Life after Official Action Indicated (OAI)

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U.S. Food and Drug Administration (FDA)

CDER Bioresearch Monitoring (BIMO) Good Clinical Practice (GCP) Compliance and Enforcement–
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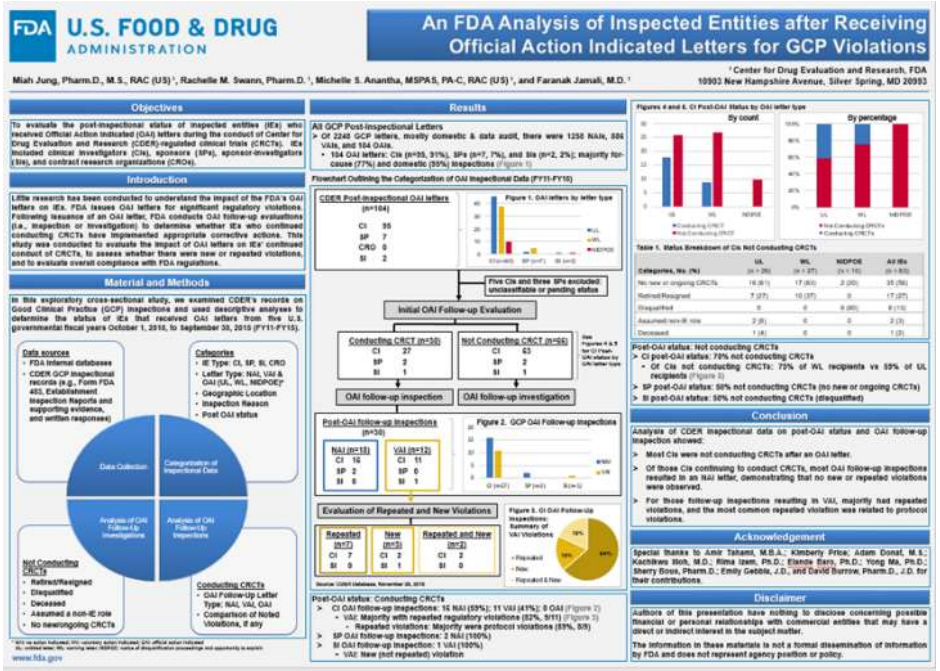

U.S. FOOD & DRUG ADMINISTRATION

An FDA Analysis of Inspected Entities after Receiving Official Action Indicated Letters for GCP Violations

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Objectives

To evaluate the post-inspectional status of inspected entities (IEs) who received Official Action Indicated (OAI) letters during the conduct of Center for Drug Evaluation and Research (CDER)-regulated clinical trials (CRCTs). IEs included clinical investigators (CIs), sponsors (SPs), sponsor-investigators (SIs), and contract research organizations (CROs).

Introduction

Little research has been conducted to understand the impact of the FDA's OAI letters on IEs. FDA issues OAI letters for significant regulatory violations. Following issuance of an OAI letter, FDA conducts OAI follow-up evaluations (i.e., inspection or investigation) to determine whether IEs who continued conducting CRCTs have implemented appropriate corrective actions. This study was conducted to evaluate the impact of OAI letters on IEs' continued conduct of CRCTs, to assess whether there were new or repeated violations, and to evaluate overall compliance with FDA regulations.

Material and Methods

In this exploratory cross-sectional study, we examined CDER's records on Good Clinical Practice (GCP) inspections and used descriptive analyses to determine the status of IEs that received OAI letters from five U.S. governmental fiscal years October 1, 2010, to September 30, 2015 (FY11-FY15).

Data sources
- FDA internal databases
- CDER GCP inspectional records (e.g., Form 483, Establishment Inspection Reports and supporting evidence, and written responses)

Categories
- IE Type: CI, SP, SI, CRO
- Letter Type: NAI, VAI & OAI (UL, WL, NIDPOE)*
- Geographic Location
- Inspection Reason
- Post-OAI status

Not Conducting CRCTs
- Retired/Resigned
- Disqualified
- Deceased
- Assumed a non-IE role
- No new/ongoing CRCTs

Conducting CRCTs
- OAI Follow-Up Letter Type: NAI, VAI, OAI
- Comparison of Noted Violations, if any

Results

All GCP Post-Inspectional Letters
- Of 2248 GCP letters, mostly domestic & data audit, there were 1258 NAIs, 886 VAIs, and 104 OAIs.
  - 104 OAI letters: CIs (n=93, 91%), SPs (n=7, 7%), and SIs (n=2, 2%); majority for-cause (77%) and domestic (89%) inspections (Figure 1).

Flowchart Outlining the Categorization of OAI Inspectional Data (FY11-FY15)

CDER Post-Inspectional OAI Letters (n=104): CI 93, SP 7, CRO 0, SI 2

Figure 1. OAI letters by letter type

Five CIs and three SPs excluded: unclassifiable or pending status

Initial OAI Follow-up Evaluation

Conducting CRCT (n=10): CI 27, SP 2, SI 1

Not Conducting CRCT (n=66): CI 63, SP 2, SI 1

OAI follow-up inspection

OAI follow-up investigation

Post-OAI follow-up inspections (n=30)

NAI (n=18): CI 16, SP 2, SI 0

VAI (n=12): CI 11, SP 0, SI 1

Figure 2. GCP OAI Follow-up Inspections

Evaluation of Repeated and New Violations

Repeated (n=7): CI 7, SI 0

New (n=5): CI 2, SI 1

Repeated and New (n=2): CI 2, SI 0

Figure 3. CI OAI Follow-Up Inspections: Summary of VAI Violations (Repeated, New, Repeated & New)

Post-OAI status: Conducting CRCTs
- CI OAI follow-up inspections: 16 NAI (89%); 11 VAI (41%); 0 OAI (Figure 2)
  - VAI: Majority with repeated regulatory violations (82%, 9/11) (Figure 3)
    - Repeated violations: Majority were protocol violations (89%, 8/9)
- SP OAI follow-up inspections: 2 NAI (100%)
- SI OAI follow-up inspection: 1 VAI (100%)
  - VAI: New (not repeated) violation

Figures 4 and 5. CI Post-OAI Status by OAI letter type

By count / By percentage

Table 1. Status Breakdown of CIs Not Conducting CRCTs

Categories, No. (%)	UL (n = 26)	WL (n = 37)	NIDPOE (n = 10)	All IEs (n = 93)
No new or ongoing CRCTs	16 (61.5)	17 (46)	2 (20)	35 (38)
Retired/Resigned	7 (27)	10 (27)	0	17 (27)
Disqualified	0	0	0 (0)	0 (1.1)
Assumed non-IE role	2 (8)	0	0	2 (2)
Deceased	1 (4)	0	0	1 (2)

Post-OAI status: Not conducting CRCTs
- CI post-OAI status: 70% not conducting CRCTs
  - Of CIs not conducting CRCTs: 75% of WL recipients vs 55% of UL recipients (Figure 5)
- SP post-OAI status: 50% not conducting CRCTs (no new or ongoing CRCTs)
- SI post-OAI status: 50% not conducting CRCTs (disqualified)

Conclusion

Analysis of CDER inspectional data on post-OAI status and OAI follow-up inspection showed:
- Most CIs were not conducting CRCTs after an OAI letter.
- Of those CIs continuing to conduct CRCTs, most OAI follow-up inspections resulted in an NAI letter, demonstrating that no new or repeated violations were observed.
- For those follow-up inspections resulting in VAI, majority had repeated violations, and the most common repeated violation was related to protocol violations.

Acknowledgement

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ORIGINAL RESEARCH

An FDA Analysis of Inspected Entities After Receiving Official Action Indicated Letters for Good Clinical Practice Violations

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Abstract

Background Limited research has been conducted to examine whether clinical investigators (CIs), sponsors (SPs), contract research organizations (CROs), and sponsor-investigators (SIs) continue conducting clinical trials following issuance of FDA Official Action Indicated (OAI) letters. FDA issues OAI letters for significant regulatory violations. The objective of this study was to evaluate the status of inspected entities who received OAI letters in the conduct of Center for Drug Evaluation and Research (CDER)-regulated clinical trials (CRCTs).

Methods This cross-sectional study included an analysis of inspectional data from CDER's Good Clinical Practice (GCP) inspections for OAI letters issued from October 1, 2010, to September 30, 2015, with an in-depth analysis of post-OAI status of inspected entities, including OAI follow-up inspections.

Results Of the 2248 GCP letters issued during this period, 104 (4.6%) OAI letters were sent: 95 (4.2%) to CIs (91% of OAIs), 7 (6.3%) to SPs (7% of OAIs), and 2 (0.08%) to SIs (2% of OAIs). Majority of OAI letters were issued as a result of a for-cause inspection. Five CIs were excluded from analysis. No OAI letters were sent to CROs. Only 30% of CIs (27 out of 90) continued to conduct CRCTs. OAI follow-up inspections were completed for these CIs resulting in 16 No Action Indicated (NAI), 11 Voluntary Action Indicated (VAI), and no OAI letters. Majority (64%) of the VAI letters noted repeated but not significant violations.

Conclusions Majority (70%) of CIs who received an OAI letter were no longer conducting CRCTs at the time of follow-up. Of the 27 CIs continuing CRCTs, 16 (59%) OAI follow-up inspections resulted in NAI classifications and 11 (41%) in VAI.

Keywords Bioresearch Monitoring (BIMO) · Clinical investigator · Form FDA 483 · Good Clinical Practice compliance · Inspection · Sponsor

The views and opinions expressed in this presentation are those of the authors and do not necessarily represent the views or policies of Food and Drug Administration or its staff, per 21 CFR 50.85(k).

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Abbreviations

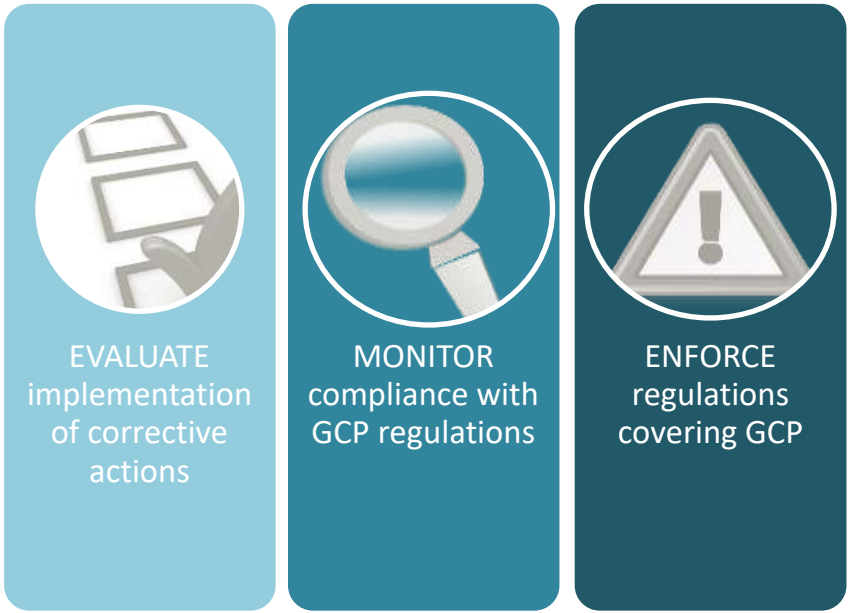
21 CFR	Title 21 of United States Code of Federal Regulations
BIMO	Bioresearch Monitoring
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	Clinical Investigator
CRCT	CDER-Regulated Clinical Trial
CRO	Contract Research Organization
EIR	Establishment Inspection Report
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
IE	Inspected Entity
IND	Investigational New Drug Application
NAI	No Action Indicated
NDA	New Drug Application

https://link.springer.com/content/pdf/10.1007/s43441-021-00267-y.pdf

Overview

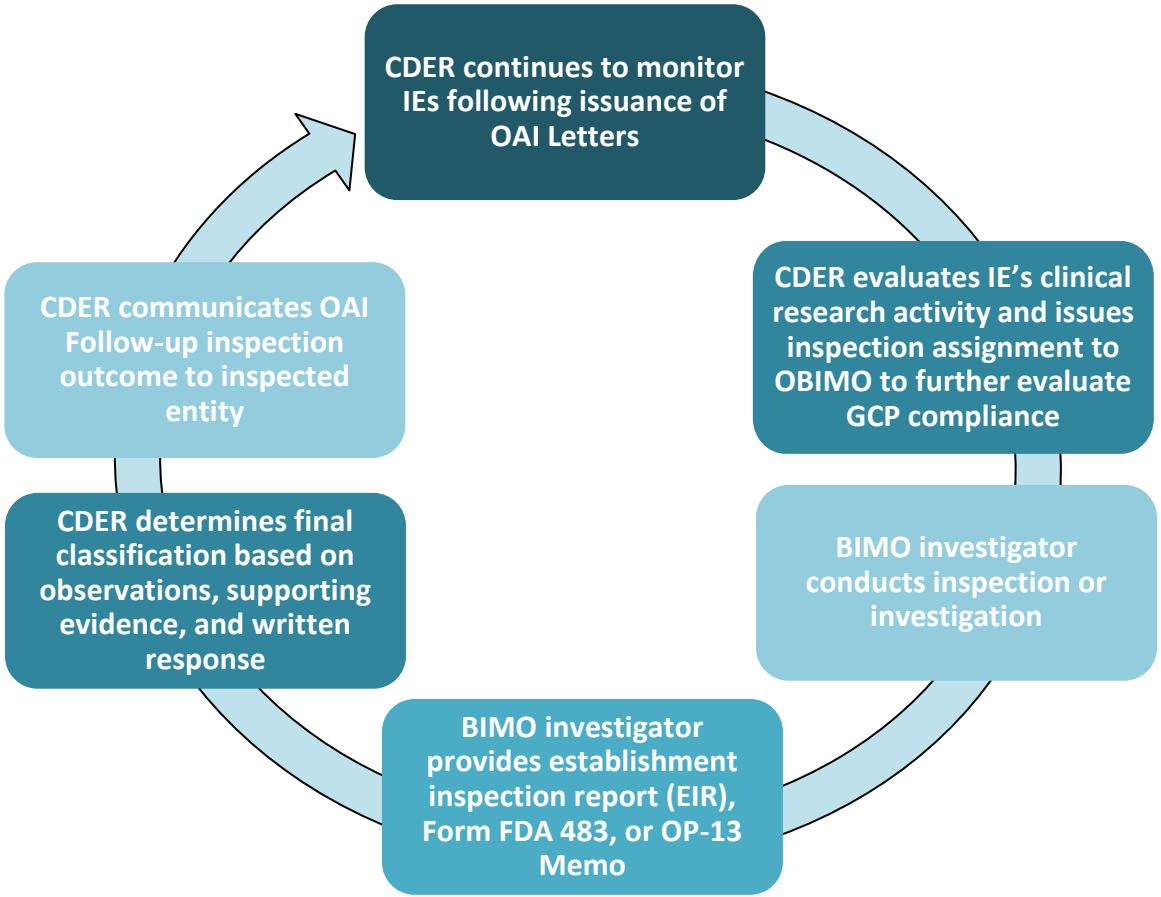
- **OAI Follow-up Objectives, Process & Procedures**
- OAI Follow-up Research – Purpose, Design & Methods
- OAI Follow-up Research – Metrics, Trends & Outcomes
- OAI Follow-up Case Examples
- Conclusions & Questions

OAI Follow-Up Objectives



- OAI follow-up inspections or investigations of inspected entities (IEs)
- Post-OAI compliance
  - Corrective actions
  - Repeat or new regulatory violations

OAI Follow-Up Process



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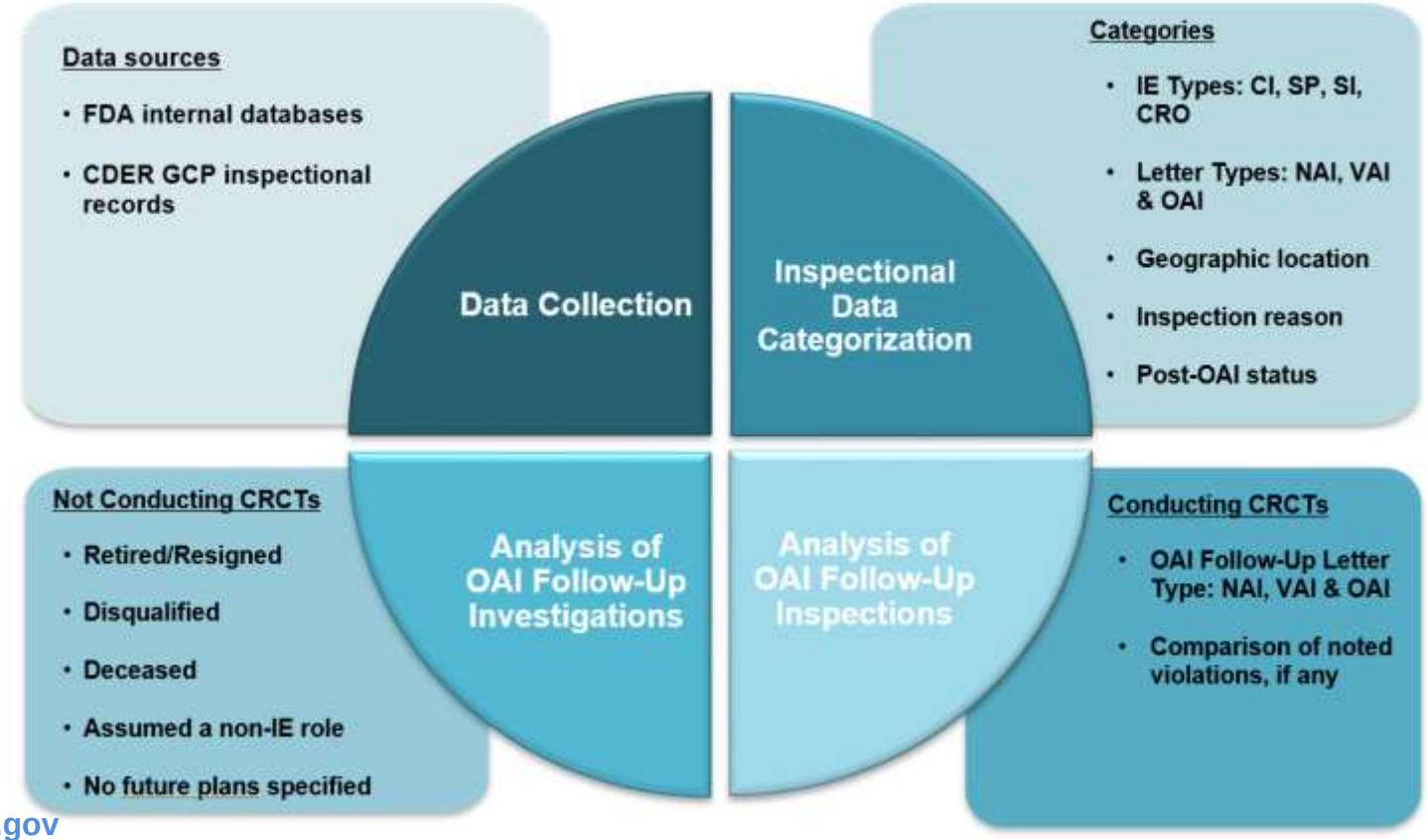
OAI Follow-Up Research Purpose

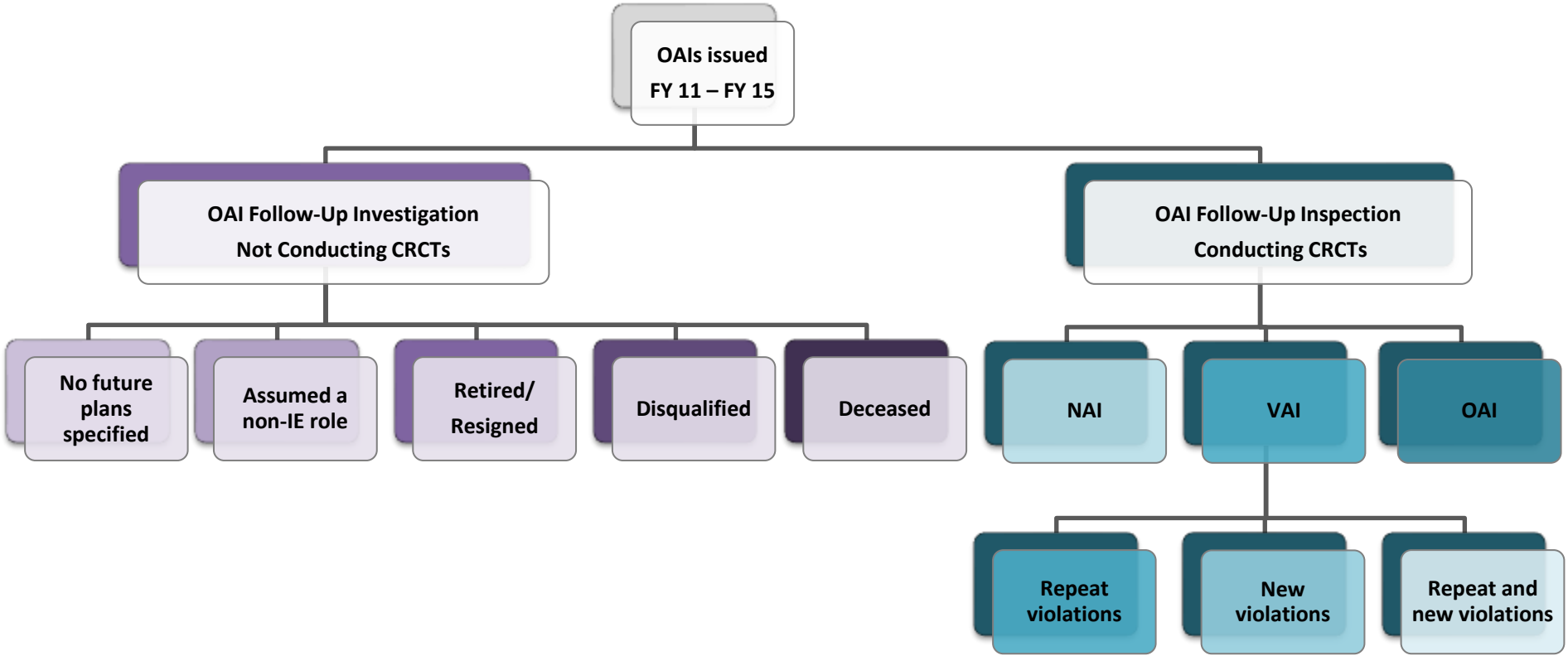
- Analysis of post-OAI inspectional status of inspected entities (IEs) for CDER-regulated clinical trials (CRCTs)
  - Clinical Investigators (CI)
  - Sponsors (Sp)
  - Sponsor-investigators (SI)
  - Contract research organizations (CRO)

OAI Follow-Up Research Study Design & Methods



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

OAI Follow-Up Research Analysis



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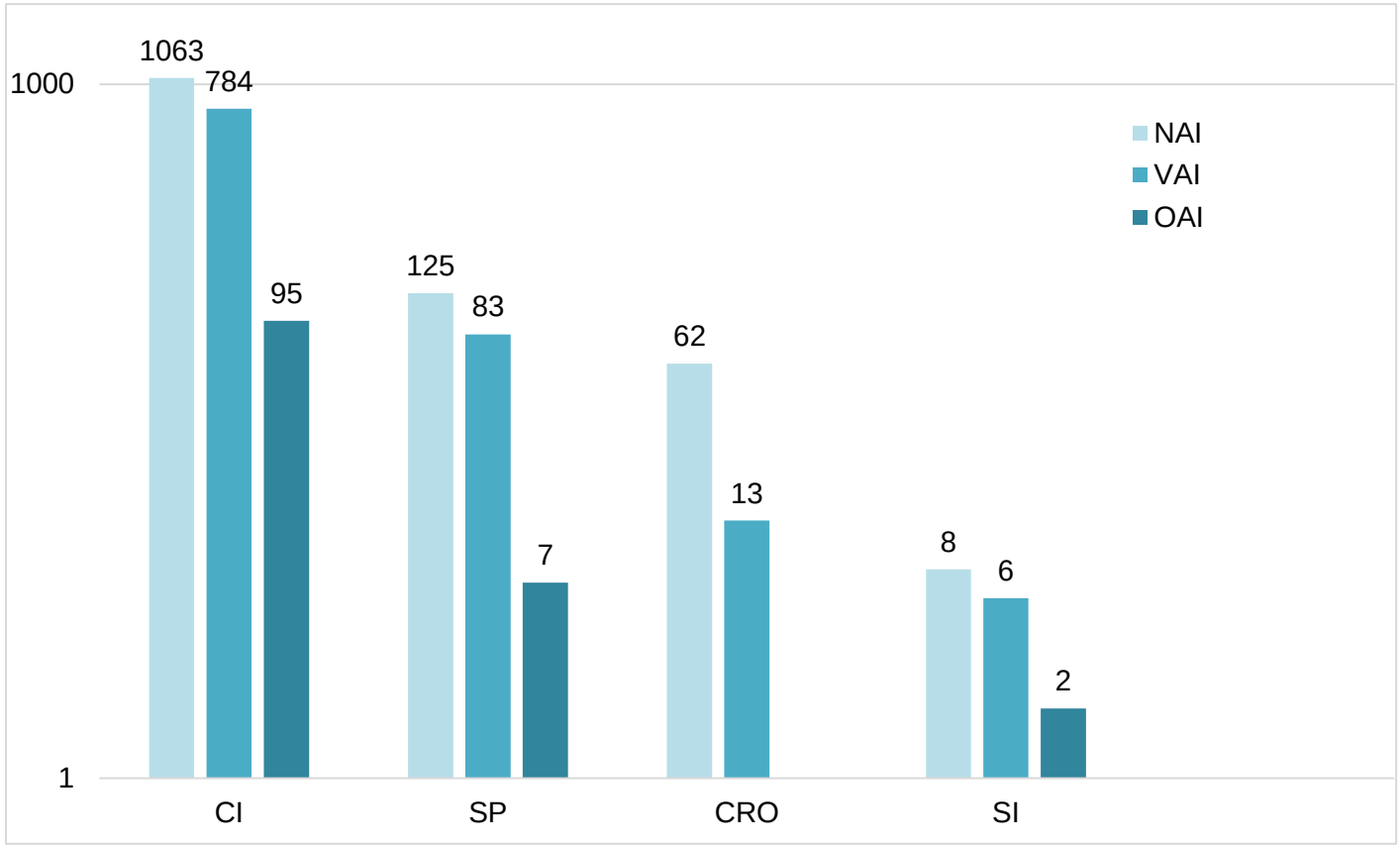
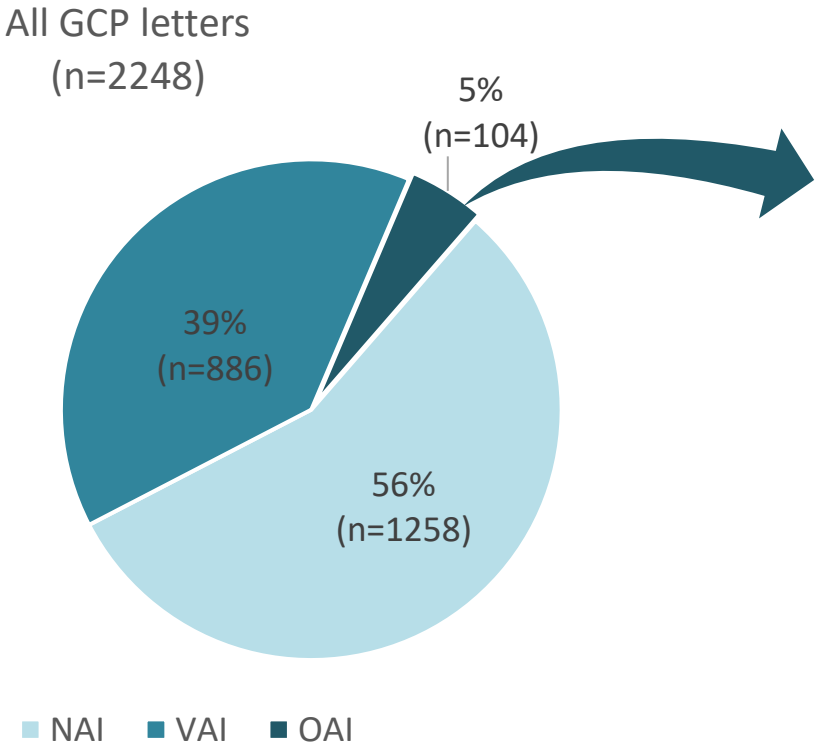
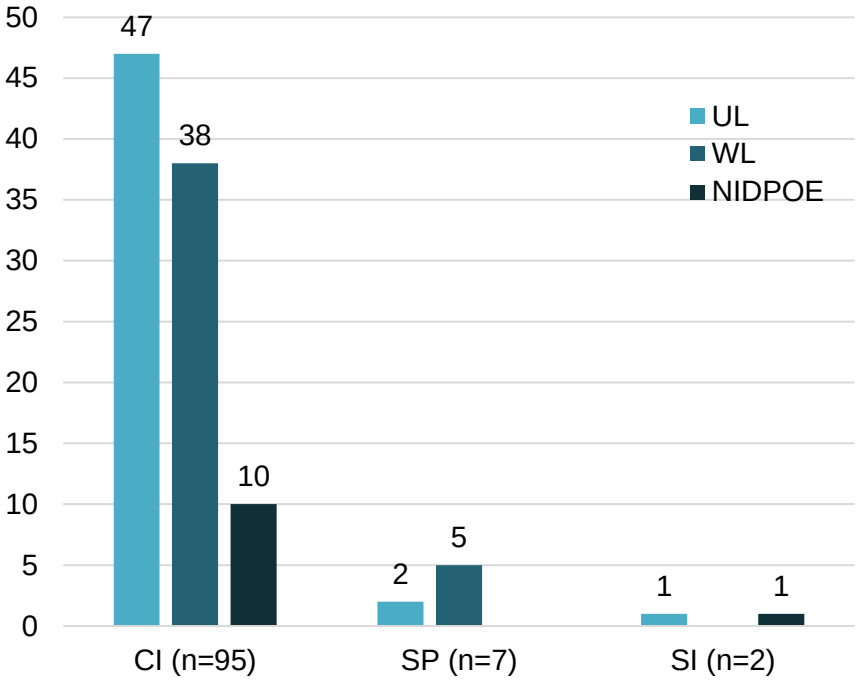
OAI Follow-Up Research Metrics & Results
Post-Inspectional Letters: All IEs FY11 – FY15



OAI Follow-Up Research Metrics & Results

Post-Inspectional Letter Classifications & IE Type: FY11 – FY15

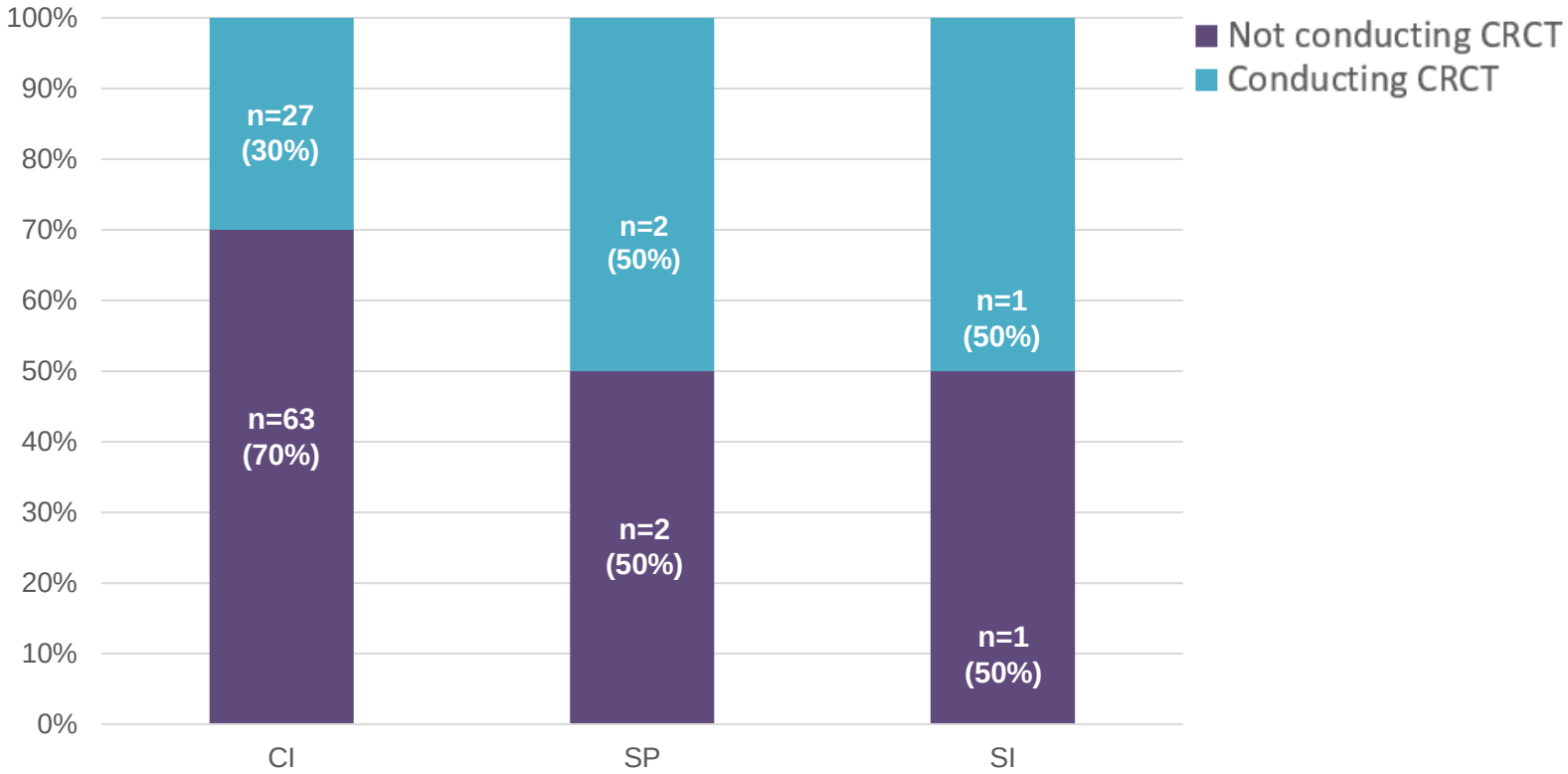




UL: Untitled Letter
WL: Warning Letter
NIDPOE: Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

OAI Follow-Up Research Metrics & Results‡

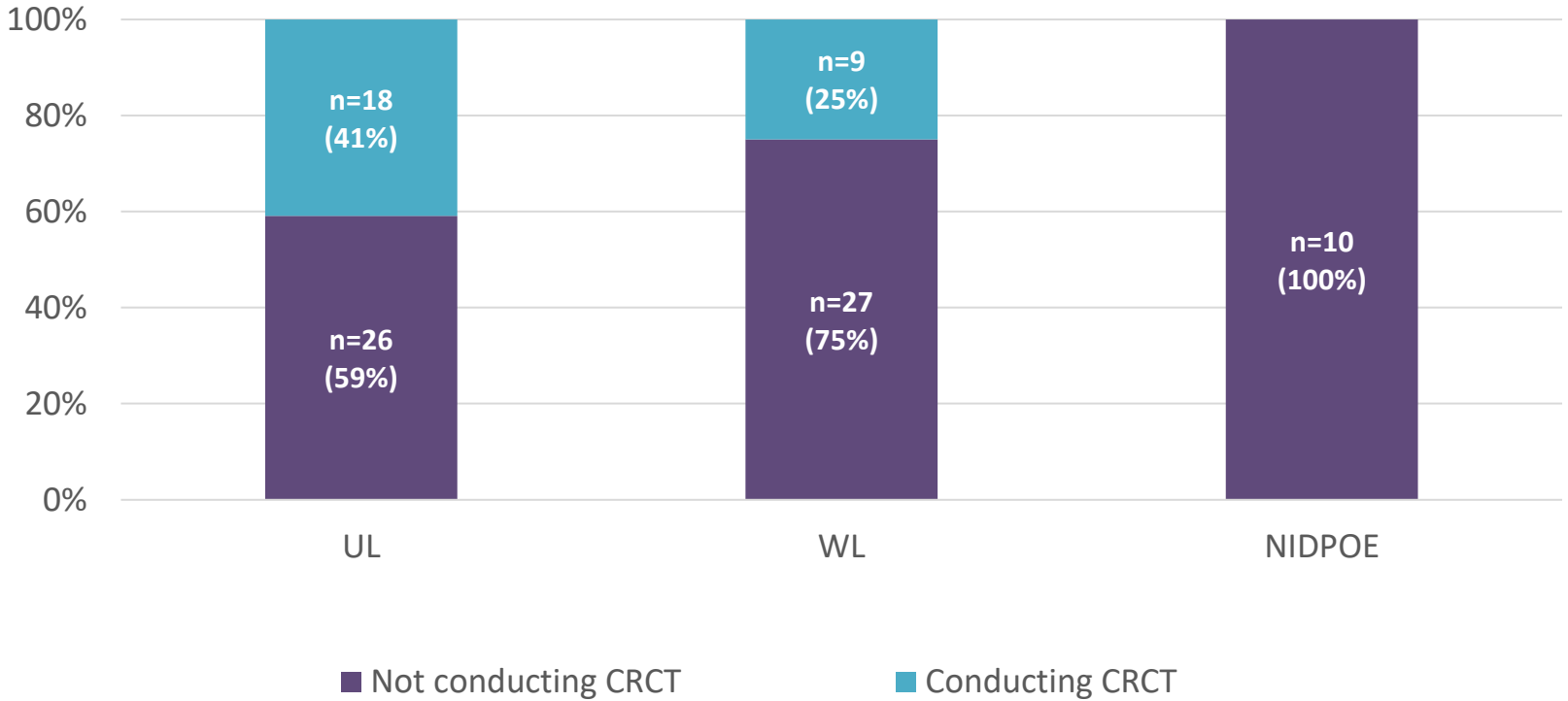
Post-OAI Status: All IEs FY11 – FY15



‡Data cut-off was November 28, 2018. Therefore, five CIs and three SPs whose status was unconfirmed by follow-up inspection or were undergoing ongoing evaluation by this date were excluded from OAI follow-up analysis

OAI Follow-Up Research Metrics & Results‡

Post-OAI Status: CI FY11 – FY15

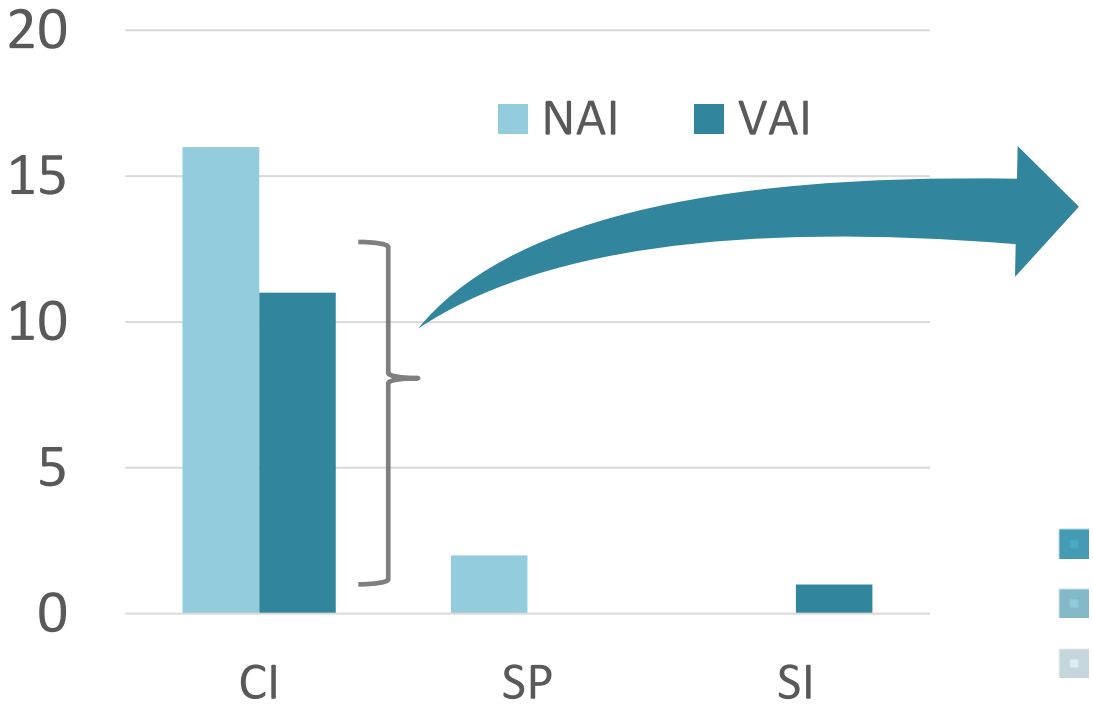


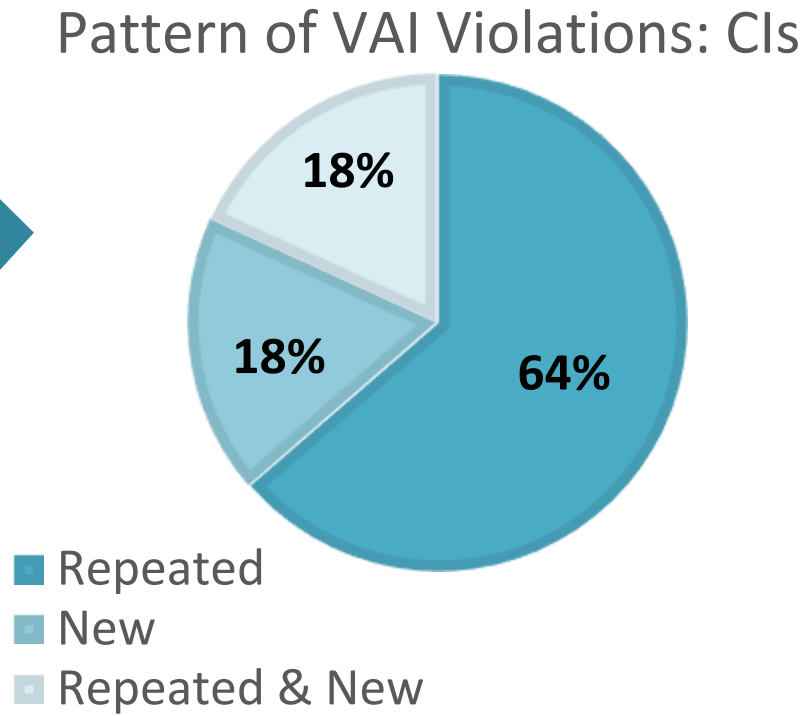
‡Data cut-off was November 28, 2018. Therefore, five CIs and three SPs whose status was unconfirmed by follow-up inspection or were undergoing ongoing evaluation by this date were excluded from OAI follow-up analysis

OAI Follow-Up Research Metrics & Results: Post-OAI Status of CIs Not Conducting CRCTs Status Breakdown: FY11 – FY15

Categories	UL (No, %)	WL (No, %)	NIDPOE (No, %)	Total (No, %)
No future plans specified	16 (61)	17 (63)	2 (20)	35 (56)
Retired/Resigned	7 (27)	10 (37)	0	17 (27)
Disqualified	0	0	8 (80)	8 (13)
Assumed non-IE role	2 (8)	0	0	2 (3)
Deceased	1 (4)	0	0	1 (2)
Total	26	27	10	63

OAI Follow-Up Research Metrics & Results
Post-OAI Inspection Outcomes FY11 – FY15





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OAI Follow-Up: Case Examples

Sample Case Studies

OAI Follow-Up Case Example #1 - CI

2015 OAI WL

- 21 CFR 312.60 protocol violations; 21 CFR 312.62(b) recordkeeping violations
- CI proposed CAPA: eligibility checklist creation, SOP development, and training

2016 OAI Follow-up Inspection

- CI continued conducting CRCTs for long-term follow-up studies post-OAI WL
- Follow-up inspection did not result in any observed regulatory violations

OAI Follow-Up Final Classification

- NAI classification – no regulatory violations

SAE: Serious Adverse Events; **CAPA**: Corrective and Preventive Actions; **SOP**: Standard Operating Procedures

OAI Follow-Up Case Example #2 - CI

2015 OAI UL

- 21 CFR 312.60 protocol violations
- CI proposed CAPA – protocol and GCP training

2016 OAI Follow-up Inspection

- CI continued conducting CRCTs post-OAI UL
- Follow-up inspection noted repeat violations, including protocol assessments not completed and discrepant case report forms

OAI Follow-Up Final Classification

- VAI classification – repeat violations noted but not significant
- CI implemented corrective actions to prevent recurrence of inspectional findings

OAI Follow-Up Case Example #3 - SP

2014 OAI WL

- 21 CFR 312.2(a), 312.20(a), 312.40(a) and (b), 312.56(a) for failure to submit an IND; 312.50 & 312.56(a) for failure to ensure proper monitoring
- Sponsor proposed CAPA – IND submission; SOP monitoring implementation

2017 OAI Follow-up Inspection

- Sponsor study still active post-OAI WL
- Follow-up inspection did not result in any observed regulatory violations

OAI Follow-Up Final Classification

- NAI classification – no regulatory violations

OAI Follow-Up Case Example #4 - CI

2014 OAI UL

- 21 CFR 312.62(b) recordkeeping violations
- CI CAPA– GCP training, revised SOPs, and utilization of quality control management

2015 OAI Follow-up Inspection

- CI continued conducting CRCTs post-OAI UL
- Follow-up inspection confirmed SOPs and GCP training implemented post-OAI UL; however, new violations noted for failure to assure continuing IRB review and approval

OAI Follow-Up Final Classification

- VAI classification – new violations noted but minimal impact
- CI implemented CAPA including submission of revised IRB questionnaire noting 2014 FDA Form 483. CI implemented revised SOPs and IRB reporting requirement training to prevent repeat violations

Challenge Question

Most CIs who were not conducting CRCTs following issuance of an OAI were disqualified CIs?

A. True

B. False

Summary

- Majority of CIs did not continue to conduct CRCTs post-OAI
- Most CI OAI follow-up inspections resulted in NAI
- Majority of CI VAIs noted repeated but not significant violations
- Most repeated regulatory violations were related to procedural noncompliance
- No OAI follow-up inspections resulted in OAI

Key Takeaway Points

- Promote and protect the public health by ensuring safe and effective drugs reach the public
- Monitor and take enforcement action for noncompliant inspected entities
- Share inspectional data and trends

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Questions?

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Abbreviations

BIMO: Bioresearch Monitoring

CDER: Center for Drug Evaluation and Research

CFR: Code of Federal Regulations

CI: Clinical Investigator

CRCT: CDER-Regulated Clinical Trial

CRO: Contract Research Organization

EIR: Establishment Inspection Report

FDA: Food and Drug Administration

GCP: Good Clinical Practice

IE: Inspected Entity

IND: Investigational New Drug Application

NAI: No Action Indicated

NIDPOE: Notice of Initiation of Disqualification Proceedings and Opportunity to Explain

OAI: Official Action Indicated

OSI: Office of Scientific Investigations

SI: Sponsor-Investigator

SP: Sponsor

UL: Untitled Letter

VAI: Voluntary Action Indicated

WL: Warning Letter


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