E-BOOK

Complete Guide to FDA Inspection Readiness

ADVARRA™

Table of Contents

Introduction

You've received a communication from the Food and Drug Administration (FDA) regarding an upcoming inspection of your organization, what's next? An announcement of an FDA inspection can create anxiety, but if the steps and expectations are known, the inspection announcement will be less stressful. In fact, an FDA inspection will provide assurance of study integrity.

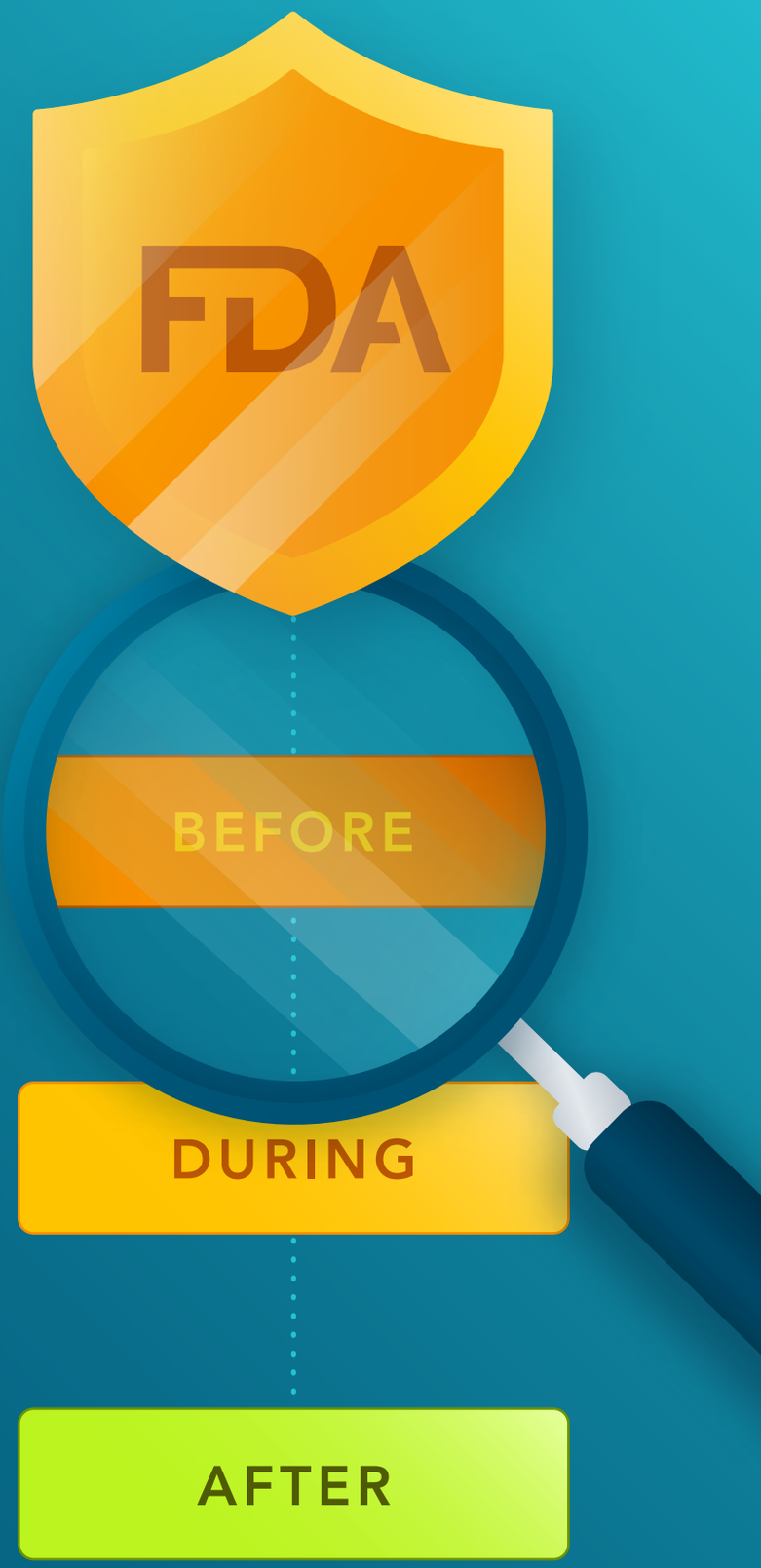
Although some inspections may come at a critical time in your clinical research journey, they are meant to protect the rights, safety, and welfare of human research subjects; to verify the accuracy and reliability of clinical trial data submitted to the FDA; and to assess compliance with FDA's regulations governing the conduct of the clinical trial. Inspections can happen for multiple reasons, including a new drug application, complaint, safety issue, or just a routine inspection. The FDA's regulations are meant to govern the conduct of a clinical trial, including regulations for investigators, informed consent, and ethical review.

This eBook is designed to help you prepare for an upcoming FDA inspection, outlining what to expect during the investigation, and strategies to employ as the investigation process comes to a close.

Preparing for an Inspection

Let’s examine the FDA inspection process. When preparing for an inspection, having a site-specific process for supporting a regulatory inspection is important as it will identify who does what before, during, and after a regulatory inspection.

Additionally, the organization should identify the most responsible person with the most accountability for the operations of the organization and responsible for compliance. It’s this person who will receive the Form FDA 482 Notice of Inspection from the inspector upon their arrival.



Even with a point person identified, all staff, including the principal investigator (PI), sub-investigator(s), study coordinators, and other pertinent team members should meet to review all activities for the study under investigation before the inspector arrives. This includes review of the protocol, the subjects enrolled, and delegation of study procedures.

Upon meeting beforehand, site personnel should plan to discuss topics such as:

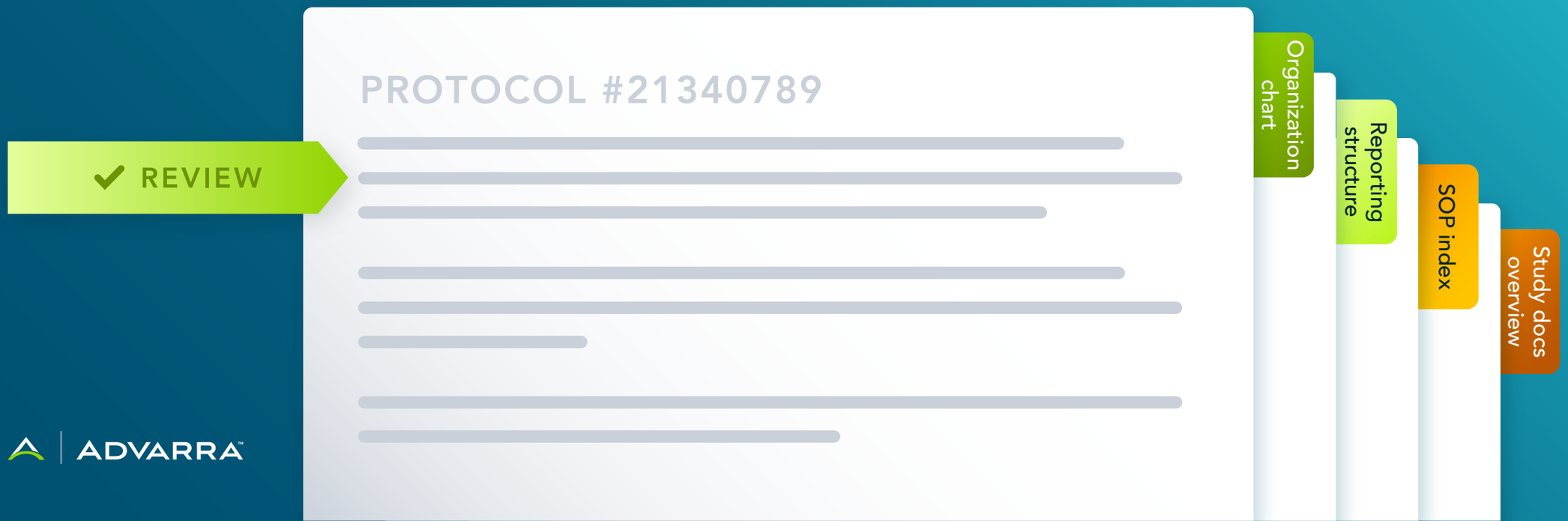
- Protocol training
- Subject recruitment
- Informed consent process
- Study-specific procedures
- Source documentation
- Data entry
- Investigational product handling
- Ethical reviews and approvals
- Monitoring

It's also important for site staff to prepare for the inspector interview. Re-read the protocol, study procedures and study manual. Recall who did what in the study. If any issues happened during the study, have an explanation. For example, were there protocol deviations? Why did they occur? What actions were taken to prevent future occurrences? Conducting mock interviews will also help staff become more at ease with answering questions related to the protocol.

Preparing beforehand for the inspector interview helps the site ensure all study documents are readily available. If study records are archived off-site, all records should be recalled and available for the inspection. Review the records to confirm they are complete and ensure the inspector can open and review any electronic records. If the site is missing any documents, check with the sponsor/contract research organization (CRO) to see if a copy is in the trial master file (TMF) and the sponsor/CRO can send a copy of the document to the site.

Sites must provide multiple documents with information about the organization. The designated host should provide the inspector with the following:

- Site's organizational chart
- Site's reporting structure
- Standard operating procedure (SOP) index
- An overview of study documentation organization



Prior to the inspection, the inspector will request to see study documents. It's imperative to only provide them with the specific documents requested. For example, if they requested to see all the signed Form 1572s, do not bring in the investigator site file (ISF) where the Form 1572s are filed. Remove the forms from the file before providing them to the inspector. Upon review of the Form 1572s, the inspector will request the principal investigator's (PI's) and all listed sub-investigators curriculum vitae (CV), medical licenses as applicable, and financial disclosure agreements.

Common documents an inspector may request to see include:

- Protocol and amendment training
- Delegation of responsibilities
- Screening and enrollment logs
- Informed consent forms (ICFs) – including ICFs for screen failures, ethical reviews, and approvals

Additionally, an inspector may select several or all participants who are screened and enrolled in a study and review their source documents, including all available medical records. If the study used an electronic data capture (EDC) system and it is still active, the inspector will request access to this system. If the database is closed, the inspector will review either data listings or they might have access to case report forms (CRFs) from the sponsor.

Inspectors will also conduct source data verification (SDV) and source data review (SDR). SDR is the review of source documentation to check on protocol compliance and staff involvement. SDV is the process by which data within the CRFs are compared to original sources of information to confirm accurate data transcription. Source data is original records and certified copies or original records of clinical findings, or observations (ICH E6 R2 1.51).

To keep the inspection moving efficientl, assign a designated copier and printer, if possible. The inspector may request copies of any of the essential documents or source documents they review.

During the Inspection

As mentioned earlier, when the inspector arrives at the site, they will present a Form 482 Notice of Inspection to the designated point person. After the Form 482 is presented, escort the inspector to the inspection room.

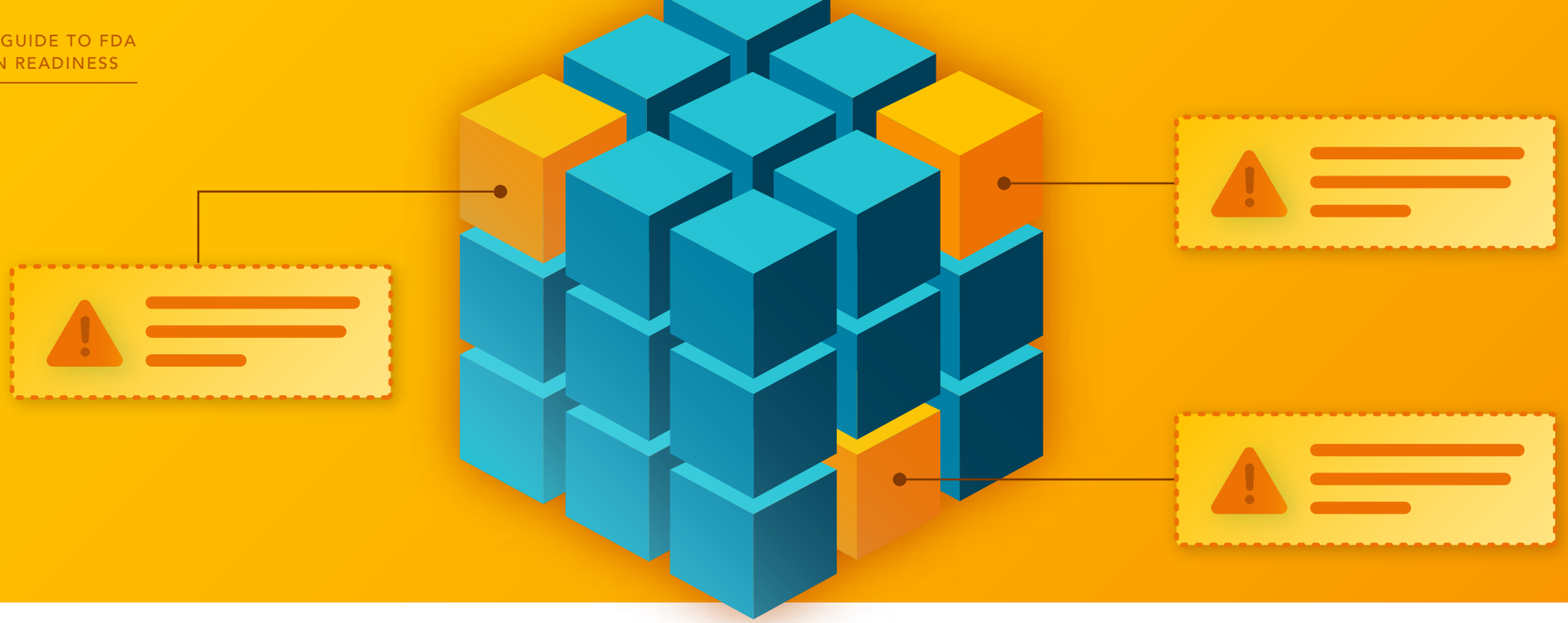
Always escort the inspector throughout the site and never let the inspector wander on their own. This is to prevent them from finding anything by chance, and keeps everyone on schedule.

The inspection will begin with an opening meeting. This meeting covers introductions of key people, a background of the organization, and confirmation of the scope of the inspection. This allows the FDA investigator to understand the organization, processes, and functions.

As the inspection progresses, the document requests will be focused on the study or studies identified in the scope and how that documentation verifies compliance with regulations and applicable SOPs. Key staff should be available for interviews.

Oftentimes the most daunting aspect of an FDA inspection, it's important to come prepared to the interview. When called to speak with the inspector, introduce yourself by stating your name, your position, and confirm the study being inspected and describe your responsibilities in that study. Make sure your ID badge is visible; if you do not have an ID badge, you may present a business card. The inspection host or another site manager will be with you during the interview, it is recommended that employees shouldn't be alone with the inspector during an interview.

It is of utmost importance to make sure you understand the questions posed during the interview so you can answer the question fully and as accurately as possible. It's okay to take your time, think through your answer before giving it, and if necessary, ask the inspector to rephrase the question. If you do not know the answer, tell the inspector that, as well as you will get them the information they are requesting.



Only answer questions relating to your role in the study. For example, a study coordinator should not answer questions directed to the PI and the PI should not defer questions to the study coordinator. Additionally, do not answer questions outside your area of responsibility, do not guess, and do not volunteer information.

Throughout the interview, the inspector will often remain silent after you are done answering your question. This is a strategic tactic they use, and you must respect the silence and let it draw out. Frequently, inspectors use this as a way to draw out more information from interviewees, as many times, people are uncomfortable by the silence and will fill it by continuing to talk and volunteer information. If you've answered the question in full, and there is nothing more to your answer, remain silent until the next question is asked.

As previously mentioned, investigators will request specific documents during the inspection. Document requests must be handled expediently and reviewed prior to presenting them to the FDA. Expect to have daily debriefs with your inspector, which typically will include document request for the following morning.

A debrief may also entail the inspector discussing any issues, observations, or making document requests for the next inspection day. The PI and site managers should respond at once to any observation and work to clarify or correct any potential errors or misunderstandings while the inspection is ongoing. Meeting with the inspector(s) for the daily debrief and addressing issues as they occur helps to minimize surprises if a Form 483 is issued at the end of an inspection.

> *2020 Investigations Operations Manual, section 5.2.3*

After the Inspection

As mentioned earlier, when the inspector arrives at the site, they will present a Form 482 Notice of Inspection to the designated point person. After the Form 482 is presented, escort the inspector to the inspection room.

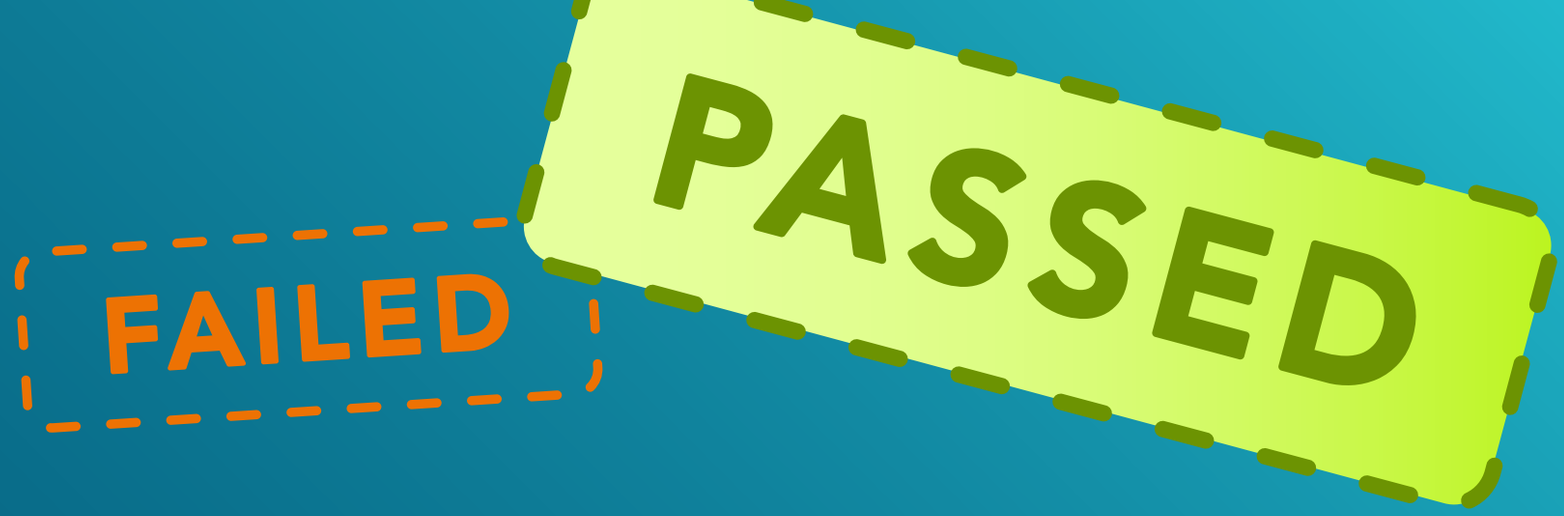
- Regulation non-compliance
- Concerns regarding subject rights, safety, or welfare
- Issues with the study or with data integrity

The FDA observation will begin with a citation of the regulation or act, following a pre-defined description of the unmet requirement, and details of the FDA observations during the inspection that deviated from the regulation or act. As the close out meeting comes to an end, site staff will have an opportunity to ask follow-up questions.

A response to the Form 483 is not required, but it is a best practice. If the organization concludes it is best to respond to the Form 483, they must respond within 15 business days. To ensure timely delivery, they should aim for 15 calendar days.

All Form 483s are reviewed at the program level and may be referred to the FDA's Compliance Branch if there are significant observations noted. The Compliance Branch will determine if and what enforcement action(s) to take. The most common enforcement action is an FDA Warning Letter, which is the agency's means of notifying regulated industry of violations and achieving correction. Site staff can review the FDA Warning Letter database to understand types of observations cited, the language used, and inadequate responses.

> *https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters*



Conclusion

While they are often stressful and sometimes unforeseen, FDA inspections are intended to ensure the protection of the human research subject rights, safety, and welfare as they are involved in FDA-regulated clinical studies; to verify the accuracy and reliability of study data submitted to FDA and to assess compliance with FDA regulations.

Understanding the expectations of the FDA, while remaining calm, confident, and cooperative during inspections can help to resolve the apprehension of an inspection and provide the landscape for a successful inspection.