FDA's Good Clinical Practice Compliance Review for NDAs and BLAs

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Clinical Investigator Training Course – December 12, 2024

Learning Objectives

- Provide an overview of FDA's Bioresearch Monitoring (BIMO) Program
- Discuss the Good Clinical Practice (GCP) inspection and review process
- Provide a case example and lessons learned from a clinical investigator (CI) inspection with data reliability findings

FDA's Bioresearch Monitoring (BIMO) Program

Comprehensive program of on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research

Objectives:

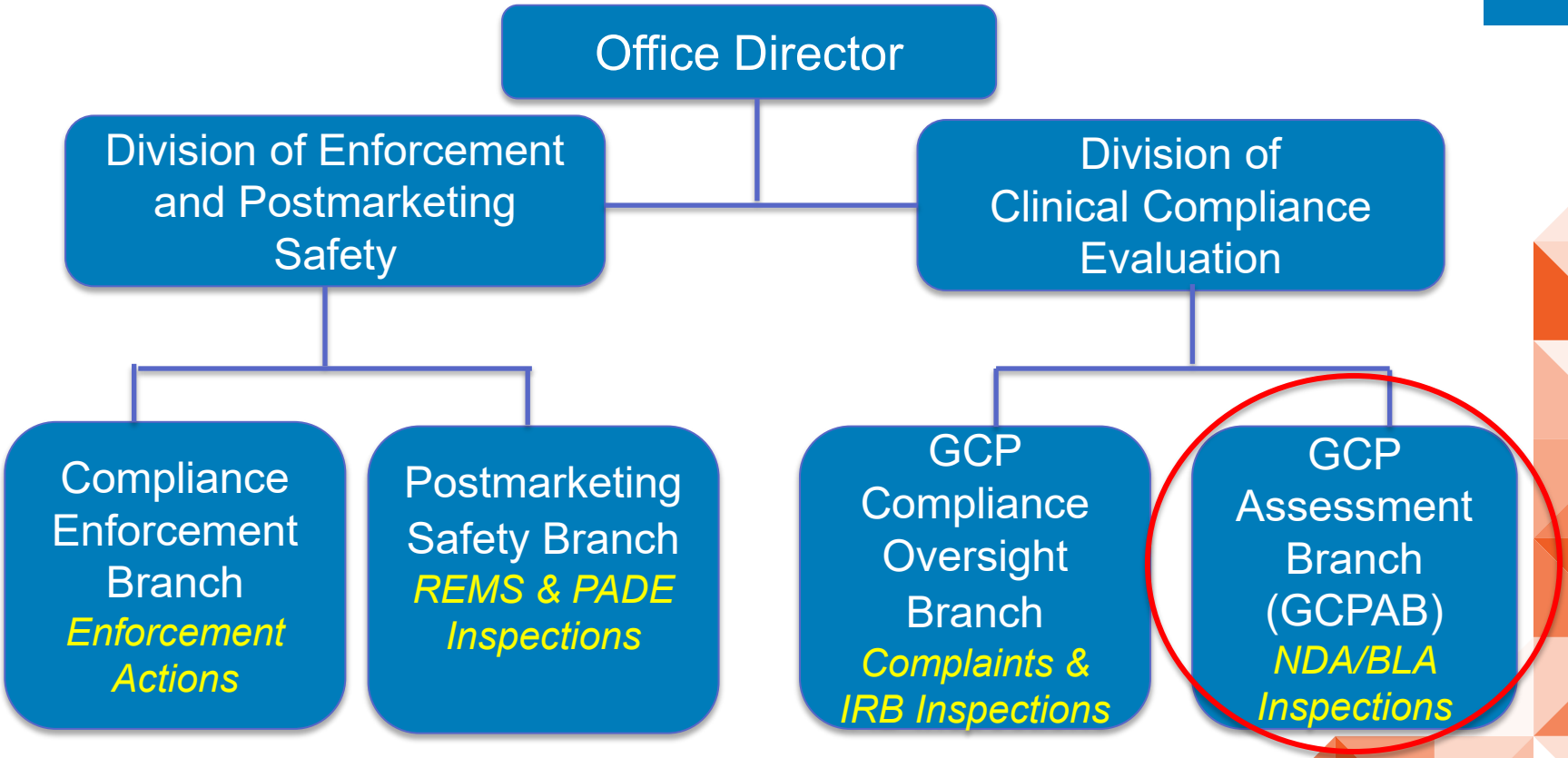
- To ensure that the rights and welfare of human research participants are protected
- To verify the quality and integrity of research data
- To ensure that FDA-regulated research is conducted in compliance with applicable regulations

BIMO Program

Over 1500 domestic and foreign inspections conducted annually involving different compliance programs including

- Clinical Investigators/Sponsors/CROs (GCP)
- Nonclinical Laboratories - Good Laboratory Practice (GLP)
- In Vivo Bioavailability-Bioequivalence Studies
- Institutional Review Boards
- Postmarketing Adverse Drug Experience (PADE)
- Risk Evaluation and Mitigation Strategies (REMS)

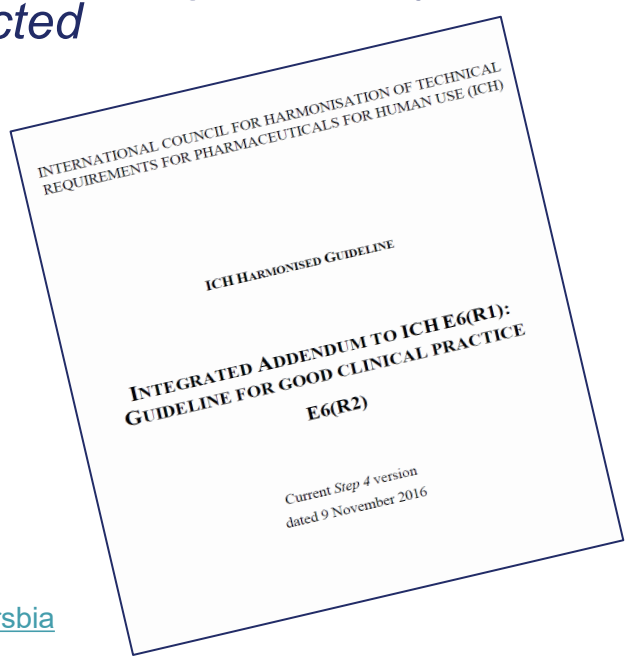
Office of Scientific Investigations



Good Clinical Practice (GCP) Inspections

Good Clinical Practice (GCP)

A standard for the planning, initiating, performing, recording, oversight, evaluation, analysis and reporting of clinical trials that provides assurance that the *data and reported results are reliable* and that the *rights, safety and well-being of trial participants are protected*


INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2)

Current *Step 4* version
dated 9 November 2016


ICH
harmonisation for better health

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

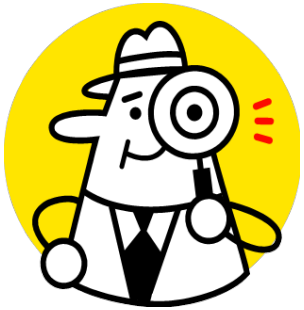
ICH HARMONISED GUIDELINE

GOOD CLINICAL PRACTICE (GCP) E6(R3)

Draft version
Endorsed on 19 May 2023
Currently under public consultation

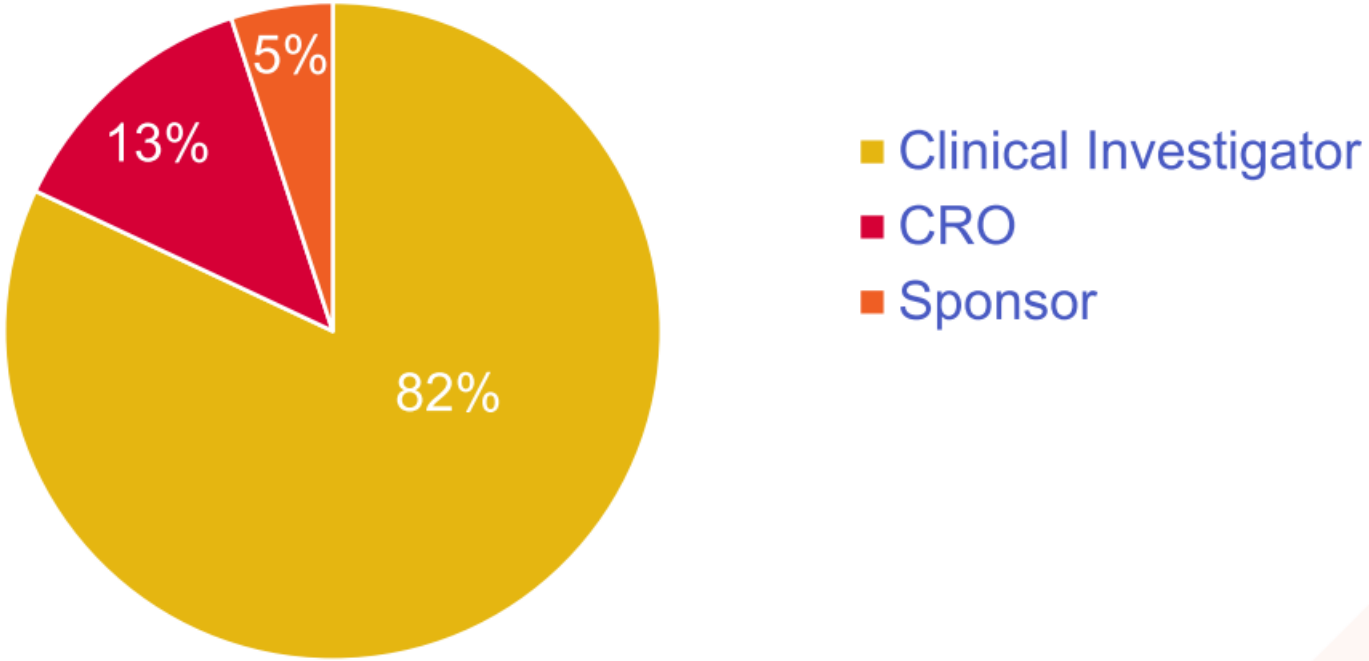
GCP Inspections

- Clinical Investigators
- Sponsors
- Sponsor-Investigators
- Contract Research Organizations (CROs)



OSI/GCPAB Inspections

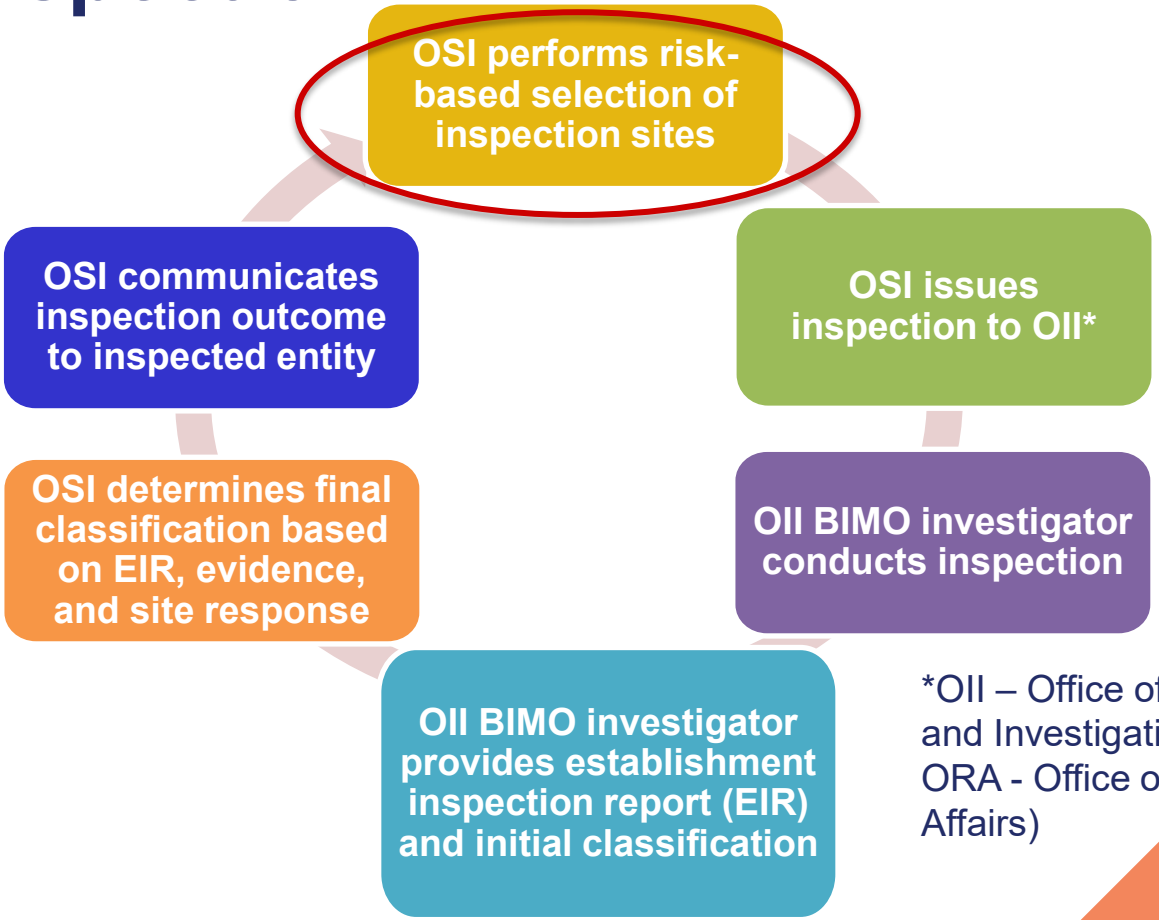
FY 2023 ~420 foreign and domestic GCP inspections



CI Inspections

- GCP inspections are not required as part of the application review process
- CI inspections usually requested
  - New molecular entities (NMEs)
  - Efficacy supplements if new dosing/population/indication
  - Other considerations: major protocol deviations, SAEs, unblinding

GCP Inspection Process



*OII – Office of Inspections and Investigations (formerly ORA - Office of Regulatory Affairs)

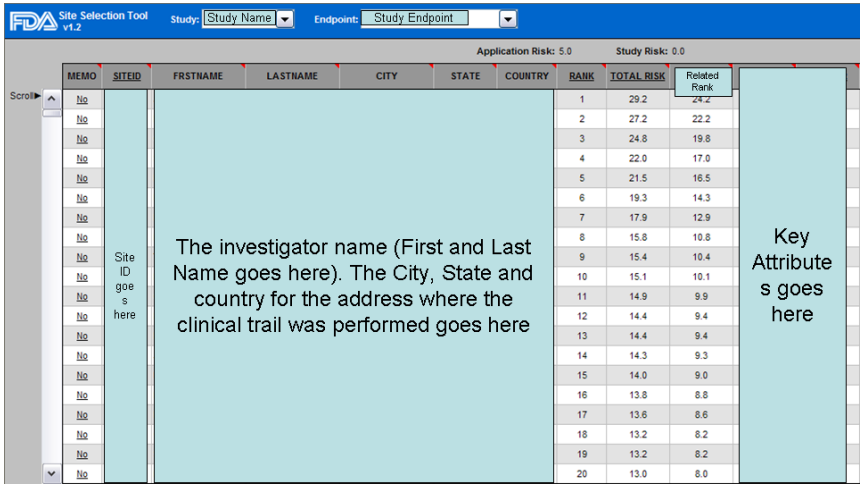
Choosing CI Sites for Inspection

- OSI works with review divisions and statisticians
- Clinical Investigator Site Selection Tool (CISST) assists the site selection process
- CISST generated from data submitted by sponsors and OSI internal metrics

CISST

Calculates total risk of each CI site based on

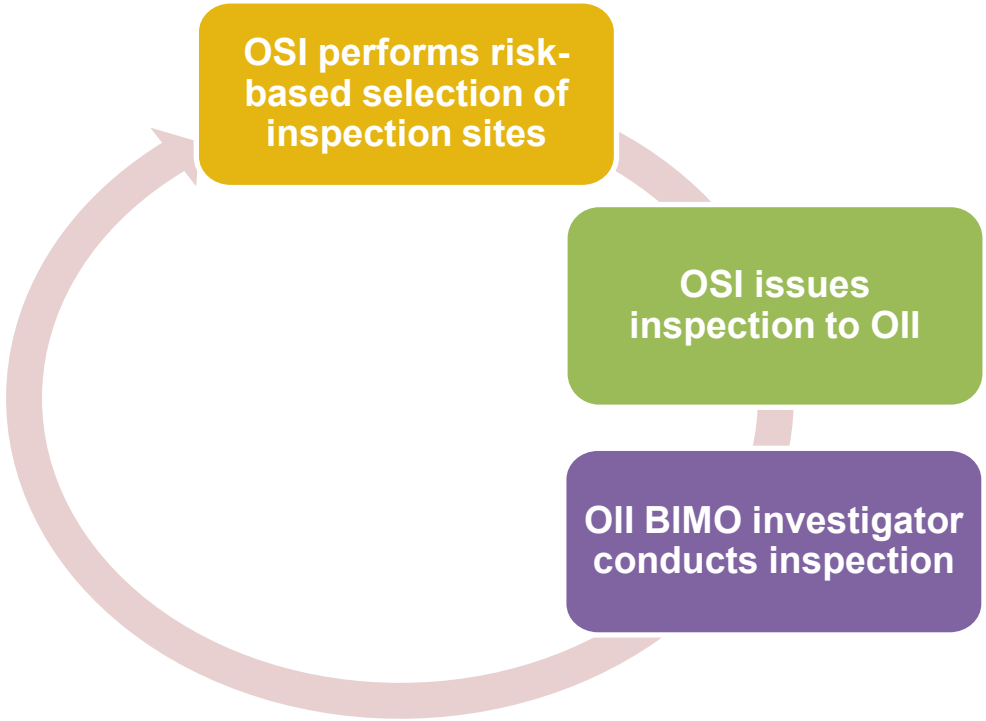
- Enrollment
- Efficacy outcome
- Complaints
- # SAEs
- # Protocol deviations
- Time since last inspection



CI Site Selection

- Other considerations for site selection not captured in CISST
  - Significance of PDs
  - Individual site impact on efficacy variables
  - GCP issues raised by sponsor (e.g. sensitivity analyses, site termination)
  - Reports of unblinding not captured as PDs

GCP Inspection Process



CI Inspections

- On average, 2-3 clinical sites per protocol chosen for inspection
- Clinical trial conduct
  - Study conducted according to protocol
  - Study conduct comply with federal regulations
- Data Verification
  - Primary/secondary efficacy data
  - Adverse events
  - Protocol deviations

CI Inspections

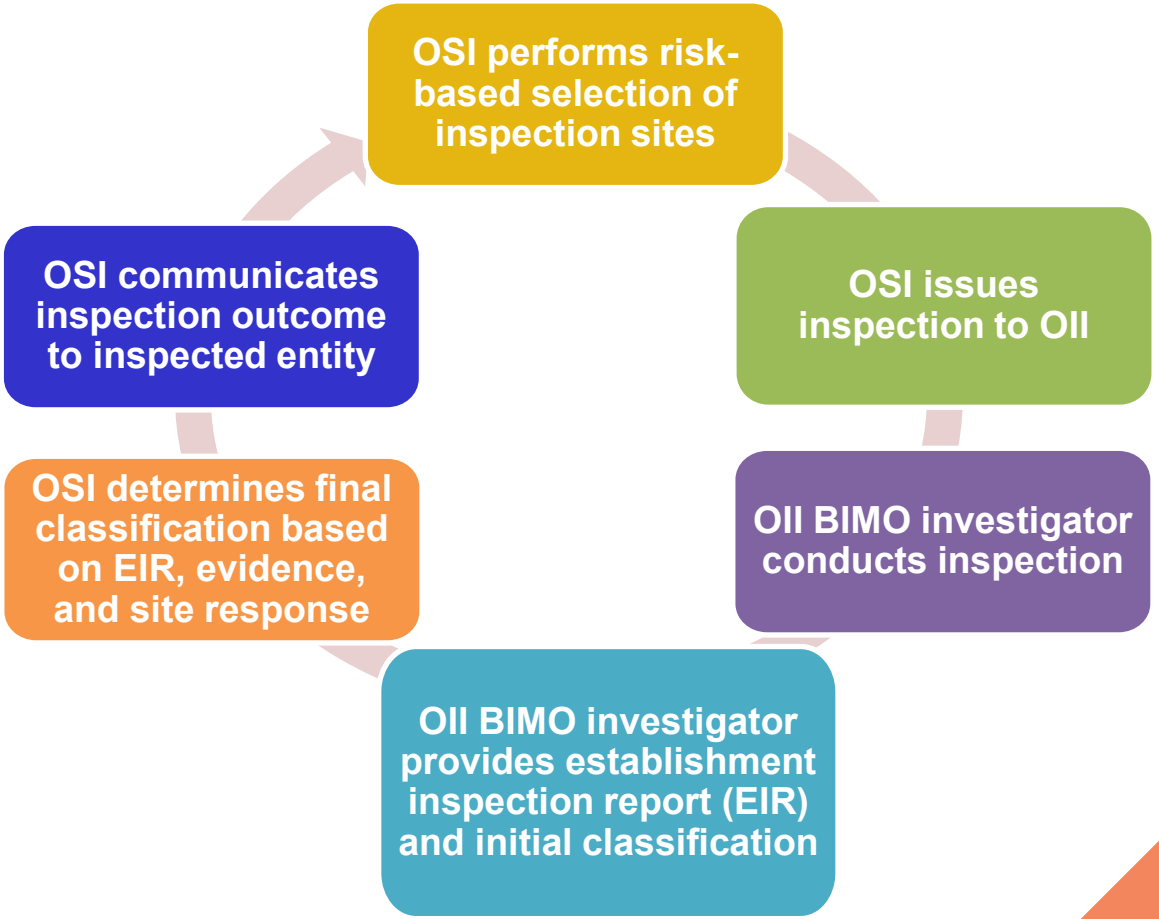
- OSI is in communication with OII before, during, and after the inspection
  - Ongoing or completed inspections may inform pending inspections
- OSI may participate in inspection as subject matter expert (SME)

GCP Compliance Review
Role of OSI

OSI Collaboration with Review Divisions

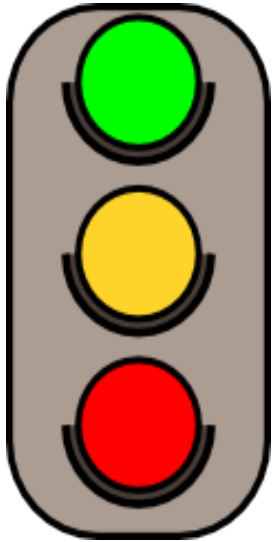
- OSI actively participates in NDA/BLA milestone meetings
- OSI communicates potentially significant inspection findings to review division *in real time*
  - Unblinding, under-reporting of significant AEs/SAEs, etc.
  - Follow up on data anomalies identified by review division
  - Depending on inspection findings
    - Additional CI sites may be inspected
    - Add sponsor and/or CRO inspection
    - Generate information requests to sponsor

GCP Inspection Process



Inspection Compliance Classifications

- No Action Indicated (NAI)
  - No objectionable conditions or practices
- Voluntary Action Indicated (VAI)
  - Objectionable conditions or practices
  - Not at threshold to take or recommend administrative or regulatory action
- Official Action Indicated (OAI)
  - Serious objectionable conditions found
  - Regulatory action recommended



Case Example

Case Example

- Randomized, double-blind, Phase 3 study
- Primary endpoint - change in a rating scale administered by an examining MD
  - 10 different domains assessed, each scored 0-6 based on severity
- Examining MD entered electronic clinical outcome assessment (eCOA) ratings into an eDevice during assessment

Case Example

- Per protocol, eCOA ratings were to be performed prior to the 3-hour investigational product (IP) IV infusion
- In case of eDevice malfunction, a paper backup process was in place

Case Example

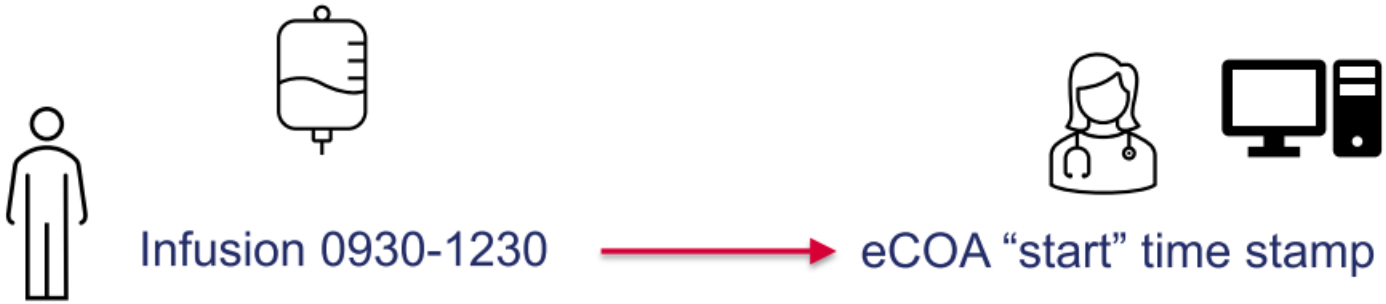
Examining MD assessment & data entry into eDevice

Investigational product administration over 3 hours

Case Example

IP administration over 3 hours

Data entry into eDevice



Infusion 0930-1230 → eCOA “start” time stamp 1245

Infusion 0940-1240 → eCOA “start” time stamp 1252

Case Example

- eCOA data entered after rather than prior to the 3-hour IP infusion
  - When was assessment performed?
  - Examining MD stated that assessment completed prior to infusion, no documentation
- No eDevice malfunction
- No paper source

Case Example

- CI stated data entered based on examining MD recall
  - eCOA involved 10 different domains assessed, each scored 0-6 based on severity
  - Ability to recall all ratings, for two or more subjects, to record in eDevice 3 hours or longer after assessment completed?

Case Example

- For some subjects, examining MD entered data into eDevice using different MD's username and login credentials
  - Importance of attribution
  - Examining MD was to be blinded with no access to subject data (e.g. AEs, labs)

Case Example

- CI inspection classified as VAI
- Impact on data reliability
  - OSI recommended sensitivity analysis
- CI and Sponsor responsibilities
    - Contemporaneous data entry
    - Not sharing login credentials

Challenge Questions

Challenge Question

When choosing CI sites for inspection, which of the following are NOT usually considered

A. Enrollment
B. Number of sub-investigators
C. Protocol deviations
D. Impact on efficacy variables

Challenge Question

Which FDA office conducts GCP inspections?

A. OND (Office of New Drugs)
B. OSE (Office of Surveillance and Epidemiology)
C. OII (Office of Inspections and Investigations)
D. OSI (Office of Scientific Investigations)

Summary

- The goal of GCP inspections is to provide assurance that the data are reliable and that the rights of trial participants are protected
- For NDA/BLA submissions, OSI collaborates with review divisions to choose sites for CI inspections
- OSI communicates inspection findings to the review division throughout the NDA/BLA review cycle and provides recommendations regarding data integrity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