U.S. FOOD & DRUG ADMINISTRATION

FDA Regulatory Requirements for Clinical Investigators and Case Examples

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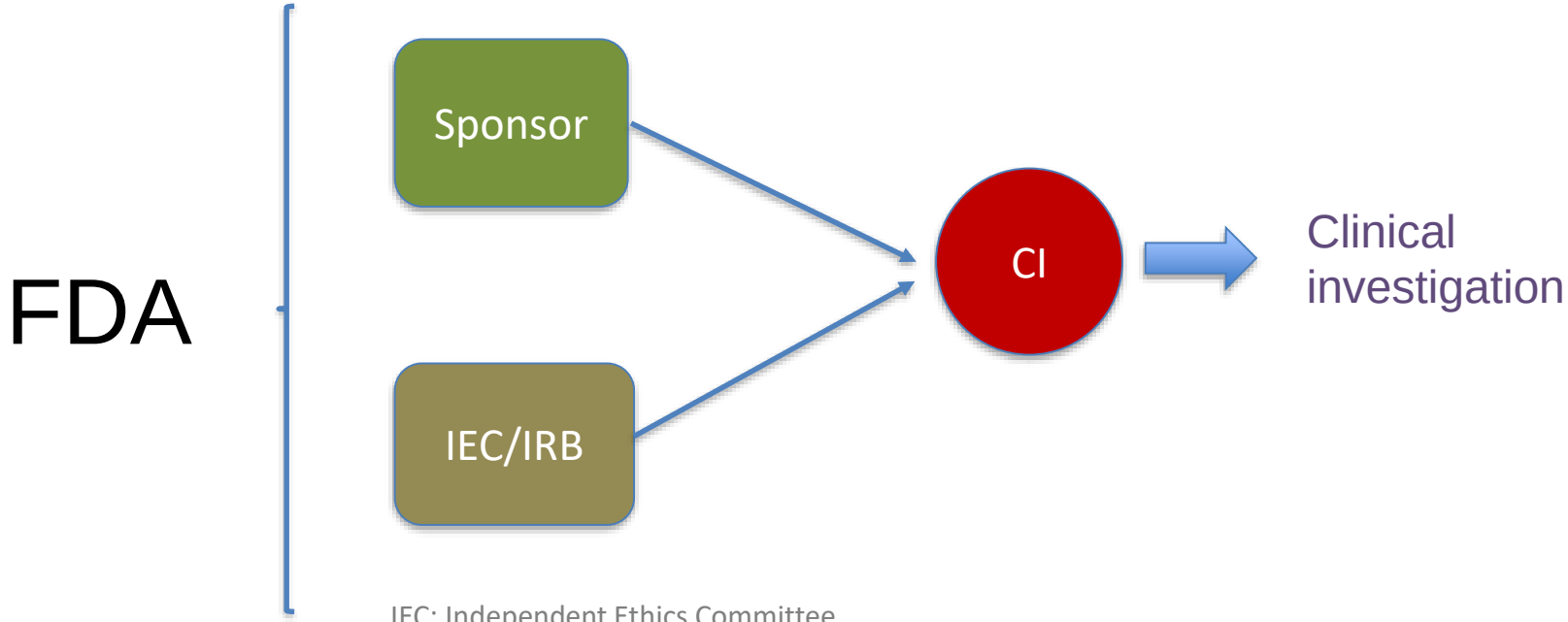
Lisa's Story

- Study protocol required exclusion of subjects with serum HCG > 5.2 mIU/mL.
- Clinical Investigator (CI) enrolled and randomized Lisa who met the exclusion criterion.
- 25 year old pregnant woman who received multiple doses of a teratogenic study drug!

Outline

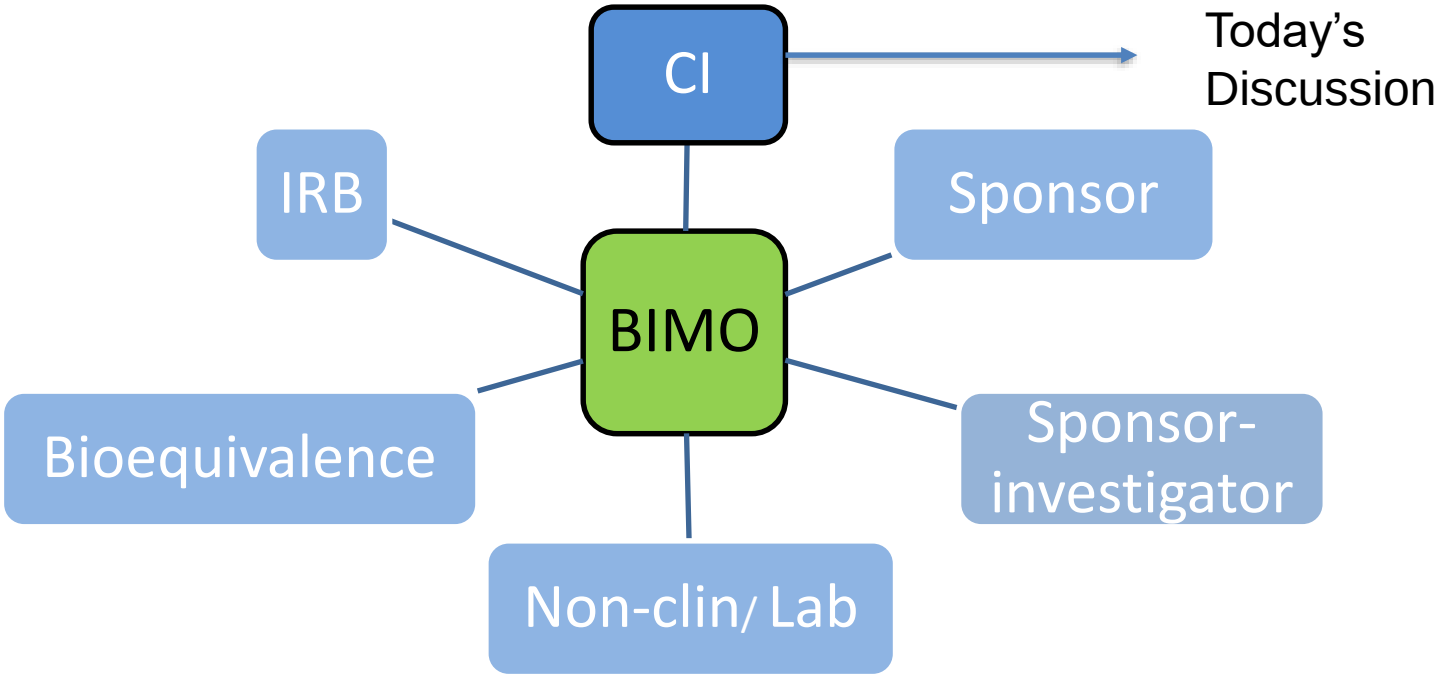
- Regulatory requirements
- Inspections and outcomes
- Case examples
- Root cause analysis
- Summary

Relationships

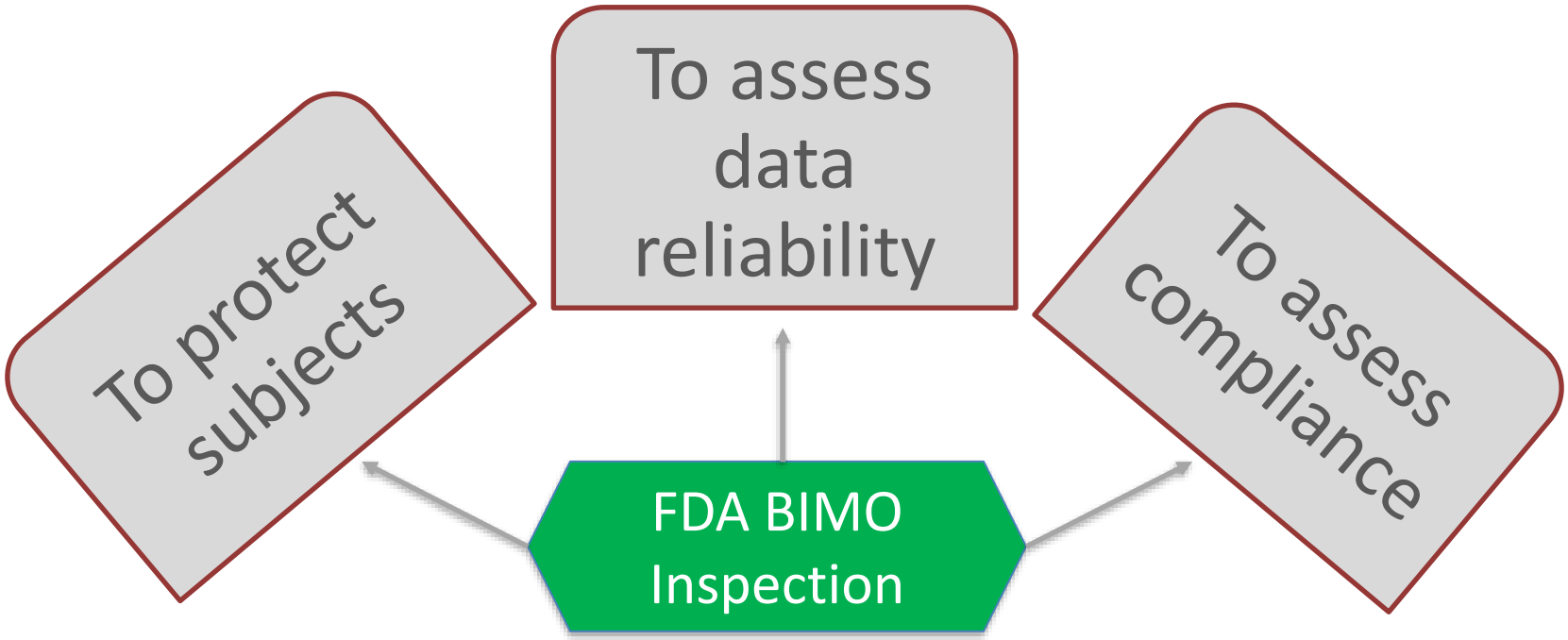


IEC: Independent Ethics Committee
IRB: Institutional Review Board

Bioresearch Monitoring Program Coverage (BIMO)



Purpose of BIMO Inspection

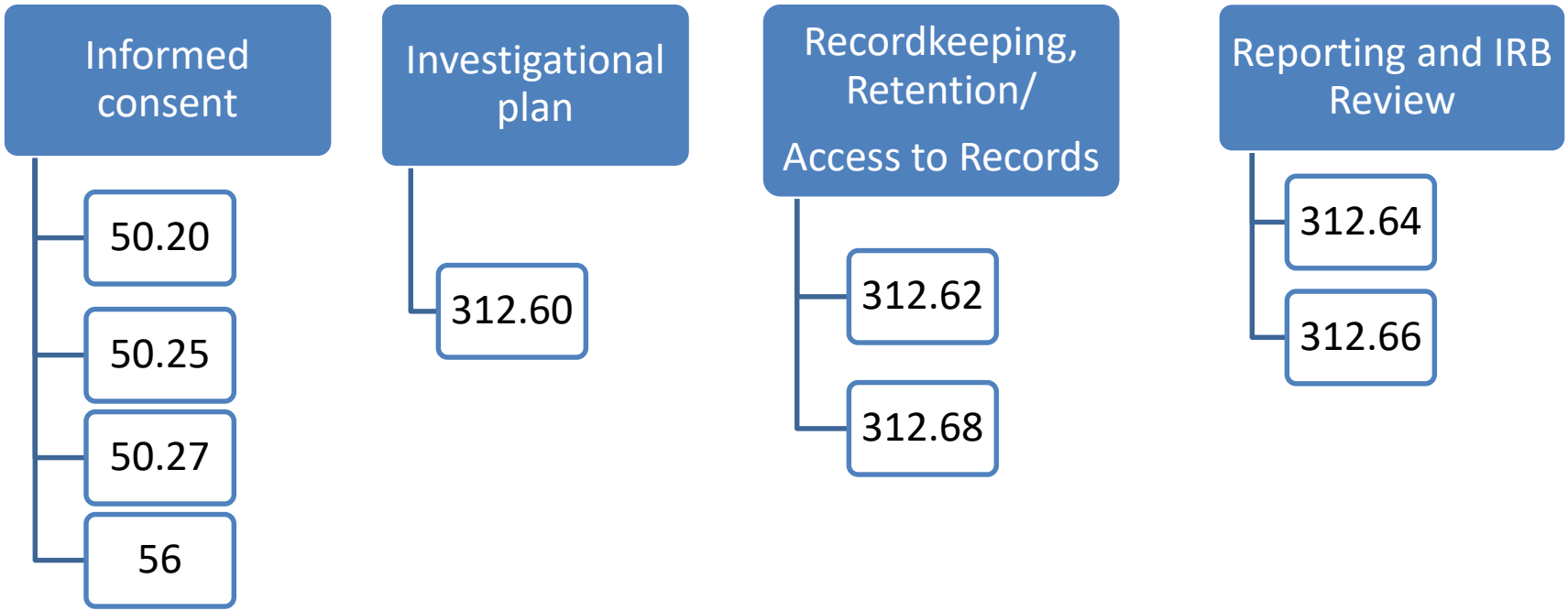


Why Clinical Investigators?

- Highest number of CDER GCP inspections
- Highest number of CDER Warning Letters (WLs)
- Responsible for the conduct of clinical studies

Frequency of CI Inspections

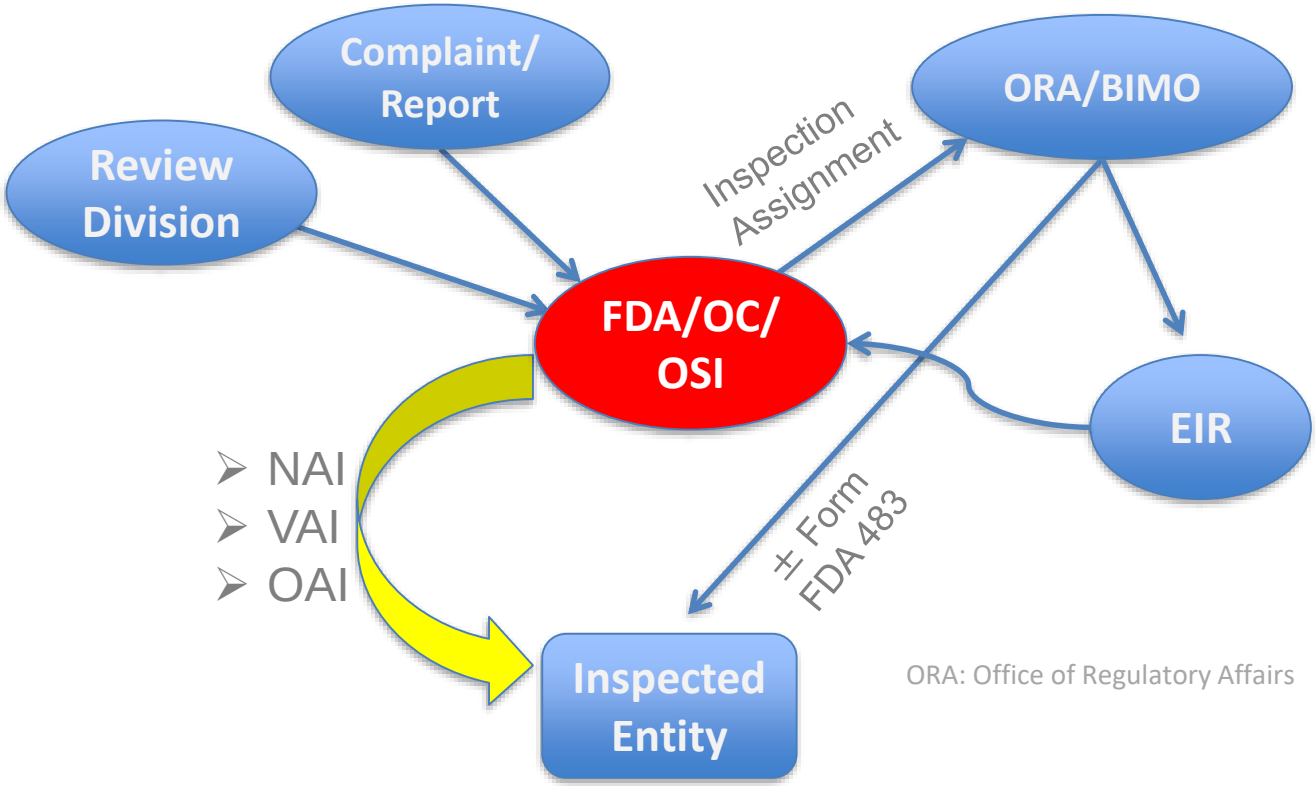
Regulatory Requirements for Clinical Investigators



Regulatory Requirements…

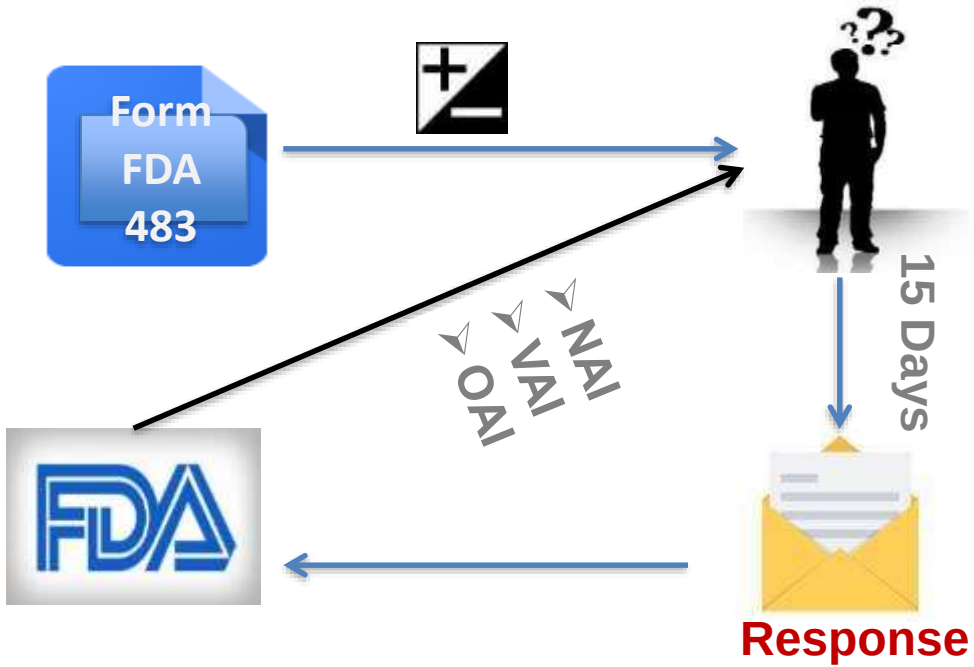
- Control of investigational drug
  - 312.61
- Handling of controlled substances
  - 312.69
- Disqualification of CI
  - 312.70

Inspection Process



ORA: Office of Regulatory Affairs

Form FDA 483 Issued?



FDA considers your response
if ≤ 15 business days

Does your response help?

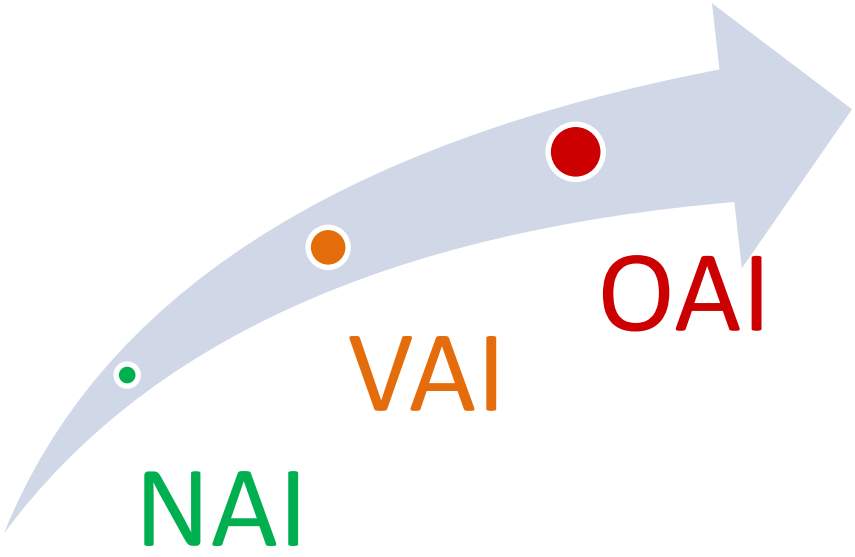
Form
FDA 483
and EIR

+

Your
Response

- Mitigates
- Disproves
- Clarifies

Final Inspection Classification



NAI: no violations identified

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

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

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

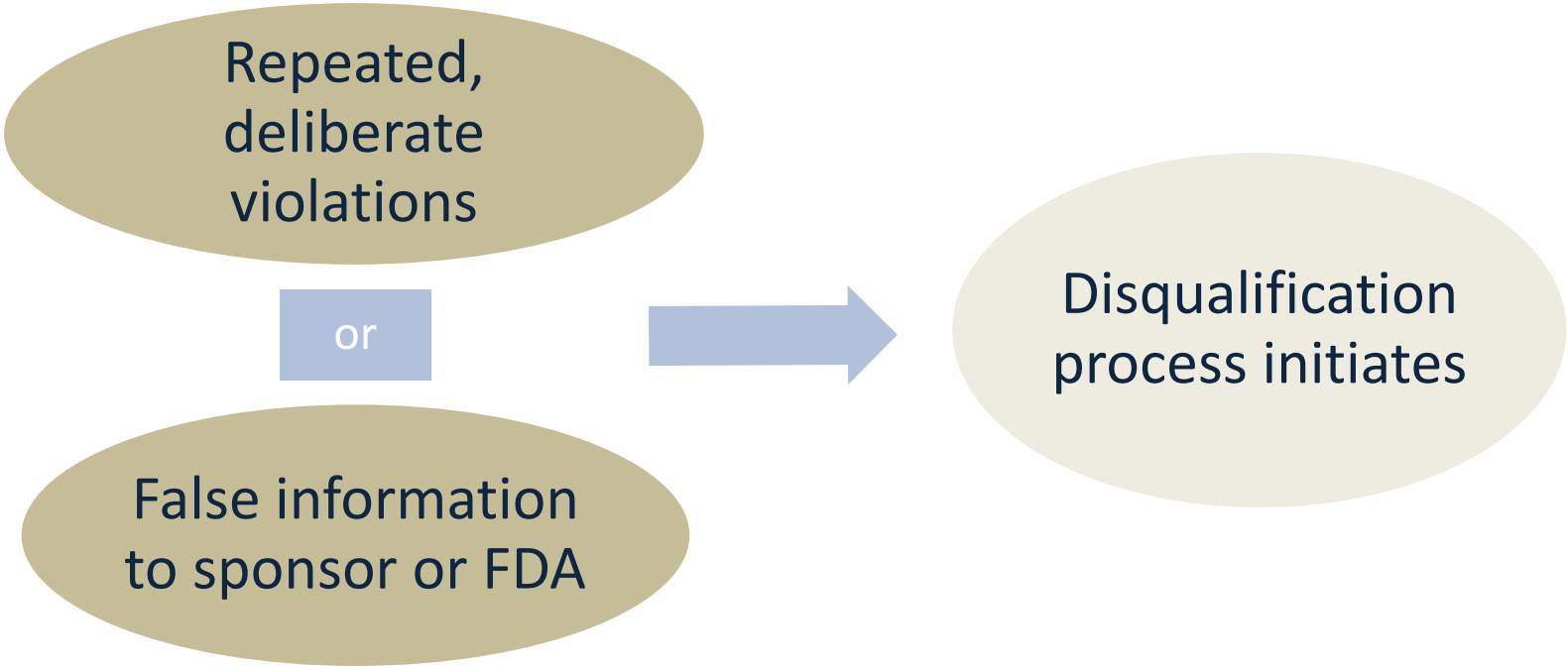
OAI – Warning Letters (WL)

- 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

OAI- NIDPOE


Repeated, deliberate violations
or
False information to sponsor or FDA
Disqualification process initiates

Case Example 1 – Report

- CI did not retain any paper or electronic records:
  - Case Report Forms
  - Source documents
  - Signed informed consent forms

Cases Example 1 – Findings

- Screened 45 and enrolled 22 subjects
- Shredded or destroyed all records 2 yrs after study termination at the site!
- Sponsor withdrew IND and terminated the study 1.5 years before FDA inspection.

Case Example 1 – Outcome

- WL for failure to retain records
- Responded to Form 483:
  - CI misunderstood the regulation!!
  - Completed GCP training
  - Promised to follow the record retention regulations
  - Promised to inform regulatory authorities and sponsor before destroying records

Case Example 2 – Report

- Sponsor's concerns about adequacy of data
  - Identification of complete vs partial responders
- Protocol required subject's assignment based on therapeutic response to study drug:
  - Complete vs partial response
  - Stable vs progressive disease

Case Example 2 – Findings

- CI enrolled 50 subjects in an oncologic study
- CI incorrectly classified therapeutic responses
- CI's interpretation different from protocol
- Resulting in significant impact on data integrity

Case Example 2 – Outcome

- WL: issued for failure to follow the protocol, and other regulatory violations…

- Follow-up: No new studies after WL

Case Example 3 – Report

- Report of scientific misconduct
- Protocol Requirements:
  - Physical exams (PE) must be done by CI
  - All PE's must be reported on Case Report Forms (CRFs)

Case Example 3 – Findings

- CI signed and dated PE CRFs, when he did not perform them and was out of state!
- Study coordinator (SC) enrolled site's employees using fabricated names and data!
- Falsified data were submitted in CRFs to sponsor and FDA!
- CI failed to adequately supervise study conduct

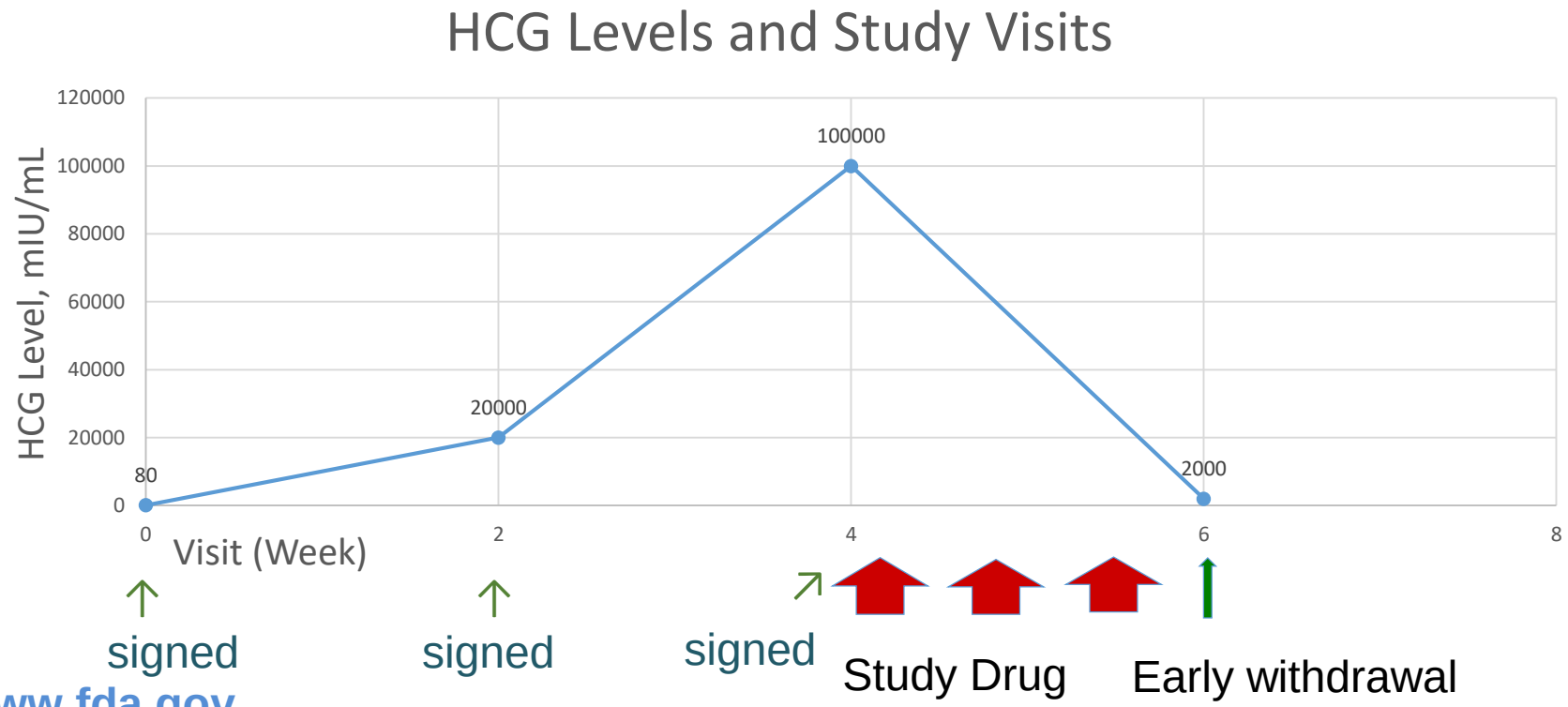
Case Example 3 – Outcome

- Disqualified:
  - Is not entitled to receive investigational drugs, animal drugs, biologics, devices, or food additives,
  - Is not entitled to conduct any further studies, intended or required for submission to FDA, of investigational articles regulated by FDA.
  - Can serve as a sub-investigator, but cannot be a CI!

Back to Lisa's Story

- Study protocol required exclusion of subjects with serum HCG > 5.2 mIU/mL.
- Clinical Investigator (CI) enrolled and randomized a subject who met the exclusion criterion.
- 25 year old pregnant woman received multiple doses of a teratogenic study drug!

What happened to Lisa?



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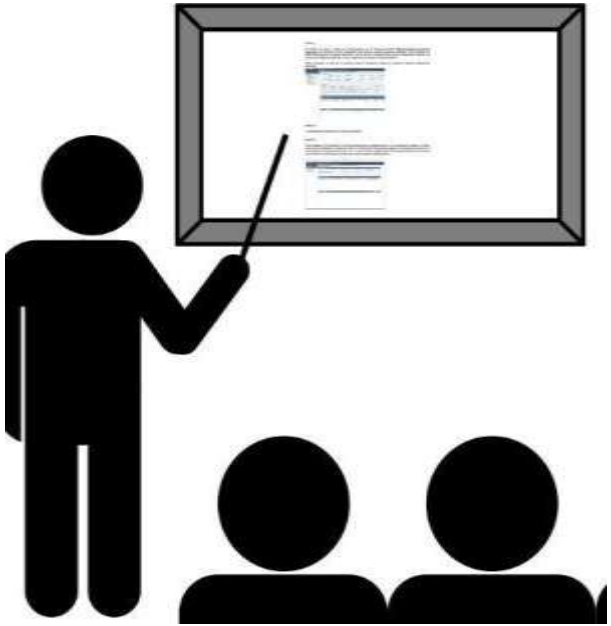
Root Cause Analysis: Non-Compliance

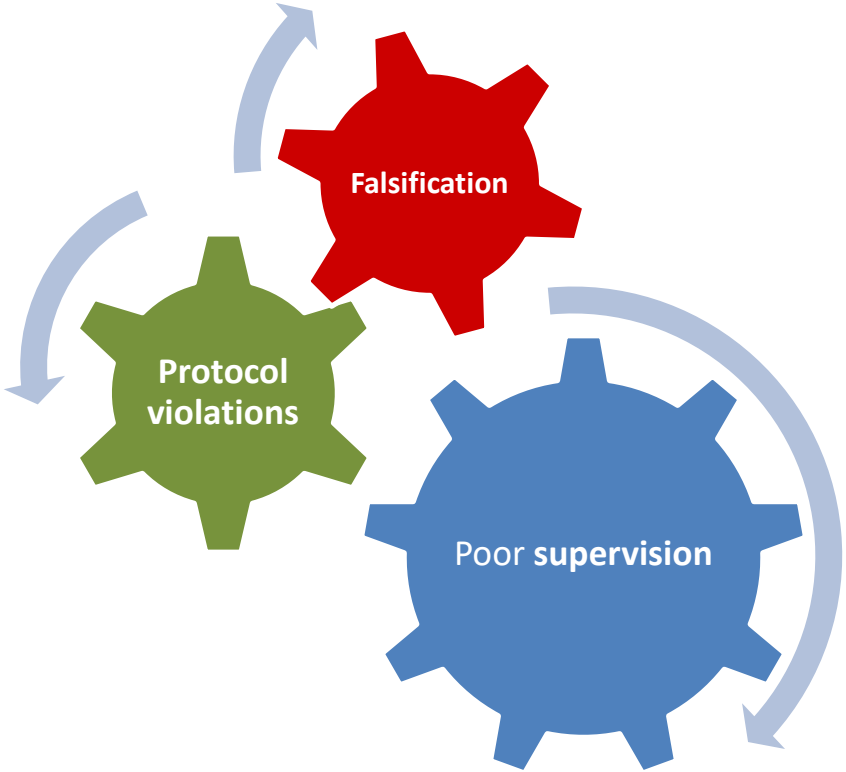
- Etiology (ies)
- Mechanism/pathophysiology
- Assessment and diagnosis
- Treatment
- Follow-up

Potential Etiologies: Non-Compliance

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

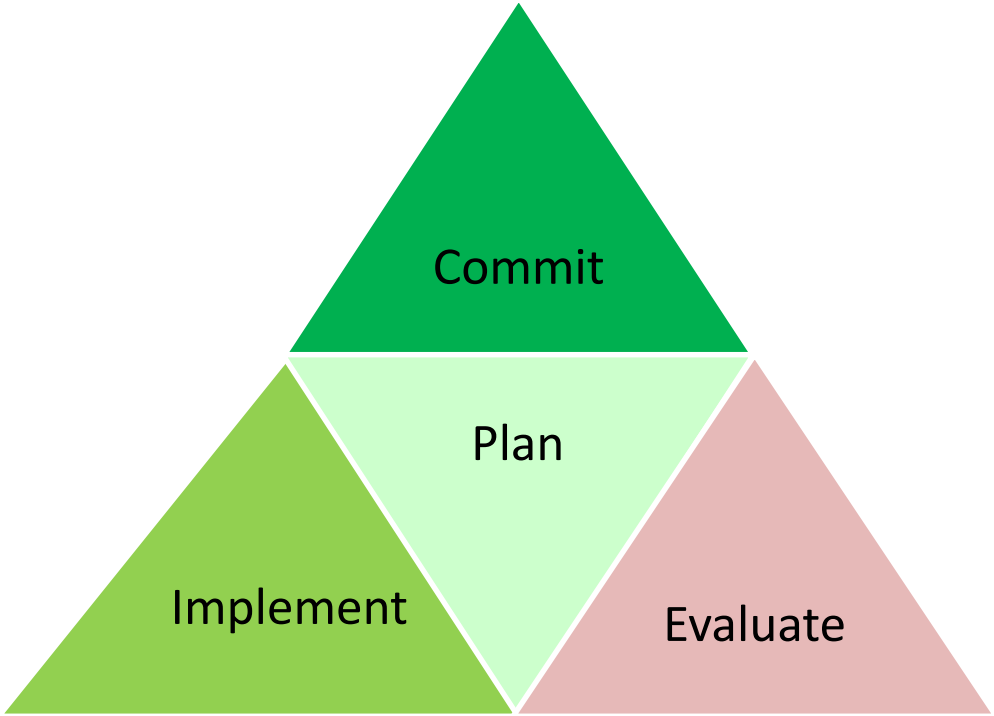


Mechanism: Chain Reaction



Treatment: Prevent and Correct

Corrective Actions and Preventive Actions (CAPA)



Tips for CAPA

Focus on violations in original OAI

Establish all GCP aspects

Hire Qualified staff

Improve Documentation: SOP, work instructions, study worksheets

Train: CI and study team

Strengthen Site Infrastructure

Design study-specific CAPA

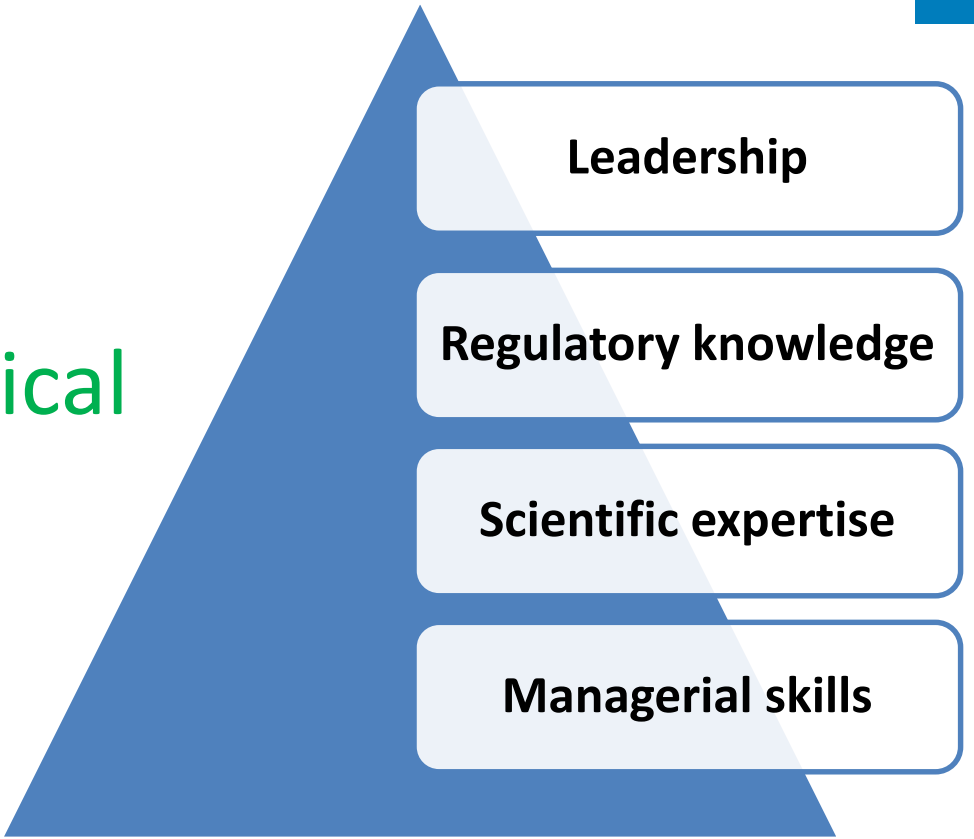
Implement and Sustain CAPA

Resources


Sponsor
Guidance
IRB
GCP Recovery
Educational conferences
Consultants

Key Elements to Better Compliance

Build a quality system for clinical research



Summary

- CI's are eventually responsible for the conduct of the study.
- Good compliance can protect subject safety and provide more reliable data.
- Non compliance can have multiple causes.
- Most non-compliance can be prevented or corrected.

Questions?

Please evaluate this session:

surveymonkey.com/r/DRG-D2S02

Closing Thought…

Build a strong infrastructure before you expose human subjects to your study drug!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