An Overview of Clinical Investigator Responsibilities and Inspectional Findings

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Disclaimer

The views expressed in this talk are those of the speaker and not necessarily those of the US Food and Drug Administration (FDA).

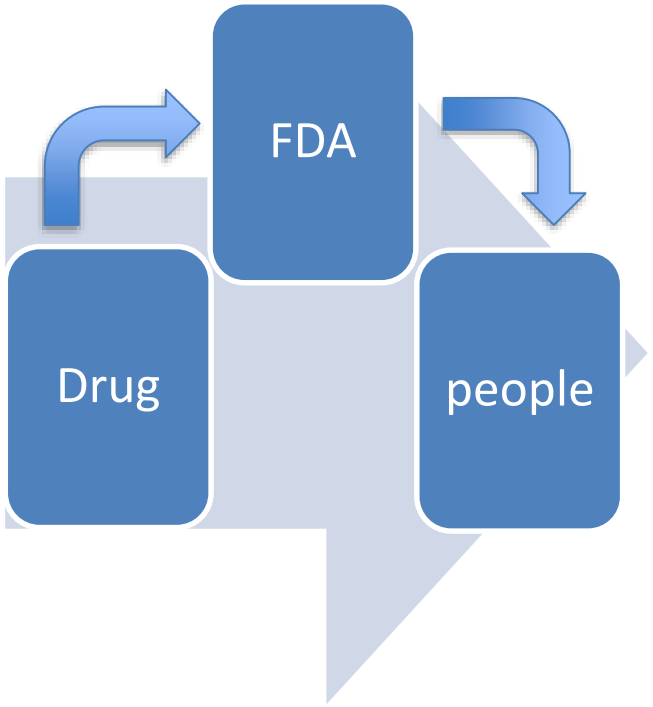
Objectives

- CDER BIMO Program
- Inspection Process for Clinical Investigators
- Highlights of CI Responsibilities
- Examples of Common GCP Regulatory Violations
- Tips for Clinical Investigators (CIs)

CDER: Center for Drug Evaluation and Research
BIMO: Bioresearch Monitoring
GCP: Good Clinical Practice

BIMO GCP Objectives

- To ensure data reliability and integrity
- To protect rights, safety, and welfare of human research subjects
- To ensure FDA-regulated research is conducted in compliance with applicable regulations



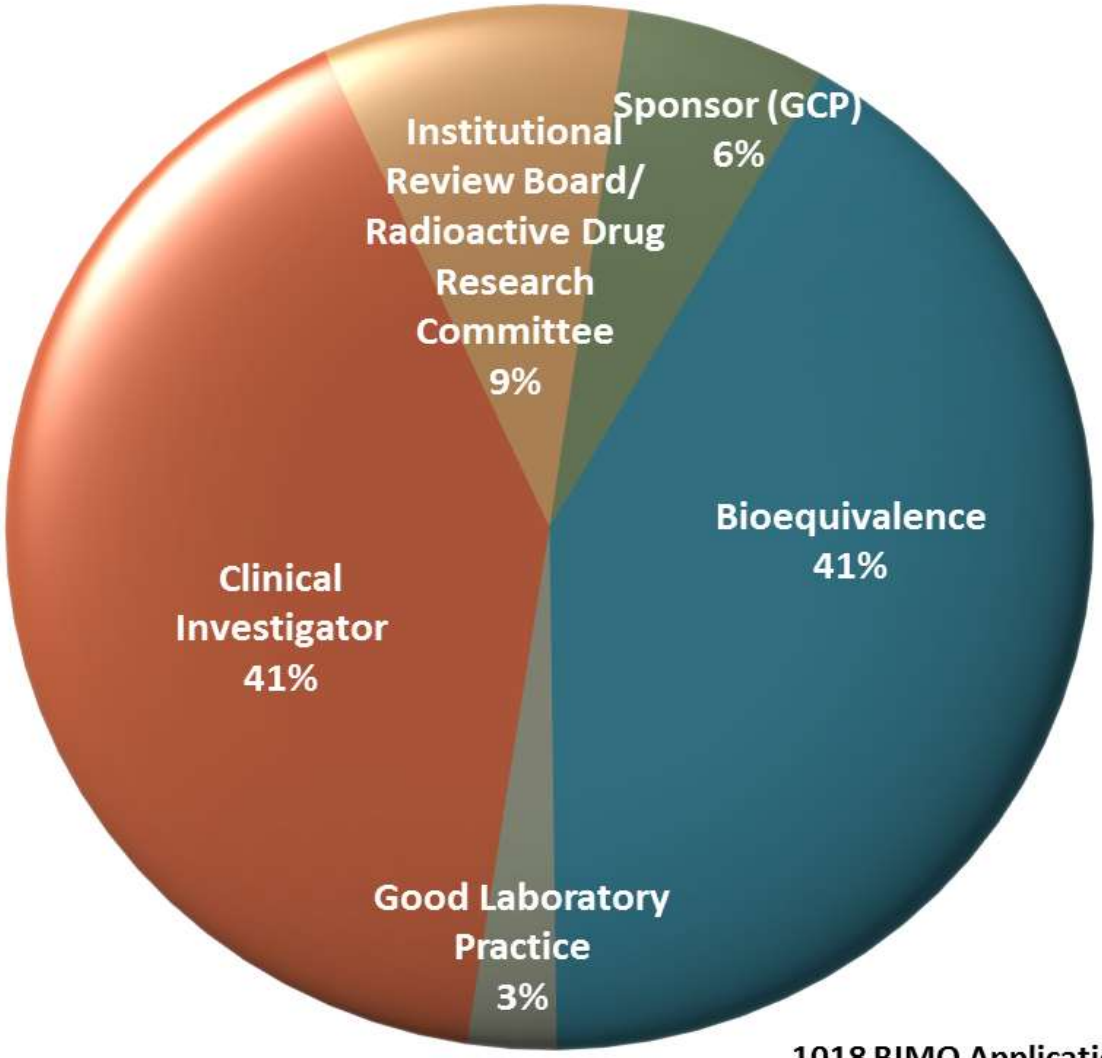
GCP Compliance Program
BIMO Coverage

- Sponsors and monitors
- Clinical Investigators (CI)
- Sponsor-Investigators

- In-vivo bioequivalence facilities
- IRBs
- Nonclinical Laboratories

CDER-BIMO Inspections

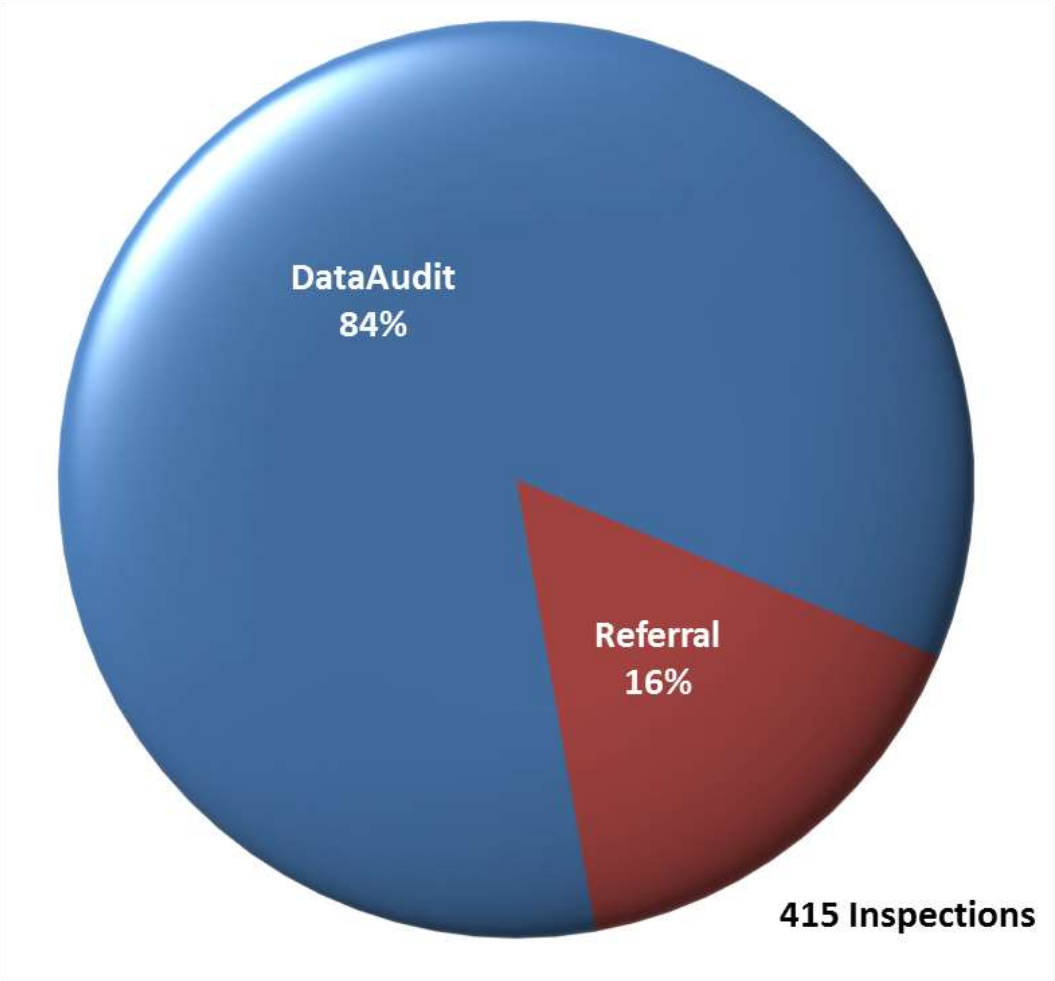
FY 2016



1018 BIMO Application-Inspections

*Based on inspection start date – [Complis database as of December 20, 2016]

Clinical Investigator Inspections CDER FY-2016



Pre-approval/Data audit/Surveillance

For-cause/Referral

Follow-up

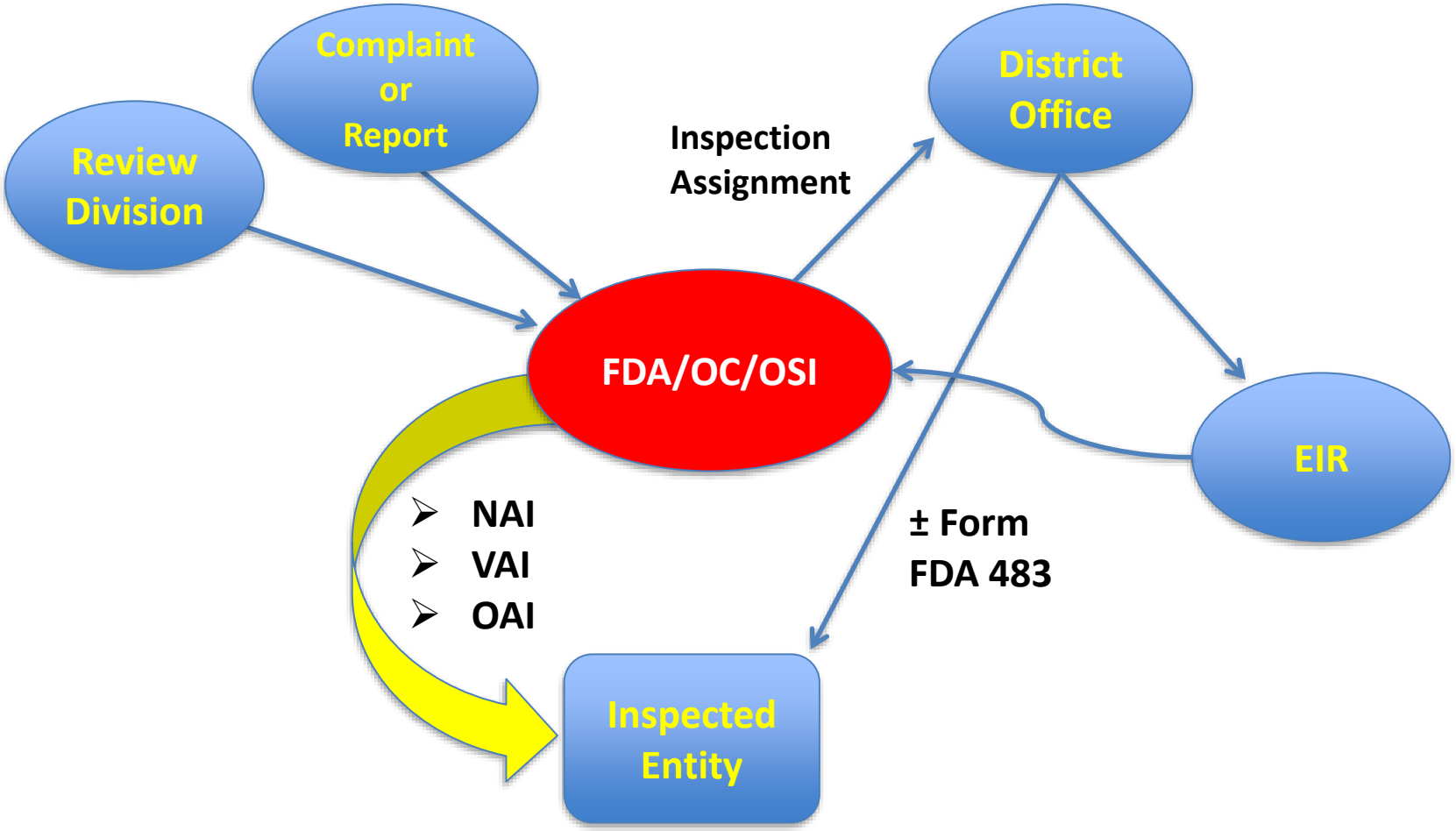
Based on inspection start date – [Complis database as of December 20, 2016]
Referrals include Complaints, Required Reports, IRB/Sponsor Notifications, and other referrals-internal and external for All OSI Branches

Poll: Role Category

Into which of these categories do you best fit?

- Sponsor
- Monitor/Contract Research Organization (CRO)
- Clinical investigator
- Sponsor-investigator
- Other

BIMO GCP Inspection Process

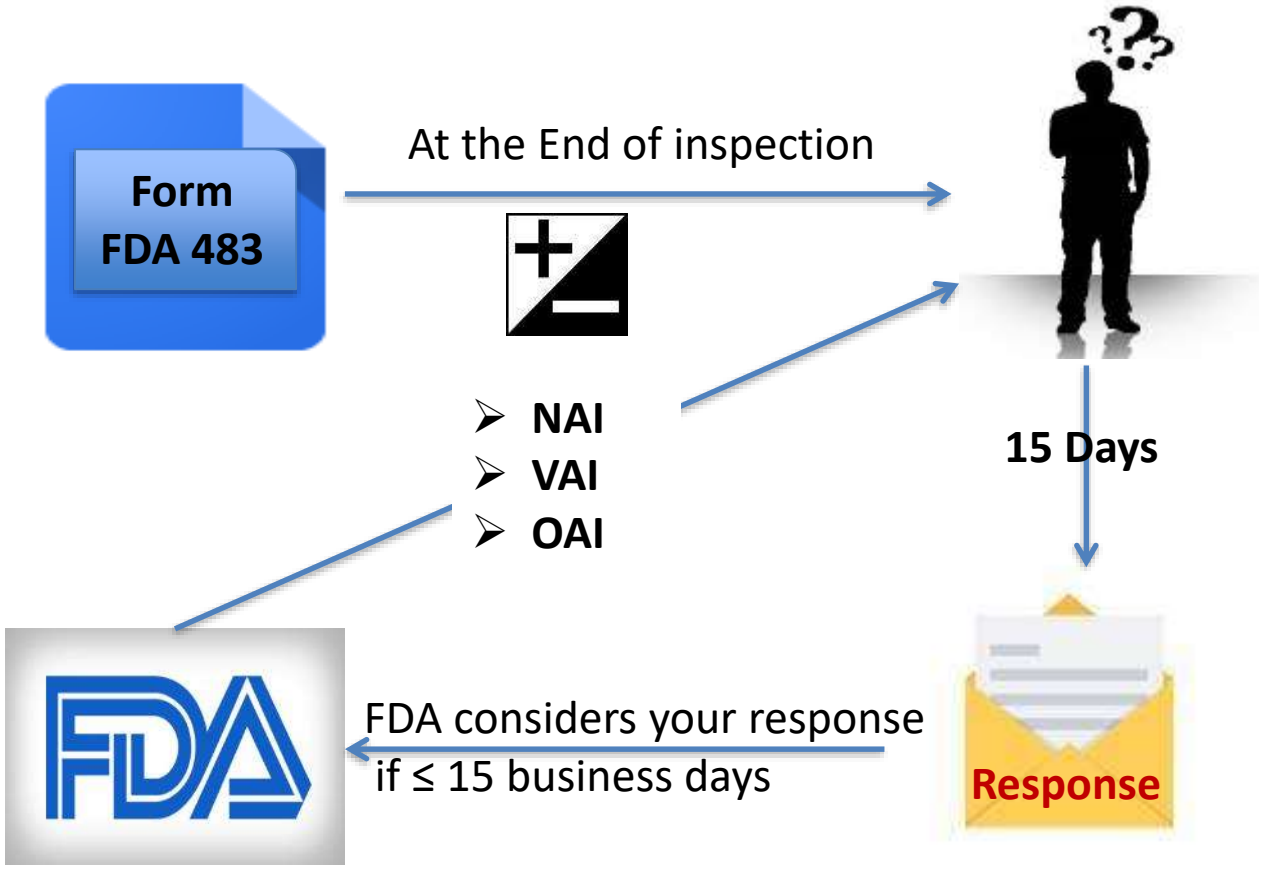


By a show of hands:

If you receive a Form FDA 483 at the end of an inspection, are you required to respond to the FDA?

- Yes
- No

Form FDA 483 Issued?



Does your response help?

Form FDA 483 and EIR

Response

- Change significance
  - Disproves
  - Mitigates
- No change

Final Inspection Classification

NAI: no violations identified

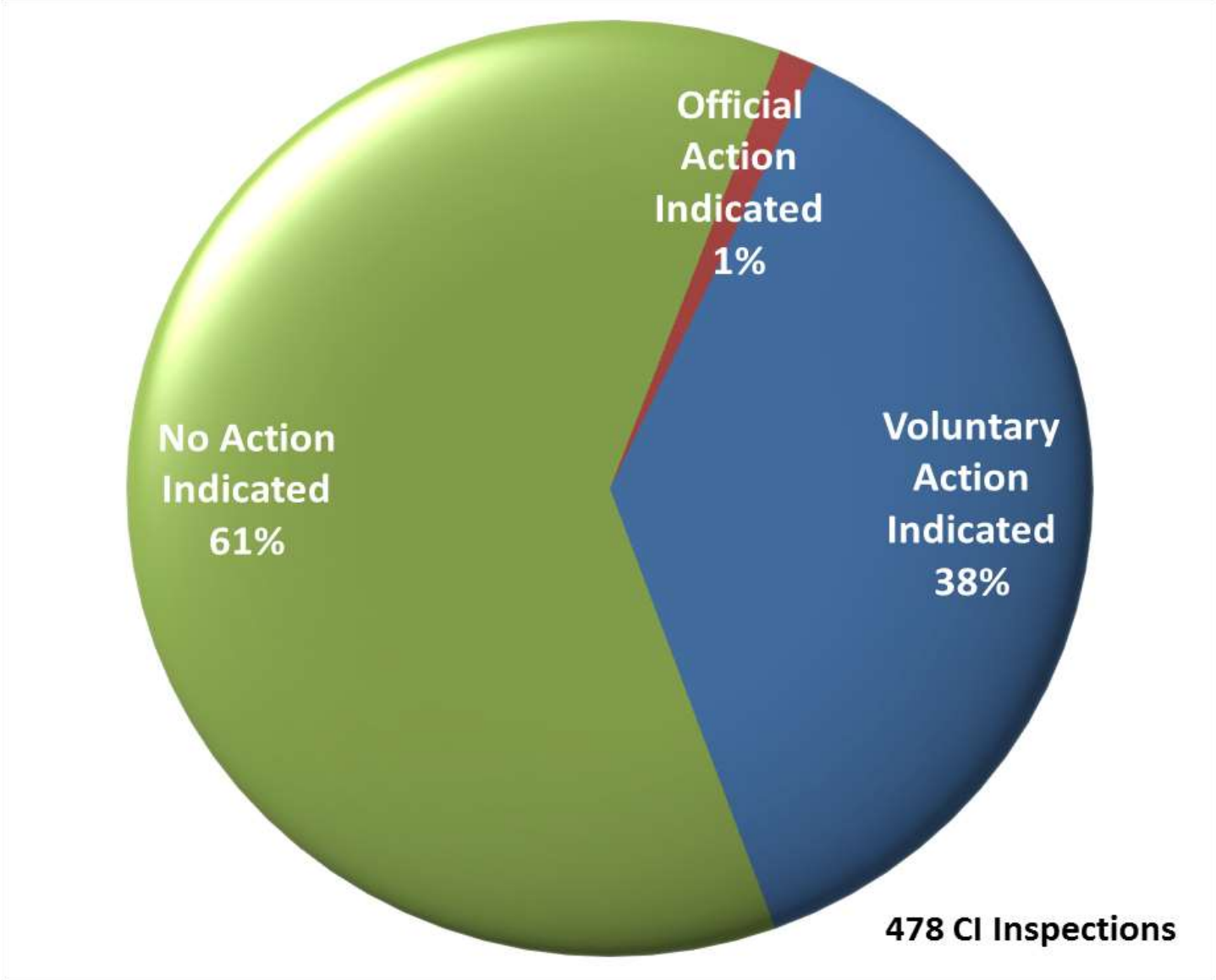
VAI: violations identified but no or minimal impact on data integrity and/or subject safety

OAI: violations identified that have significant impact on data integrity and/or subject safety

NAI: No Action Indicated
VAI: Voluntary Action Indicated
OAI: Official Action Indicated

CI Inspections by Classification

CDER- FY 2016



OAI – Warning Letters (WL)

- Informal and advisory
- Issued for: violations of regulatory significance
- Purpose: to give opportunity to take voluntary and prompt corrective action before an enforcement action is initiated.
- Does not commit FDA to take enforcement action
- Is not a pre-requisite to take enforcement action

Follow-up Inspection

- ✓To ensure violations are not repeated
- ✓To verify promised CAs are implemented
- ✓To ensure compliance is sustained

Close-out Letter

Records reviewed in a CI inspection

- CDER regulated clinical studies:
  - Form FDA 1572
  - Informed consent processes
  - Subjects' records and Case Report Forms (CRFs)
  - Protocols and amendments
  - Sponsor and IRB correspondences
  - …

Poll Question

For how long is a clinical investigator is required to retain the study related records?

- 2 years
- 4 years
- 10 years
- Indefinitely

Form FDA 1572 –Commitments

- **Conduct** the study in accordance with the protocol
- **Personally conduct** or **Supervise**
- **Inform patients** about investigational purposes
- **Report** adverse experiences to sponsor
- **Inform Staff** about their obligations

You commit when you sign:

Form FDA 1572

21 CFR 312.60
21 CFR 312.50,56
21 CFR 312.64

Poll Question

When does a Form FDA 1572 need to be completed?

- Any time during the study
- Every month during the study
- Any time a new clinical investigator is selected by the sponsor to conduct the study

Form FDA 1572 –Commitments

- **Maintain** adequate/ accurate records; and and **Retain** records
- **Make records** available for inspection
- **Ensure IRB review** of the initial & continuing application
- **Comply** with all other obligations of CI's

Form FDA 1572

21 CFR 312.62
21 CFR 312.68
21 CFR 312.66

By a show of hands:

Do you have to be a physician to conduct a clinical study as a clinical investigator?

- Yes
- No

Assurance of IRB Review

- Review and approval of
  - original protocol
  - any changes to the protocol
  - revisions in informed consent document
- Reporting all unanticipated problems involving risks to human subjects

Adequate Informed Consent

- Approved by IRB
- Signed/dated by subject or subject's LAR
- Language understandable to subjects
- Required information

50.20: General Requirements
50.25: Basic Elements
50.27: Documentation of Informed Consent

Adherence to investigational plan

- Screening evaluations
- Subject eligibility
- Study design and procedures
- Dosage and administration
- Reporting Serious Adverse Events (SAEs)

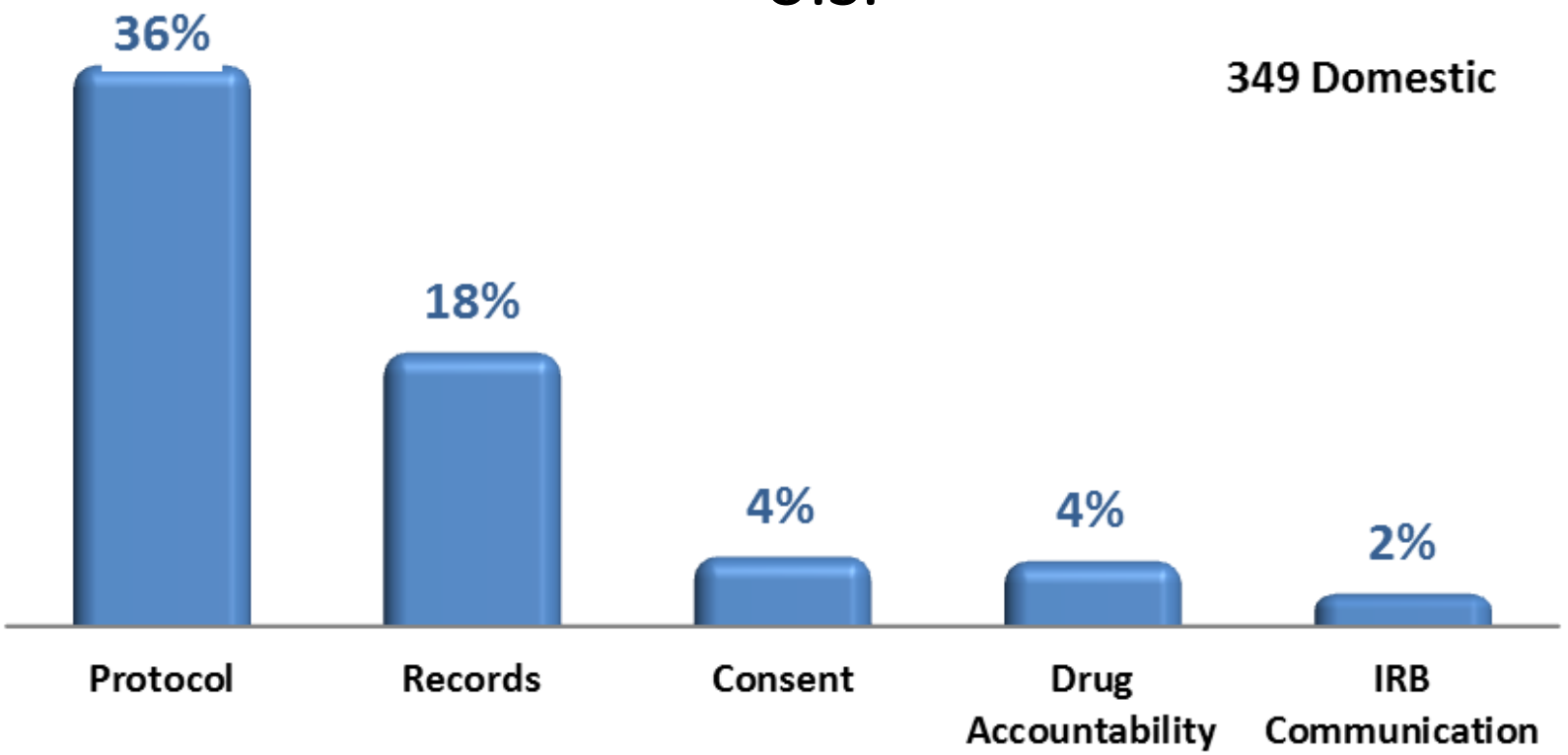
Adequate documentation

- ✓ Accurate, original, contemporaneous, legible, attributable
- ✓ Initialed/signed and dated
- ✓ Study data transferred correctly into Case Report Forms (CRFs)

Regulatory Violations – All Letters

CDER- FY 2016

U.S.

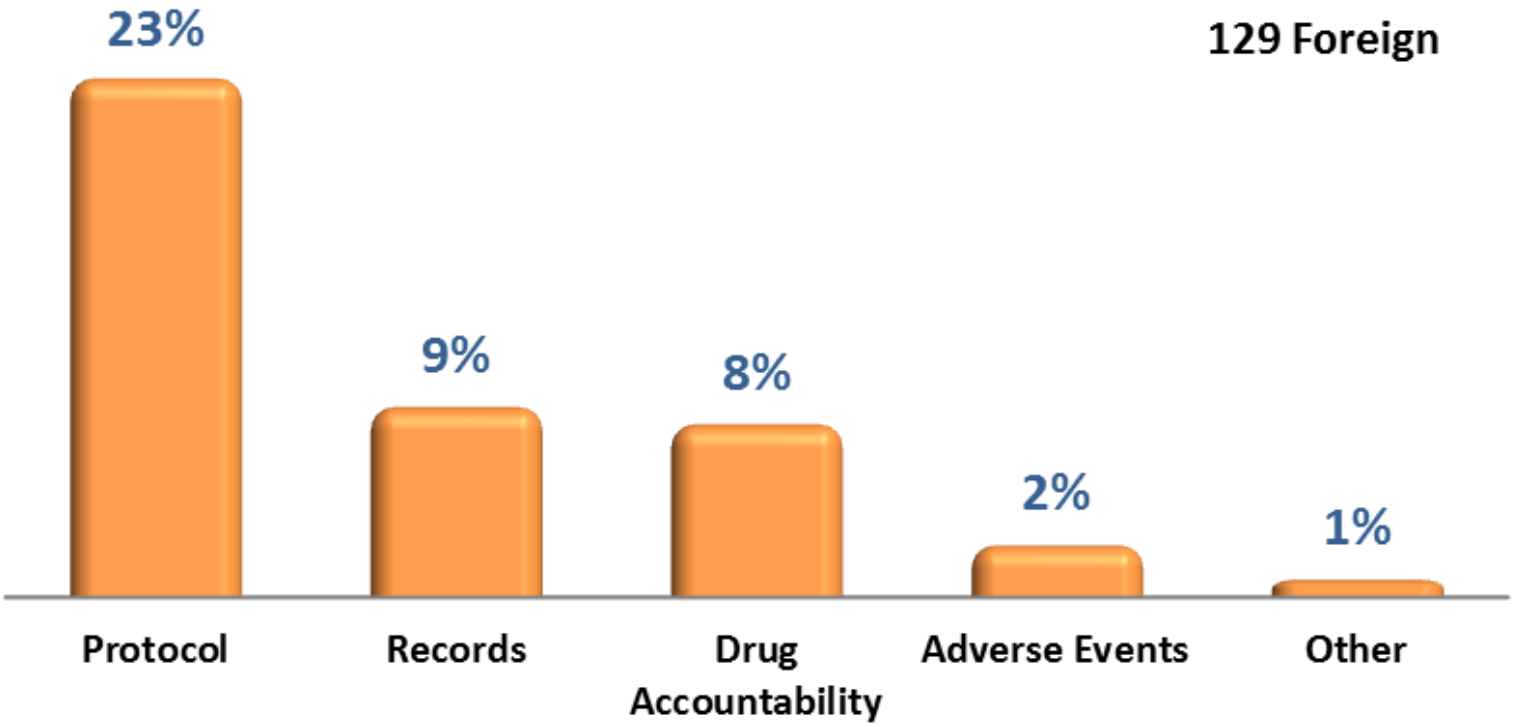


Based on letter issue date. Inspections may have multiple deficiencies. Includes OAI untitled letters. [Complis database as of December20, 2016]
Note: this does not denote number of inspections completed, but rather number of inspection reports evaluated and closed.

Regulatory Violations – All Letters

CDER- FY 2016

International



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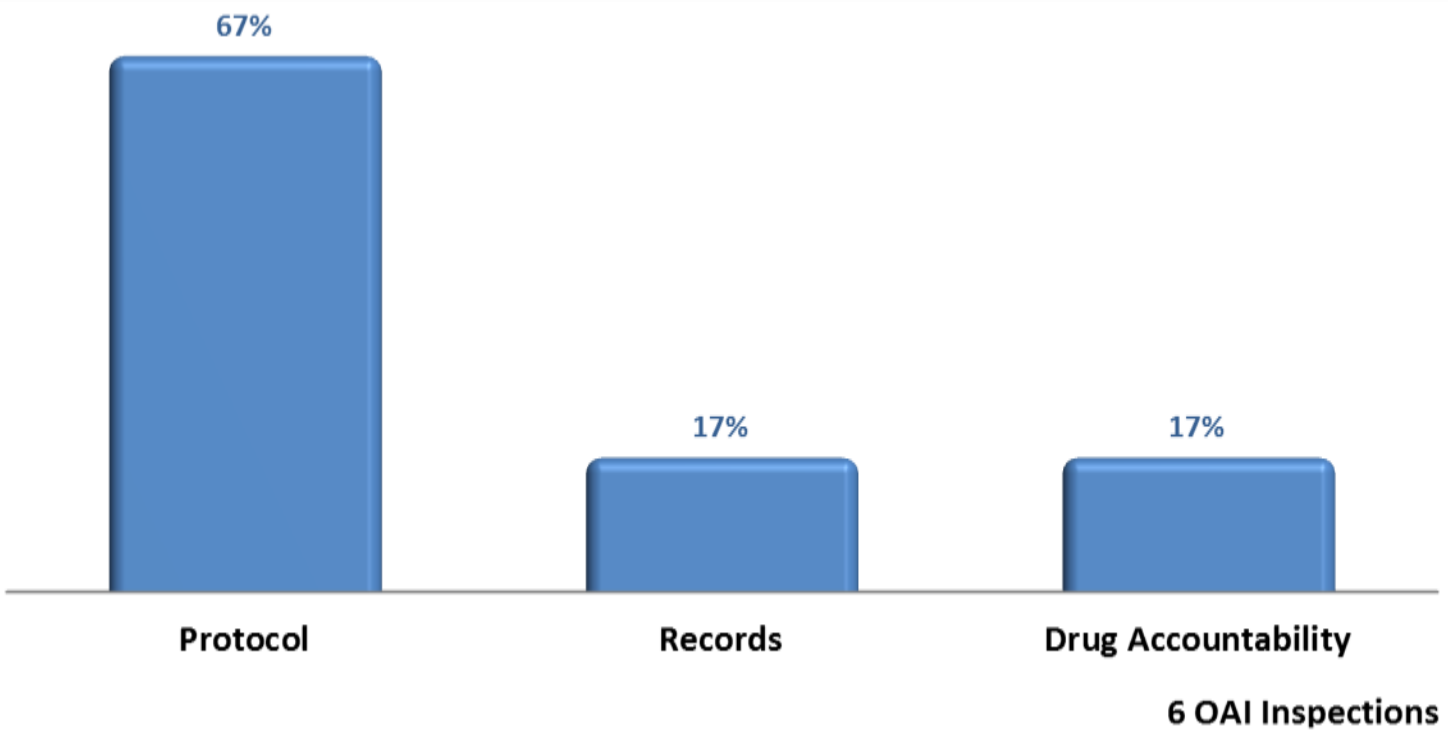
Regulatory violations – OAI letters



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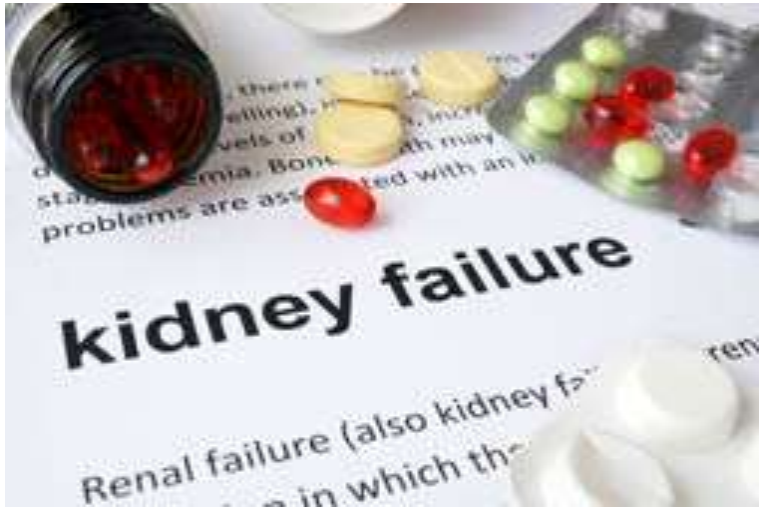
EXAMPLE

Protocol Violations - Eligibility

- Protocol required exclusion of subjects with severe renal insufficiency



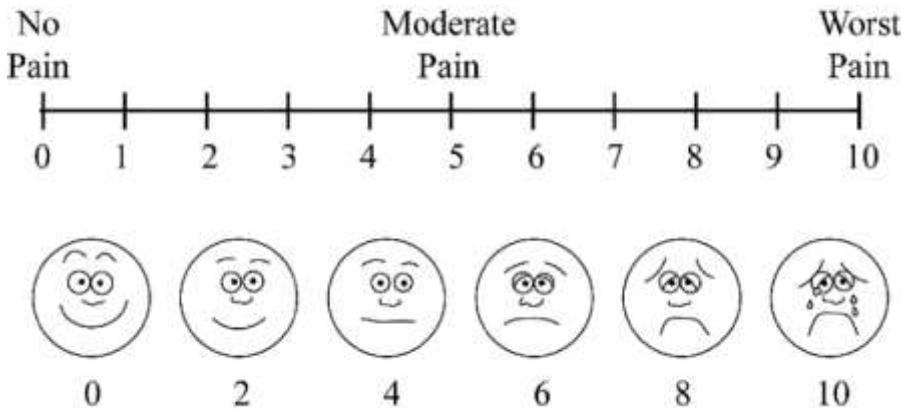
- Medical history records showed that subject had chronic renal failure prior to enrollment into the study.

Protocol violations – Screening

- Protocol required collection of serum creatinine values at screening and randomization visit
- 20 subjects were enrolled and received study drug prior to receipt of their serum creatinine values.

Protocol violations – Study Procedures

- Protocol required that pain assessment be documented by the subjects on an electronic handheld device prior to surgery.
- Pain assessments for subjects were entered by the study coordinator, rather than by the subjects.



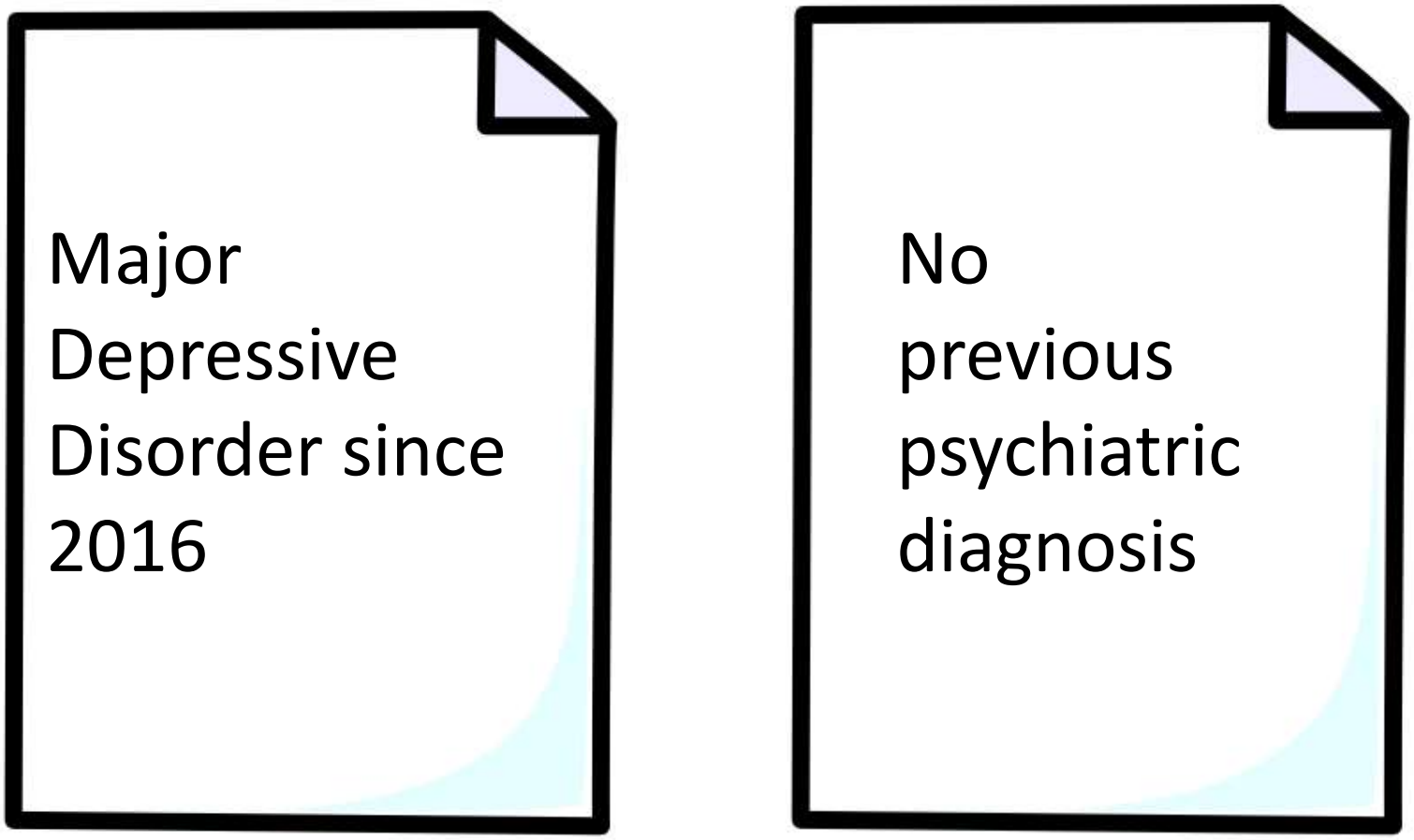
Protocol violations – Subject Safety

- If Fasting Plasma Glucose (FPG) ≥ 250 mg/dL → administer hyperglycemia rescue medication

- Subject had FPG levels: 350 mg/dL, and 304 mg/dL
- No rescue medication administered

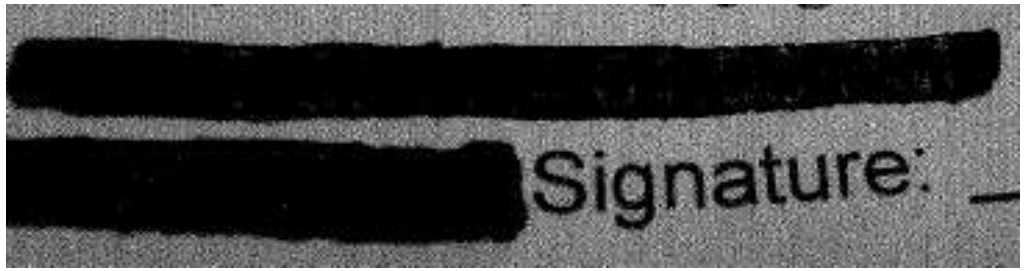
Inadequate documentation

Source document → **CRF**



Inadequate documentation Case 2

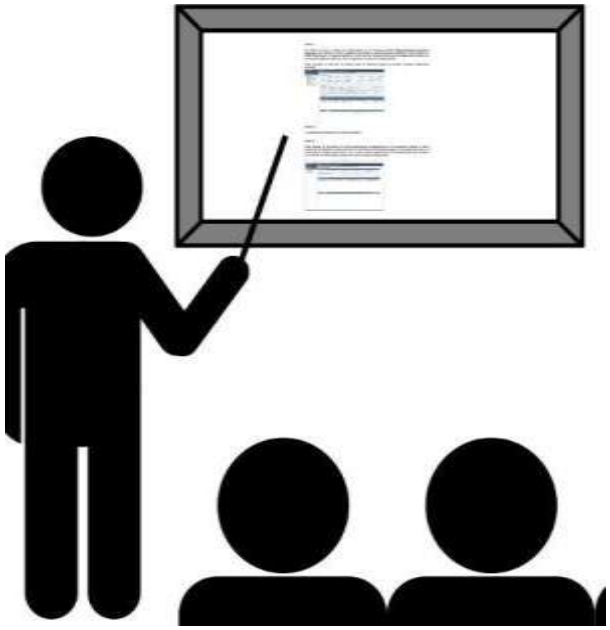
- Obscured original subject ID data for multiple subjects
- Different subject ID handwritten on those records on which original data was obscured



If you don’t strategize…

Root Cause Analysis

- Insufficient training/awareness
- Overlapping responsibilities
- Fear/desire
- Misunderstanding of the regulations
- Inadequate delegation

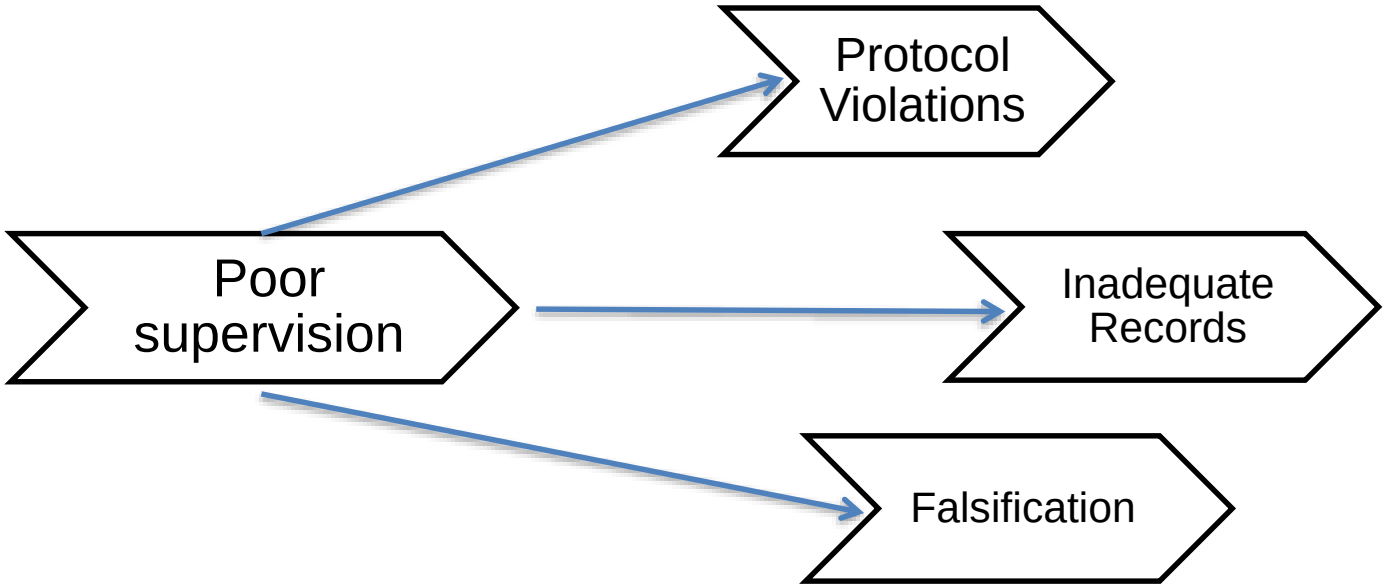


Unqualified Study Team

- Lymphoma
- Pre-eclampsia
- Bone fractures
- Periodontitis

- Dentist
- Podiatrist
- Ophthalmologist
- Physical therapist

Chain Reaction



What can you do to correct?

A Few Tips

- Commit to change or stop
- Make a comprehensive plan with defined steps
- Support with documentation (SOP, work instructions, training)
- Set a timeline for completion of your CAPs
- Implement your CAP
- Evaluate the implementation of CAP

Summary

- CDER GCP BIMO Program
- Regulatory Requirements for CIs
- Inspection Classifications and Regulatory Actions
- Common Regulatory Violations and Examples
- Root cause analysis and Tips for CIs

Please complete the session survey:

surveymonkey.com/r/DRG-D2S04

Key Elements

- Write a complete and articulated protocol
- Select a qualified team
- Train your staff
- Adhere to the protocol
- Supervise
- Communicate
- Anticipate
- Act promptly
- Re-evaluate

Helpful Resources

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

  http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM214282.pdf

- 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

- Clinical Investigator Administrative Actions – Disqualification

  https://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidanceInformationSheetsandNotices/default.htm

Thank You

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