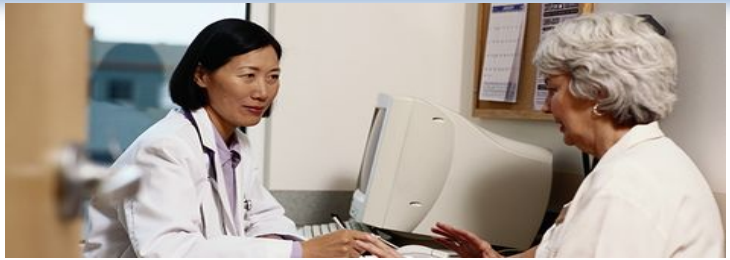
U.S. FOOD & DRUG ADMINISTRATION

# Investigator Responsibilities – Regulation and Clinical Trials



**Cynthia F. Kleppinger, M.D.**
**Office of Scientific Investigations**
**Office of Compliance, CDER**
FDA Clinical Investigator Training Course
November 14, 2018

# 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?

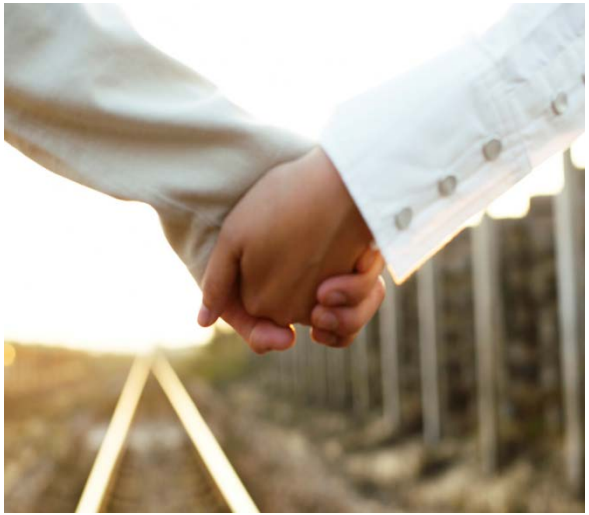
- An individual **who actually conducts a clinical investigation** (i.e., under whose immediate direction the drug is dispensed to a subject.)

- 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]

# QUESTION

- Can there be co-investigators?



***ANSWER:*** **Yes and No.**

**Yes, for your needs but**

**<u>NO for regulatory purposes</u>.**

**Each co-investigator is fully responsible for fulfilling all of the obligations of an investigator; each must sign a separate Form FDA- 1572.**

# Sponsor-Investigator

- 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]

# QUESTION

- *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

# Clinical Trial Environment

# Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations

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## 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

# Know the laws of your state

- *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**

# Reference

- **Institute of Medicine Report**

Ethical Conduct of Clinical Research Involving Children

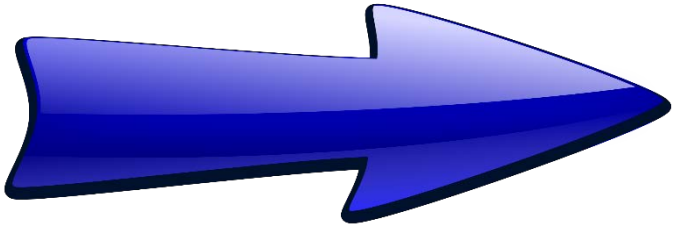
*See Appendix B:*

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



National Archives and Records Administration

code of federal regulations

# Expectations

If you don't like doing paperwork…

***Run as fast as you can towards the door.***

# Statement of Investigator Form FDA 1572

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)]

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

# STATEMENT OF INVESTIGATOR

***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)***

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: April 30, 2015
*See OMB Statement on Reverse.*

**NOTE:** 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)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Principal Investigator

| Address 1 | | Address 2 | |
|---|---|---|---|
| City | State/Province/Region | Country | ZIP or Postal Code |

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 — **CONTINUATION PAGE for Item 3**

Name of Medical School, Hospital, or Other Research Facility

| Address 1 | | Address 2 | |
|---|---|---|---|
| City | State/Province/Region | Country | ZIP or Postal Code |

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — **CONTINUATION PAGE for Item 4**

Name of Clinical Laboratory Facility

| Address 1 | | Address 2 | |
|---|---|---|---|
| City | State/Province/Region | Country | ZIP or Postal Code |

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES) — **CONTINUATION PAGE for Item 5**

Name of IRB

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 Sign |
|---|---|

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

FDA

Warning

# 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.***

# Commitments (cont.)

- 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

# Form FDA 1572

- 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

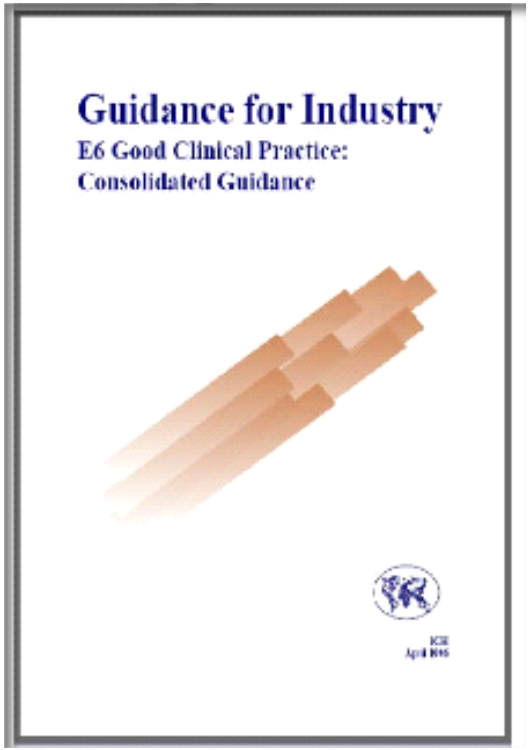
## Frequently Asked Questions – Statement of Investigator (Form FDA 1572)

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

# E6 Good Clinical Practice: Consolidated Guideline

- 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".

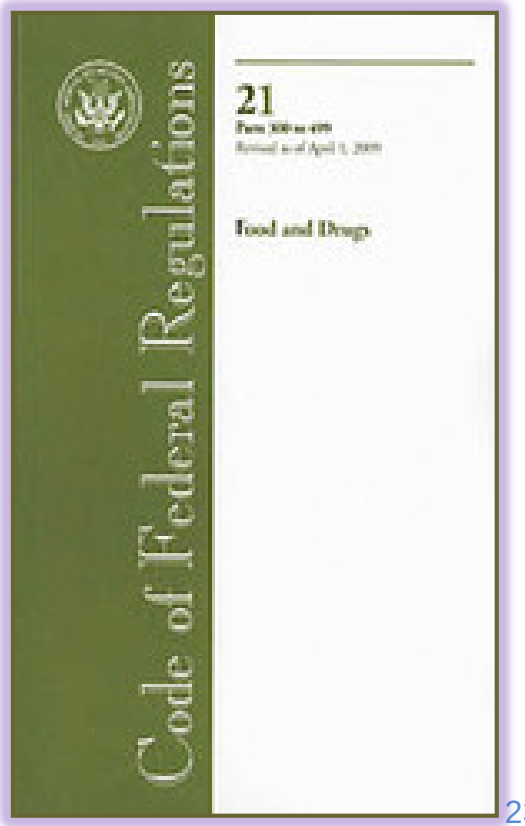


# E6: Integrated Addendum

- 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**

# In General…E6 More Detailed

- 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



# QUESTION

- Do FDA regulations allow for delegation of the informed consent?

# Answer: Not really but…

- 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*

# Who's in Charge at the Study Site?

- 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

# What if Not Compliant?

- **Penalties** for significant noncompliance
  - Warning Letters (posted on FDA website)
  - Disqualifications/Restrictions/ Debarments (posted on FDA website)
  - Criminal prosecutions/prison/fines

# Historical Perspective

- 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

# Consequences

## 1,200 U.S. DOCTORS GOT BANNED PILL FOR TESTS

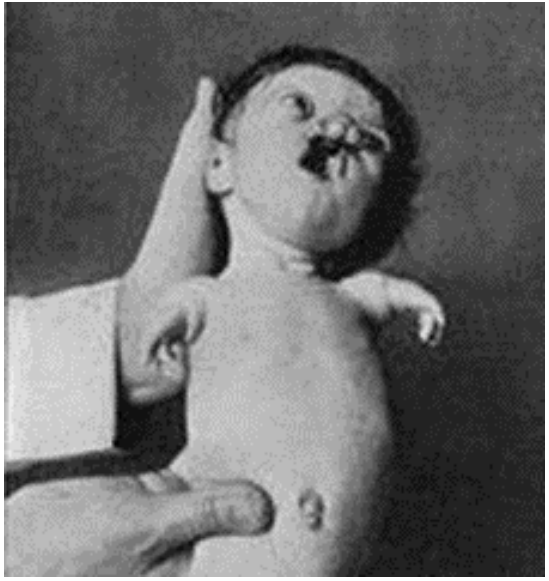
Thalidomide, the sleeping pill that has caused thousands of infant malformations in Europe had been distributed to 1,200 physicians in the United States for investigational use since 1959, before it was banned in the United States.

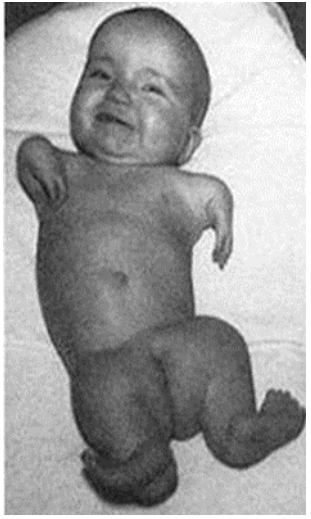
This figure has been supplied by the William S. Merrell Co. of Cincinnati, manufacturer of the drug, to the Food and Drug Administration here. FDA inspectors are now checking the physicians to make sure they have returned or destroyed their supplies of the drug, as requested by the Merrell Company in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

***Thalidomide tragedy***





# Action

- ***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

# Additional Actions

- ***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

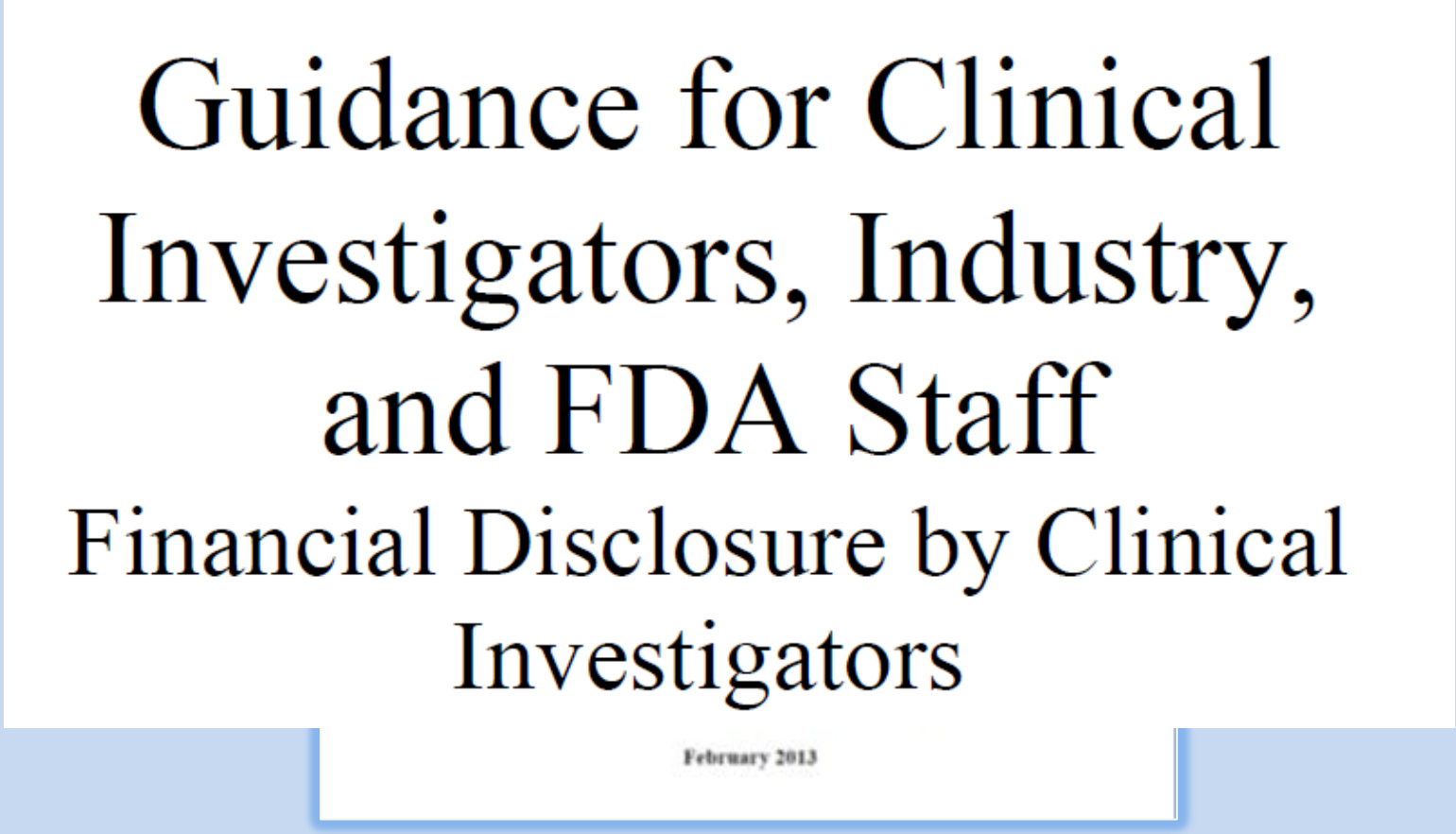
- Record keeping and retention (312.62)
  - An investigator is responsible for:
    - Maintaining adequate records of the **disposition of the drug**
    - Accurate **case histories** that record all observations, and
    - **Other data pertinent to the investigation** on each individual administered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

# Responsibilities (cont.)

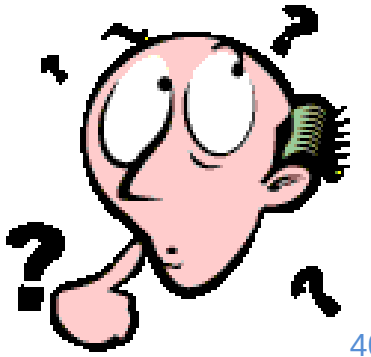
- Investigator reports (312.64)
  - Progress reports to sponsor
  - Safety reports
    - Immediately report any adverse event that is alarming (e.g. an unexpected event that is serious or life-threatening)
    - Record nonserious adverse events and report them to the sponsor according to the timetable 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




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

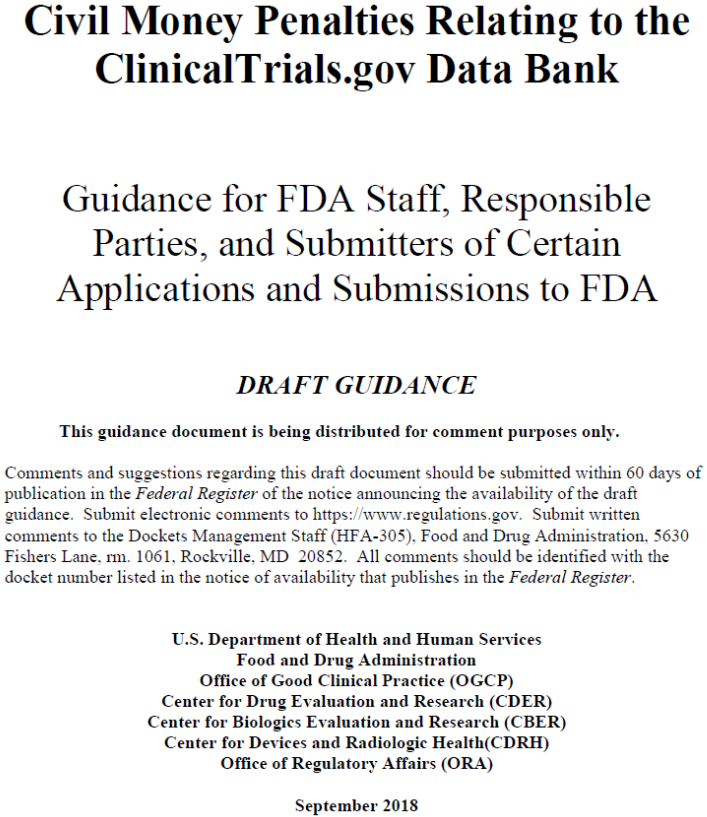


# ClinicalTrials.gov

- **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 heath 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

# Final Rule 42 CFR part 11



**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 Biologics Evaluation and Research (CBER)**
**Center for Devices and Radiologic Health(CDRH)**
**Office of Regulatory Affairs (ORA)**

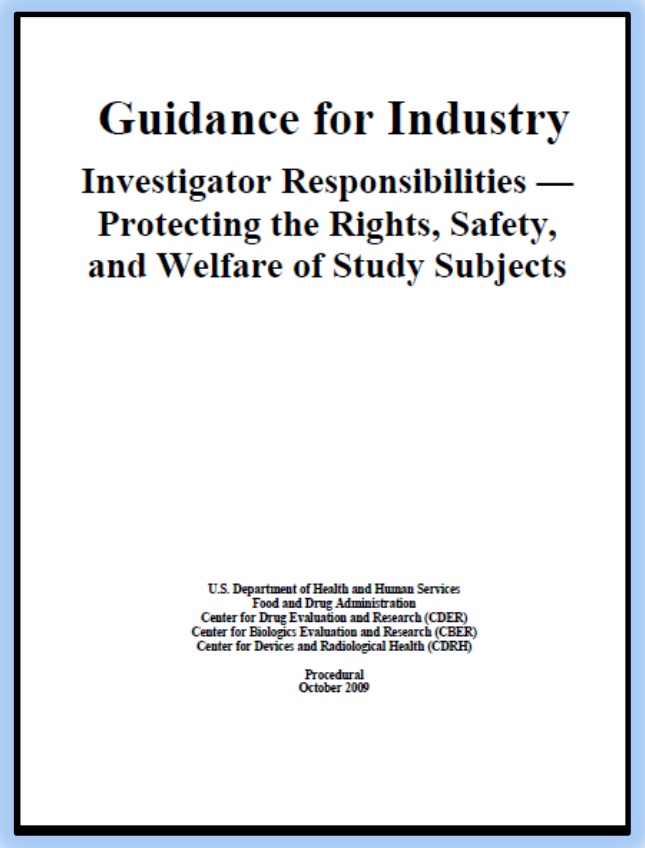
**September 2018**

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

# 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
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

Procedural
October 2009

- 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

# QUESTION

- *Can the investigator delegate the activities around investigational product?*

# Answer

- 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)."

*FDA Guidance Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects*

# 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

# Article of Interest

## Research Misconduct Among Clinical Trial Staff

**Barbara K. Redman,**[1,2] **Thomas N. Templin**[2] **and Jon F. Merz**[1]

[1]*Dept of Medical Ethics, University of Pennsylvania, USA;* [2] *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*

Science and Engineering Ethics, Volume 12, Issue 3, 2006

# 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*

# Institutional Corrections

- 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

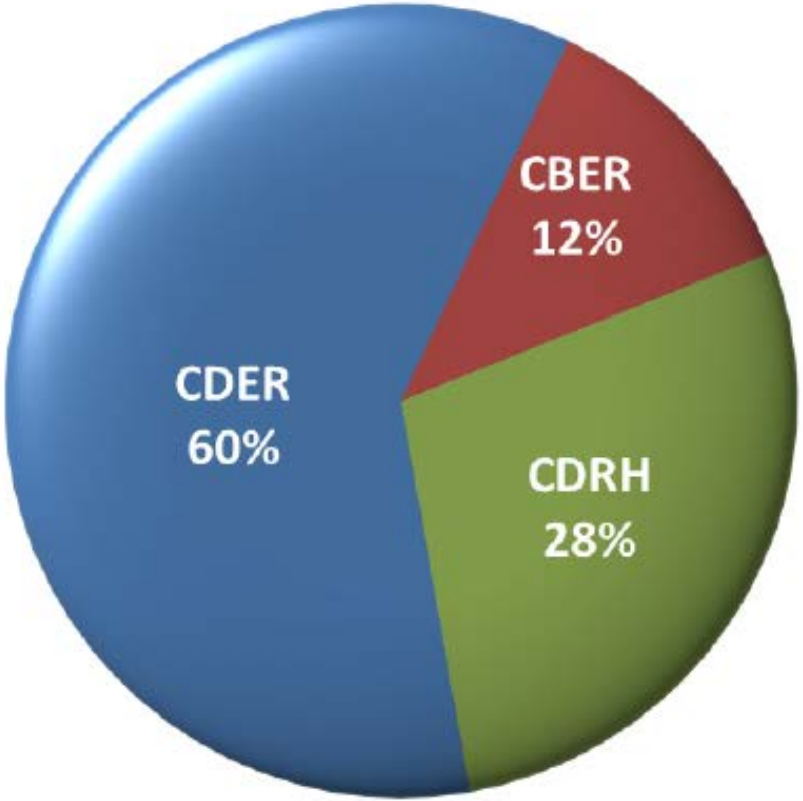
- Section 505(k)(2) of the Food, Drug, and Cosmetic Act mandates that FDA shall have access to and copy and verify the required clinical study records.

**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)

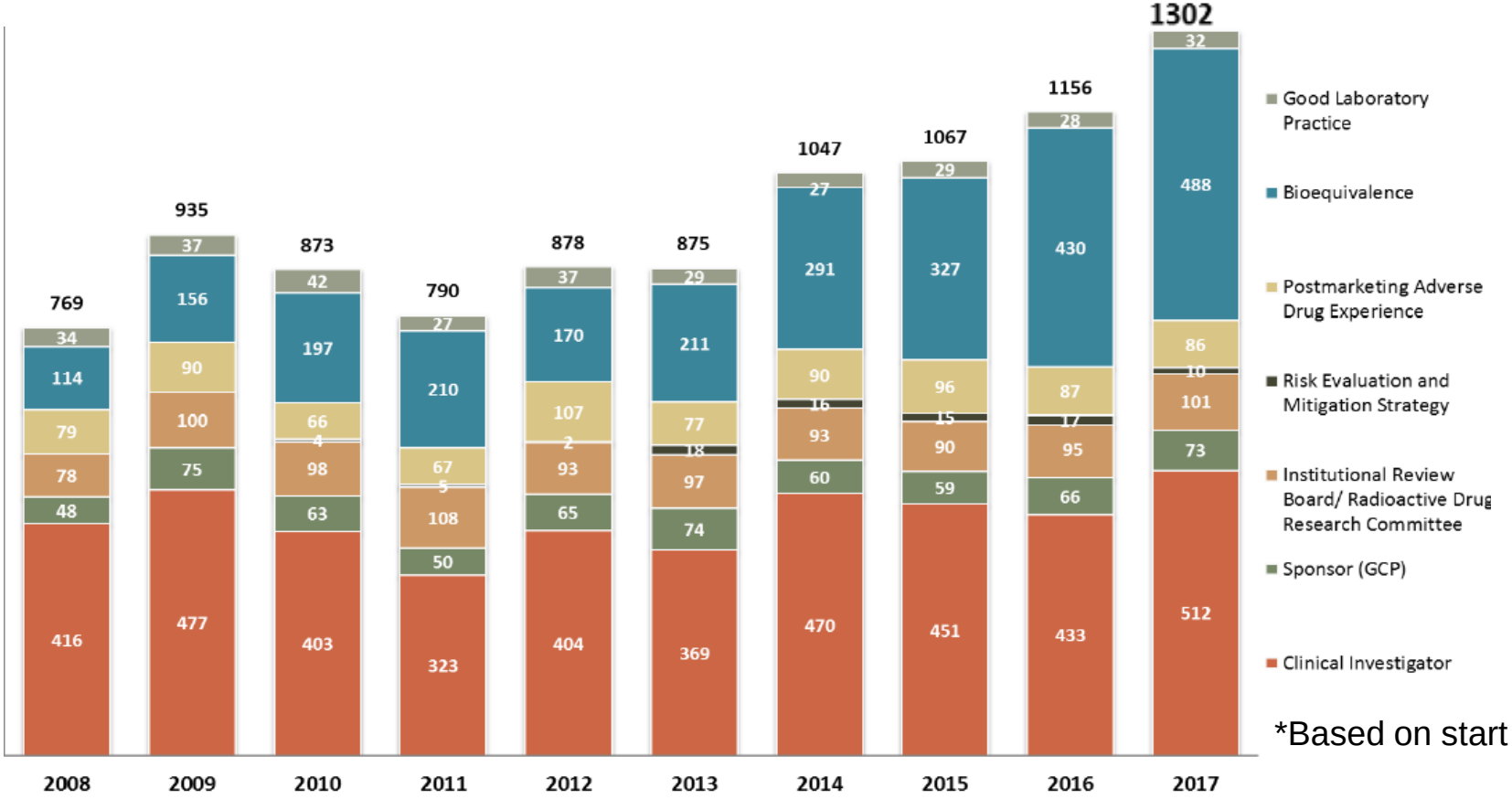



| | |
|---|---|
| CDER | 418 |
| CBER | 84 |
| CDRH | 198 |
| Total | 700 |

*Based on final classification

# Inspections Overseen by OSI/OSIS*

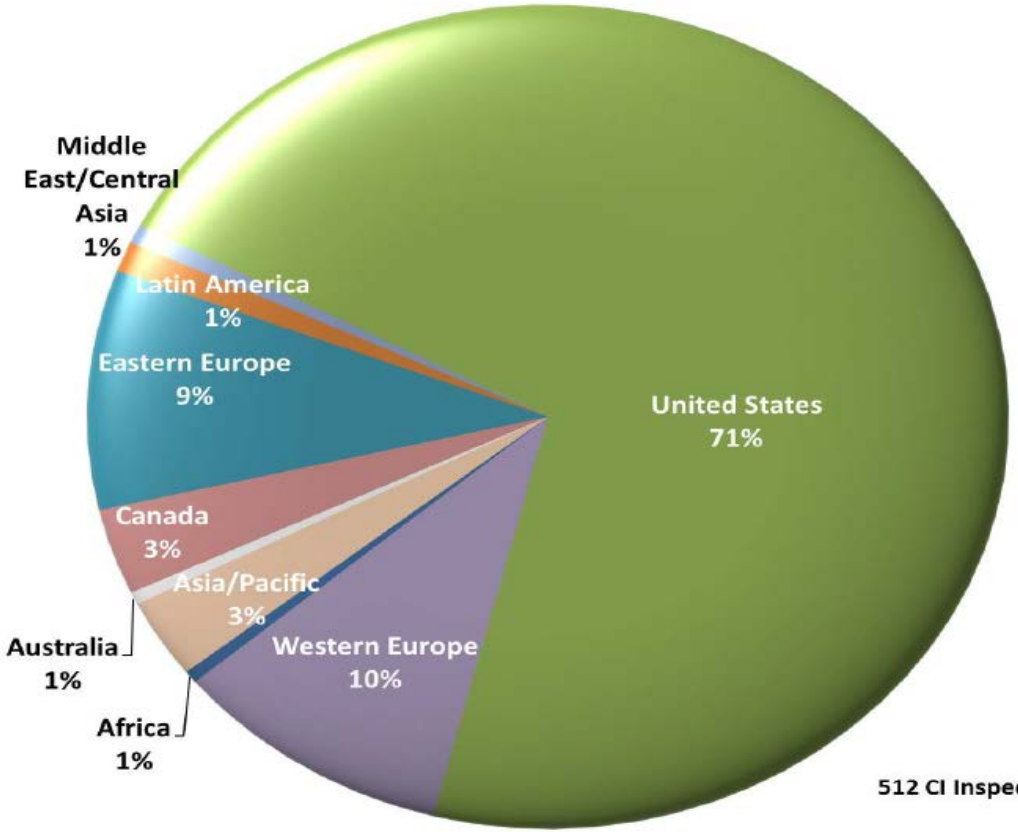
## (CDER, FY 2008 - FY 2017)




*Based on start date

# Clinical Investigator Inspections by Location*

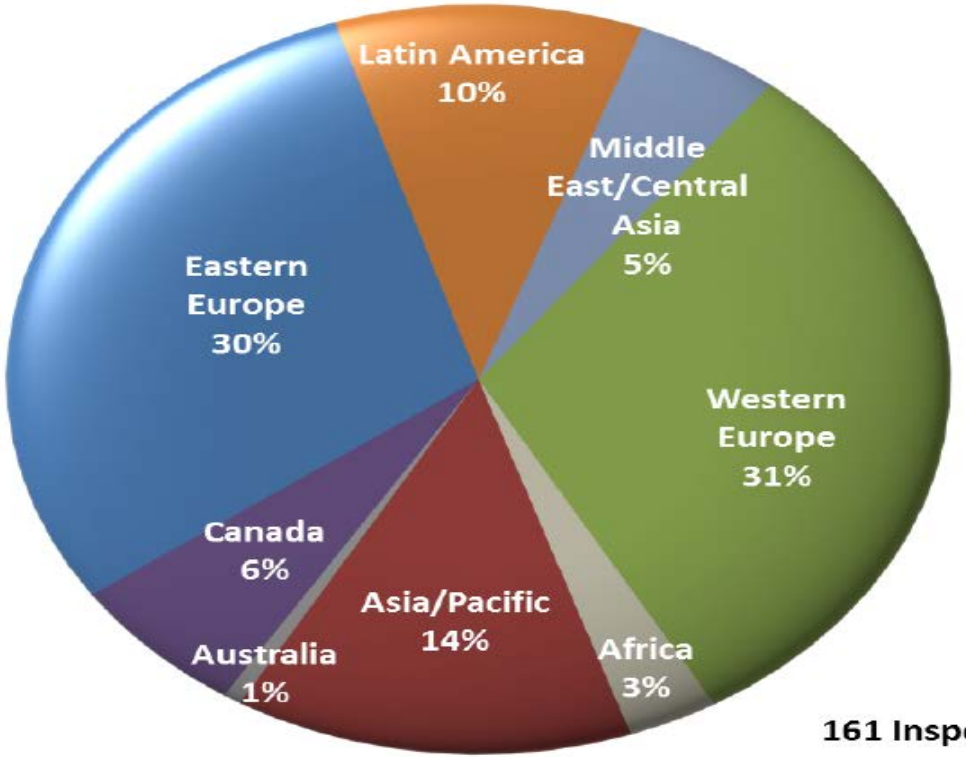
## (CDER, FY 2017)




512 CI Inspections *Based on start date

# International Clinical Investigator Inspections by Location*

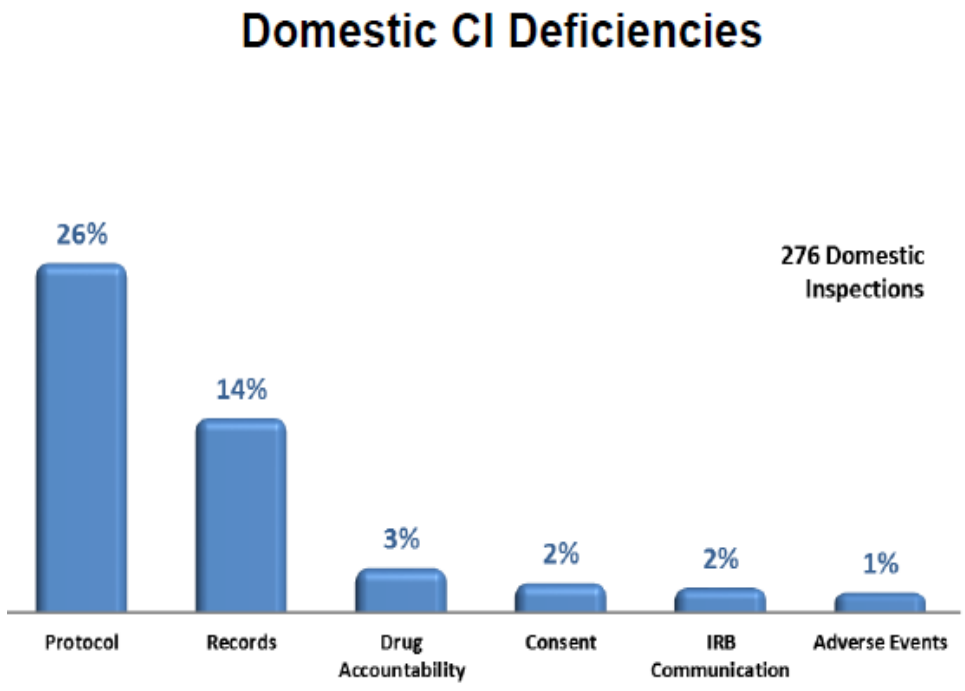
(CDER, FY 2017)

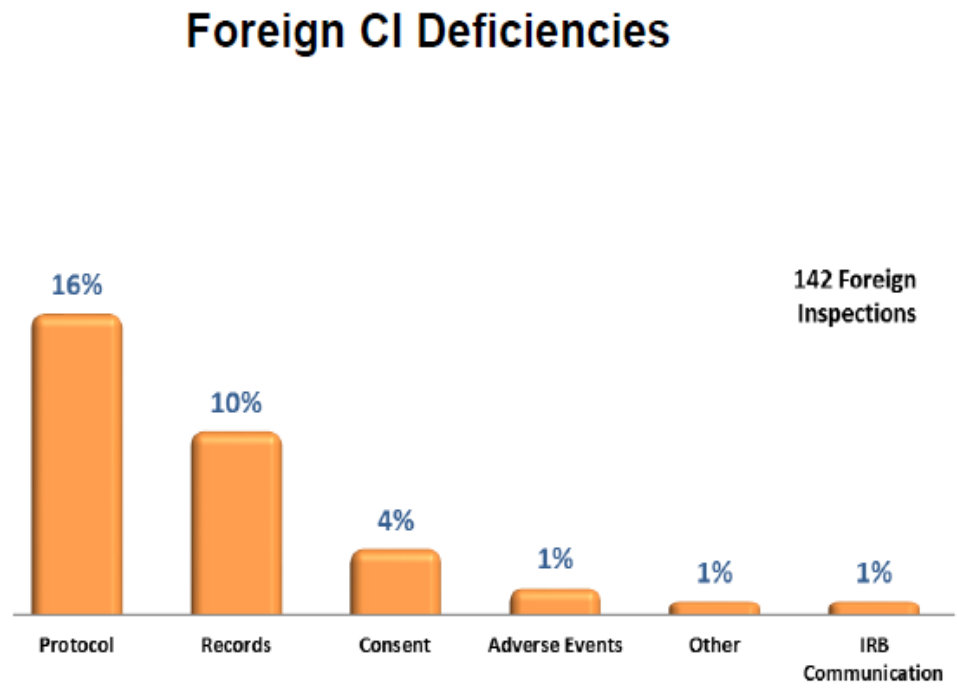



*Based on start date

# Frequency of Clinical Investigator-Related Deficiencies Based on Post-Inspection Correspondence Issued

(CDER, FY 2017)



# Compliance Classifications

**NAI** - No Action Indicated

Inspected Entity is in compliance

**VAI** - Voluntary Action Indicated

Minor deviation(s) from the regulations

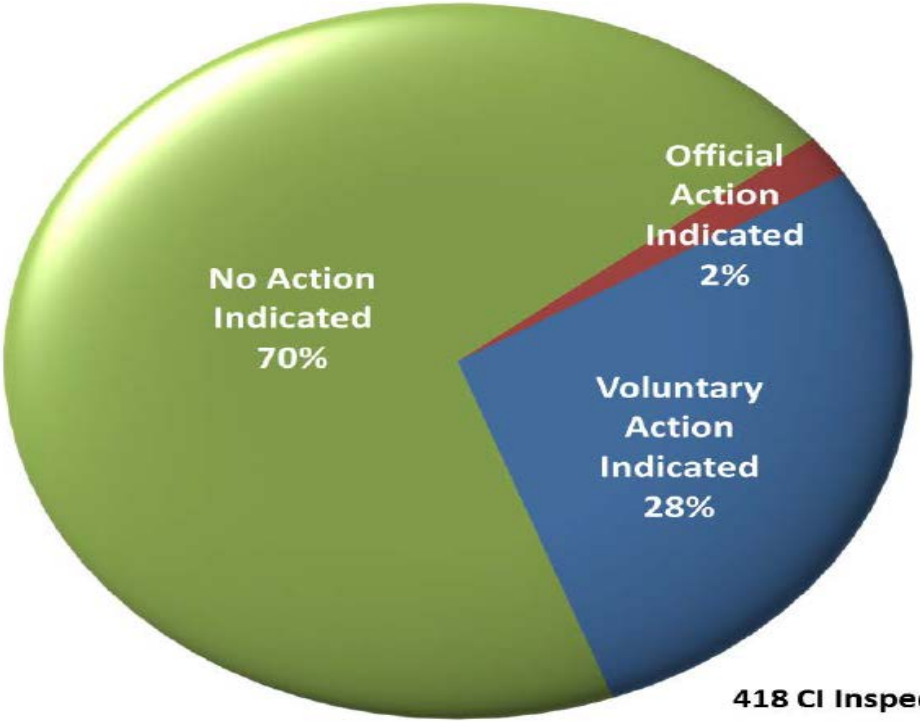
Voluntary correction is requested

**OAI** - Official Action Indicated

Serious non-compliance requiring regulatory or administrative action by FDA

# Clinical Investigator Inspections Final Classification*

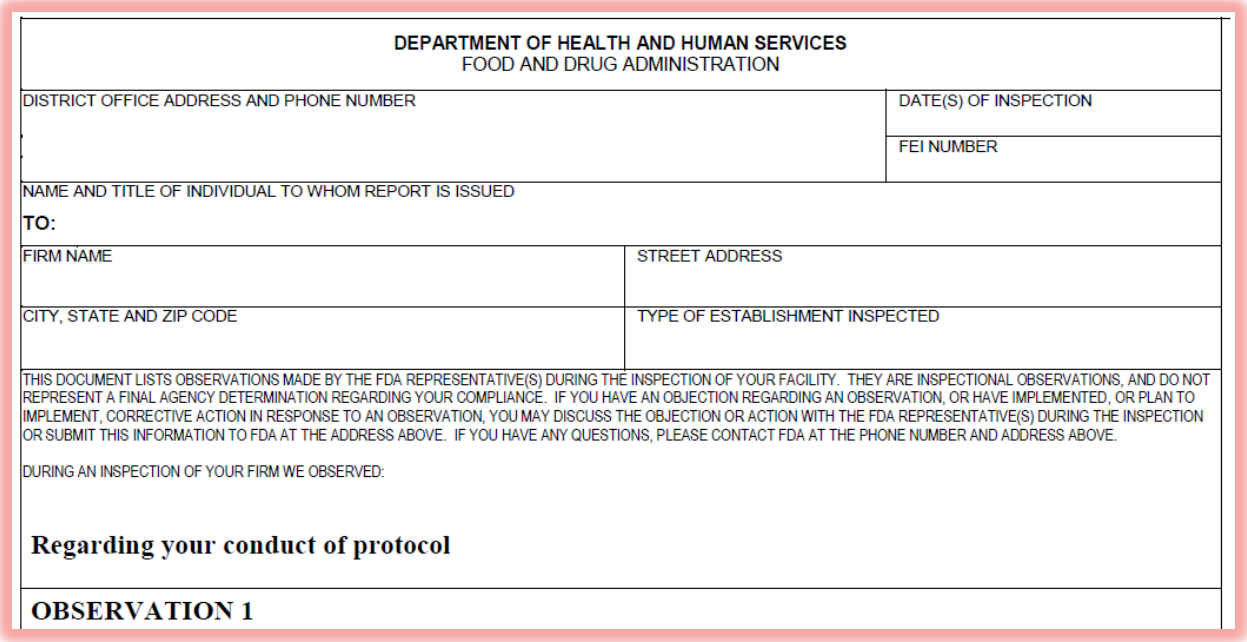
(CDER, FY 2017)




*Based on final classification

# Inspectional Outcomes

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



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION

| DISTRICT OFFICE ADDRESS AND PHONE NUMBER | DATE(S) OF INSPECTION |
|---|---|
| | FEI NUMBER |

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

**TO:**

| FIRM NAME | STREET ADDRESS |
|---|---|
| CITY, STATE AND ZIP CODE | TYPE OF ESTABLISHMENT INSPECTED |

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

**Regarding your conduct of protocol**

**OBSERVATION 1**

# Reference

- 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

# Reference

- 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

# Form FDA 483 Response

- 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.*

# Inadequate Response

- 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.*

# Warning Letter Language

- “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.”

# Reference

- List of Warning Letters

  https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm

- Regulatory Procedures Manual Section on Warning Letters

  https://www.fda.gov/downloads/iceci/compliancemanuals/regulatoryproceduresmanual/ucm074330.pdf

# Investigator Disqualification

- 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

# Reference

- **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

| | | | |
|---|---|---|---|
| Balin, Howard, MD | CDER | Disqualified | 03/19/1975 |
| Baratta, Vincent J, MD | CDER | Disqualified | 11/13/1985 |
| Batshaw, Mark L., MD | CBER | Restrictions Removed | 10/01/2007 |
| Bazo, Albert J., MD | CDER | Restricted | 11/04/1981 |
| Bender, Sheldon R., MD | CDER | Disqualified | 02/17/1969 |
| Berger, Daniel S., MD | CDER | Restrictions Removed | 09/10/2014 |
| Berger, Michael Dean, MD | CBER | Disqualified | 06/20/2014 |
| Bigg, Daniel, MD | CBER | Disqualified | 05/18/2007 |
| Bilezikian, John P., MD | CDER | Not Disqualified | 11/27/2015 |
| Blunck, Jr., Carl E., MD | CDER | Disqualified | 07/07/1979 |
| Borison, Richard L., MD | CDER | Disqualified | 11/10/1998 |

# Part of Letter

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.

# And More…

- 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.

# Debarment List

- **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

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA–2013–N–0333]**

**Richard M. Fleming; Denial of Hearing; Final Debarment Order**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is denying a request for a hearing submitted by Richard M. Fleming (Fleming) and is issuing an order under the Federal Food, Drug, and Cosmetic Act (FD&C Act) debarring Fleming for 10 years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this order on a finding that Fleming was convicted of two felonies under Federal law that 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.

Federal Register / Vol. 83, No. 189 / Friday, September 28, 2018

# Medicaid and Medicare Fraud

- 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.*

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA–2013–N–1018]**

**Isachi Gil; Denial of Hearing; Final Debarment Order**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is denying Isachi Gil's (Gil's) request for a hearing and issuing an order under the Federal Food, Drug, and Cosmetic Act (FD&C Act) debarring Gil for 6 years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this order on findings that Gil was convicted of 12 felonies under Federal Law involving fraud or falsification and that Gil has demonstrated a pattern of conduct sufficient to find that there is reason to believe she may violate requirements under the FD&C Act relating to drug products. In

On May 24, 2011, a jury found Gil guilty of 12 felonies. On September 28, 2011, the U.S. District Court for the Southern District of Florida entered judgment against her for five counts of felony healthcare fraud, in violation of 18 U.S.C. 1347, and seven counts of felony false statements related to healthcare matters, in violation of 18 U.S.C. 1035(a)(2). The court sentenced Gil to 43 months in prison, with 3 years of supervised release.

FDA

**Registered nurse in the home health field**

Federal Register /Vol. 83, No. 201 /Wednesday, October 17, 2018

# 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

# Northstar doctor, FDA reach deal

BY SAMUEL WORLEY

Dr. Daniel Berger, who has been the subject of a Food and Drug Administration (FDA) investigation following alleged improprieties at his Northstar Medical Center, has reached an agreement with the FDA that will allow him to continue coordinating HIV/AIDS drug trials. Berger told Windy City Times about the agreement last week, two days after a Chicago Tribune article said the FDA was "seeking to disqualify" Berger from future studies.

Berger was informed of the investigation last November in a letter from FDA investigator Leslie K. Ball. Ball wrote that a spring 2009 audit of Northstar had found that the clinic "repeatedly or deliberately submitted false information to the sponsor in a required report," and that Berger "failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects."

The "sponsors" of Berger's trials were pharmaceutical companies developing drugs to treat HIV/AIDS. Berger and Northstar Medical Center, have been heralded for HIV/AIDS treatment and clinical drug research. Berger is the director of Northstar, which he founded in 1991.

Although the letter acknowledged that the fraudulent activity had been undertaken by Berger's study coordinator—an employee who, Berger alleges, also embezzled money from the clinic—Ball said that, as the principle investigator in the drug trials, Berger was "ultimately responsible" for the errors.

Berger fired the study coordinator, whom he identified as Wesley McQuerry, when the extent of the fraud became clear.

Berger told Windy City Times that, under the terms of the agreement reached with the FDA, his clinic will submit to regular monitoring by an independent agency, the details of which

# *Abuses Endangered Veterans In Cancer Drug Experiments*

By DEBORAH SONTAG

ALBANY — Carl M. Steubing, a decorated Battle of the Bulge veteran whose experience of war made him a pacifist but also instilled in him a zest for living life at full tilt, took his diagnosis of gastroesophageal cancer in 2001 as a challenge.

With a thatch of white hair and a rich baritone voice, Mr. Steubing, at 78, was not ready to succumb to illness. A retired music educator and wedding photographer, he remained active as a church choir director, expert cook, painter, golfer and fisherman. He was married to a woman 24 years his junior, and they had seven children and three grandchildren between them.

Mr. Steubing jumped at the chance to participate in an experimental 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 kidney function, Mr. Steubing was not even eligible to participate in the experiment, according to government documents. Mr. Kornak, however, brushed that obstacle aside. He altered Mr. Steubing's medical records, according to prosecutors, and enrolled him in the study. He also posed as a doctor.

IN HARM'S WAY
*Research, Fraud and the V.A.*

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 glared at Mr. Kornak, 53, as he pleaded guilty to fraud, making false statements and criminally negligent homicide in the death of an Air Force veteran, James DiGeorgio. When Mr. Kornak admitted 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 investigation of the hospital's cancer research 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 abuse in the hospital's cancer research program predated Mr. Kornak, and employees say that administrators not only dismissed their concerns, but harassed them for standing up for the veterans.

"Research violations were a way of life at Stratton for 10 years," said Jeffrey Fudin, a pharmacist 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 prevented."

According to Mr. Kornak's lawyer, E. Stewart Jones, there was a "clear systems failure," permitting a research culture where "rules weren't followed, protocols weren't applied and supervision was nonexistent."

It was also a culture whose de-

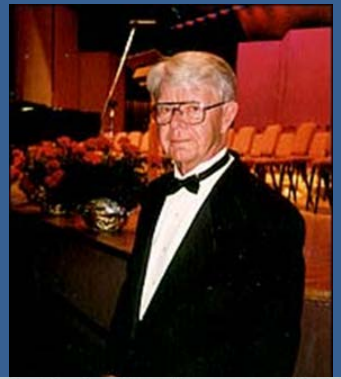
Paul H. Kornak, who posed as a doctor for veterans, in 1999.

*Continued on Page 18*

The New York Times



SUNDAY, FEBRUARY 6, 2005



In September, however, the Food and Drug Administration started proceedings to disqualify Dr. Holland from conducting further clinical research because he had "failed to protect" subjects under his care in Albany.

According to the F.D.A., patients' medical records were altered in at least five experimental drug studies, enabling veterans like Mr. Steubing to be enrolled in studies for which they were either too sick or too healthy to qualify. A patient with coronary disease, for instance, was enrolled in a study that excluded heart patients because of a risk of hemorrhages. A patient with impaired renal function was administered a drug toxic to kidneys that probably contributed to his death, the agency said.

## Routine Visit Leads to an Inquiry

In December 2001, a clinical research associate 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 conducting 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, according 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 pathology report for a biopsy are dated prior to the biopsy being taken — something seemed off."

The discrepancies led to an audit by Ilex. In the spring of 2002, the Albany hospital began an internal review of the cancer research 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.

# QUESTION

- *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).

# Improve Process — Be Proactive

- **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

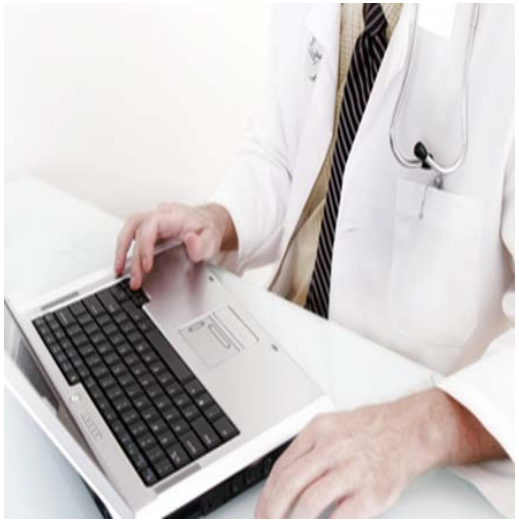
- Insist on training and then refresh
- Have a disaster plan (for staff turnover, floods, etc.)
- Do beta-testing/dry-runs
- Have weekly team meetings/calls
- Audit yourself — be open and honest
- Think very carefully about unblinding procedures ***Many examples of errors!***

# 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

# Webpage for Sponsor-Investigators

- 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.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

# 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

# FDA Sites of Interest

- 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**

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf

- **Guidance for Industry-Investigator Responsibilities**

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf

# 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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