Magi Clinical Research
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FDA Inspections: Always Be Ready and What to Do When They Actually Come Knocking on Your Door!

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What to Expect, What to Do, and What Not to Do

- Learn from other people's mistakes: Common findings from 483s, FDA warning letters, and trends
- Learn from the Compliance Program Guidance Manual: Instructions for conducting FDA inspections
- Before, during and after inspection: What you need to know and what you need to do to prepare

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This is Not Where You Start

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Before FDA Arrives…

- Operational Model Designed to Always Be Compliant!
  - Have the appropriate staffing
  - Provide training to staff on regulatory requirements, specific protocol requirements, any processes or procedures
  - Facilitate open communications with Designated Subject Matter Experts
  - Not just the what, but the why on compliance matters
  - Assume all studies conducted will be inspected
- Be prepared for an inspection
  - Have procedures for how to handle an inspection
  - Mock inspections with staff; use sponsor visits as a tool

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Violations Can Be Avoided

- Ensuring Staff understand the Protocol and Regulatory requirements will aid in conducting research in compliance with the regulations

- Training
  - Make Training effective for your staff to understand expectations
  - Most sites provide training and yet there are still violations – Why?
  - Not just standard GCP training, but training tailored to the study requirements
  - Know that the protocol was not written for your site or with you procedures in mind
  - Research Records tell a story about how the study was conducted
    - Do they reflect everything that happened including errors and corrections?
    - Do they show PI input and oversight ?
    - Do they have Gaps Due to turnover –Need to Always have a Transition Plan?
  - Full Understanding of Protocol needs to be addressed at SIV

* Note – in Holy Cross Study ConMeds were not required to be collected (Per Protocol) – But was corrected By Monitoring Staff (Because it did not make sense).

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Clinical Research is a "Protocol Centric" Endeavor

- The Quality of the Protocol Dictates the Quality of Study
- The FDA Requires Strict Adherence to the Protocol except when patient safety is a concern
- The FDA allows flexibility to be written into the Protocol
- The PI is responsible for assessing the feasibility of performing the study at his or her Institution.
- Recent FDA focus has been on Protocol Adherence
- Be aware of any Systemic Obstacles to Adherence
  - Example: Centralized Clinical Trial Center/Delays in Test Results
  - Do a walk through before enrolling subjects

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Are you Maintaining Strong Communication and Reporting relations with OHRP, FDA, etc.

- **Do they know you/your institution**
- **How do you Assess Whether Internal Findings are Reportable**
- **Don't be afraid to ask questions and seek guidance**
- **Report unanticipated problems**
- **Attend educational sessions involving FDA/OHRP Reps – they keep track of which institutions attend.**
- How Do you Control Contact with Feds?
  - Does this Approach ensure Consistent and Appropriate Communication or does this Practice Prevent Good Relations?
- Learn From Unique Models for Reducing Risks
  - Centralized model
  - IND/IDE Office

**Many institutions require communication through Regulatory or IRB Office

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Basic Questions to Ask Yourself

- **Do you Have Well Designed SOP's**
- **Are you doing what your policies and SOP's say**
  - **Review frequently with staff (when is the last time you went over SOP's)**
    - **Are they in line with current guidance (Changes to Common Rule)**
- **Do your SOP's and the Protocol Conflict?**
  - **Are you keeping an eye out for differences between Institutional SOP's and Protocol and Contract**
  - **Which takes precedent?**
    - **Recent 483 – Institution did not recognize protocol reporting times to IRB were shorter than SOP's**

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Review SOP's to Assess Whether They Create Non-Compliance

Strive for improving your processes.

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Support Your PI's But Make Sure Make Sure PI's Are on Board For Full Compliance

- Training (updated regularly)
- Monitoring (with Corrective Measures)
- Communication (Set aside Time)

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Does the PI Understand His/Her Responsibilities FDA Form 1572

- Will assure that the study will not start prior to review and approval by the IRB
- Will conduct and personally supervise the study according to the relevant protocol
- Will only change the protocol after notifying the sponsor and obtaining IRB approval prior to implementing the change
- Will seek a properly constituted IRB and obtain initial and on-going review
- Will obtain informed consent of subjects and submit progress reports to the IRB at intervals not to exceed 1 year
- Will prepare and maintain adequate and accurate case histories designed to record all pertinent observations for each subject
- Will prepare and maintain adequate and accurate drug accountability records
- Will collect and report the data in a way to accurately and completely reflect the observations noted during the study

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FDA Form 1572

- Will report immediately and promptly if adverse events are alarming
- Will communicate to sub-investigators information on scientific matters of importance related to the investigation
- Will ensure that the drug is administered according to the stated dosing regime, including dose, route, rate, and duration, and maintains records documenting such facts
- Will certify that the drugs are being tested for investigational purposes and will obtain informed consent of subjects or their representative prior to enrollment
- **PI Can Delegate Tasks BUT NOT Responsibility**
- **These Responsibilities Directly Correlate to Common FDA Inspection Findings Listed Above**

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Lessons Learned from FDA and OPRR/OHRP Closures and Findings

- **Keep up on Recent Guidance (FDA and OHRP)**
- **Read any previous FDA Inspection reports or OHRP determination letters regarding your institution (Beware of repeat problems)**
- **Read Common findings and Determination Letters (IRB Focus)**
  - https://www.hhs.gov/ohrp/compliance-and-reporting/determination-letters/index.html
- Read FDA 483s and FDA Warning Letters (including responses)
- Read OHRP Determination Letters
- Read your FWA
- Does your Clinical Research Support Office Participate in all Regulatory Visits?

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Common Clinical Investigator Inspectional Observations*

- Failure to follow the investigational plan; protocol deviations
- Inadequate and/or inaccurate case history records; inadequate study records
- Inadequate accountability and/or control of the investigational product
- Failure to comply with Form FDA 1572 requirements
- Inadequate subject protection; informed consent issues
- Safety reporting; failure to report and/or record adverse events
- Failure to comply with 21CFRpart 56 (IRB)requirements.

- **www.fda.gov**
- *Most common observations collected from issued FDA Form 483s 2020

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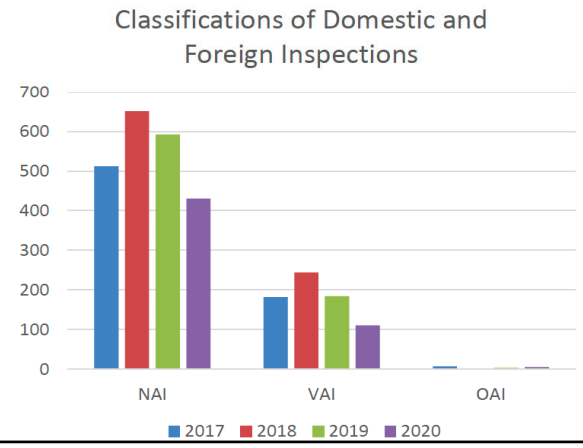
Final Classifications for Clinical Investigator Inspections FY 2017-2020



	2017	2018	2019	2020
NAI	512	651	592	430
VAI	182	244	184	110
OAI	7	1	3	5

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Common Institutional Review Board Inspectional Observations*

- Failure to conduct initial and/or continuing review of research
- Failure to have minutes of IRB meetings in sufficient detail to show attendance at the meeting; vote actions, quorum issues
- Failure to conform to membership criteria listed in 21 CFR 56.107; membership list
- Failure to follow FDA regulations regarding expedited review procedures
- Inadequate written procedures for prompt reporting of non-compliance, suspension or termination
- Failure to prepare and maintain documentation of IRB activities; inadequate copies of research proposals and related documents

Most common observations collected from issued FDA Form 483s 10

www.fda.gov

*Individual Study Concerns can result in shutdown as finding expand the scope of original Study Inspection to IRB Inspection

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Common Sponsor-Investigator Inspectional Observations*

- Failure to select qualified investigators and/or monitors, ensure proper monitoring of the study and ensure the study is conducted in accordance with the protocol and/or investigational plan. (General responsibilities of sponsors)
- Failure to submit an Investigational New Drug (IND) application
- Failure to maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product; Investigator Statement (FDA 1572); Financial disclosures.
- Inadequate subject protection; informed consent issues
- Failure to notify FDA of termination of investigator

*Most common observations collected from issued FDA Form 483s
www.fda.gov

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Understand the Most Common Findings 483's and Warning Letters

Common Findings

1. Failure to follow the investigational plan and/or regulations **[21 CFR 312.60]** **[21 CFR 812.100 & 21 CFR 812.110(b)]** was cited in 3 of 3 Warning Letters to Medical Device CIs.
2. Protocol deviations including so called alleged approval
3. Inadequate recordkeeping **-** [21 CFR 312.62(b)]. & [21 CFR 812.140(a)(3)] was included in 2 of 3 Warning Letters issued in 2014 & 2015.
4. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)].
5. Procedures for design change have not been adequately established, per 21 CFR 820.30(i). Inadequate subject protection – failure to report AEs and informed consent issues
   a) Procedures for corrective and preventive actions have not been adequately established, as required by 21 CFR 820.100.

Warning Letters

1. Eligibility Violations - including unacceptable ECG results, a subject previously enrolled in a study and received a treatment that was disqualifying, prohibited prior/ConMeds, (+) pregnancy test. - Randomization prior to receipt/evaluation of Eligibility Data & some subjects had already completed the study.
2. **Device- "**…MRI and X-rays were taken over six (6) months prior to implantation of the investigational device."
3. Dosing Errors – including overdosing, under-dosing, dispensing wrong drug, etc. Missed Efficacy and/or Safety Assessments blood, urine, and/or stool specimens, ECGs, scans - Out of Window Tests/Assessments
4. **Ref: 08-HFD-45-1001.** Discrepancies were noted among the lists that recorded the initials of subjects who were enrolled in the study …and received study drug -As a result of these discrepancies, it is not possible to determine which patients actually received study drug.
   a) **Ref: 08-HFD-45-1001.** a. Operating room pharmacy log were not kept. There were no records for the preparation and dispensing of **[redacted]** for subjects in protocols **[redacted]** and **[redacted]**
5. **Device -**Failure to submit complete and accurate progress reports [21 CFR 812.150(b)(5)].
6. Failure to maintain accurate, complete, and current records of shipment, receipt, use, or disposition of a device and failure to maintain the records during the investigation and for a period of 2 years after the date on which the investigation is terminated or completed [21 CFR 812.140(a)(2)(i) and (iii), 21 CFR 812.140(b)(2), and 21 CFR 812.140(d)]..

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Most Significant Violations

- Enrollment of ineligible subjects
- Violation of protocol affecting safety
- Extensive data corrections and questionable changes
- Inadequate oversight of study personnel
  - *Inappropriate delegation of authority*
  - *Poor oversight of satellite sites*
- No informed consent
- Failure to communicate with IRB
- Falsification

  - **Example: Jesse Gelsinger –UPenn Death in Gene Transfer Research**
    - Conflicts of Interest - PI Developed adenovirus vector
    - Unreported Deaths and Injuries
    - Changes to Protocol w/o IRB (and FDA) Approval
  - **Result: Media Attention – Congressional Hearings – Distrust**

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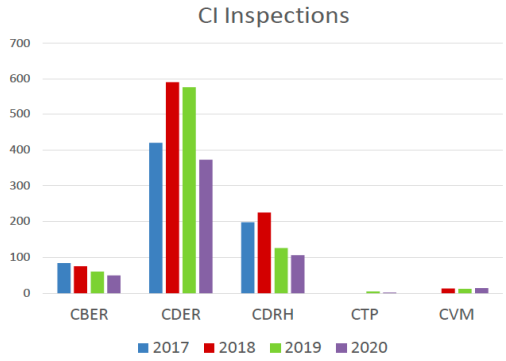
Clinical Investigator Inspections by Center FY 2017- 2020*



Center	2017	2018	2019	2020*
CBER	84	75	60	50
CDER	419	591	574	372
CDRH	198	225	126	106
CTP	0	0	5	2
CVM	0	13	12	14

* Due to the COVID-19 pandemic, RRAs (not reflected in the above table) were conducted. See slide 31 for more details.

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The Best Training and Education Program Includes Auditing/Monitoring

What Are Your Resources For: Monitoring/Auditing/Training/Education

- **Do you have an auditing or monitoring program**
  - Who Performs follow-up on Corrective and Preventative Action Plans to confirm compliance with Plan
    - Do not just audit for improved audit outcomes
    - Who should audit CAPA adherence (Compliance Office)
    - Confirm CAPA is being followed
- **Do you provide a pre-audit service to assist investigators**
  - **Educate - how to be audit ready**
  - **How to *Manage* an FDA audit**
  - **Identify potential study 483 issues prior to audit**
  - **Address where possible prior to Audit**

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What to Do?

How Do I Prepare Once I Receive Notice of an Inspection

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Preparation- Using Existing Monitoring Resources To Prepare

- Preparation begins before study initiation BUT…
  - **It is never too late to prepare**
- Pre-Audit – Make sure you know potential issues before you are audited –document, resolve, CAPA
- Have a Plan for Managing the Audit – Professional approach and Demeanor is recognized and appreciated
- Prepare the players – who is the in room assist and who is doing document prep
- Prepare the PI and Administration (Have a Notification List)

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Familiarize Yourself (and your Team) with FDA Guide on Inspections

- FDA Follows specific Guidelines on How to Run an Inspection- Review those guidelines
  - https://www.fda.gov/downloads/iceci/inspections/ucm142981.pdf
- What is your policy on Managing Audits
  - Who do you notify?
  - How Do you prepare?
  - Do you have space?
  - Who on your audit team does what?
  - Who is in the Room with Inspector? (Take Minutes)
  - Prepare for the Unexpected – (Hypothetical Worst Case)

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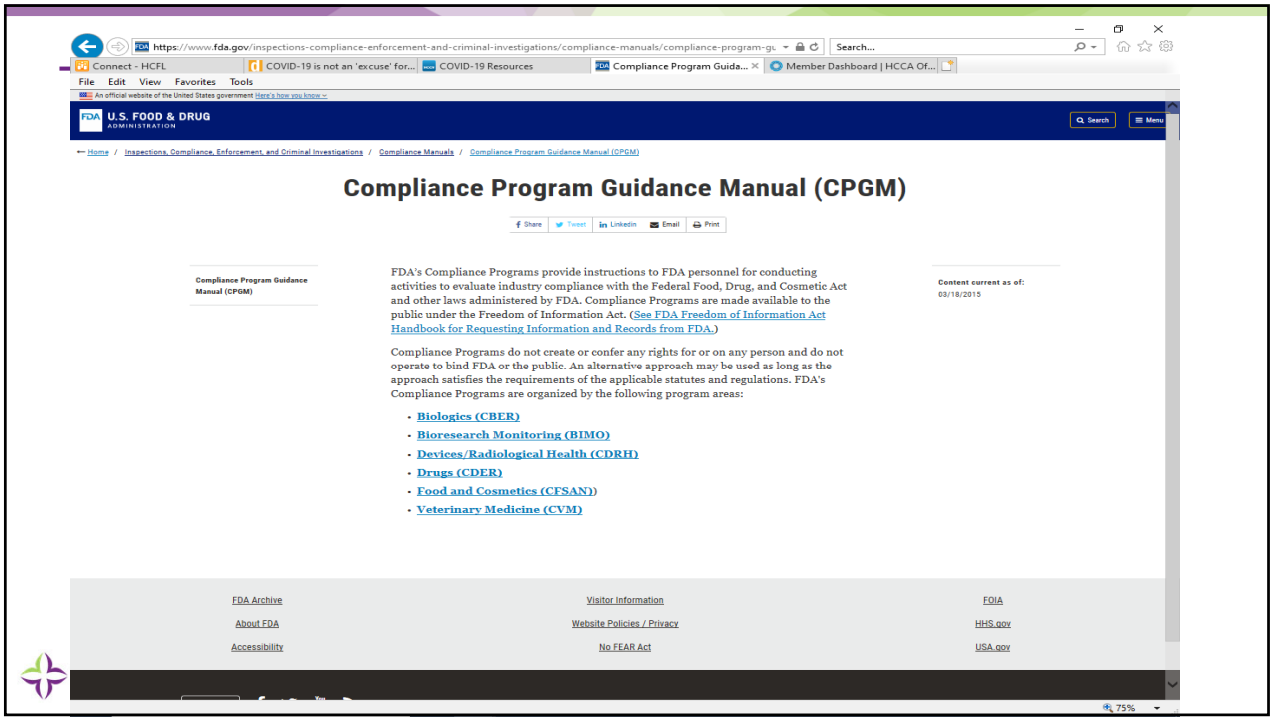

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When the Call Comes

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When you Don't Have a Plan

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“We are the Government and We are Here to Help You.”

- Form FDA 482 – Notice of Inspection

Follow your SOP.

- Usually a few days notice – can ask for minor delay
- Ask to see official ID
- Ask the purpose of the visit
- Assemble your team
- Do not refuse to permit inspection
- Know who to notify.
- Know what to say and not to say.
- Manage The Inspection
- Have confidence in your team and the quality of your work based on pre-inspection preparedness and training
- Beware FDA OCI - Primary responsibility for criminal investigations (e.g. Report of more than $10,000 worth of Investigational Drug Unaccounted for)

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While FDA is on-site

- Opening meeting
  - Scope of inspection
  - Schedule
  - Explain roles and responsibilities, study conduct
  - Explain records, organization, access
- Objective is to ensure investigator and site staff have clear communication and expectations

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Preparing for an inspection

- Team approach
  - Leader
    - Primary contact for FDA investigator
    - Primary responder to questions
    - Inspection coordinator
    - Note taker
  - Runner
    - Document retriever, reviewer, and copier
    - Note taker
  - Others
    - Available to answer specific questions

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Develop a Story-Board of Your Operation to Present at Inspection

- Paint a Picture of Your Operational Model
  - Make sure that it is real and not just on Paper!
- Organizational charts
- Job Titles/description and training schedule/records
- Documents to show who is responsible for specific operations, clinical studies, or regulatory documents (Reporting matrices, RACI diagrams, etc.)
- Overview of the quality system (including a Quality Manual, if you have one)
- Quality Policy and Objectives
- Key procedures, such as those governing complaint handling, CAPA, document control, and change control.
- How Do you Measure Whether a CAPA is Effective?

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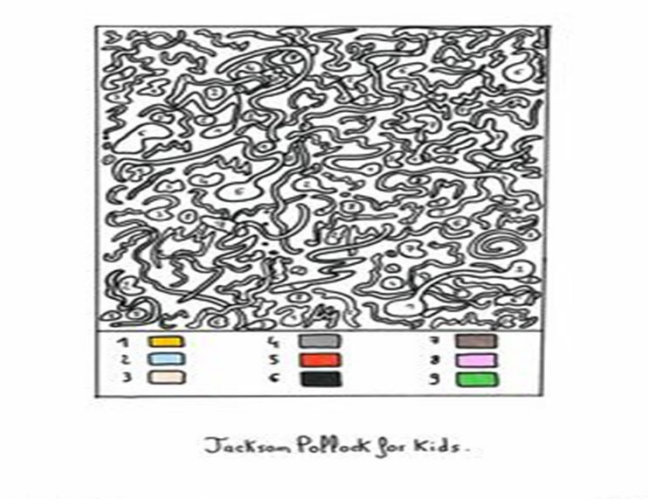
Story Board Your Operation

(FYI - It should not look like this)



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Basic Rules

- **DO** answer the question, only the question.
- **DON'T** offer more information than what is asked or requested by FDA
- **DO** ask FDA for clarifications to make sure you understand what an investigator is asking
- **DON'T** lie, guess, or make up an answer. It is OK not to know everything. A simple, "I don't know, but I will find out for you" will suffice.

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FDA Inspector reviews the following for investigators:

- SOPs
- Adherence to Protocol*
- Authority to conduct
- Subjects' records
- Informed consent*
- IRB documentation*
- Adverse event reporting
- Drug/Device accountability
- Records retention
- Electronic records

* Be prepared for Post COVID Reviews

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Additional items FDA investigator Reviews for a sponsor (Investigator/Sponsor):

- Selection & monitoring of clinical investigators
- Adverse event reporting
- Data collection and handling
- Data tabulations
- Record retention
- Test article and accountability

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Expectations during an inspection

- What the PI should expect of the FDA
  - Discuss all observations as they occur or at least daily
  - Minimize surprises, errors, and misunderstandings
- What FDA expects of the PI
  - Knows the Protocol thoroughly – fully engaged
  - Ask questions about observations
  - Request and Provide clarification
  - What corrections have been or will be made

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While FDA is on-site

- During the inspection
  - Be accessible to answer questions, provide copies
  - Don't delay unnecessarily, if time is needed to retrieve records/answer, explain why
- Daily wrap up
  - Questions?
  - Concerns?
  - Communication
  - Plan for following day

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As the inspection closes

- Schedule close out meeting, ensure responsible/knowledgeable parties available
- Is there an FDA 483?
  - Observations clear?
  - Do you have additional documentation not reviewed during inspection?
  - Verbal response? Will be included in Establishment Inspection Report
  - Plan to respond in writing?

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After the Inspection has Ended

- If there was an FDA 483 – should respond in writing
  - Recap observation
  - Provide explanation if appropriate
  - Describe corrective actions considered and when they will be implemented including any SOP revisions, staff training
  - Consider impact on any other on-going or future studies
- No FDA 483, but discussion items?
  - Consider any impacts and corrective actions you may need to do
  - Consider a written response, the items will be reported in the Establishment Inspection Report and reviewed
  - Even If No 483 ask – What could we do Better?

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Why submit a 483 response

- May mitigate further FDA compliance action
- Demonstrates to FDA an understanding and acknowledgement of the observations
- Demonstrates to FDA a commitment to correct, voluntarily comply
- Establishes credibility with FDA

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Types of Post Inspection Letters from FDA

- An *Informational* or *Untitled Letter* - identifies deviations from statutes and regulations that do not meet the threshold of regulatory significance for a Warning Letter. Such letters may request a written response from the clinical investigator.
- A *Warning Letter* - identifies serious deviations from applicable statutes and regulations. Issued for violations of regulatory significance. Significant violations are those violations that may lead to enforcement action if not promptly and adequately corrected. Issued to achieve voluntary compliance, and include a request for correction and a written response to the agency.
- A *Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)* - process to disqualify the clinical investigator from receiving investigational new drugs or biologics, or investigational devices if the investigator has repeatedly or deliberately failed to comply with applicable regulatory requirements or has deliberately or repeatedly submitted false information to the sponsor or FDA in any required report.

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Elements of an effective response

1. Include a commitment/statement from senior leadership
2. Address each observation separately – Identify Root Cause where applicable
3. Note whether you agree or disagree with the observation
4. Provide corrective action accomplished and/or planned; tell FDA the plan
5. Provide time frames for corrections
6. Provide method of verification and/or monitoring for corrections and by whom at Site
7. Consider submitting to FDA documentation of corrections where reasonable and feasible
8. Be timely – or communicate a reason for delay

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Questions?

Thank you

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