U.S. FOOD & DRUG ADMINISTRATION

Clinical Investigator Inspection Readiness

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FDA Clinical Investigator Training Course – December 12, 2024

Poll Question

Which of the following best describes your current role:

A. Clinical Investigator

B. Study Coordinator or other staff member at a clinical research site

C. Employed by a sponsor/firm or contract research organization

D. Other

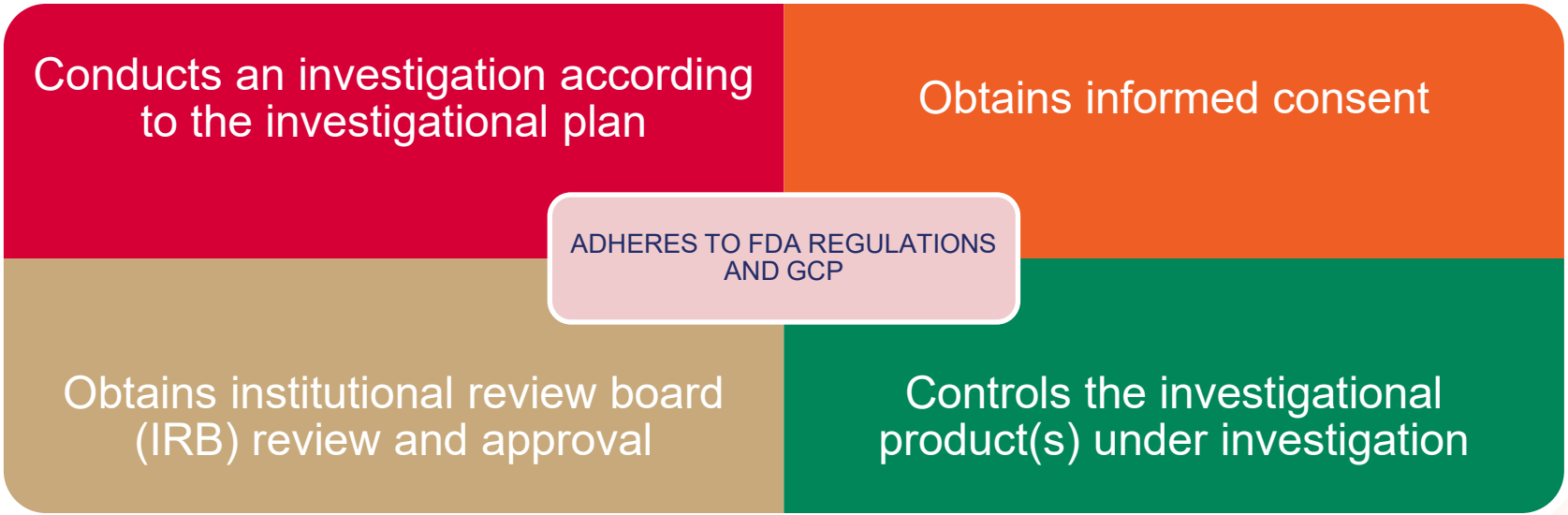
Learning Objectives

- Describe the purposes, focuses, and types of clinical investigator (CI) inspections
- Explain the inspection timeline and activities
- List potential enforcement actions
- Provide case examples of for-cause inspections classified as Official Action Indicated (OAI)

Purposes, Focuses, and Types of CI Inspections

Purposes of CI Inspections

Ensure that the CI:



Focuses of CI Inspections

Was the study conducted according to the protocol?

- Inclusion/exclusion (eligibility) criteria
- Randomization and blinding procedures
- Study visits, procedures, evaluations
- Administration of investigational product

Did the study comply with FDA regulations?

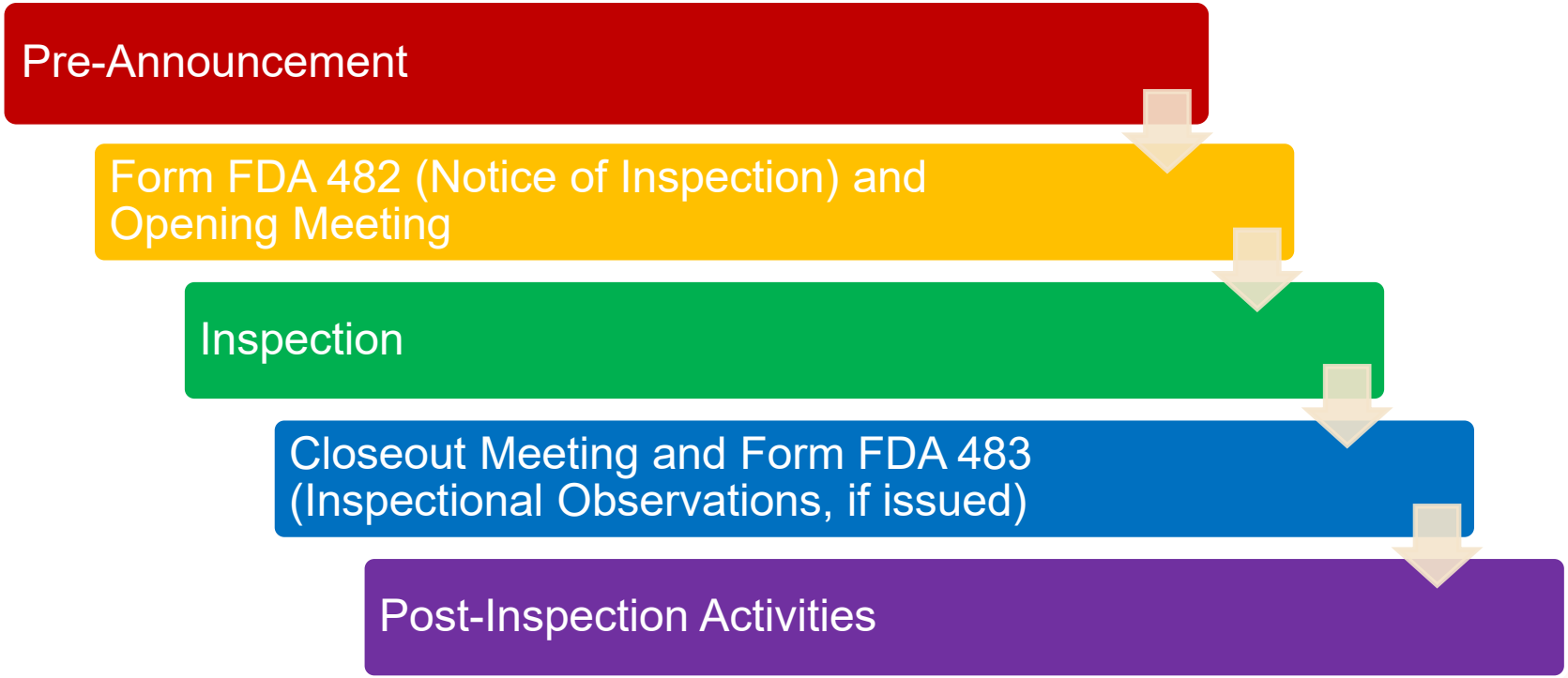
- Protocol adherence
- Adverse event (AE) and serious adverse event (SAE) reporting
- IRB approvals and communications
- Informed consent procedures
- Financial disclosures
- Paper and/or electronic records management
- Investigational product accountability

Types of CI Inspections

- Routine/surveillance
  - Pre-marketing application review
  - Assess compliance with FDA regulations
- For cause
  - Investigate allegations of potential regulatory violations
  - Referrals from FDA sources
  - Reports from IRBs, sponsors
  - Complaints from study staff, subject(s)

CI Inspection Timeline and Activities

Overview


Pre-Announcement
Form FDA 482 (Notice of Inspection) and Opening Meeting
Inspection
Closeout Meeting and Form FDA 483 (Inspectional Observations, if issued)
Post-Inspection Activities

Pre-Announcement

- Generally pre-announced unless otherwise instructed in inspection assignment
- Made up to 5 days prior to start of inspection
- Scope and logistics:
  - Protocols to be covered
  - Location of records (storage/retrieval, computer system access)
  - Anticipated length of inspection
  - Access to workspace, internet, scanner, and personnel
  - Involvement of other parties

Form FDA 482 (Notice of Inspection) and Opening Meeting

- Form FDA 482 (Notice of Inspection)
- Presentation of FDA credentials
- Performed by an Office of Inspections and Investigations (OII) investigator, sometimes accompanied by a Subject Matter Expert from the relevant Center

Inspection

- Examples of **study** records reviewed (not an exhaustive list)
  - Protocols and amendments
  - Investigational product accountability records
  - IRB approvals and correspondence
  - Signed investigator statements (Form FDA 1572)
  - Financial disclosure forms
- Examples of **subject** records reviewed (not an exhaustive list)
  - Informed consent documents
  - Source documents (e.g., visit worksheets, progress notes, laboratory reports)
  - Case report forms
  - AE and SAE reports
  - Investigational product accountability records (dosing and administration)

Inspection

- Interviews
- Site walk-through
- A word about access to electronic systems
- Daily discussions
- Resources
  - Clinical Investigators and Sponsor-Investigators Compliance Program (CP) 7348.811
  - Investigations Operations Manual (IOM) – Section 5.14 Bioresearch Monitoring (BIMO)

Closeout Meeting and Form FDA 483 (Inspectional Observations, if issued)

- Summary of inspectional findings

Form FDA 483 items are OII investigator's observations of possible deviations from federal regulations, and not necessarily regulatory violations

  - Center determines whether each observation is a regulatory violation, and if a regulatory violation, will determine the violation's impact on data integrity and subject safety

- Form FDA 483 issued to the inspected entity at the end of the inspection
- CI may provide verbal response to Form FDA 483 during Closeout Meeting

Post-Inspection Activities

- Two perspectives: CI and FDA
- CI – Written Response to Form FDA 483
- FDA – Final Classification

Written Response to Form FDA 483

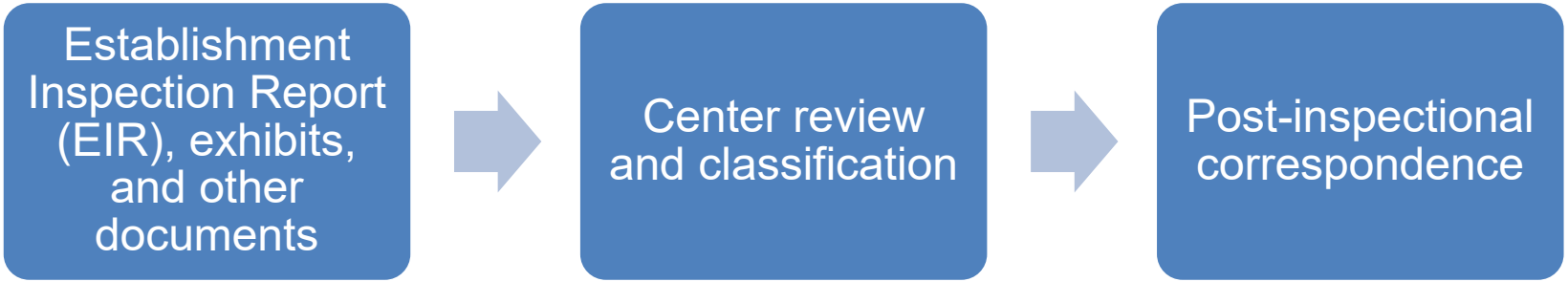
- Optional, but good reasons to submit a written response
  - ✓ Demonstrates your acknowledgement and understanding of the inspectional observations to FDA
  - ✓ Demonstrates your commitment to correct (and prevent the recurrence of) the inspectional observations
  - ✓ Opportunity to submit information for determining whether an inspectional observation is a supportable regulatory violation
  - ✓ May be considered in the final FDA compliance decision
- Must be received by OII Investigator's office within 15 business days after close of the inspection

Post-Inspection Activities

Suggested Contents of a Written Response to Form FDA 483

- ✓ Address each inspectional observation separately
- ✓ Indicate whether you agree or disagree with each inspectional observation
- ✓ Submit a corrective and preventive action plan (CAPA) for each inspectional observation, noting which actions are already completed (and when) and which actions are planned
- ✓ Provide a realistic timeline for completion of each planned action
- ✓ Provide a method of verifying or monitoring the effectiveness of the actions
- ✓ Submit supporting documentation (e.g., training records, standard operating procedures (SOPs))
- ✓ Consider including a commitment from senior leadership
- ✓ *Ensure the written response is well-reasoned, easy to follow, comprehensive, and submitted timely*

Final Classification – Flow



Final Classification – Common Inspectional Findings

Finding	Regulation
Investigation not conducted in accordance with the Investigational plan	21 CFR 312.60
Failure to prepare and maintain adequate and accurate case histories	21 CFR 312.62(b)
Failure to obtain informed consent in accordance with 21 CFR part 50	21 CFR 312.60
Failure to maintain adequate drug disposition records, Including dates, quantity, and use by subjects	21 CFR 312.62(a)
Failure to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to subjects	21 CFR 312.66

Final Classification – Objectionable Conditions

- Subjects exposed to unreasonable and significant risk of injury
- Subjects' rights, welfare, and safety compromised
- Data integrity or reliability compromised

Final Classification

- **No Action Indicated (NAI)**

No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action)

- **Voluntary Action Indicated (VAI)**

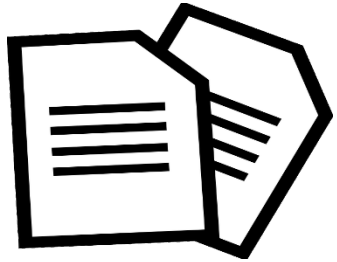
Objectionable conditions were found and documented, but the Center is not prepared to take or recommend any regulatory action since the objectionable conditions do not meet the threshold for regulatory action

- **Official Action Indicated (OAI)**

Objectionable conditions were found and regulatory action is recommended

Potential Enforcement Actions

OAI Outcomes



- **Untitled Letter**
- **Warning Letter**
  - Regulatory Procedures Manual, Chapter 4 (Advisory Actions)
  - FDA Warning Letters
- **Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE) Letter**
  - CI Disqualification Proceedings database

Case Examples

Inspection with Final Classification of OAI

Regulatory Violation in the Warning Letter:

- Regulatory violation of failure to ensure that the investigation was conducted according to the investigational plan **in a pediatric population which is considered a vulnerable population**
- Protocol required investigational drug to be administered according to a subject's weight and in accordance with the protocol's titration schedule for the 20-week Titration Phase
  - The Titration Phase consists of specific dose increases at each study visit; at Visit 2, **subjects 12 to <18 years old were to receive modified dosing**, not to exceed 12.5 mg per day
  - Doses exceeded the weight-based dose required by the protocol-specified titration schedule; in fact, the per protocol daily doses were substantially exceeded and were **approximately 10X the maximum daily dose**. This considerably **increased risk of adverse events,** such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome.
- **Overdose in the vulnerable pediatric population raises significant concerns about subject safety**

Inspection with Final Classification of OAI

Evaluation of CI's Written Response to Form FDA 483 in the Warning Letter:

- CI promptly confirmed no adverse events occurred
  - CI provided instructions to reduce the drug dosage to the correct amount and arranged unscheduled visits
  - CI stated that the sponsor did not provide an electronic dose calculator and that the electronic dispensing algorithm lacked safeguards to prevent errors
- CI submitted a CAPA consisting of an SOP for medication dispensation processes and procedures
- FDA unable to determine whether the CAPA is adequate to prevent similar violations in the future
  - Response **did not provide sufficient details about procedures implemented at the site** to ensure compliance with protocol dosing procedures
  - FDA requested follow-up documentation of these procedures

Inspection with Final Classification of OAI

Regulatory Violation in the Warning Letter:

- Regulatory violation of failure to ensure that the investigation was conducted according to the investigational plan
- Protocol required clinician-administered assessments related to study-defined efficacy endpoints to be completed by a **rater blinded to the safety assessments**
  - Blinded assessor responsible for administering protocol-required efficacy assessments, including MADRS[1], at certain study visits
    - Primary objective of the protocol was to assess efficacy of the investigational drug compared to placebo as assessed by change in MADRS score from Baseline to Week 4 (Day 29)
  - Blinded assessor would **not have access to EDC[2] system and subject source data** that could potentially unblind the assessor to a subject's treatment assignment
  - Blinded assessor **conducted MADRS assessments but was not blinded to certain safety assessments** (e.g., blood pressure, heart rate, body temperature) and performed a physical examination
- **Unblinding raises significant concerns about the reliability and integrity of the data collected at the site**

[1] Montgomery-Asberg Depression Rating Scale
[2] Electronic data capture

Inspection with Final Classification of OAI

Evaluation of CI's Written Response to Form FDA 483 in the Warning Letter:

- CI filed a protocol deviation and did not conduct any additional MADRS assessments
- CI submitted a CAPA
  - Clear identification of protocol requirements that concern blinding and annotation of worksheets to clearly identify blinded assessments
  - Consultation with both the sponsor and quality consulting group to provide clarity in understanding ambiguities in the protocol
  - CI and site personnel participation in various clinical research compliance trainings
- FDA unable to determine whether the CAPA is adequate to prevent similar violations in the future
  - Response **did not provide sufficient details about CAPA, such as implementation of proposed practices being instituted at the site** to ensure compliance with protocols (including requirements for blinding procedures) when conducting future clinical investigations

Challenge Questions

Challenge Question #1

Which of the following statements is NOT true?

A. Submitting a written response to Form FDA 483 is optional, but is in your best interest.

B. Components of a written response include items such as a CAPA for each observation and supporting documentation.

C. The most serious final inspection classification is OAI.

D. Items listed on Form FDA 483 are always regulatory violations.

Challenge Question #2

Which of the following choices BEST completes the sequence of the inspection?

Pre-Announcement → _____ → Inspection → Closeout Meeting and Form FDA 483 → Post-Inspection Activities

A. Call the lawyer
B. Gather relevant study records
C. Form FDA 482 and Opening Meeting
D. Contact your institution or the sponsor

Summary

- The overall purpose of FDA inspections of CIs is to ensure adherence to FDA regulations and GCP
- The sequence of events in FDA inspections of CIs is standard and predictable
- If Form FDA 483 is issued, there are benefits in submitting a written response to it
- Final classifications of inspections are NAI, VAI, or OAI

Closing Thought

The best way to successfully navigate an FDA inspection is to always be prepared for one!

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Questions?

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