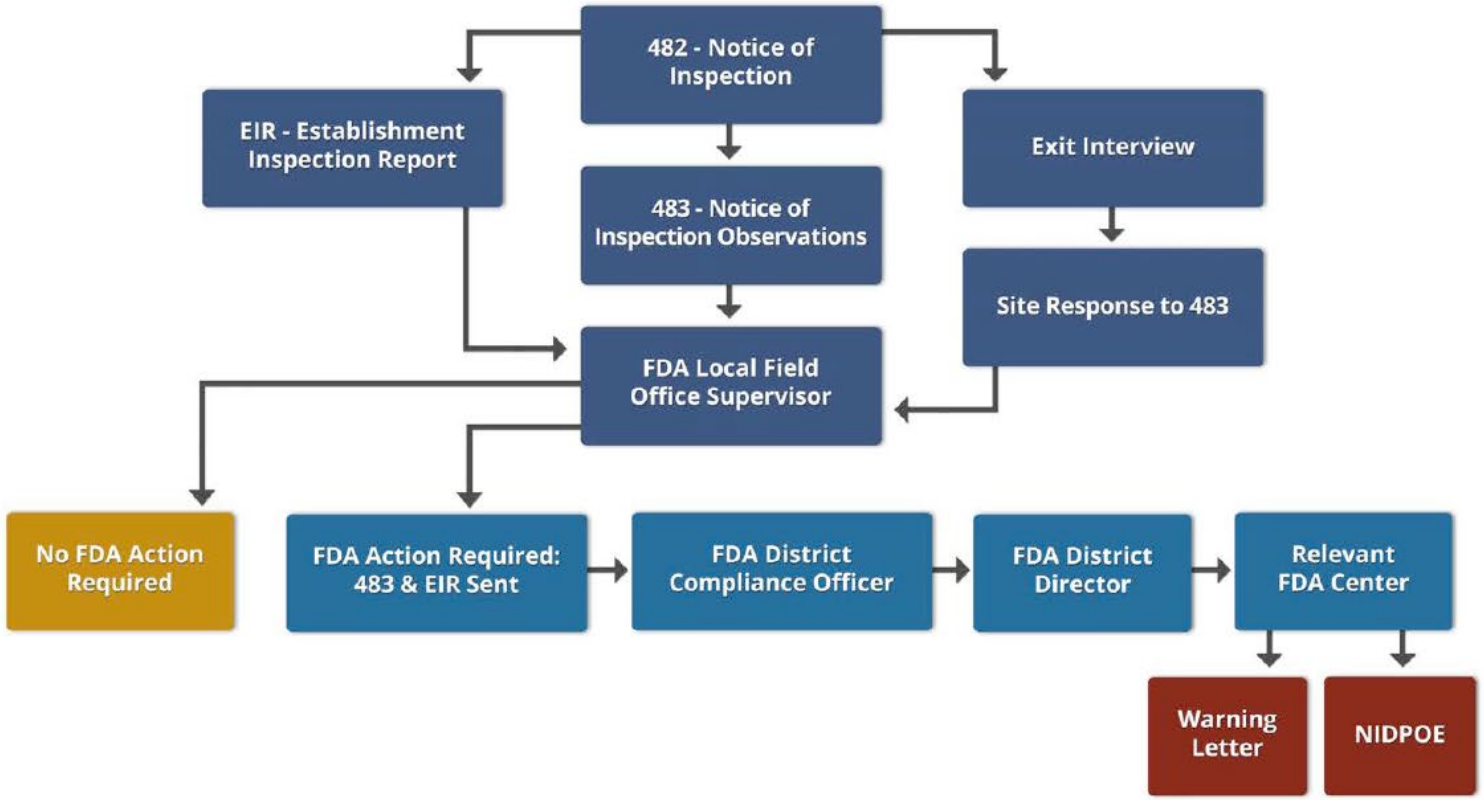
Part 3: After the Inspection

FDA Inspection Series - Research Matters

FDA Inspection Process



FDA. 2020. "FDA Bioresearch Monitoring Information."; FDA. 2020. "Form 483 Frequently Asked Questions."

Chart obtained from CITI Program Webinar presented by Dr. Theresa A. O'Lonergan on March 15, 2022

Topics Covered:

- FDA Inspection Process and Possible Outcomes
- Issuance of FDA Form 483
- Responding to FDA Form 483
- Resolution and Beyond

Possible outcomes at District Office

Site's written response to 483 → FDA Field Office (not the inspector) → District Office.

UTSW HRPP is available to provide guidance at all stages of the FDA Inspection Process.

Possible outcomes from District Office to relevant FDA Center -

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)

Possible outcomes at relevant FDA Center – Final Classification

The four most common actions -

- Letter stating general compliance with pertinent regulations.
- An **Informational or Untitled Letter** Identifying deviations that do not meet threshold of regulatory significance.
- A **Warning Letter** identifying serious deviations requiring immediate voluntary compliance to correct deviations.
- A **Notice of Initiation of Disqualification Proceedings and Opportunity to Explain** (NIDPOE).

UTSW HRPP is available to provide guidance at all stages of the FDA Inspection Process.

FDA. 2010. “Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators.”

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Issuance of FDA Form 483

If issued, the FDA field office will send the 483 to -

- Research study team

PI is responsible for sharing all documents (483 and/or EIR, if not already shared) with –

- Research site compliance office
- UTSW HRPP office
- Other recipients (e.g., sponsor) based on institutional policy

Common Observations in 483

- Staff performing procedures that are not listed in IRB-approved protocol.
- Documentation of study visits is incomplete or inaccurate.
- Drug accountability is insufficient to show careful handling and dispensing.
- Other standard operating procedures (SOPs) are not being followed (for example, SAE not reported in a timely manner).

Example of a 483 Observation

Observation
"An investigation was not conducted in accordance with the investigational plan.

Specifically,

a. Serious Adverse Events (SAE) were not reported in a timely fashion to the IRB as required by the Institutional Review Board (IRB) written procedures and IRB study approval letters. IRB written procedure . . . requires all serious adverse events related to the study treatment . . . be reported within five working days of knowledge of the event."

483 lists the observation

483 lists the specific details – this is what the investigator can respond to in the written response

FDA Form 483. 2019. "Hennepin Healthcare Inc."

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Responding to FDA Form 483

HIGHEST PRIORITY

ASK QUESTIONS BEFORE INSPECTOR FINALIZES FORM 483 DRAFT AND LEAVES YOUR FACILITY

SET A FIRM AND DEFINITIVE TIMELINE TO DRAFT RESPONSE – 15 BUSINESS DAYS

IDENTIFY ROOT CAUSE

DISPUTING OR ACCEPTING A VIOLATION

CORRECTIVE ACTIONS

DRAFT RESPONSE

FINAL DRAFT RESPONSE SHOULD BE SENT TO UTSW HRPP BEFORE SUBMISSION TO FDA

Responding to FDA Form 483 - Drafting the response

Do's –

- Briefly explain the approach used to review the 483.
- Provide separate response for each violation using 483 as a template.
- Use respectful and neutral language.
- Clarify if site agrees or disagrees with each item.
- Use concise and clear sentences.

Responding to FDA Form 483 - Drafting the response

Examples of appropriate responses -

- “After carefully reviewing the list of deviations, we agree in part and disagree in part with FDA inspector’s findings.”
- “We did miss collecting blood specimen on Month-3 visit for 2 subjects. PI discovered this after the second occurrence. Please see CAPA for remedial measures.”
- “Temperature log was not maintained between 12/25/21 to 1/5/22. Please see temperature recordings maintained by the central pharmacy to ensure there were no excursions along with CAPA.”

Responding to FDA Form 483 - Drafting the response

Don’t -

- Question the knowledge, qualifications or attitude of the inspector.
- Invalidate the seriousness/ importance of deviations as not important or being nit-picky.
- Demand or express need for less federal bureaucracy and mandates.
- Threaten to contact your congressman or other higher authorities to complain.

Responding to FDA Form 483 - Drafting the response

Examples of inappropriate responses –

- “Just one missing blood draw collection for Month-3 visit is not serious because patients were doing fine, and no adverse events were noted.”
- “The inspector was argumentative and seemed to be determined to make our program look bad.”
- “Only 10 days of temperature recordings were missing out of the 3 years of continuous temperature monitoring.”
- “Inspectors did not know what they were talking about. With my references brought in, I would like re-evaluation of the citied violations to discuss incorrect findings.”

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Resolution and Beyond

Use the 483 as an opportunity to improve

- Addressing all violations is only the first step
- Identify the behaviors that caused them
- Examine processes, training and oversight of study
- Create CAPA for now and future study activities

Maintain all documentation related to the FDA Inspection in study binders

References

”Understanding 483s and How to Survive them” CITI Program Webinar; Presented March 15, 2022, by Theresa A. O'Lonergan, PhD, MA, Velocity Clinical Research.

UTSW FDA Inspection Preparation Guide. UTSW HRPP v2.0_09-2019

”The FDA Just Completed Its Inspection... Now What?”; May 12, 2016, David R. Butcher, Marketing Communications, MasterControl

Any questions?

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