled, including administration of 6 cycles of an investigational drug to a subject after closure of the study. Adequate review of the chemotherapy orders could have prevented misadministrations, or at a minimum allowed you to discover flaws in your systems that led to repeated departures from the investigational protocol. Adequate supervision also could have prevented or minimized repeated failures to report adverse events and to conduct procedures required by the protocol. We note that your staff reported to Investigator Garmendia that you were not present at the clinical site for a majority of the study, and that you live outside of the State of Florida for six months of the year. It is apparent that procedures were not in place to compensate for your absence.

FDA PI Warning Letter 2/2/09

1. You failed to personally conduct or to supervise the clinical investigation [21 CFR 312.60].

When you signed the investigator statements (Form FDA 1572) for the above-referenced clinical investigations, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities include ensuring that the investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation (21 CFR 312.60). You specifically agreed to personally conduct the clinical studies or to supervise those aspects of the studies that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you may not delegate your general responsibilities.

Our investigation indicates that you permitted individuals to conduct study tasks which they had not been delegated the authority to execute, and that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan, and applicable regulations, and in a manner that protected the rights, safety, and welfare of human subjects.

A. The following violations were noted for Protocol [(b)(4)]

1. We note that per the "Delegation of Duties & Authorized Signatures Form," you and/or your sub-investigator were the only individuals at your site designated by you to make trial-related medical decisions and to perform critical trial-related procedures. You informed FDA Investigator Torres, however, that you gave to your study coordinator Ms. [(b)(6)] the responsibility to determine subject eligibility into the study; the fact that she made such determinations is also evident in the medical and study records. Determination of subject eligibility is a trial-related medical decision, as well as a critical trial-related procedure. As such, this study task was not delegated to Ms. [(b)(6)] Permitting Ms. [(b)(6)] to conduct study tasks for which she did not have authorization demonstrates your failure to conduct the study in accordance with the study plan and applicable regulations.

How do you manage
delegation, training and
supervision?

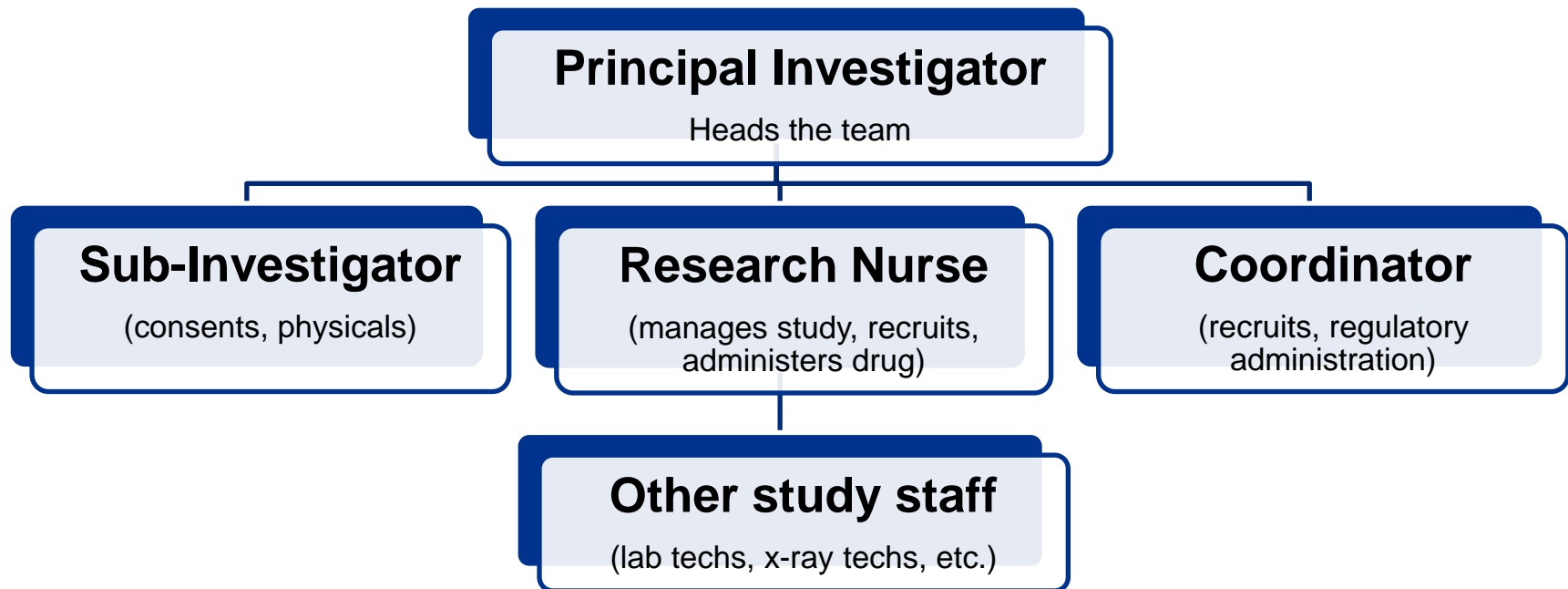
Tools to manage delegation, training and supervision - documenting

- Maintain a list of study staff and what study-specific tasks have been delegated
 - Describe the delegated tasks
 - Identify qualifying training
 - Identify dates of involvement in the study

Tools for managing

Create an organization chart

- Identify study team members including specific job responsibilities
- Review responsibilities and determine review intervals



Sample study specific task list

Study Task	Specific Actions	Individual Responsible
Screening	Telephone screening of interested participants	RC
	Complete screening checklist	RN/RC
Eligibility	Initial review with potential participant	RN/Sub-I
	Final eligibility	PI
Consent	Obtain informed consent	RN/Sub-I
Clinical Procedures	Draw blood	RN
	Complete history/physical exam	PI/Sub-I
Data management	Complete case report forms	RN/RC

Sample staff signature and delegation of responsibility log

Staff Signature and Delegation of Responsibility Log

Page 1 of ____

Principal Investigator: _____

Protocol Title: _____

IRB Number: _____

Print Name	Signature	Initials	Responsibilities*	HSP Certification	Start Date	End Date	PI Initials

End of Study / Page Completion

Principal Investigator Signature: _____ Date: _____

Responsibilities* (list all that apply)

- | | | | |
|-----------------------------------|--------------------------------|---------------------------------------------------------------------------|-------------------------|
| 1) PI | 4) Research Nursing | 7) Administration | 10) Patient Examination |
| 2) Co-Investigator | 5) Laboratory Analysis | 8) Patient Consent (requires Certification in Human Subjects Protections) | |
| 3) Clinical Research Coordination | 6) Regulatory Activities (IRB) | 9) Data Entry | |

Tools to manage delegation, training and supervision

- Research Standard Operating Procedures (SOPs)
 - FDA Inspection of Investigators
 - Site Initiation Visit
 - Maintenance of Research Regulatory Documents and Other Essential Documents
- Office of Research Compliance and Education website (Uhhospitals.org/ccrt)
 - AE summary logs
 - Delegation of authority/staff signature log
 - Device accountability log
 - Screening/enrollment log

Examples of inappropriate delegation of study-related tasks

- Assessment of inclusion/exclusion criteria by individuals with inadequate medical training
- Physical examination performed by unqualified personnel
- Evaluation of adverse events by individuals lacking appropriate medical training or knowledge of the clinical protocol or study agent
- Informed consent obtained by individuals who lack the training and knowledge of the protocol need to discuss risks and benefits of study

Elements of a supervisory plan:

- Routine meetings with staff and sponsor's monitors
- Procedure for timely correction and documentation of identified problems
- Procedures for:
 - Documenting review of performance of delegated tasks
 - Ensuring informed consent is being done appropriately.
 - Ensuring that source data are accurate

Key Messages

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practices (GCP) in research
 - It is important have a clear understanding of responsibilities under FDA regulations
- At stake is public confidence and participation in the clinical trials and ultimately the availability of safe and effective products

U. S. Food and Drug Administration

5600 Fishers Lane, Rockville MD 20857-0001

1-888-INFO-FDA (1-888-463-6332)

Drug Information Number: 301-827-4570 (8:00 AM - 4:30 PM)

<http://www.fda.gov/cder/guidance/index.htm>

