

# What to Expect When You're Inspected by the FDA

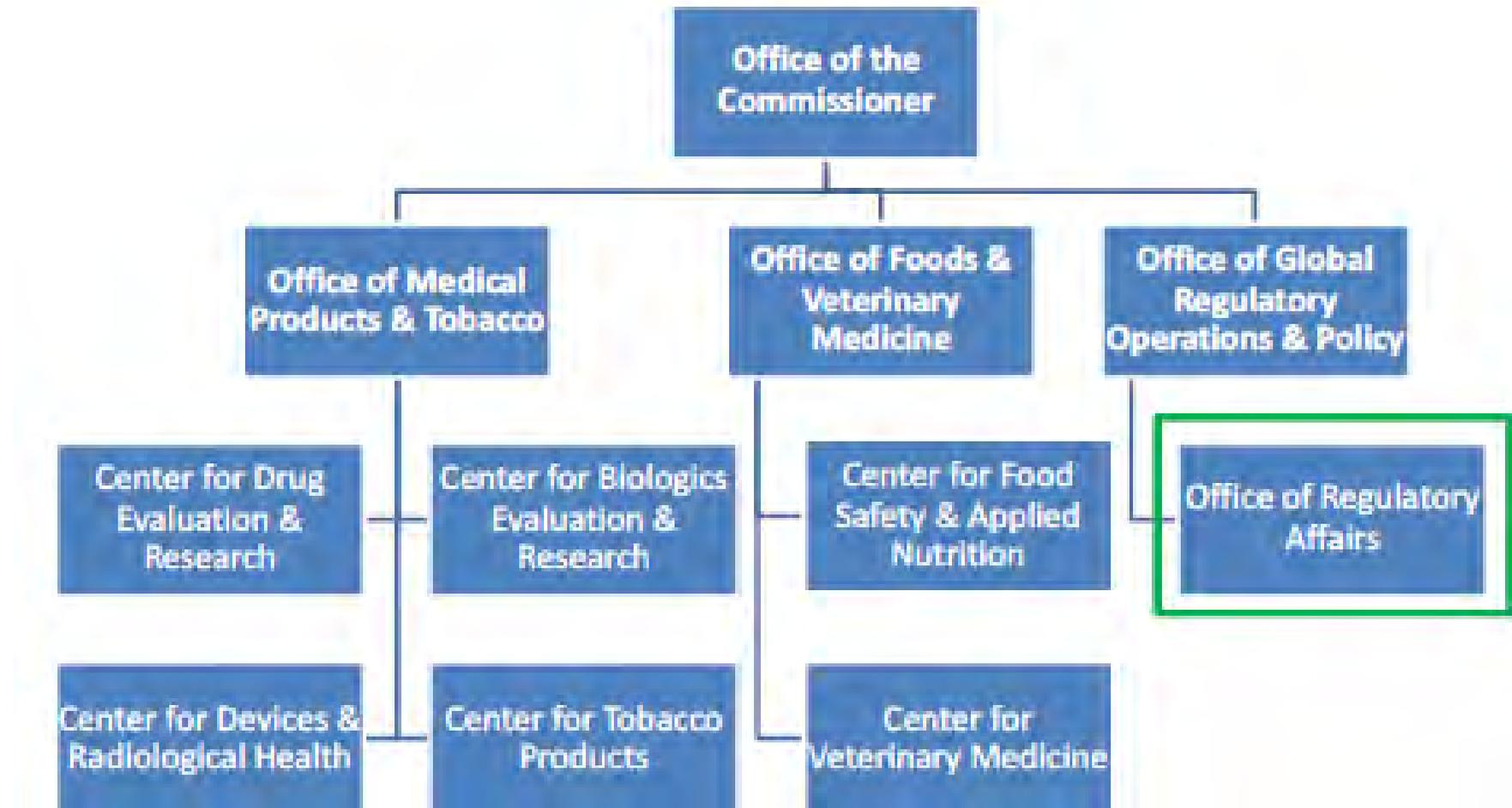
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March 24, 2021

# Overview

- Scope and Purpose of FDA Inspections
- COVID-19 Pandemic Considerations
- Inspection Readiness
- Inspection Process
  - Notification
  - Preparation
  - On-site visit
  - Post-inspection
- IRB Resources
- Q&A

# U.S. Food and Drug Administration (FDA)



# Bioresearch Monitoring (*BIMO*) program

BIMO Division I (East) & BIMO Division II (West)

## Perform inspections of:

- Clinical Investigators
- Sponsors
- Institutional Review Boards

## Evaluate compliance of:

- FDA regulations
- Subject protection
- Data verification

# Site/PI Selection for Inspection

- Routine surveillance
- High-enrolling study site
- Coinciding with review of a marketing application
- Based upon current and ongoing public health issues
- Data outliers
- As a result of complaints or reports of non-compliance
- Inspection history

# FDA BIMO Inspection Metrics

- Common Clinical Investigator Inspectional Observations
  - Failure to follow the investigational plan; protocol deviations
  - Failure to comply with Form 1572/investigator agreement requirements
  - Inadequate and/or inaccurate case history records; inadequate study records
  - Inadequate accountability for the investigational product
  - Inadequate subject protection; informed consent issues
  - Safety reporting; failure to report and/or record adverse events
  - Failure to comply with 21 CFR part 56 (IRB) requirements

# FDA BIMO Inspection Metrics

- Common Sponsor-Investigator Inspectional Observations
  - Same as investigator observations
  - Failure to submit an Investigational New Drug (IND) application
  - Failure to ensure proper monitoring of the clinical investigation

<https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/bimo-inspection-metrics>

# FDA Inspections During the COVID-19 Pandemic

- On-site inspections are still occurring, even if the facility is closed to visitors
  - Critical for pre-approval or for-cause
  - Routine: COVID-19 Advisory Rating System
- Voluntary remote record reviews are also being done
  - Not official inspections, but a work-around for marketing application approvals
- Communicate campus COVID-19 protocols before inspection date



# Inspection Readiness

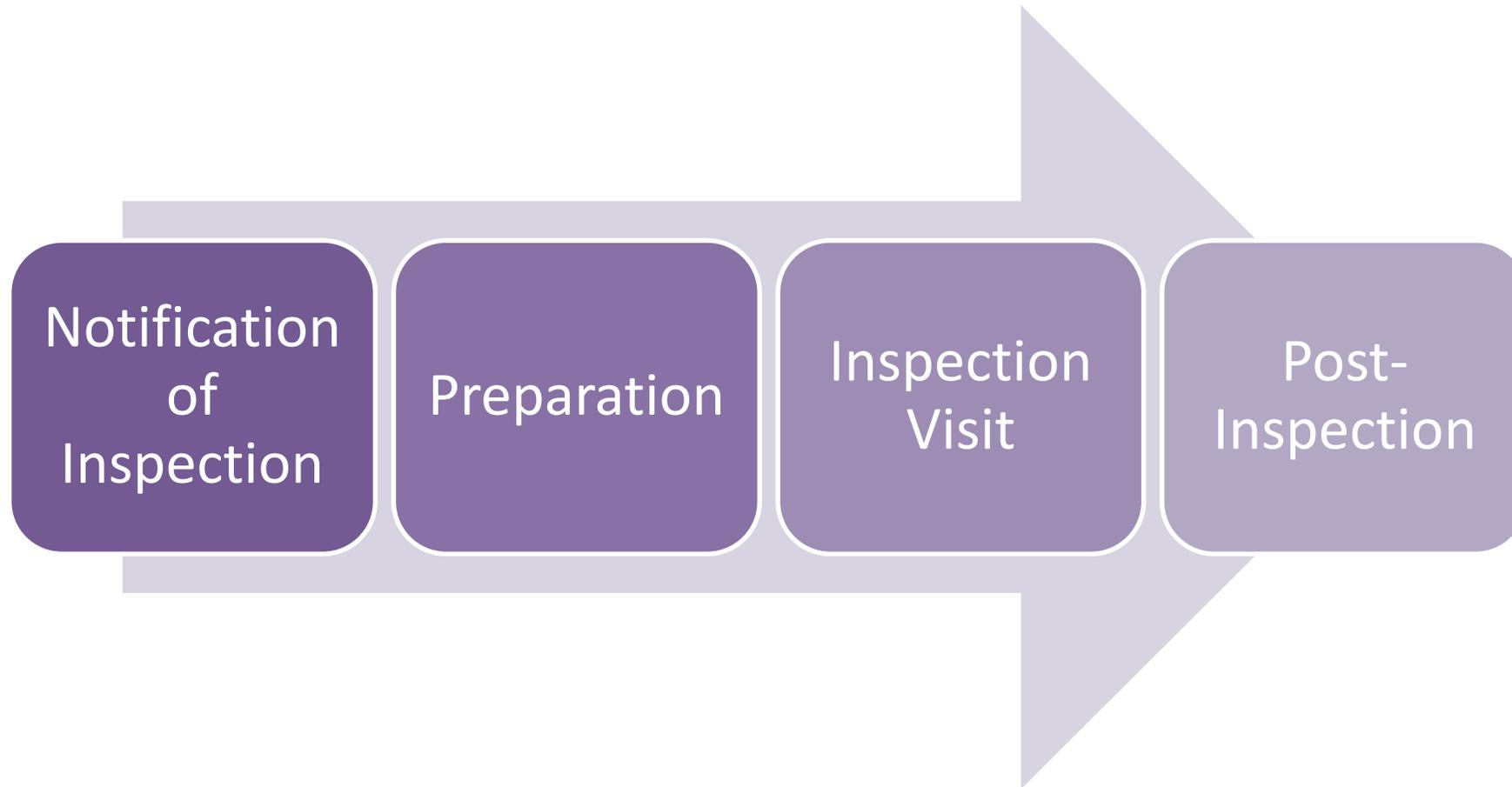
## What's the secret to being prepared for an inspection?

- Maintain compliance throughout your study
- Provide effective training to staff on regulatory requirements, specific protocol requirements, and processes or procedures
- Create a plan ahead of time for how inspections will be handled
- Assume your study will undergo an inspection, and that it can happen at any time
- **DOCUMENTATION, DOCUMENTATION, DOCUMENTATION**

# Good Documentation – “ALCOA”

- Attributable - it should be clear who has documented the data
- Legible - readable, permanent (no pencil), and signatures identifiable
- Contemporaneous - the information should be documented in the correct time frame along with the flow of events
- Original - original or exact copy of the first record made
- Accurate - accurate, consistent and real representation of facts

# FDA Inspection Process



# FDA Site Inspection Guidance

**[HRP-1910 – FDA Site Inspection Guidance](https://www.irb.northwestern.edu/fda-site-inspection-guidance/)**: a comprehensive and detailed guidance for a successful FDA site inspection. It includes recommendations, best practices, and what to expect for receipt of an inspection notification, preparing for an inspection, and during and after an inspection.

<https://www.irb.northwestern.edu/fda-site-inspection-guidance/>

## FDA Site Inspection Guidance

The U.S. Food and Drug Administration (FDA) conducts inspections to protect the rights, safety, and welfare of research study participants, verify the accuracy and reliability of study data, and assess compliance with FDA regulations for the conduct of clinical trials. FDA inspections, or audits, are in-person site visits that may be performed on clinical investigators, study sponsors, or IRBs.

### What kind of inspections does the FDA conduct on investigators?

The FDA conducts site inspections on FDA-regulated clinical trials to verify data submitted to the FDA and to determine if investigators are in compliance with FDA regulations and the protocol.

# RING RING...FDA Calling!



Don't panic! Take notes

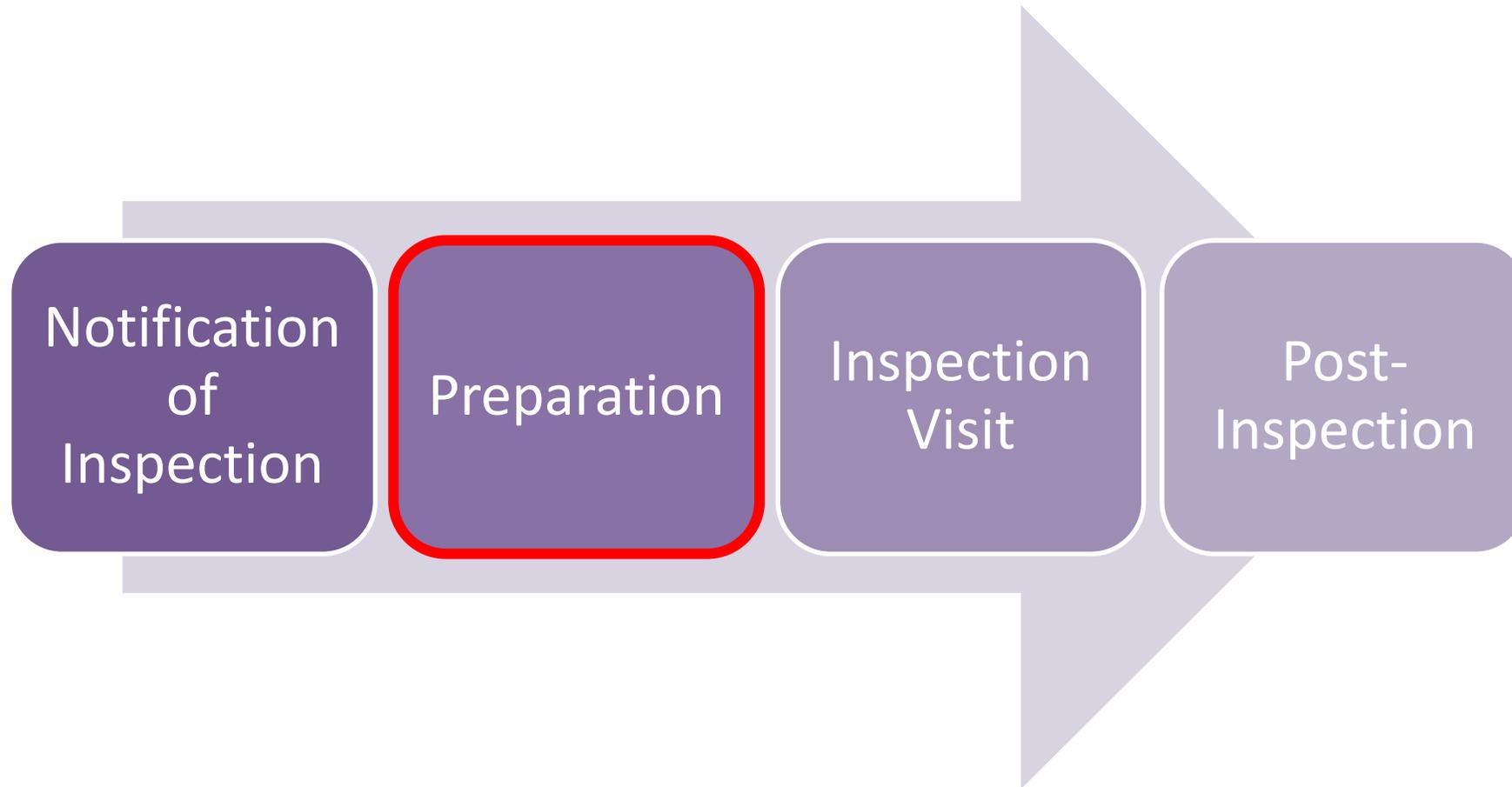
# Record Notification Information

- Estimated date and duration of the inspection
  - How long will the inspector(s) be on site? Are the dates flexible?
- FDA inspector(s) contact information
- Purpose and scope of the inspection
  - Protocol or investigator? Multiple protocols? Routine or for-cause?
- Inspector's requests (specific personnel, documents, etc.)
- Is information is needed before the inspection? If yes, by when?

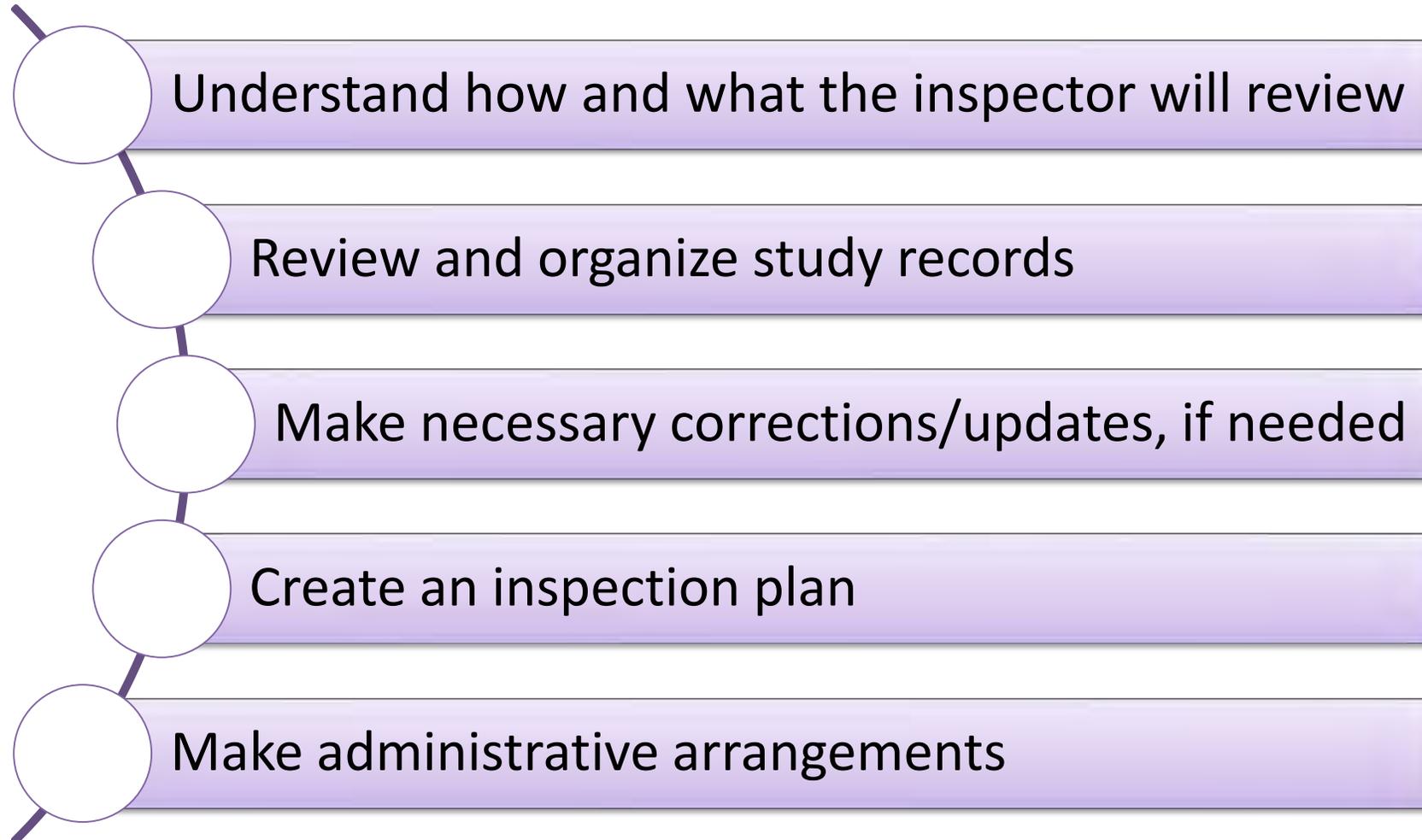
# Notify Stakeholders of Inspection

- Investigators and staff
- PI's direct supervisor
- Sponsor/CRO
- Directors of clinics or centers
- Staff in clinic spaces that may be visited
- Local ancillary support services
- Other relevant staff or administrators
- IRB Office
- OSR
  - [SponsoredResearch@northwestern.edu](mailto:SponsoredResearch@northwestern.edu)
- External IRB
- Investigational Pharmacy
  - [invdrugser@nm.org](mailto:invdrugser@nm.org)
- FSM Office for Research
  - Abby Cosentino-Boehm, Director of Administrative Operations  
([a-cosentino-boehm@northwestern.edu](mailto:a-cosentino-boehm@northwestern.edu))

# FDA Inspection Process



# Inspection Preparation



# How the inspector will review...

- [FDA Inspections of Clinical Investigators: Information Sheet Guidance](#)
  - How and why the FDA conducts inspections
- [FDA Compliance Program – Bioresearch Monitoring](#)
  - Inspector handbook: detailed guidance for FDA inspectors on how they are to conduct inspections of clinical investigators and sponsor-investigators and the regulations that guide their inspections, and may be useful to anticipate the scope of review

# What the inspector will review...

- Protocol
- Subject records (medical records, case report forms, informed consent)
- IRB documentation/communication
- Clinicaltrials.gov requirements
- Electronic records and signatures
- Progress/sponsor reports (adverse events, protocol deviations)
- Monitoring logs
- 1572/Clinical investigator agreement
- Device/Drug accountability records
- Financial disclosure forms
- Study staff interviews

# Review and organize study records...

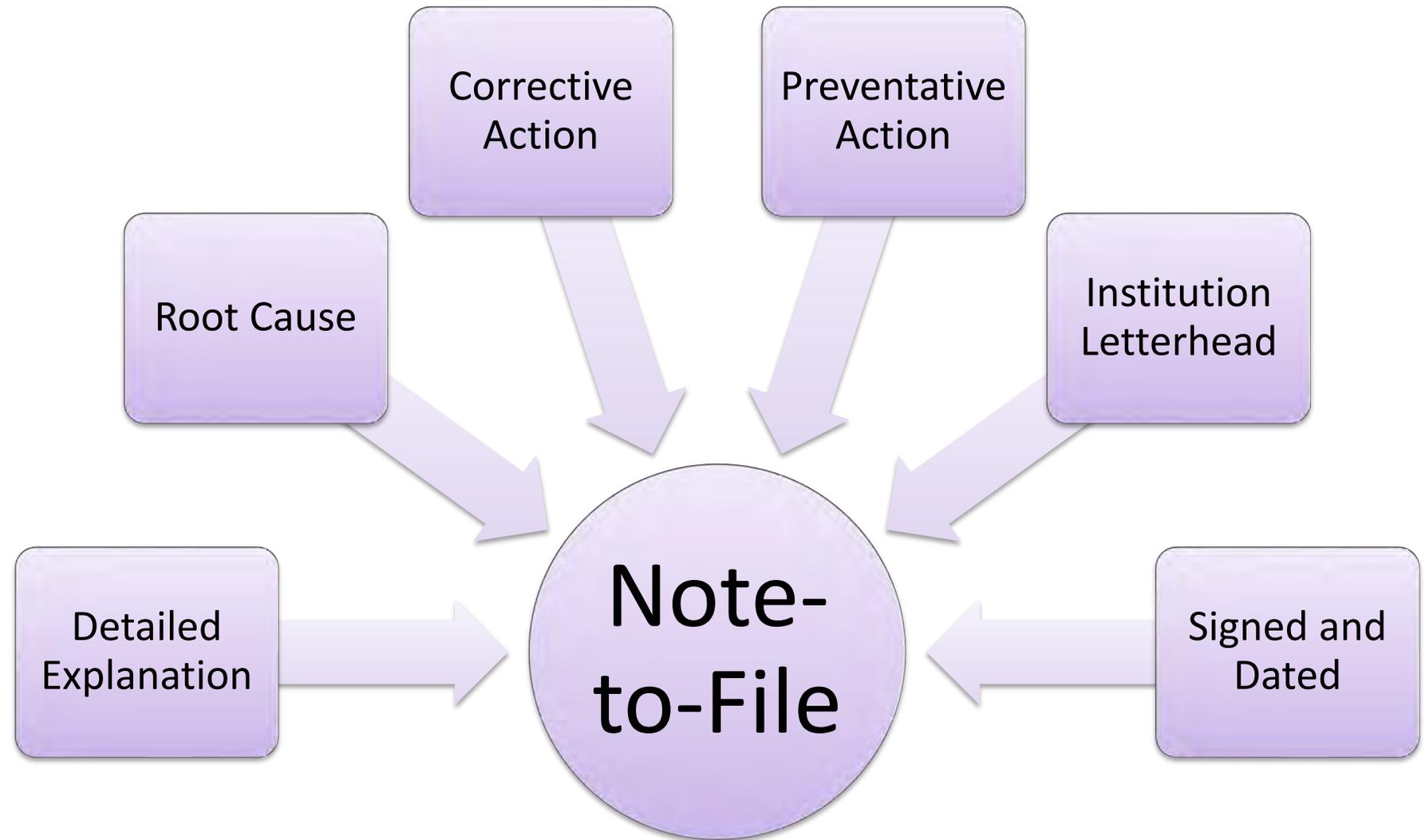
- Applicable [Post-Approval Monitoring Checklists](#)
- FDA Site Inspection Supplemental Checklist
- Prepare a summary of the study, site, responsibilities, facilities
- Create a list of PI's FDA-regulated studies
- Make all study records readily available
  - Print, prepare flash drive, or plan for over-the-shoulder review for documents in systems (EMR, eCRFs, etc.)
- Records should be easy to follow
- [Study Support Resources and Templates](#)

# Make corrections or updates...

- **File missing documentation**
- **Identify weakness or gaps**
  - Explain corrective and preventative action with a note-to-file
- **Correct minor issues**
  - Use appropriate correction methods
- **Resolve any prior findings**
- **Limit major corrections and updates**
  - Protocol amendments or data corrections
  - Create internal list to address after inspection

# Memos or Notes-to-File (NTF)

Provide context or additional information and for items that may need clarity within the file (not a substitute for corrective action).



# The Correct Way to Make Corrections

- 1. Single line through incorrect information**
  - No white out, original entry still visible
- 2. Enter the correct information**
  - Based on a source document
- 3. Initial and date the correction**
- 4. Document why the correction was made or delayed**

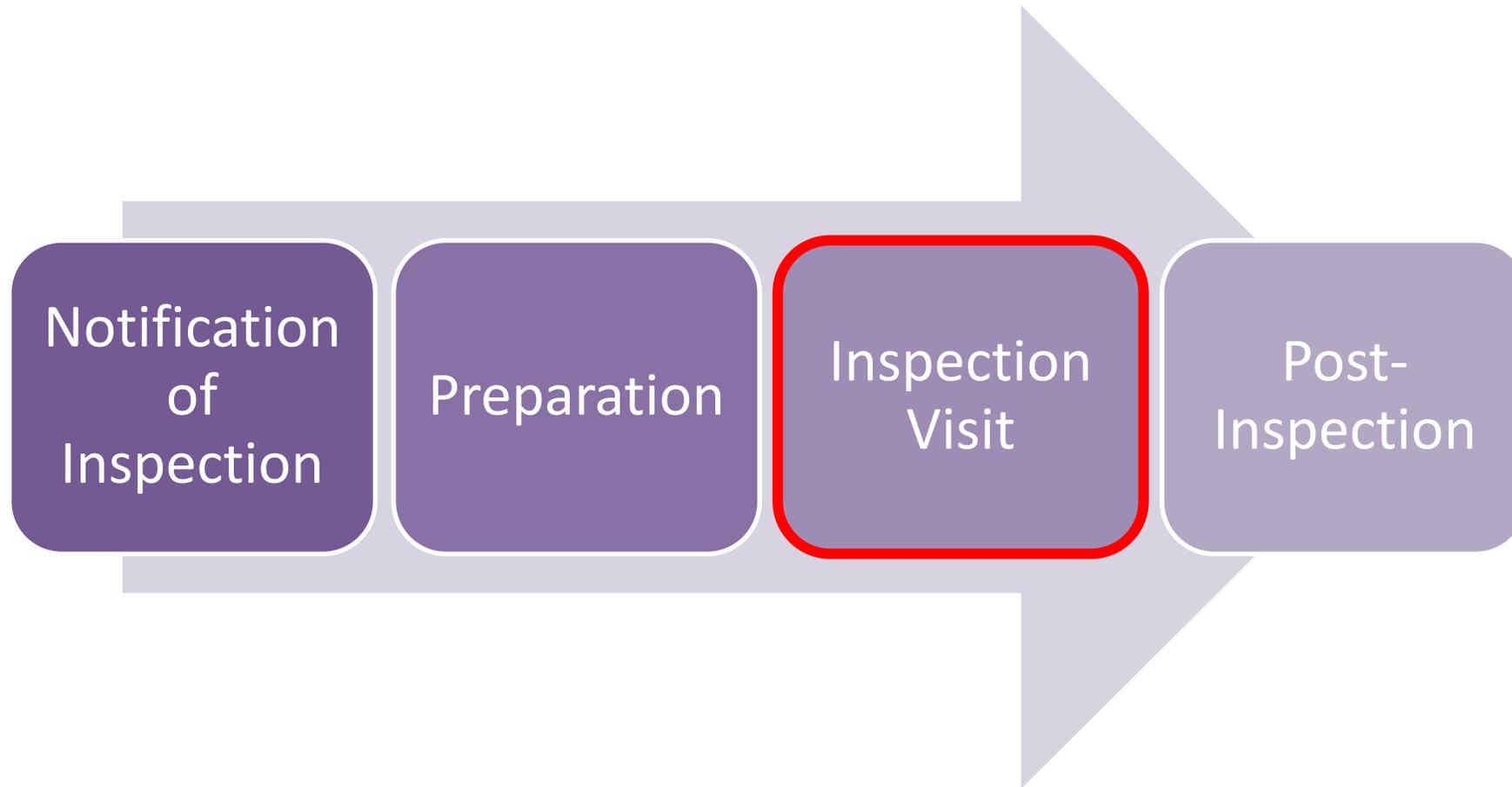
## Create an inspection plan...

- Inspection coordinator(s) to oversee and be inspector's contact
- Inspection assistant(s) to take notes, make copies, locate personnel, document runner, etc.
- Prepare [inspection tracking logs](#) to track inspector requests
- Prepare a “shadow binder” to track document copies provided
- Create and share inspection file location and process with study staff
- Plan a tour of research facilities

# Administrative arrangements...

- Reserve a private room, free of other records
- Invite PI and primary team members to the opening interview
- Inform the inspector where to arrive (include directions, parking, etc.)
- Inform the inspector if there is a sponsor/CRO representative
- Inform study staff and tour location staff of visit guidelines
- Ensure area near inspection room has sensitive documents/items out of sight

# FDA Inspection Process



# Basic Guidelines

- **Limit idle business conversation by ALL staff**
- Be calm, courteous, and professional
- Accompany the inspector on facility tours
- Ensure someone is always readily available for questions/requests
- Don't delay unnecessarily
  - If time is needed to obtain records or an answer, explain why
- Take detailed notes of all meetings, requests, questions, answers
- PI should attend end-of-day meetings and be available for questions

# Opening Interview

- The inspector **must** present their badge/credentials and a Notice of Inspection (Form 482)
- The inspector will explain the intended purpose and scope of the inspection and their anticipated schedule
- PI will summarize the study, site, roles/responsibilities, facilities
- Set expectations for communication and end-of-day meetings
- Provide inspection coordinator/assistant contact information

# Study Record Review

- The inspector will request specific files for review
- Log requests (documents, questions, interviews, etc.) as received and addressed
- Do **not** offer up information or documents that are not specifically requested
- Inspectors are generally not permitted to receive direct log-in credentials for EMR/eCRF systems
- Provide photocopies or electronic copies only of documents specifically requested by the inspector
  - “Shadow binder”

# Interacting with the Inspector

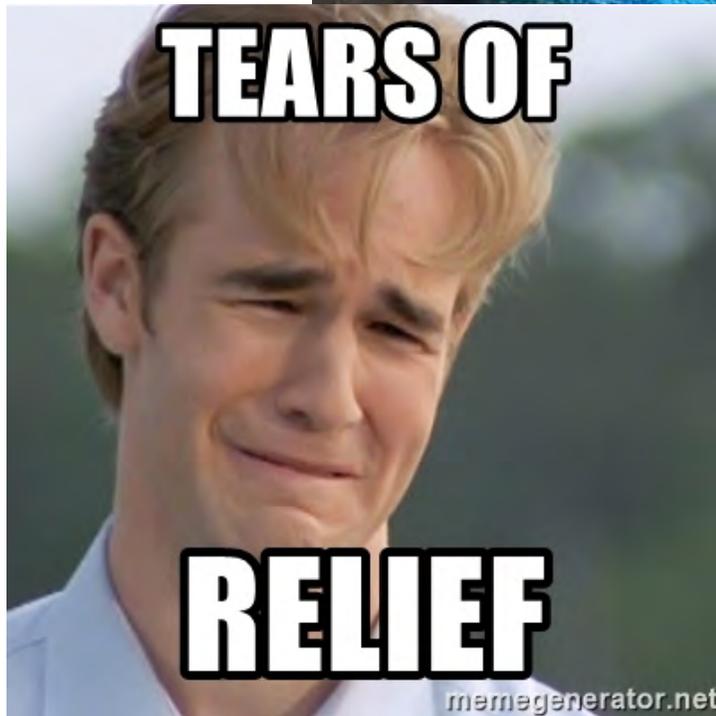
- Ask for clarification
- Be truthful and clear
- Stop when you have fully answered the question
- Answer only the question the inspector asks
- Use documents already provided for support of answers
- If you do not know the answer to a question, write it down and refer it to the correct person
- Once you have answered, wait for the next question

## 8 Appendix I: Questions Frequently Asked by FDA Inspectors

- 8.1 Provide an overview of the study including background, objectives, study design, duration of the study, participant population, and number of participants enrolled.
- 8.2 What responsibilities are delegated to other members of study team?
- 8.3 How are potential participants identified?
- 8.4 Who screens and recruits participants?
- 8.5 Were all methods and materials used for recruitment IRB approved?
- 8.6 Who verifies inclusion and exclusion criteria?
- 8.7 Who obtains consent/assent?
- 8.8 Was written documentation of consent required?
- 8.9 Is the informed consent process documented in the medical record?
- 8.10 Was assent required? (Include age of assent)
- 8.11 Were there any research participants who were wards of the state?
- 8.12 How are screening/enrollment logs used and maintained during the conduct of the study?
- 8.13 Where were study procedures conducted? (e.g., inpatient or outpatient)
- 8.14 What are the study start and/or completion dates?
- 8.15 How do you communicate protocol or study design changes to study staff, pharmacy, and/or ancillary department staff?
- 8.16 How do you obtain, record, secure, and retain data?

# Inspection Closeout – Exit Interview

- Ensure PI and primary study team members present
- Inspector will discuss findings
- Clarify and seek to correct any errors in the findings
- If possible, respond to any deficiencies
- If your opinion differs from the inspector, ask them to indicate the associated regulation or guidance
- Record all discussion points
- **FDA Form 483** - official list of serious inspectional observations or deficiencies

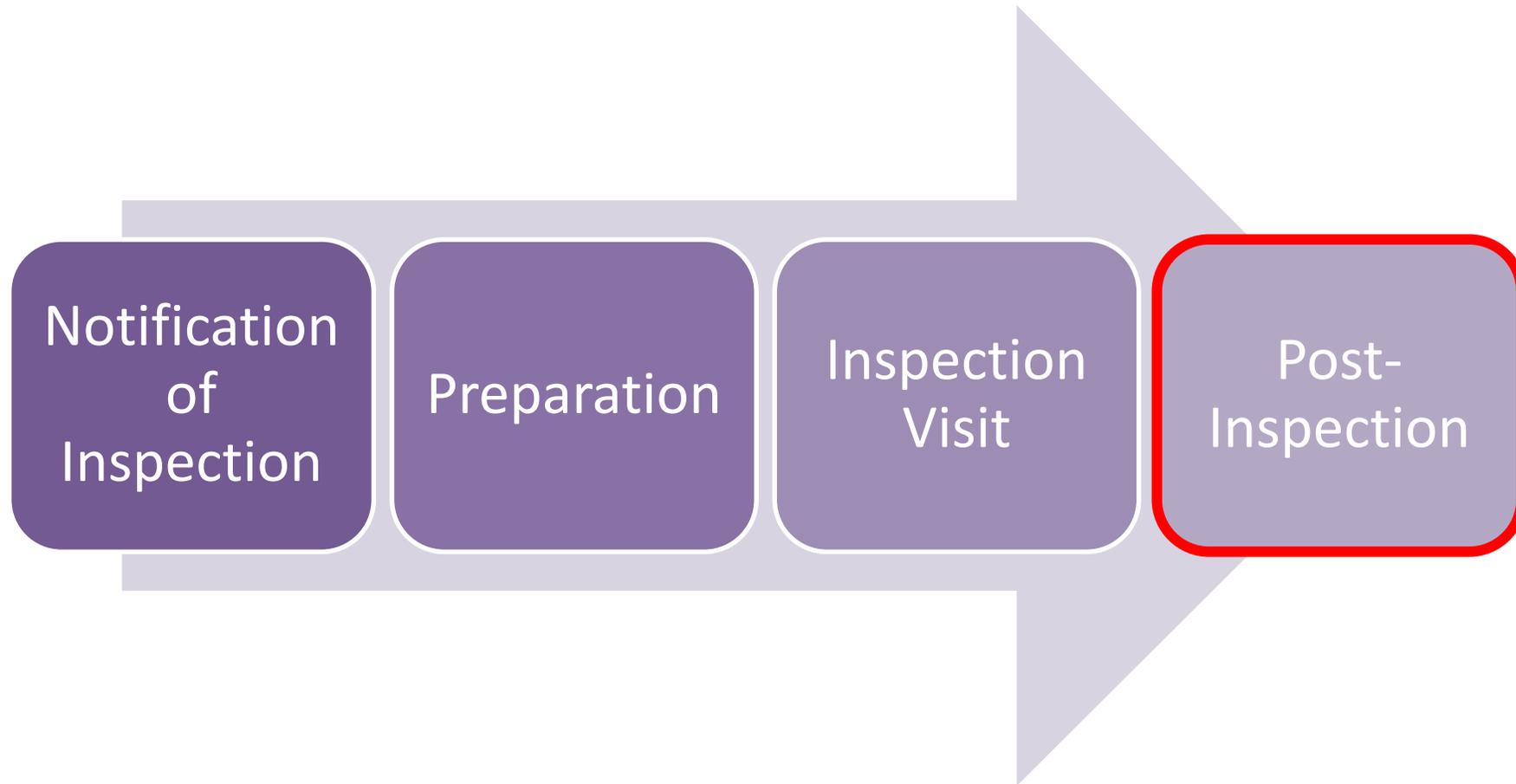


**TEARS OF**

**RELIEF**

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# FDA Inspection Process



# Post-Inspection

- If a Form 483 is issued, the PI must submit a written a response **within 15 working days**
- If no Form 483 is issued, but the FDA requests voluntary actions or has discussion items, it's important to still send a written response

**The FDA does not make a final determination until carefully considering the response.**

**A comprehensive response may downgrade final determination, prevent a Warning Letter, or prevent other action.**

# Written Response to Observations

- Provide a point-by-point response
- Provide explanation or root cause
- Establish specific, timely, and measurable corrective AND preventative actions
- If the PI disagrees with an observation, respond factually, providing clear and verifiable evidence

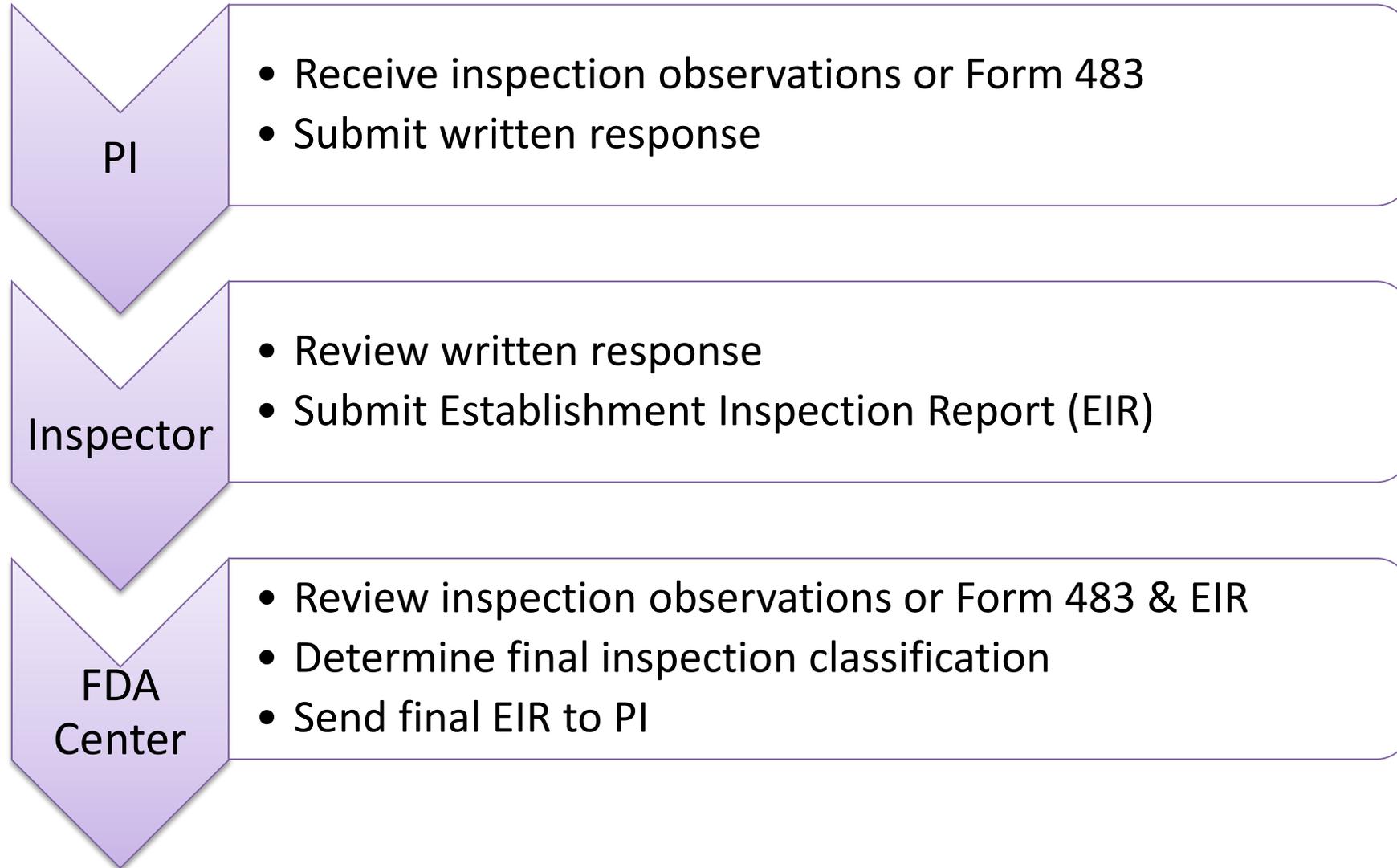
# Written Response to Observations

Follow the 4 Cs:

- **Clear** – document exactly what you plan on doing
- **Concise** and precise
- **Compelling** – tell your story to make sure the actions taken come across as appropriate
- **Complete** – include prevention plan

Submit via email to BIMO Division II (West): [ORABIMOW.Correspondence@fda.hhs.gov](mailto:ORABIMOW.Correspondence@fda.hhs.gov)

# Inspection Closeout



# Inspection Classifications

- **NAI - No Action Indicated**
  - No objectionable conditions or findings
- **VAI - Voluntary Action Indicated**
  - Objectionable conditions or findings, but not serious enough to recommend regulatory action
- **OAI - Official Action Indicated**
  - Serious objectionable conditions, and/or regulatory action recommended

Posted online after inspection closeout:

<https://www.accessdata.fda.gov/scripts/inspsearch/>

# Possible Enforcement Actions

Disallowed data

Warning letter (posted on FDA website)

Untitled letter (not posted on FDA website)

Notice of Initiation of Disqualification Proceedings and Opportunity to Explain letter (NIDPOE)

Criminal prosecution

# Notify the IRB of Inspection Outcome

- Submit Reportable New Information (RNI) to IRB if:
  - issued FDA 483
  - inspection identified information that indicates participants were placed at increased risk of harm or that participants' rights or welfare were adversely affected (even if no FDA 483)
  - Include FDA 483 or inspection report, and PI's draft or official response to the FDA
- RNI is not needed if:
  - NO Form 483 and NO issues identified with participant risk/rights/welfare
  - still inform the IRB Office of the outcome via email
    - copy of the final report or written communication from the FDA inspector

# How do I remember all of this?

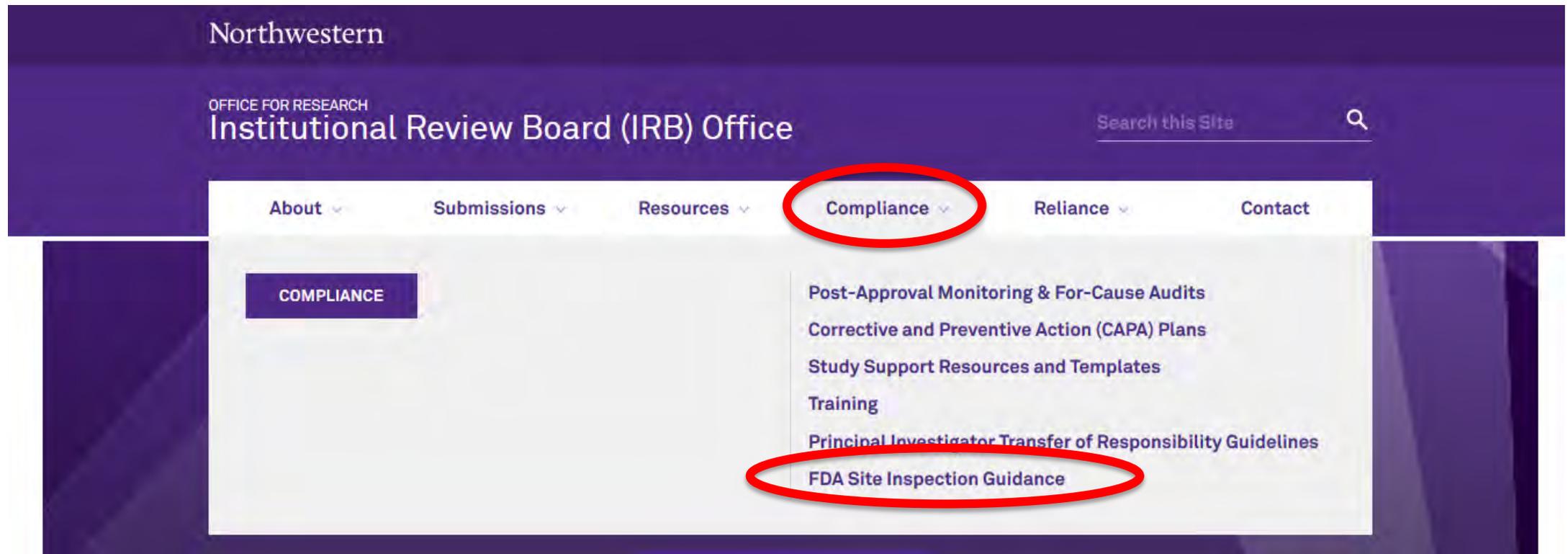


# FDA Site Inspection Guidance

- [HRP-1910 – FDA Site Inspection Guidance](#)
  - Includes recommendations, best practices, and what to expect for receipt of an inspection notification, preparing for an inspection, and during and after an inspection
- [HRP-2020 – FDA Site Inspection Preparation Checklist](#)
  - Condensed checklist of recommended steps for the notice of inspection and inspection preparation information
- [HRP-2021 – Inspection Request Tracking Log Template](#)
  - Template log that study teams may use, customize, or reference to track all requests made by an FDA inspector

# FDA Site Inspection Guidance

<https://www.irb.northwestern.edu/fda-site-inspection-guidance/>



# Contact Information and Other Resources

- IRB Compliance: [irbcompliance@northwestern.edu](mailto:irbcompliance@northwestern.edu)
- IRB Office: [irb@northwestern.edu](mailto:irb@northwestern.edu) or (312) 503-9338
- Post Approval Monitoring Checklists:  
<https://irb.northwestern.edu/templates-forms/templates-forms-sops#checklist>
- Study Support Resources and Templates:  
<https://irb.northwestern.edu/policies/study-support-resources-and-templates>
- Writing Corrective and Preventive Action (CAPA) Plans:  
<https://www.irb.northwestern.edu/writing-an-effective-corrective-action-plan/>

