Objectives

Identify the federal regulations covering clinical research and clinical investigator obligations

Discuss specific problems seen during FDA inspections at clinical sites

Discuss various methods that can be used to ensure compliance with federal regulations and study protocol requirements
Who is an investigator?

- An individual **who actually conducts a clinical investigation** (i.e., under whose immediate direction the drug is dispensed to a subject.)

- 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]
Can there be co-investigators?

**ANSWER:** Yes and No.

Yes, for your needs but NO for regulatory purposes.

Each co-investigator is fully responsible for fulfilling all of the obligations of an investigator; each must sign a separate Form FDA-1572.
An individual who **both initiates and conducts an investigation**, and under whose immediate direction the investigational drug is administered or dispensed

- The term does not include any person other than an individual
- The requirements applicable to a sponsor-investigator include both those applicable to an investigator and those applicable to a sponsor

[21 CFR 312.3]
Does the investigator have to be a medical doctor?

**ANSWER: NO** A physician can be a subinvestigator to perform those study functions requiring the appropriate level of medical expertise.

[21 CFR 312.53]
Legal Framework

Federal Food, Drug, and Cosmetic Act (FD&C Act)
- Section 505(i) is the statutory authority for FDA’s oversight of clinical investigations to test safety and effectiveness

Code of Federal Regulations (CFR)
- Regulations promulgated under Section 505(i) describing FDA’s authority over the conduct of clinical investigations including
  - Sponsor responsibilities
  - Clinical Investigator responsibilities

Guidances
- Advisory only, to assist clinical investigators and sponsors in complying with the regulations
Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations

Guidance for Sponsors, Investigators, and Institutional Review Boards
U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)

October 2018

https://www.fda.gov/RegulatoryInformation/Guidances/ucm623197.htm
Example: What is the legal age for consent to enroll in a clinical trial?

Answer: Depends on the applicable law of the jurisdiction in which the investigation will be conducted. [21 CFR 50.3(o)]

- Certain life events like military service, marriage, pregnancy and childbirth may allow consent
Institute of Medicine Report
Ethical Conduct of Clinical Research Involving Children

See Appendix B:
STATE REGULATION OF MEDICAL RESEARCH WITH CHILDREN AND ADOLESCENTS: OVERVIEW AND ANALYSIS

https://www.nap.edu/catalog/10958/ethical-conduct-of-clinical-research-involving-children
FDA Expectations of Clinical Investigators

- Adherence to Code of Federal Regulations
  - Knowledge of Clinical Investigator regulations
  - Understanding of Clinical Investigator responsibilities
Expectations

If you don’t like doing paperwork...

Run as fast as you can towards the door.
No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572

[21 CFR 312.53(c)]
# Statement of Investigator

**Title 21, Code of Federal Regulations (CFR) Part 312**

### 1. Name and Address of Investigator

<table>
<thead>
<tr>
<th>Name of Principal Investigator</th>
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<tbody>
<tr>
<td>Address 1</td>
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<td>Address 2</td>
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<td>ZIP or Postal Code</td>
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</table>

### 2. Education, Training, and Experience that Qualify the Investigator as an Expert in the Clinical Investigation of the Drug for the Use Under Investigation. One of the Following is Provided (Select one of the following.)

- [ ] Curriculum Vitae
- [ ] Other Statement of Qualifications

### 3. Name and Address of Any Medical School, Hospital, or Other Research Facility Where the Clinical Investigation(s) Will Be Conducted

<table>
<thead>
<tr>
<th>Name of Medical School, Hospital, or Other Research Facility</th>
</tr>
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<tbody>
<tr>
<td>Address 1</td>
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<tr>
<td>Address 2</td>
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<tr>
<td>Country</td>
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<tr>
<td>ZIP or Postal Code</td>
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### 4. Name and Address of Any Clinical Laboratory Facilities to Be Used in the Study

<table>
<thead>
<tr>
<th>Name of Clinical Laboratory Facility</th>
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<tbody>
<tr>
<td>Address 1</td>
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<tr>
<td>Address 2</td>
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<td>State/Province/Region</td>
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<tr>
<td>Country</td>
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<td>ZIP or Postal Code</td>
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</tbody>
</table>

### 5. Name and Address of the Institutional Review Board (IRB) That is Responsible for Review and Approval of the Study(IES)

<table>
<thead>
<tr>
<th>Name of IRB</th>
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</thead>
<tbody>
<tr>
<td>Address 1</td>
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<tr>
<td>Address 2</td>
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<tr>
<td>City</td>
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<td>State/Province/Region</td>
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<tr>
<td>Country</td>
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<tr>
<td>ZIP or Postal Code</td>
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</tbody>
</table>
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.

10. DATE (mm/dd/yyyy)  11. SIGNATURE OF INVESTIGATOR

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)
Commitments on 1572

- Personally conduct or supervise investigation
- Follow protocol- only make changes after notifying the sponsor unless subject at risk
- Ensure all persons assisting with the study are informed of obligations
- Inform subjects that drugs are being used for investigational purposes
- Ensure informed consent (21 CFR Part 50) and IRB review, approval and reporting (21 CFR Part 56)
- Report to sponsor adverse events (21 CFR 312.64); read and understand the IB.
Maintain adequate and accurate records (21 CFR 312.62) and make them available for inspection in accordance with 21 CFR 312.68

Ensure initial and continuing review by an IRB and report all changes to research and unanticipated problems involving risks to subjects, not make any changes without IRB approval except where necessary to eliminate immediate hazards

Comply with other requirements in 21 CFR 312
If a clinical study is conducted outside of the U.S. and is not conducted under an investigational new drug application (IND), then the investigator need not sign a 1572.

If a foreign clinical study is conducted under an IND, then all FDA IND regulations, including the requirement to obtain a signed 1572, must be met.

If local laws or regulations prohibit the signing of a 1572, FDA would expect the sites to operate as non-IND sites.
Information Sheet
Guidance for
Sponsors, Clinical
Investigators, and
IRBs

Frequently Asked Questions –
Statement of Investigator
(Form FDA 1572)

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2010
Procedural
Published as official guidance in U.S. Federal Register (May 1997)

- “The objective of this ICH GCP guidance is to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions”. 
Amended to add detail, encourage innovation and to keep up with evolutions in technology and risk management processes

- Additional **definitions** such as certified copy, validation of computerized systems
- Added **additional investigator responsibilities**
- Added standards regarding **electronic records and essential documents** have been updated
- Added discussion of **quality management and risked-based monitoring**
Differences can especially be seen in the area of sponsor responsibilities

- ICH E6 more detailed for monitoring and quality assurance

However, FDA regulations are more explicit in the institutional review board (IRB) sections
Do FDA regulations allow for delegation of the informed consent?
FDA has no regulations concerning delegation of this duty

- Discussed in the FDA Information Sheets: “FDA does not require the investigator to personally conduct the consent interview.”

http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm

ICH allows the delegation of the informed consent process to a designee

- “The investigator, or a person designated by the investigator, should fully inform the subject...”
**QUESTION**

Does the investigator have to sign the informed consent?

**ANSWER:** NO Signing/dating by person conducting the informed consent discussion is part of ICH-GCP but not FDA regulations.
Role of Clinical Investigators

Good Clinical Practice (GCP) in FDA-regulated research is not the same as good clinical practice in caring for patients.

**CLINICAL CARE:** Goal is benefit to the individual. Care is individualized to each patient. New knowledge generated is incidental.

**RESEARCH:** Goal is new knowledge that can help future patients. Balancing of risks and benefits. Standardized procedures for all study participants. Procedures must be consistent and data must be reproducible. Additional expectations of documentation in research. Course of care is outlined in the IRB-approved protocol.
Important Caveat

Standards for clinical care of patients ≠ Standards for academic research ≠ Standards for FDA regulated research

“Therapeutic experimentation did not begin to gain a true foothold in modern medicine until the U.S. legal system stopped equating experimentation with medical malpractice”.

- Overview on FDA History
The clinical investigator is in charge **and** held accountable

- FDA regulations permit sponsors to transfer their responsibilities to contract research organizations (CROs) but do **not** permit clinical investigators to transfer their general responsibilities to CROs or site management organizations, subinvestigators, or study staff.
Penalties for significant noncompliance

- Warning Letters (posted on FDA website)
- Disqualifications/Restrictions/Debarments (posted on FDA website)
- Criminal prosecutions/prison/fines
Loopholes in the Food, Drug and Cosmetic Act of 1938:
Companies could distribute unapproved drugs for experimental purposes
- Did not require notification to patients of investigational status
- Did not require companies or doctors to keep track of distribution
- Did not require FDA to be notified of experimental use
- Did not require records to be kept
- Did not require demonstration of drug effectiveness
Thalidomide tragedy

Thalidomide, the sleeping pill that has caused thousands of infant malformations in Europe had been distributed to 1,200 physicians in the United States for investigational use since 1959, before it was banned in the United States.

This figure has been supplied by the William S. Merrell Co. of Cincinnati, manufacturer of the drug, to the Food and Drug Administration here. FDA inspectors are now checking the physicians to make sure they have returned or destroyed their supplies of the drug, as requested by the Merrell Company in March.

The investigational use of the drug in the United States dates to 1959. It is not known by FDA if the drug was used experimentally during early pregnancy, the critical period in which the malformations are caused.

Several malformed infants in the United States have been linked to their mothers’ use of the drug. In none of these publicly-reported cases, however, was the drug given by a licensed physician in the United States.
1962: Kefauver-Harris Amendments

- Approval based on demonstration of **efficacy** as well as safety (*1938 Food, Drug, and Cosmetic Act only required safety evaluation*)
- Expanded inspectional authority - FDA can inspect company records regarding development and clinical testing
  - FDA must be notified before clinical trials could be conducted
  - Rulemaking authority over "Investigational New Drugs"
  - Gave FDA the power to halt clinical trials
IND Regulations of 1963

- Created the current framework of clinical trials
- Investigations must be “adequate” and “well-controlled”
- Investigators qualified by scientific training and experience
- Recordkeeping requirements
- Informed consent of subjects (one year before the Declaration of Helsinki)
General Clinical Investigator Responsibilities
[21 CFR 312.60]

- Ensuring that an investigation is conducted according to the
  - Signed investigator statement (Form 1572)
  - Investigational plan
  - Applicable regulations

- Protecting the rights, safety, and welfare of subjects under the investigator's care

- Control of drugs under investigation

- Ensuring that informed consent is adequately obtained according to 21 CFR 50

- Ensuring IRB review, approval and reporting requirements are met per 21 CFR 56
Investigator Responsibilities

- Record keeping and retention (312.62)
  - An investigator is responsible for:
    - Maintaining adequate records of the **disposition of the drug**
    - Accurate **case histories** that record all observations, and
    - **Other data pertinent to the investigation** on each individual administered the investigational drug or employed as a control in the investigation
Investigator Responsibilities

- An investigator is required to maintain investigation records for:
  - 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated
  - 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication
Investigator reports (312.64)

- Progress reports to sponsor
- Safety reports
  - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
  - Record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol
- Final report to sponsor
- Financial disclosure to sponsor (21 CFR 54)
  - Promptly update as needed during the course of the investigation and for 1 year following study completion
Guidance for Clinical Investigators, Industry, and FDA Staff
Financial Disclosure by Clinical Investigators

February 2013

FORMS FDA 3454 (Certification of no disclosable financial interests) and 3455 (Disclosure Statement [21 CFR § 54.4(a)]) are available on the Web at the following Internet address: http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
QUESTION

- You must disclose significant equity interest in the sponsor of a covered study.
  - What is the monetary amount of stock in a nonpublicly traded corporation?
    - Any amount
  - What is considered for a publicly traded corporation?
    - $50,000
  - To whom does this apply?
    - Investigator, subinvestigator, spouses and dependent children
U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007/FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain “applicable clinical trials”

- Trials of drugs and biologics: controlled clinical investigations, other than Phase 1 investigations, subject to FDA regulation
- Trials of devices: Controlled trials with health outcomes of devices subject to FDA regulation, other than small feasibility studies, and pediatric postmarket surveillance required by FDA

http://clinicaltrials.gov/ct2/manage-recs/fdaaa
Civil Money Penalties Relating to the ClinicalTrials.gov Data Bank

Guidance for FDA Staff, Responsible Parties, and Submitters of Certain Applications and Submissions to FDA

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Good Clinical Practice (OGCP)
Center for Drug Evaluation and Research (CDER)
Center for Biologies Evaluation and Research (CBER)
Center for Devices and Radiologic Health (CDRH)
Office of Regulatory Affairs (ORA)

September 2018

The Final Rule clarifies and expands the regulatory requirements and procedures for submitting registration and results information for certain trials to ClinicalTrials.gov, in accordance with FDAAA 801. The Final Rule has been in effect since January 18, 2017. Responsible parties have been required to be in compliance starting April 18, 2017.
Sponsor Responsibilities

Sponsors are responsible for (21 CFR 312.50):

- Selecting qualified investigators
- Providing investigators with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation
- Ensuring that the investigation is conducted in accordance with the general investigational plan
- Maintaining an effective IND
- Ensuring that the FDA and all participating investigators are promptly informed of significant new adverse effects or risks
Outlines FDA expectations for study oversight

- **Delegation** of study tasks
- **Training** of study staff
- **Supervision** of conduct of ongoing study
- **Oversight of third parties** involved in the study (e.g. SMOs, outside labs specifically retained to conduct study assessments)
Guidance (cont.)

- Outlines FDA expectations for protecting the rights, safety, and welfare of subjects
  - Provision of reasonable medical care for issues related to study participation (e.g. to manage an adverse event)
  - Facilitation of care for other health issues that might arise during the study
  - Avoiding exposure of subjects to unreasonable risks
Can the investigator delegate the activities around investigational product?
FDA has no regulation concerning delegation of these duties

- The investigator should ensure that any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task

(per FDA Investigator Guidance 2009)

ICH allows the delegation of study drug dispensing, patient counselling, and drug accountability to an “appropriate” designee
Definition: Inappropriate Delegation

“Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with inadequate medical training (e.g., a medical assistant).”
What NOT to Do
DON’T

- Over-delegate to non-physicians (e.g., diagnosis that qualifies/determines eligibility for entry into the study)
- Erase, white-out or obliterate original data entry
- Accept suggested changes to study data without checking the source documents or without justification for such changes
- Backdate the consent forms and signatures
DON’T

- Forget to obtain IRB approval of consent form revisions
- Revise the protocol without obtaining the sponsor’s written concurrence
- Use your staff as subjects in a study not having the condition(s) under investigation
- Destroy study records
Research Misconduct Among Clinical Trial Staff

Barbara K. Redman, Thomas N. Templin and Jon F. Merz

Dept of Medical Ethics, University of Pennsylvania, USA; Wayne State University, USA

Keywords: research misconduct

ABSTRACT: Between 1993 and 2002, 39 clinical trial staff were investigated for scientific misconduct by the Office of Research Integrity (ORI). Analysis of ORI case
Summary of Findings

- Only one staff person certified as a Clinical Research Coordinator

- Motivation: job retention and productivity; the ability to earn extra pay, *typically involving the use of pay incentives for subject recruitment*

- Three types of problems were identified in the cases: deficiencies in management, supervision, and training.
Deficiencies in Management

- Over-delegation of responsibility
- Overwhelming workload
  - One coordinator was managing more than twenty trials with eight investigators
  - In one instance of a five year employee, the only individual who interviewed participants and entered data, so many records had been falsified or fabricated that it took the research team two years to recover from the damage.

Principal investigators asserted that quality control of records lay with the data safety monitoring committee in a multi-center trial and not with them; thus the PIs failed to provide any local supervision.
Strengthened project controls such as: Principal Investigator (PI) signature on all forms, weekly meetings of the PI and project coordinator with monthly records review, and PI observation of trial procedures.

Audit of all trials, further documented training in research methods and compliance, and re-audit to see if study oversight, data management and supervision of personnel had improved.
Regulatory Authority to Conduct Inspections/Audits

- Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have access to and copy and verify the required clinical study records.

21 CFR 312.68

- “An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator...”
Clinical Investigator Inspections*
(All Center, FY 2017)

- CDER: 418
- CBER: 84
- CDRH: 198
- Total: 700

*Based on final classification
Inspections Overseen by OSI/OSIS* (CDER, FY 2008 - FY 2017)

*Based on start date
Clinical Investigator Inspections by Location*
(CDER, FY 2017)

- United States: 71%
- Western Europe: 10%
- Eastern Europe: 9%
- Asia/Pacific: 3%
- Canada: 3%
- Latin America: 1%
- Middle East/Central Asia: 1%
- Australia: 1%
- Africa: 1%

512 CI Inspections *Based on start date
International Clinical Investigator Inspections by Location*

(CDER, FY 2017)

*Based on start date

- Eastern Europe: 30%
- Latin America: 10%
- Western Europe: 31%
- Asia/Pacific: 14%
- Middle East/Central Asia: 5%
- Canada: 6%
- Australia: 1%
- Africa: 3%

161 Inspections
Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued (CDER, FY 2017)

**Domestic CI Deficiencies**
- Protocol: 26%
- Records: 14%
- Drug Accountability: 3%
- Consent: 2%
- IRB Communication: 2%
- Adverse Events: 1%

276 Domestic Inspections

**Foreign CI Deficiencies**
- Protocol: 16%
- Records: 10%
- Consent: 4%
- Adverse Events: 1%
- Other: 1%

142 Foreign Inspections
Compliance Classifications

**NAI** - No Action Indicated
Inspected Entity is in compliance

**VAI** - Voluntary Action Indicated
Minor deviation(s) from the regulations
Voluntary correction is requested

**OAI** - Official Action Indicated
Serious non-compliance requiring regulatory or administrative action by FDA
Clinical Investigator Inspections
Final Classification*

(CDER, FY 2017)

- No Action Indicated: 70%
- Official Action Indicated: 2%
- Voluntary Action Indicated: 28%

*Based on final classification

418 CI Inspections
Inspectional Outcomes

- No Action Indicated
- Form FDA 483 – 15 business days to reply
Inspection Observations

- Spreadsheets summarizing the areas of regulation cited on FDA's system-generated 483s by fiscal year
  https://www.fda.gov/ICECI/Inspections/ucm250720.htm

- Examples of inspectional observations
  https://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ora/oraelectronicreadingroom/default.htm
Inspections Classification Database and Search (Oct. 2008–Sept 2018)

- Final inspection classification for inspections related to currently marketed FDA-regulated products. (Some information may be withheld from posting as to not interfere with enforcement action).

http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm
Common mistakes – Risk factors for non-compliance

- Poor supervision and training of study staff
- Insufficient investigator involvement in study conduct
- Inappropriate delegation of study tasks to unqualified persons
- Failure to adequate protect study subjects
- Overworked investigator and study staff (e.g., too many subjects, complex study with large data collection, too many concurrent studies)
Regulatory Actions

- Warning Letter
- Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
- Disqualification of clinical investigator
- Criminal Investigation by Office of Criminal Investigations (OCI)
  - Debarment
Engage in verbal discussion at close-out
Send written response within 15 business days

What not to say:

- “The study monitor failed to inform the staff of IRB approval of a new version of Protocol XX”. *It is your responsibility as the investigator (not the monitor’s responsibility) to ensure that the IRB has approved any changes in the research prior to implementing those changes.*
- The study coordinator miscalculated the WOMAC pain subscale. *Your response is inadequate because...you have submitted no documentation of the retraining.*
Screening ferritin value of 881.4 ng/ml was significantly higher than the protocol-allowed maximum value of 100 ng/ml.

- “No deviation occurred with reference to randomizing this subject because the subject was randomized per protocol prior to receiving central lab results; when I received the central lab results, I felt that the subject was stable enough to continue with the study. I monitored the subject closely and felt my clinical judgment was correct”. Protocol XX does not allow enrollment of subjects based solely on the clinical investigator’s judgment when the subject does not meet required inclusion criteria.
“It is your responsibility to ensure adherence to each requirement of the law and relevant FDA regulations. You should address these deficiencies and establish procedures to ensure that any ongoing or future studies will be in compliance with FDA regulations.”

“Within fifteen (15) working days of your receipt of this letter, you should notify this office in writing of the actions you have taken to prevent similar violations in the future. Failure to address the violations noted above adequately and promptly may result in regulatory action without further notice.”
List of Warning Letters
https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

Regulatory Procedures Manual Section on Warning Letters
21 CFR 312.70

- Repeated and deliberate failure to comply with the requirements
- FDA provides notice of matter to investigator and provides opportunity to explain (informal hearing)
- Opportunity for formal hearing
- May result in ineligibility to receive investigational drugs
Clinical Investigators- Disqualification Proceedings

Provides a list of clinical investigators who are or have been subject to an administrative clinical investigator disqualification action and indicates the current status of that action; links to related FDA regulatory documents

http://www.fda.gov/ICECI/EnforcementActions/ucm321308.htm
<table>
<thead>
<tr>
<th>Name</th>
<th>Agency</th>
<th>Status</th>
<th>Date</th>
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<tbody>
<tr>
<td>Balin, Howard, MD</td>
<td>CDER</td>
<td>Disqualified</td>
<td>03/19/1975</td>
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<tr>
<td>Baratta, Vincent J, MD</td>
<td>CDER</td>
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<td>11/13/1985</td>
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<td>Batshaw, Mark L., MD</td>
<td>CBER</td>
<td>Restrictions Removed</td>
<td>10/01/2007</td>
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<td>Bazo, Albert J., MD</td>
<td>CDER</td>
<td>Restricted</td>
<td>11/04/1981</td>
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<td>Bender, Sheldon R., MD</td>
<td>CDER</td>
<td>Disqualified</td>
<td>02/17/1969</td>
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<tr>
<td>Berger, Daniel S., MD</td>
<td>CDER</td>
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<td>09/10/2014</td>
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<td>Berger, Michael Dean, MD</td>
<td>CBER</td>
<td>Disqualified</td>
<td>06/20/2014</td>
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<td>Bigg, Daniel, MD</td>
<td>CBER</td>
<td>Disqualified</td>
<td>05/18/2007</td>
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<td>Bilezikian, John P., MD</td>
<td>CDER</td>
<td>Not Disqualified</td>
<td>11/27/2015</td>
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<td>Blunck, Jr., Carl E., MD</td>
<td>CDER</td>
<td>Disqualified</td>
<td>07/07/1979</td>
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<tr>
<td>Borison, Richard L., MD</td>
<td>CDER</td>
<td>Disqualified</td>
<td>11/10/1998</td>
</tr>
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</table>
informed about their obligations. **While you may delegate certain study tasks to individuals qualified to perform them, as clinical investigator, you must adequately supervise those to whom you delegate authority.** Our inspection indicates that you failed to personally conduct or supervise the clinical investigation. Our inspection revealed that you had little personal involvement in the conduct of the study beyond conducting a limited number of physical examinations, reviewing a limited number of electrocardiograms (ECGs), and treating study related emergencies, and 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, the investigational plan, and applicable regulations, in a manner that protected the rights, safety, and welfare of human subjects.
Submission of false information [21 CFR 312.70].

The inspection report indicates that the FDA investigator conducted a phone interview with a subject on 11/14/2006 and the subject stated that he was only at the site for two visits. Review of the CRFs revealed that there were entries for a total of six visits for this subject. The CRFs document a screening visit on 1/19/06 and a baseline visit conducted on 2/9/06. Additional entries were made in the electronic CRFs for the week one, week two, month one and month 2, none of which were attended by the subject.
FDA Debarment List (Drug Product Applications)

Firms or individuals convicted of a felony under Federal law for conduct (by a firm) relating to the development or approval of any drug product or abbreviated drug application

http://www.fda.gov/ICECI/EnforcementActions/FDADebarmentList/default.htm
involved fraud. Additionally, Fleming has demonstrated a pattern of conduct sufficient to find that there is reason to believe that he may violate requirements under the FD&C Act relating to drug products. In determining the appropriateness and period of Fleming’s debarment, FDA considered the relevant factors listed in the FD&C Act. Fleming failed to file with the Agency information and analyses sufficient to create a basis for a hearing concerning this action.
Pled guilty to one count of felony healthcare fraud in violation of 18 U.S.C. 1347 and one count of felony mail fraud in violation of 18 U.S.C. 1341.

Proposed debarment period of 10 years was based on both felony fraud convictions.

These convictions establish Fleming’s disregard for his professional obligations and the law and provide reason to believe that, if he were to provide services to a person that has an approved or pending drug application, he may violate requirements under the FD&C Act relating to drug products.

Registered nurse in the home health field
Case Study: Lax Supervision

- Study coordinator enrolled ineligible subjects into oncology clinical trials
- Study 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 any future involvement in FDA regulated research
- Dr. Holland – 5 years probation, $500,000 restitution to defrauded drug companies, disqualified
Abuses Endangered Veterans
In Cancer Drug Experiments

BY DEBORAH SONTAG

ALBANY — Carl M. Steubing, a decorated Battle of the Bulge vet-
eran whose experience of war made him a pacifist but also in-
structed him in a zest for living life at full tilt, took his diagnosis of
gastrointestinal cancer in 2000 as a challenge.

With a mouth of white hair and a
rich baritone voice, Mr. Steubing
at 76, was not ready to suc-
cumb to illness. A retired music
educator and wedding photographer,
he remained active as a church choir director, expert
conductor, painter, golfer and fisher-
man. He was married to a woman
24 years his junior, and they had
seven children and three grand-
children between them.

Mr. Steubing jumped at the
chance to participate in an exper-
imental drug study at the Stratton
Veterans Affairs Medical Center
in Albany, believing it offered him
the hope of surviving longer. The
research coordinator, Paul H.
Kornak, told Mr. Steubing that he
was “just a perfect specimen,”
with the body of a man half his
age, according to Jayne Steubing,
Mr. Steubing’s widow.

He was not. Though. Because of
a previous cancer and poor lidi-
ney function, Mr. Steubing was not
even eligible to participate in the
experiment, according to govern-
ment documents. Mr. Kornak, how-
ever, brushed that obstacle aside.
He altered Mr. Steubing’s
medicinal records, according to
prosecutors, and enrolled him in
the study. He also posed as a doc-
tor.

In 2001, Mr. Steubing endured
about six periodic treatments with an aggressive three-drug chemotherapy combination. Each infusion made him violently ill and forced his hospitalization. He died in March 2002.

Last month, at the federal
courthouse in Albany, Mrs. Steubing
graced Mr. Kornak, 59, as he
pleaded guilty to fraud, making false statements and criminally
rogueeic in the death of an Air Force veteran, James DeCerfaro. When Mr. Kornak ad-
mitted to falsifying the medical data of "subject initials CMS" — Carl M. Steubing — Mrs. Steubing’s face crumpled.

Mr. Kornak, who is scheduled to
be sentenced in May, also agreed to cooperate in a widening inves-
tigation of the hospital’s cancer re-
search program. From 1999 to 2003, when he worked there, scores of veterans were, at the least, put at risk. But allegations of
carelessness, fraud and patient
suffering in the hospital’s cancer
research program prompted Mr. Kornak and numerous other
that administrators not only dis-
missed their concerns, but har
assed them for sounding the
alarm for the veterans.

“Research violations were a
way of life at Stratton for 10
years,” said Jeffro Fein, a
pharmacists at the hospital.
“Stratton officials turned a blind
eye to unethical cancer research practices and punished those who spoke out against them. The whole Kornak episode could have been avoided.”

According to Mr. Kornak’s
lawyer, E. Stewart Jones, there was a feeling in Stratton that any investigat-
ing a research culture where patients and employees’ rights weren’t applied and supervision was nonexistent.

It was also a culture whose de-
Continued on Page 18

Route Visit Leads to an Inquiry

In December 2001, a clinical research as-
sociate for Ilex Oncology made a routine
visit to the Albany veterans’ hospital, where
Ilex was sponsoring a bladder cancer study.

Ilex, a cancer drug company, was offering
the Albany research program $2,500 for
each study subject. Such payments are a
standard practice, and many researchers
say that they barely cover the cost of con-
ducting the studies. Critics of drug-testing
practices, however, consider the payments
a threat to scientific integrity.

Ilex’s research associate discovered
some paperwork that raised suspicions, ac-
cording to Caren Arnstein, a spokeswoman
for the Genzyme Corporation, which bought
Ilex at the end of last year.

“Things about the dates didn’t look right,”
Ms. Arnstein said. “If the results of a pathol-
ogy report for a biopsy are dated prior to the
liver being taken — something seemed off.”

The discrepancies led to an audit by Ilex.
In the spring of 2002, the Albany hospital be-
gan an internal review of the cancer re-
search program, eventually referring the
matter to the inspector general, according
to The Times Union.

Ilex shut down the Albany study and alerted
the F.D.A. The agency had also received
another complaint, an F.D.A. official said.
Do you need a delegation log?

**ANSWER: NO** Such a log is not an FDA requirement and is not listed in the list of essential documents in ICH E6 (although signature sheets are included).
Address human factors in systems

- Hire experienced, qualified staff
- Avoid conflicts of interest/financial incentives
- Assess ability to comply with protocol visits; laboratory testing; electronic systems for data capture, archiving and transmission to sponsor; maintaining records, drug accountability, inspections by FDA
- Write down all procedures (SOPs). Use checklists.
Improve Process

- Insist on training and then refresh
- Have a disaster plan (for staff turnover, floods, etc.)
- Do beta-testing/dry-runs
- Have weekly team meetings/calls
- Audit yourself — be open and honest
- Think very carefully about unblinding procedures *Many examples of errors!*
Emergency Unblinding

- Code breaks should occur only in exceptional circumstances
- If unblinding is deemed to be necessary, use the system for emergency unblinding
- The actual allocation should NOT be disclosed to the patient and/or other study personnel including other site personnel, monitors, sponsors or project office staff
- There should not be any written or verbal disclosure of the code in any of the corresponding subject documents
- Report all code breaks to the sponsor, including accidental
Implement System to Detect and Correct Errors

- Do real-time cleaning of the data
- Pay attention to monitoring queries and respond promptly *Close loops*
- Audit trail of changes should make clear what was changed, who changed it, and why it was changed
- Evaluate need for system-wide corrections and training
Investigator-Initiated Investigational New Drug (IND) Applications webpage

- Brief explanations about various aspects of IND application submissions and procedures with links to guidances, references, and forms.

Key Messages

- Clinical investigators play a critical role in ensuring high quality studies
- Good care of patients is not the same as Good Clinical Practice (GCP) in research
  - Ensure that all staff 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
FDA Sites of Interest

- Regulations: Good Clinical Practice and Clinical Trials
  https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm

- FDA Basics for Industry
  http://www.fda.gov/ForIndustry/FDABasicsforIndustry/default.htm

- Sign up for Updates
  http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234630.htm
Replies to Inquiries to FDA on Good Clinical Practice

- Designed to simplify the search for copies of e-mail messages (including the original inquiry and associated replies) that have been submitted by the public to the Good Clinical Practice Program's gcp.questions@fda.hhs.gov e-mail account.

http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/RepliestoInquiriestoFDAonGoodClinicalPractice/default.htm
Guidances of Interest

- FDA Inspections of Clinical Investigators - Information sheet

- Guidance for Industry-Investigator Responsibilities
General Information Sheets

- Charging for Investigational Products
- Cooperative Research - Information Sheet
- Informed Consent, A Guide to
- Non-local IRB Review - Information Sheet
- Payment to Research Subjects
- Recruiting Study Subjects - Information Sheet
- Screening Tests Prior to Study Enrollment
- Sponsor - Investigator - IRB Interrelationship
- Use of Investigational Products When Subjects Enter a Second Institution

http://www.fda.gov/RegulatoryInformation/Guidances/ucm122046.htm
Thank you for your attention