BIMO Inspections of Device Sponsors

FDA Small Business Regulatory Education for Industry (REdI)

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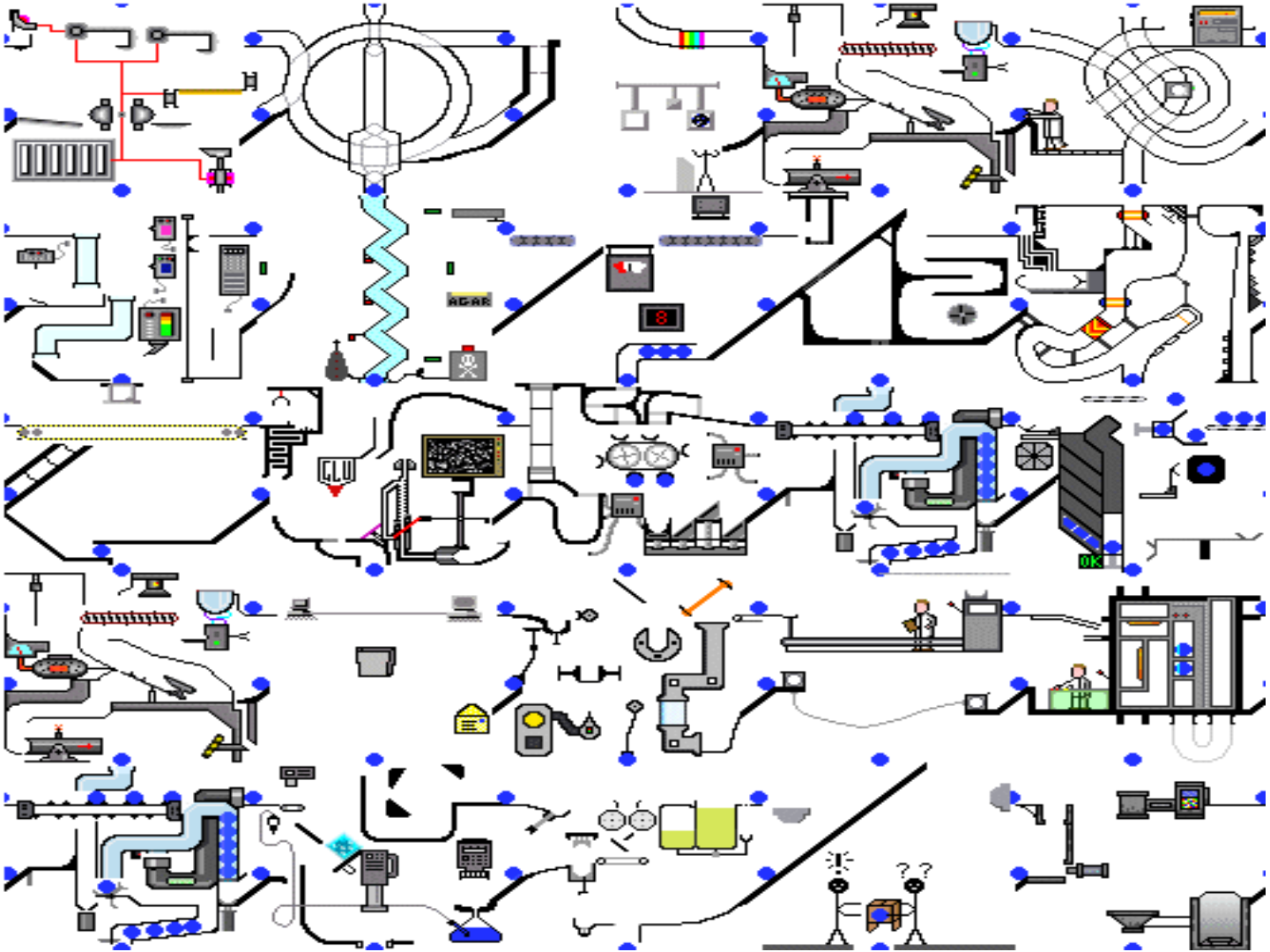
Adam Donat, JD, MS

Deputy Director
Division of Clinical Science and Quality
Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration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Learning Objectives

- Identify the roles and responsibilities of sponsors
- Describe what to expect during an inspection
- Discuss common inspection finding and tips for the conduct of a high-quality study

Roles and Responsibilities of Sponsors

Roles and Responsibilities

Sponsor – 812.3(n)

- A person who initiates, but who does not actually conduct, the investigation.
- The regulations indicate that the investigational device is administered, dispensed, or used under the immediate direction of another individual.

Roles and Responsibilities

Clinical Investigator – 812.3(i)

- An individual who actually conducts a clinical investigation, under whose immediate direction the test article is administered, dispensed, or used.

Note: The terms investigator, principal investigator, clinical investigator, and acronym CI are sometimes used interchangeably.

Roles and Responsibilities

Sponsor-Investigator – 812.3(o)

- Dual Role: An individual who both initiates and actually conducts the study.
- Obligations under Part 812 include those of an investigator and sponsor

Summary of Sponsor Responsibilities

General Responsibilities – 812.40

- Select qualified investigators, ensure proper monitoring, submit IDE to FDA

Records – 812.140(b)

- Maintain records of correspondence, device shipment and disposition, ADEs and complaints

Summary of Sponsor Responsibilities

Inspections – 812.145

- Allow FDA access to establishment, allow inspection of records

Reports – 812.150(b)

- Reporting of UADEs, withdrawal of IRB approval, progress reports

Summary of CI Responsibilities

General Responsibilities – 812.100

- Follow investigational plan and FDA regulations, protect subject safety, obtain informed consent

Specific Responsibilities – 812.110

- Await IRB and FDA approval, supervise device use, provide financial disclosure

Summary of CI Responsibilities

Records – 812.140(a)

- Maintain records of correspondence, device accountability, subjects' case histories, consent

Inspections – 812.145

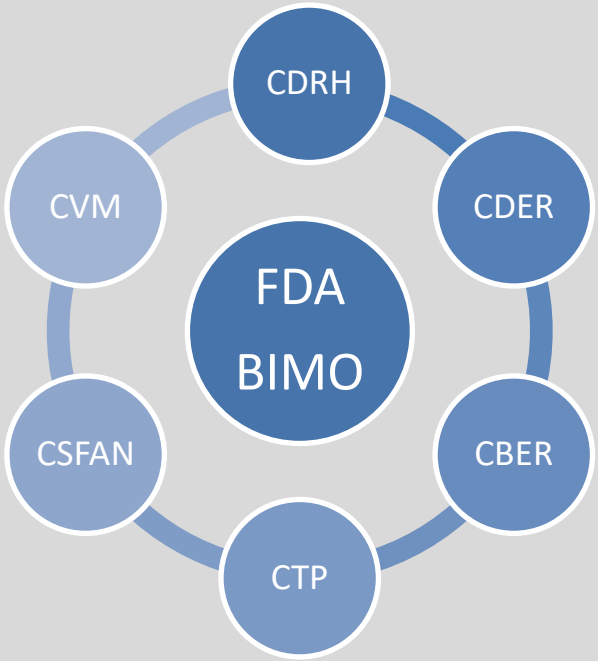
- Allow FDA access, inspection of documents and subject records

Reports – 812.150(a)

- Withdrawal of IRB approval, protocol deviations, UADEs

Bioresearch Monitoring (BIMO)

- What is the BIMO Program?



BIMO Objectives

- Protect rights, safety, and welfare of human research subjects
- Verify accuracy, reliability, and integrity of clinical and non-clinical trials data submitted to FDA
- Assess compliance with FDA's regulations governing conduct of clinical and non-clinical trials

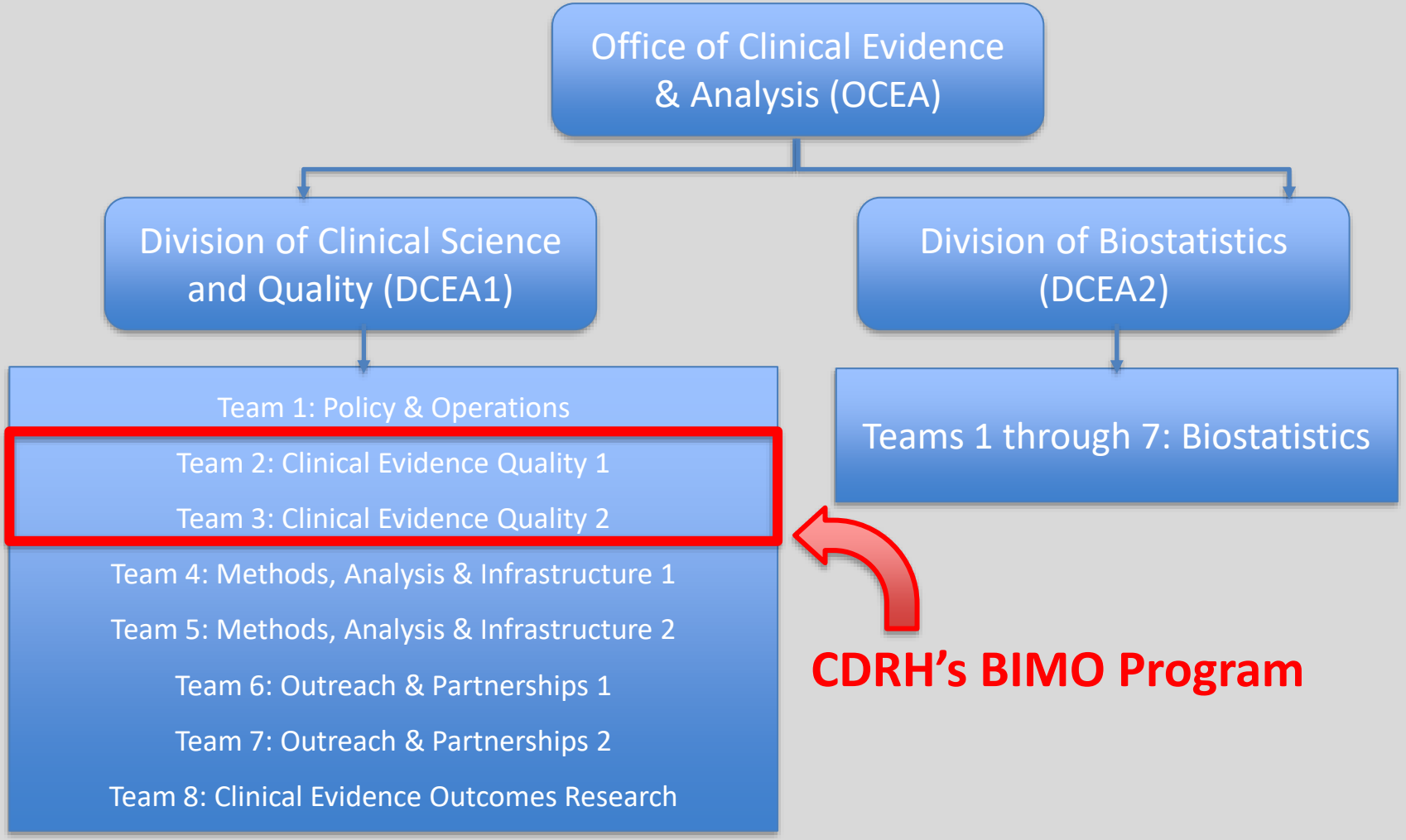
BIMO Regulations

Medical Devices

- 21 CFR 812: Investigational Device Exemption (IDE)

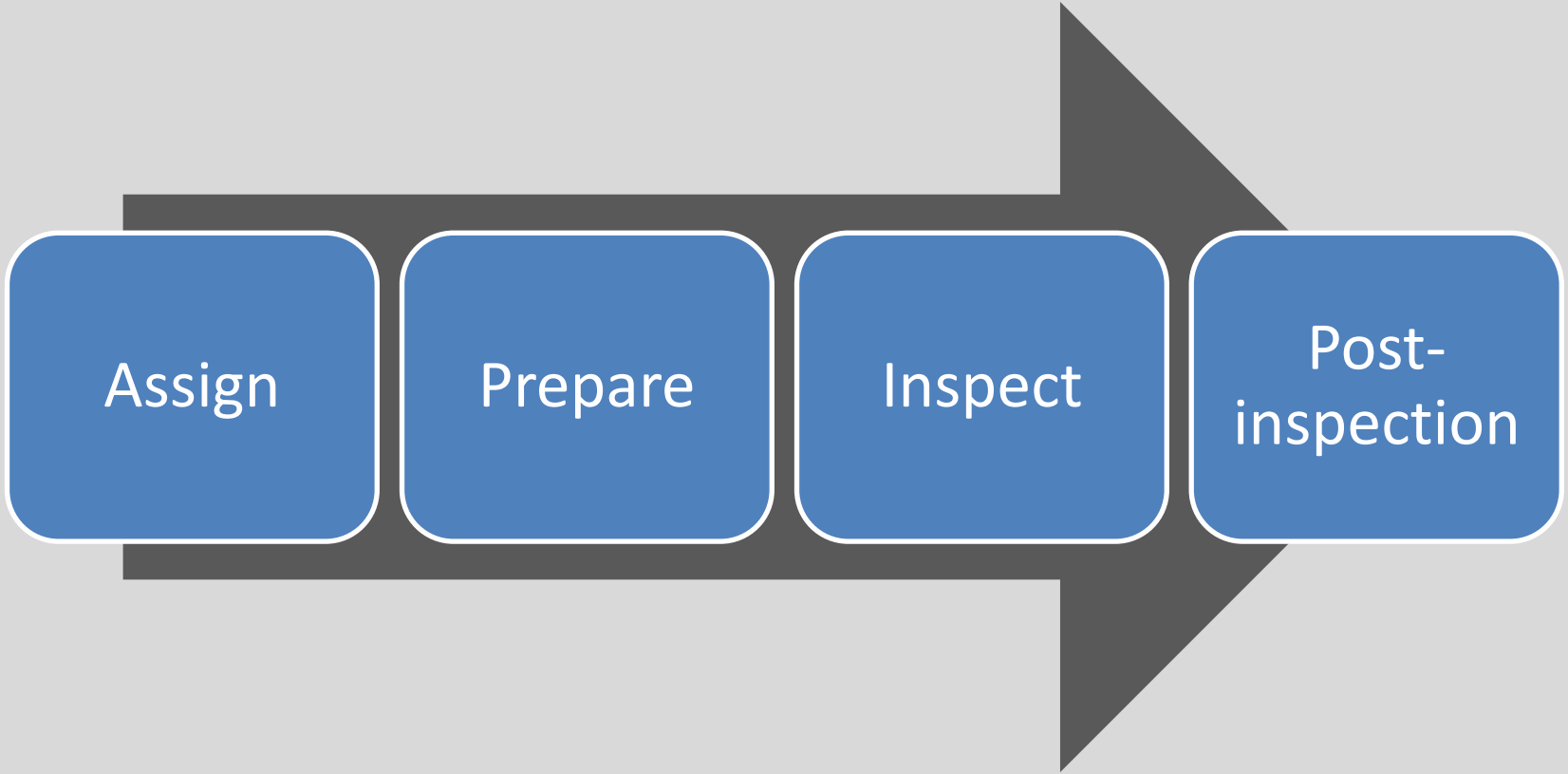
FDA-Wide

- 21 CFR 50: Protection of Human Subjects
- 21 CFR 54: Financial Disclosure
- 21 CFR 56: Institutional Review Boards
- 21 CFR 58: Good Laboratory Practice for Non-Clinical Laboratory Studies


Office of Clinical Evidence & Analysis (OCEA)
Division of Clinical Science and Quality (DCEA1)
Division of Biostatistics (DCEA2)
Team 1: Policy & Operations
Team 2: Clinical Evidence Quality 1
Team 3: Clinical Evidence Quality 2
Team 4: Methods, Analysis & Infrastructure 1
Team 5: Methods, Analysis & Infrastructure 2
Team 6: Outreach & Partnerships 1
Team 7: Outreach & Partnerships 2
Team 8: Clinical Evidence Outcomes Research
Teams 1 through 7: Biostatistics
CDRH's BIMO Program

What Happens During an Inspection

BIMO Inspection Process



Prepare for BIMO Inspection

Center

- Send inspection assignment to District Office

District

- *Usually* call inspection site 3-5 days in advance to pre-announce

Site

- Prepare staff
- Ensure all required records are available

Inspection Review of Records

- Study protocol and revisions
- Informed consent versions
- Subject records (medical records, case report forms)
- Progress reports (adverse events, protocol deviations)
- Monitoring logs

Inspection Review of Records

- Clinical investigator agreement
- Study procedures
- Device accountability records
- Financial disclosure, Form FDA 3454
- Correspondence between sponsor, IRB, CIs, FDA

Post-Inspection Next Steps

Site

- Discuss inspection findings or receive FDA Form 483
- Respond to FDA Form 483 with corrective action plan

District

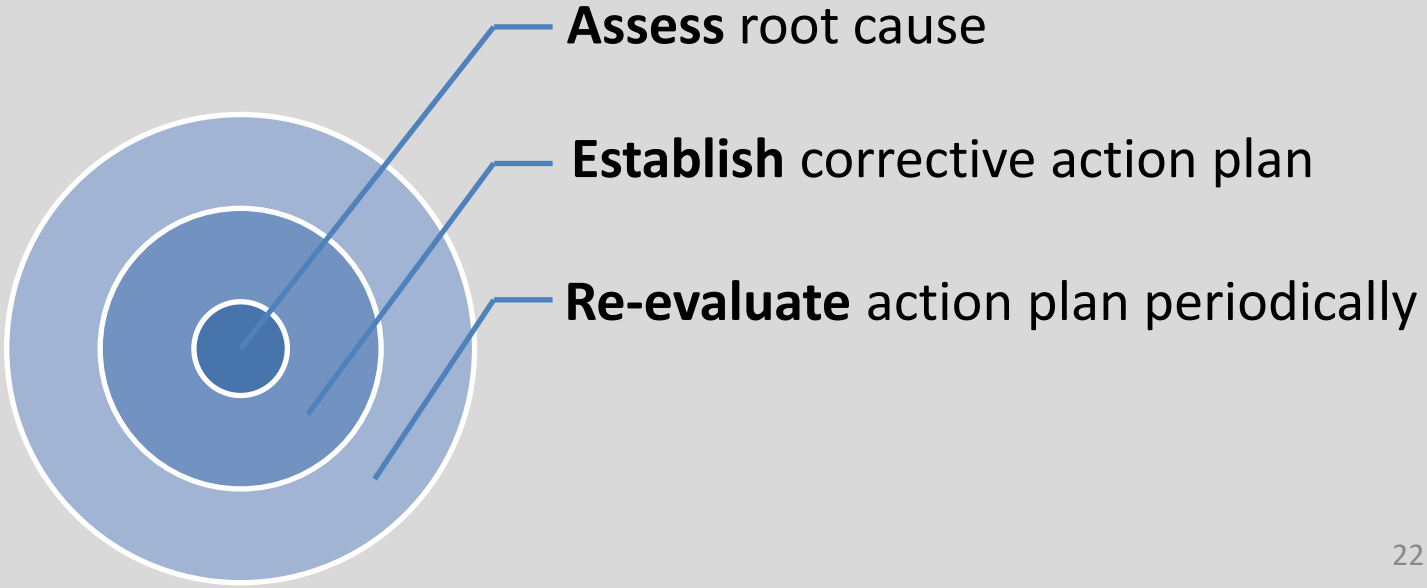
- Complete an Establishment Inspection Report (EIR)

Center

- Review EIR and FDA Form 483 to determine final classification
- Send post-inspection letter to site
- Communicate inspection findings to premarket review team

Response to 483 Observations

- **If an FDA Form 483 is issued at end of inspection:**
  - Consider providing a written response for each observation:



Example of An Inadequate Response

Form FDA 483 Citation:

- **Failure to secure the investigator's compliance with the signed investigator agreement, the investigational plan, applicable FDA regulations, and any other conditions of approval imposed by the reviewing Institutional Review Board (IRB) or FDA. [21 CFR 812.46(a)]**
  - You failed to secure investigator compliance with the investigational plan and applicable FDA regulations.

Inadequate Response

- *"…virtually all of the serious documentation problems appear to have been the work of a single research coordinator who was delinquent in fulfilling her assigned study duties."*

Example: Acceptable Response

Failure to follow the investigational plan

Response: *"We have now prepared and adopted a formal written procedure that will help us and our staff to assure compliance with written study protocols and the obligations we accept as clinical investigators for FDA-regulated trials. A copy of the approved SOP is attached. We have reviewed this new procedure at a meeting held on ___ with all research staff (attendance sign-in sheet attached). After 3 months, this corrective action will be evaluated for effectiveness."*

Knowledge Check

FDA regulations require a sponsor to respond to an FDA Form 483?

True / False

BIMO Inspection Findings and Tips

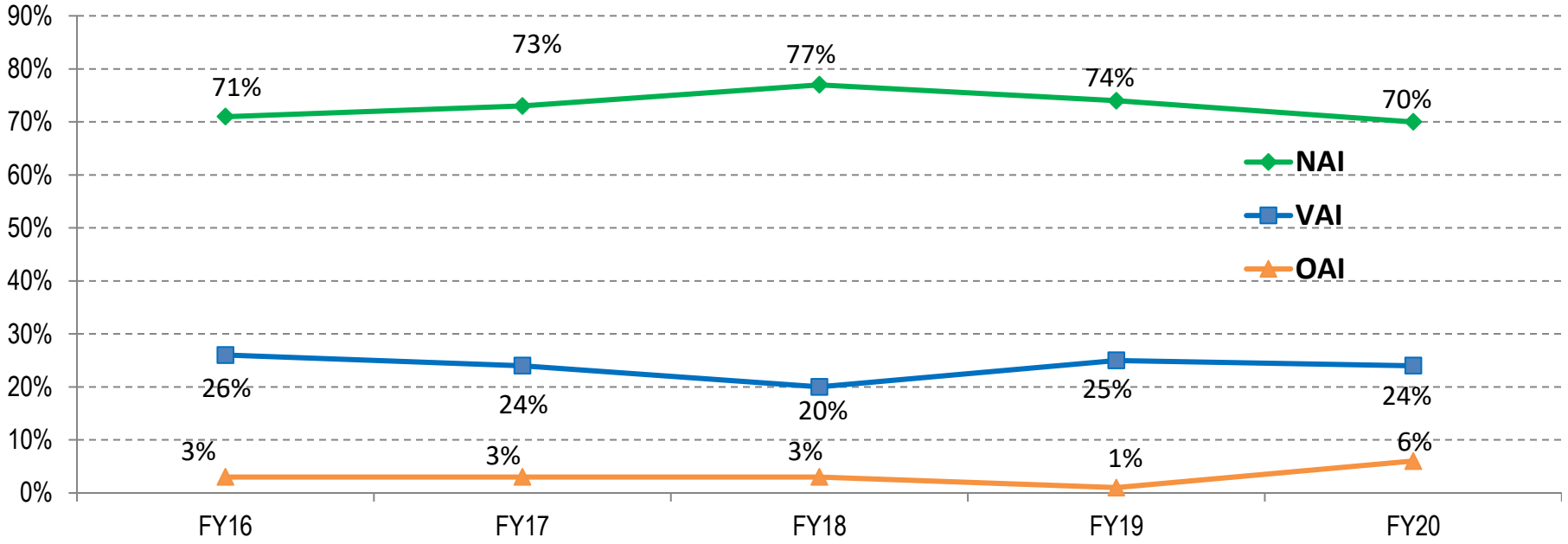
Inspections Classified FY16 to FY20

	FY16	FY17	FY18	FY19	FY20
Sponsor	48	47	53	38	13
CI	198	199	227	132	110
IRB	35	35	55	36	27
GLP	5	6	12	9	7
Total	286	288	347	215	157

Compliance Classifications

- **No Action Indicated (NAI)**
  - No or minor objectionable conditions or practices
- **Voluntary Action Indicated (VAI)**
  - Objectionable conditions/practices were observed
  - Isolated, low-risk
  - Establishment should be able to correct without official action
- **Official Action Indicated (OAI)**
  - Significant or egregious violations of regulations
  - Regulatory action recommended

Compliance Trends



Common Observations for Sponsors

- Monitoring
- Device shipment/disposition records
- Signed investigator agreement
- Financial disclosure form
- Investigator compliance
- Record retention
- Progress reports to FDA and IRB

Tips for a Successful Study

- Select qualified study personnel
- Ensure monitoring and conduct a “mock” audit
- Adopt a “quality system” approach to your study
- Consider only necessary medical procedures when designing a study

Tips for a Successful Study

- Consider incorporating comprehensive data management plan in study protocol
- Identify and address conflicts of interest
- Consult potential investigators and FDA during design phase
- Prepare for inspection by discussing with staff and organizing records

Knowledge Check

Conducting a “mock” audit of clinical investigator sites is a useful tool in ensuring a quality study.

True / False

Resources

- **CDRH Homepage:** www.fda.gov/medical-devices
- **CDRH Learn:** www.fda.gov/training-and-continuing-education/cdrh-learn
- **Device Advice:** www.fda.gov/DeviceAdvice
- **Bioresearch Monitoring:** www.fda.gov/medical-devices/overview-device-regulation/bioresearch-monitoring
- **Bioresearch Monitoring Inspection Metrics:** www.fda.gov/science-research/clinical-trials-and-human-subject-protection/bimo-inspection-metrics
- **Clinical Trials Guidance Documents:** www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trials-guidance-documents
- **Medical Device Guidance Documents** www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products
- **Clinical Trials and IDE Guidance Documents** www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-guidance

Contact Information

General Inquiries

- Division of Industry and Consumer Education (DICE)
- Email: DICE@fda.hhs.gov
- Phone: (800) 638-2014

Clinical Trials and Human Subject Protection

- CDRH Clinical Evidence Quality Teams
- Email: BIMO-CDRH@fda.hhs.gov
- Phone: (301) 796-5490

Summary

- Sponsors play a critical role in ensuring conduct of quality studies.
- FDA's BIMO program helps review the quality of studies primarily through on-site inspections.
- By looking at common problem areas, we've identified tips for ensuring the quality of device studies.

Questions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