

# Bioresearch Monitoring and Good Clinical Practice Inspections

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# Disclosures

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I have no relevant financial relationship(s) in connection with this educational activity.

# Topic Outline

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- **Bioresearch Monitoring Overview**
- GCP Inspection Process
- COVID-19 and the BIMO Program
- Questions

# Learning Objectives

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- To understand the objectives of the FDA's Bioresearch Monitoring Program
- List three potential outcomes from a Good Clinical Practice (GCP) inspection
- Identify an alternative approach to on-site inspections being used to inform decisions regarding pending applications during the COVID-19 public health emergency.

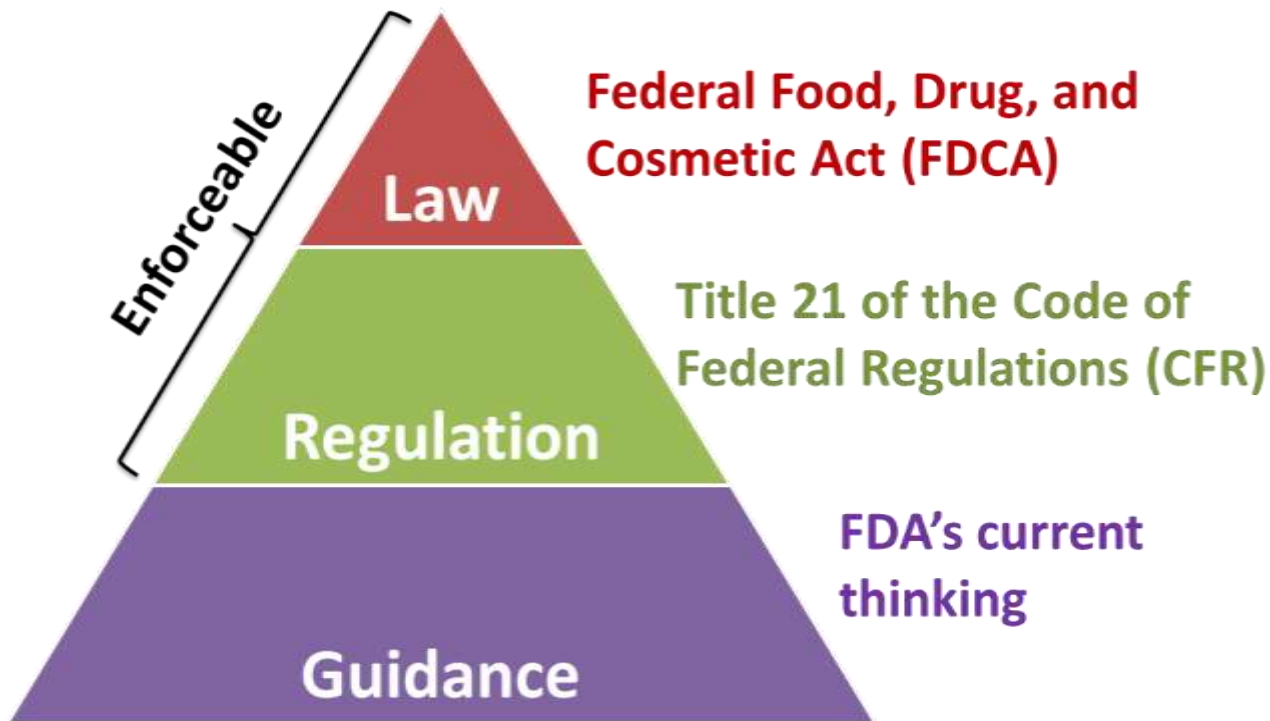
# Bioresearch Monitoring (BIMO) Program

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A comprehensive, agency-wide program of on-site inspections and data audits, designed to monitor all aspects of the conduct and reporting of FDA-regulated research



# Governing Framework



# What are the regulations most relevant to Good Clinical Practice?

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- 21 CFR 11 – Electronic records and signatures
- 21 CFR 50 – Protection of human subjects
- 21 CFR 54 – Financial disclosure
- 21 CFR 56 – Institutional Review Boards
- 21 CFR 312 – Investigational new drug application
- 21 CFR 314 – Applications for FDA approval to market a new drug
- 21 CFR 320 - Bioequivalence

# Good Clinical Practice (GCP)



## **E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry**

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

March 2018  
Precedence

CDER Control No. 0950-0545 Expiration Date 03/30/2028  
See additional FDA statements in section 9 of this guidance.

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

## **1.24 Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.



# GCP Inspections under the BIMO Program

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- Clinical Investigators
- Sponsors
- Sponsor-Investigators
- Contract Research Organizations
- Institutional Review Boards

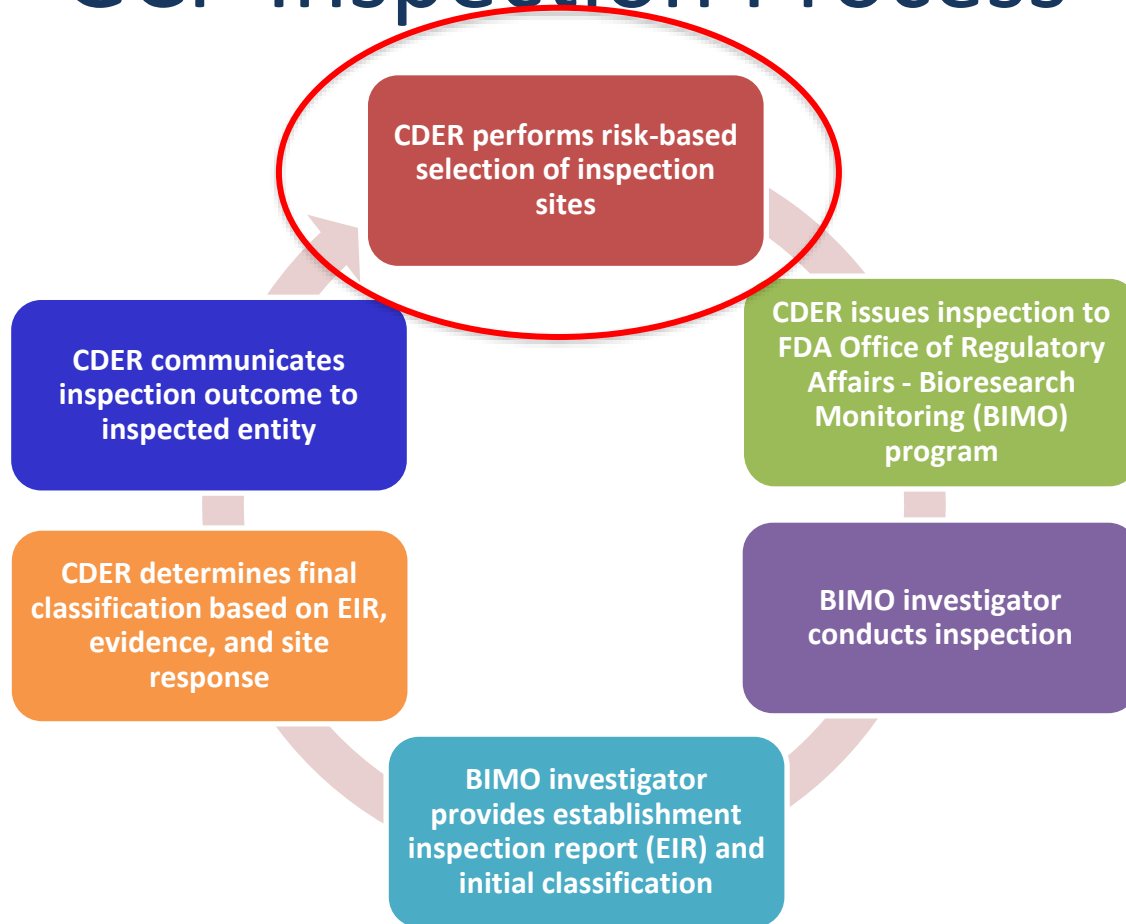


# Topic Outline

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# GCP Inspection Process



# What Triggers a GCP Inspection

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- New Drug Application (Data Validation)
  - ~70% of clinical investigator inspections are associated with NDA/BLA
  - May be linked with a sponsor/CRO inspection
- Complaint (“For Cause” Inspection)
  - ~30% of clinical investigator inspections follow a complaint
  - Complaints come from any source
- Routine Surveillance Inspections
  - Institutional Review Boards

# CI Site Selection Tool (CISST)

FDA Site Selection Tool v1.2 Study:  Endpoint:

Application Risk: 5.0 Study Risk: 0.0

MEMO	SITEID	FIRSTNAME	LASTNAME	CITY	STATE	COUNTRY	RANK	TOTAL RISK	Related Rank
							1	29.2	24.2
							2	27.2	22.2
							3	24.8	19.8
							4	22.0	17.0
							5	21.5	16.5
							6	19.3	14.3
							7	17.9	12.9
							8	15.8	10.8
							9	15.4	10.4
							10	15.1	10.1
							11	14.9	9.9
							12	14.4	9.4
							13	14.4	9.4
							14	14.3	9.3
							15	14.0	9.0
							16	13.8	8.8
							17	13.6	8.6
							18	13.2	8.2
							19	13.2	8.2
							20	13.0	8.0

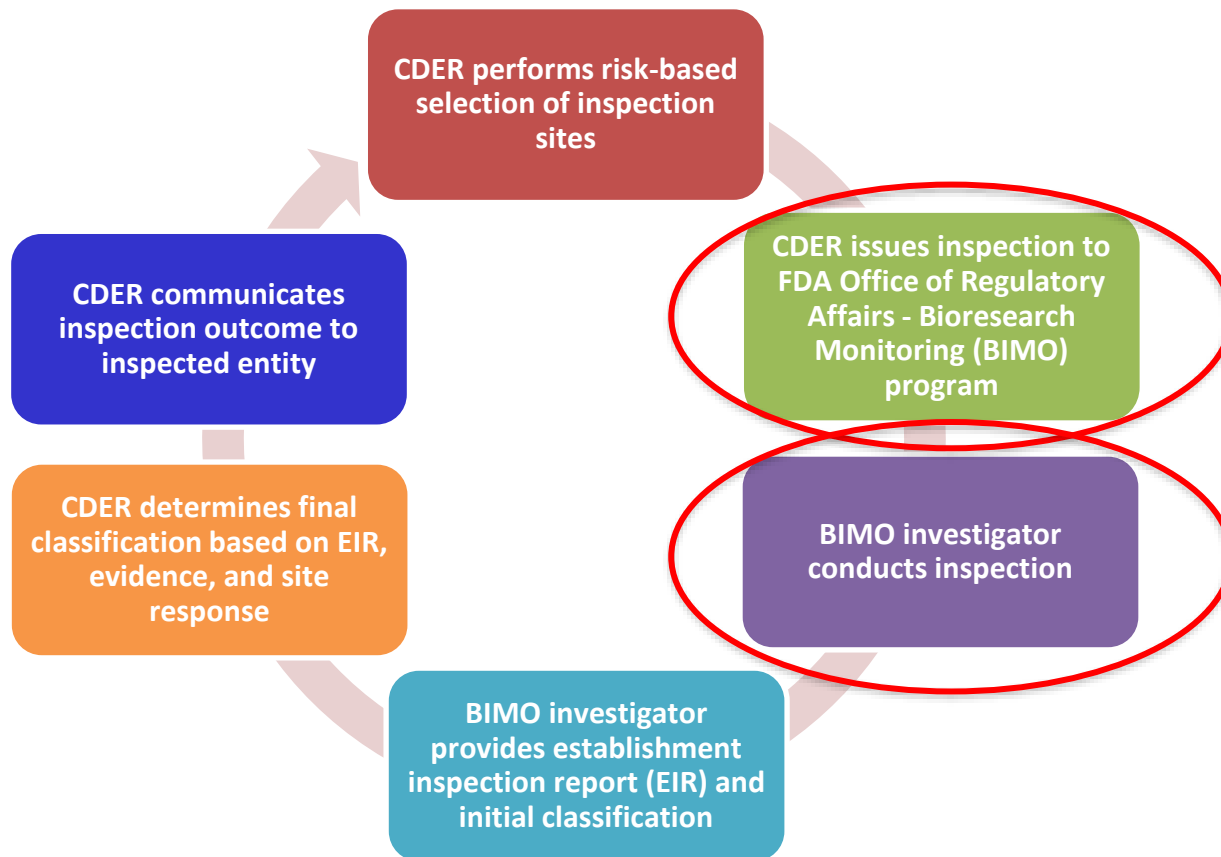
MEMO: The investigator name (First and Last Name goes here). The City, State and country for the address where the clinical trial was performed goes here

SITEID: Site ID goes here

Related Rank: Key Attributes goes here

- Assists in choosing CI sites for inspection
- Calculates the total risk of each CI site based on a variety of factors such as:
  - Enrollment
  - Efficacy outcome
  - Complaints
  - SAEs/deaths
  - Protocol deviations
  - Discontinuations
  - Time since last inspection
  - Financial disclosures
  - # of INDs

# GCP Inspection Process



# Starting an Inspection

[illegible]

- Inspection assignments sent to Office of Bioresearch Monitoring Operations (OBIMO) within the Office of Regulatory Affairs (ORA)
- FDA investigator calls site to pre-announce:
  - usually three to five days in advance
  - allows the study site to ensure that all required records are available
- FDA investigator presents credentials and “Notice of Inspection” (Form FDA 482)

# What do inspections look at?

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## Trial conduct

Was study conducted according to the protocol?

- Inclusion/exclusion criteria
- Randomization scheme
- Blinding procedures
- Data flow
- Study visits, procedures, evaluations
- Administration of study drug

Did study conduct comply with regulations?

- IRB approvals/communications
- Consent procedures
- Financial disclosures
- Electronic records management
- Study drug accountability
- Site training/site monitoring

## Data verification

Comparison of the data submitted by the sponsor with the source documents at the site

- Primary endpoint data
- Adverse events
- Protocol deviations



# COMPLETION OF INSPECTION

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- FDA Form 483 observations and/or discussion items, if applicable
- Form 483:
  - Issued to highest management official available at end of inspection
  - List of inspection observations –
    - **Form FDA 483 items are field 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 violation's impact on data integrity and subject safety
- Submit written response within 15 business days after the close of the inspection

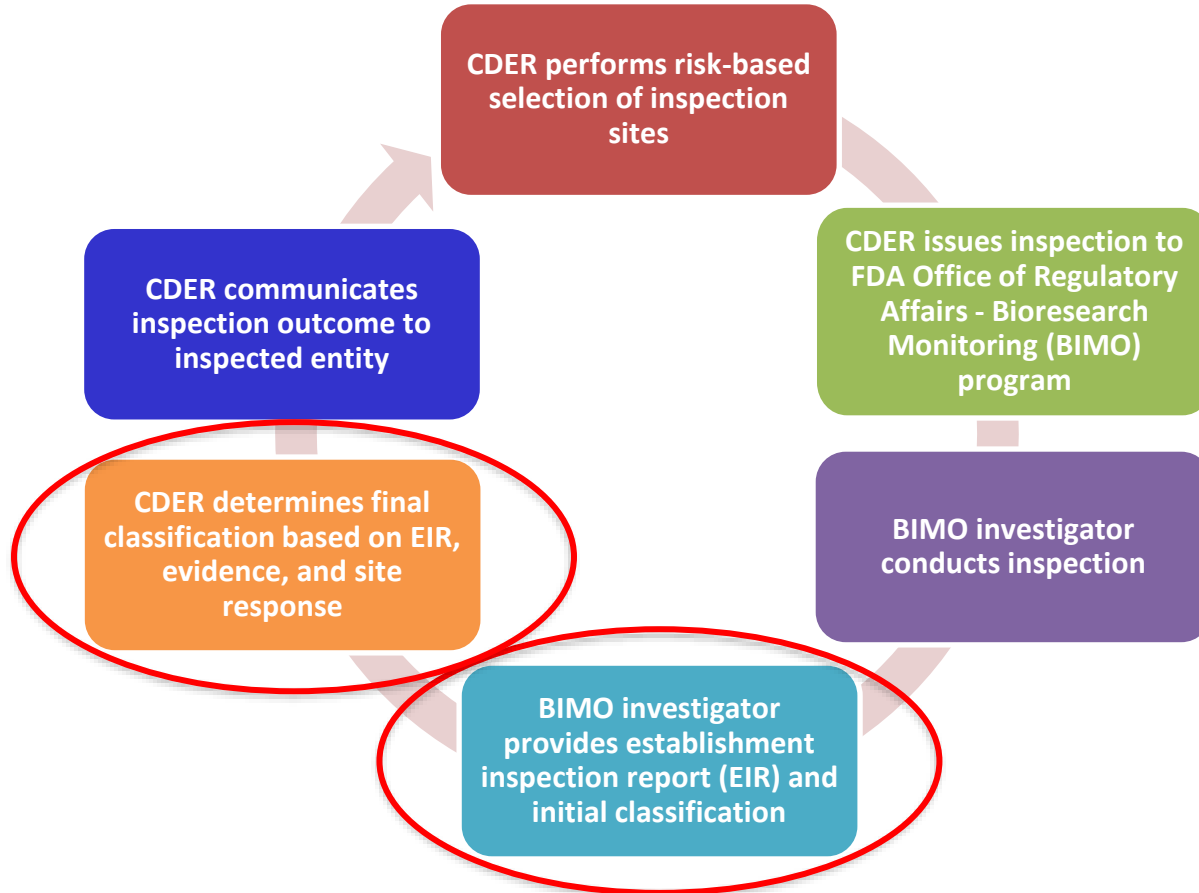
# Responding to Form FDA 483

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- There is no regulatory requirement for you to respond to the FDA Form 483

*However, a well-reasoned, complete, and timely 483 response is in your best interest*

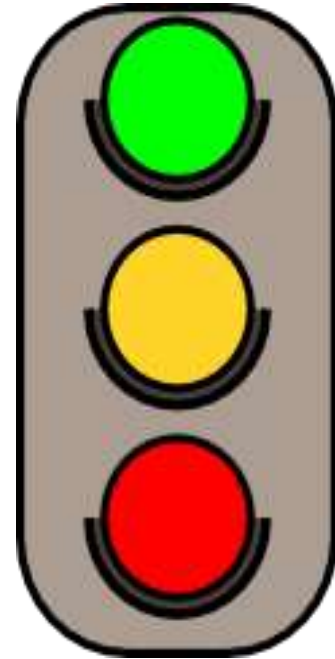
# GCP Inspection Process



# Compliance Classifications

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- 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



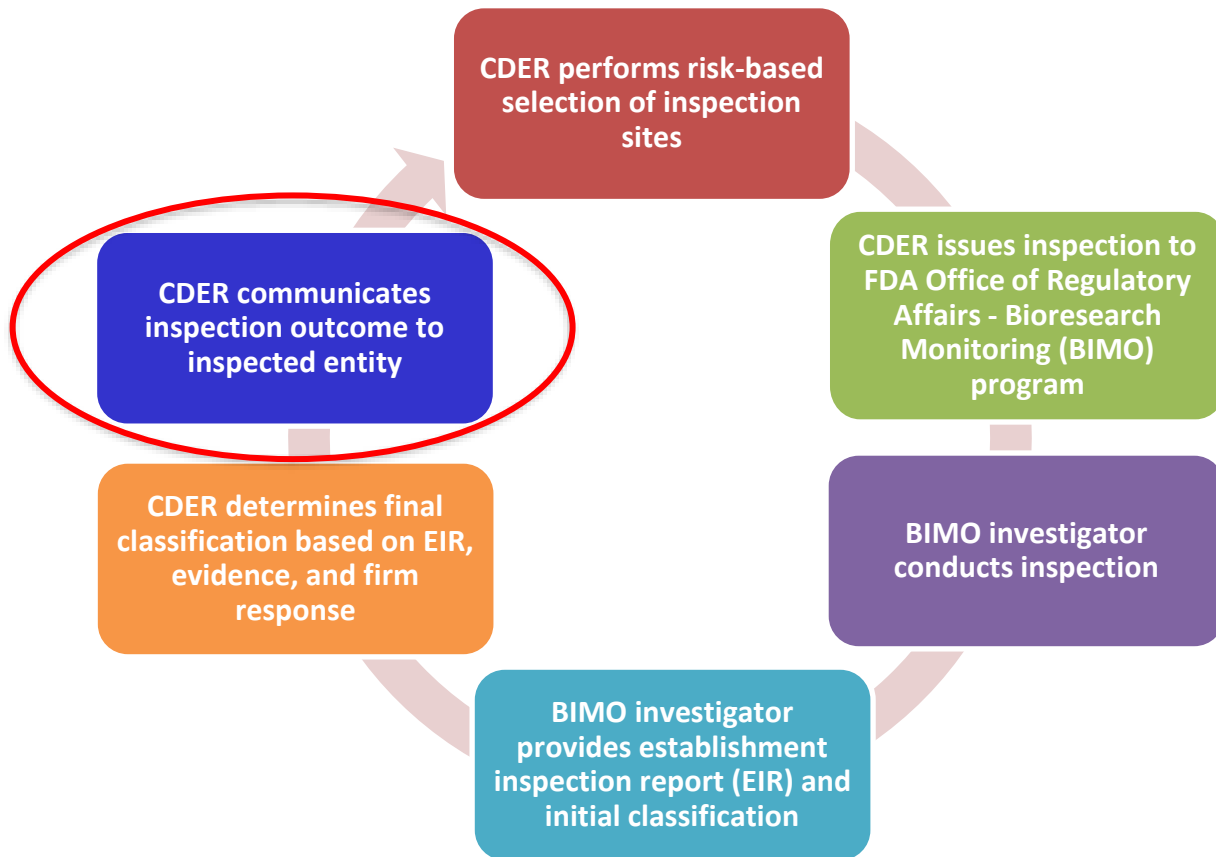
# Official Action Indicated (OAI)

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- Regulatory violations uncovered during the inspection is/are **repeated, deliberate, and/or** involve **submission of false information** to FDA or the sponsor in any required report.
- Regulatory violations are **significant/serious** and/**or numerous**, and the **scope, severity, or pattern** of violations support a finding that:
  - Subjects have been (or would be) exposed to an unreasonable and significant risk of illness or injury.
  - Subjects' rights have been (or would be) seriously compromised.
  - Data integrity or reliability has been compromised.

# GCP Inspection Process



# Compliance actions

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- NIDPOE/NOOH
- Office of Criminal Investigations Referral
- Warning Letter
- Untitled Letter
- *Data Rejection*
- *Clinical Hold*

Regulatory Procedures Manual

<https://www.fda.gov/iceci/compliancemanuals/regulatoryproceduresmanual/>

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- **COVID-19 and the BIMO Program**
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# GCP Inspections and COVID-19

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- Pre-approval and for-cause assignments deemed mission-critical are being considered for inspection on a case-by-case basis.
- ORA is using a COVID-19 Advisory Rating system to determine when other inspections may be conducted (i.e., surveillance and other non-mission critical inspections) in a given geographic region.
- Where possible, other pathways are being used to inform decisions regarding pending applications including requesting existing inspection reports from other competent authorities, requesting information from applicants, and requesting records from facilities and other inspected entities directly.
- Postponed inspections are being prioritized for completion when travel restrictions are lifted.

# Remote Interactive Evaluations (RIE)

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- RIE may be used to support regulatory decisions and oversight of establishments, while limiting unnecessary contact. FDA applies risk management methods and tools to determine when to request a facility's participation in a remote interactive evaluation.
- RIE process may include:
  - Review of documents, records, and other information via electronic systems
  - Use of livestream and or pre-recorded video to examine facilities, operations, and other information
  - Interviews and meetings to address questions and concerns
- RIEs outcomes may:
  - Support FDA's assessment of pending applications
  - Preclude the need for an inspection in follow-up and/or inform the timing for future inspections
  - Support regulatory meetings, warning letters, and other compliance and enforcement actions

# GCP Compliance and COVID-19

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- FDA recognizes that the COVID-19 pandemic may impact the conduct of clinical trials
  - IP distribution and administration
  - Protocol-mandated visits (for safety and efficacy assessments)
  - Laboratory and diagnostic testing
- FDA received many questions from sponsors, CIs, IRBs, general public

# GCP Compliance and COVID-19

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## *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*

- Provides general considerations to assist in assuring the safety of trial participants, maintaining compliance with GCP, and minimizing risks to trial integrity during the COVID-19 pandemic
- Ensuring the safety of trial participants is paramount and trial participants should be kept informed of any changes to the study as a result of COVID-19
- Engage with IRBs as early as possible when changes to the protocol or ICD anticipated.
- Documentation is key
- Optimize use of central and remote monitoring programs to maintain oversight of clinical sites

# Clinical Studies and COVID-19

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- Research studies involving human participants must generally be conducted under an investigational new drug application (IND) if the research involves a drug and is a clinical investigation
  - Criteria for the exemption of studies with marketed drug products
- INDs are reviewed by FDA:
  - To assure the safety and rights of subjects in all phases of an investigation
  - To help assure that the quality of the scientific evaluation is adequate to permit an evaluation of the drugs effectiveness and safety
- Clinical investigations of drugs for the prevention and/or treatment of COVID19 would generally require an IND
- Common violation cited in FDA warning letters to sponsor-investigators:
  - You failed to submit an IND for the conduct of clinical investigations with an investigational new drug that is subject to 21 CFR 312.2(a)

# Summary

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- FDA's Bioresearch Monitoring Program monitors all aspects of the conduct and reporting of FDA-regulated research to ensure trials are being conducted in a way that ensures the reliability of the data and that the rights of participants in clinical trials are being protected.
  - Inspections are an important component of the BIMO program.
- FDA continues to have oversight of clinical trial conduct during the PHE, both through on-site inspections and through alternative approaches.
- FDA recognizes that the COVID-19 pandemic may impact the conduct of clinical trials and stakeholders should review the guidance on the Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency for more information.
- Clinical investigations of drugs must generally be conducted under an IND, including studies for the prevention and/or treatment of COVID-19.



# Challenge Question #1

**If you receive an FDA Form 483 at the close out of an inspection, you have how many business days to provide a written response:**

- A. 7 days
- B. 15 days
- C. 30 days
- D. There is no timeline to respond to a 483



## Challenge Question #2

**Which types of inspections are NOT covered in the BIMO program?**

- A. Clinical investigator, sponsor, and contract research organizations
- B. Drug manufacturing
- C. Postmarketing adverse event reporting and Risk Evaluation and Mitigation Strategies (REMS)
- D. Institutional review boards



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Thank you!

- Office of Scientific Investigations (OSI)
  - <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-scientific-investigations>
- Code of Federal Regulations Title 21
  - <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>
- BIMO Compliance Programs
  - <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-guidance-manual-cpgm/bioresearch-monitoring-program-bimo-compliance-programs>
- FDA Guidance Documents
  - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

