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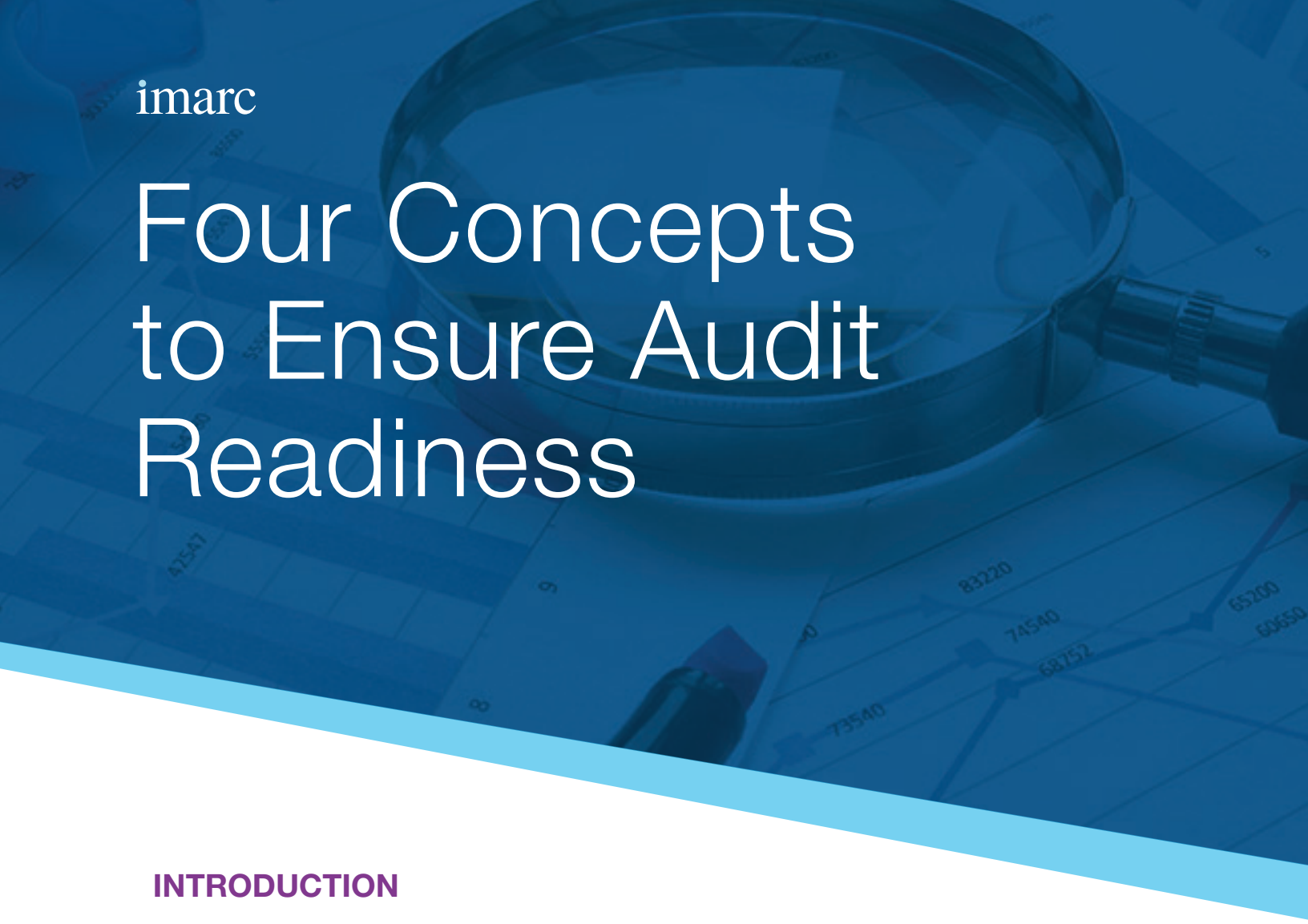
Four Concepts to Ensure Audit Readiness



INTRODUCTION

"Audit ready" is a typical clinical research buzz phrase that can elicit either eyerolls or cold sweat, depending on how confident the study team feels about the overall quality of their clinical study. But what does being "audit ready" truly entail? Most audit preparation occurs at the end of a study and focuses on preparation in the short-term, which often leads everyone on the study team scrambling to "get ready."

Instead, this whitepaper will describe how audit readiness can and should be exercised from the beginning of each study. Understanding the basics of auditing, studying the roadmap that the FDA provides, and following four main concepts will position study teams to be in an "audit ready" state from Day 1.

THE BASICS

Monitoring vs. Auditing

Auditing and monitoring are two distinct and separate processes. One way to think about the difference is that monitors look at each leaf of the clinical study tree, examining the details of each subject and situation at each site, whereas auditors look at the overall forest and big-picture items to evaluate and determine if there are any systemic issues.

Monitoring is the real-time quality control process that oversees the progress of clinical sites and ensures they are performing, reporting and documenting the study in accordance with federal regulations, agreements, protocol, and IRB requirements. Monitors are also responsible for identifying and helping remedy areas of non-compliance with the sponsor and the site while performing routine site visits detailed in accordance with the study's monitoring plan.

The goal of monitoring is to ensure patient safety and valid clinical data throughout the duration of the study and to prepare the site for potential audits.

Auditing, on the other hand, is a quality assurance function intended to ensure the rights, safety and welfare of study subjects, to verify the quality and accuracy of study data, and to assess compliance with regulations and the study protocol. Audits are typically performed by individuals not affiliated or associated with the trial. Many sponsors proactively plan to conduct an audit or a series of audits throughout the study, especially if the study is high-risk, high-enrolling or the product being studied is novel to the industry.

Sponsors may also conduct "pre-BIMO" audits to ensure their study teams are ready should an FDA inspector call. The purpose of these audits is to identify any findings or deficiencies and implement corrective and/or preventative action plans as appropriate.

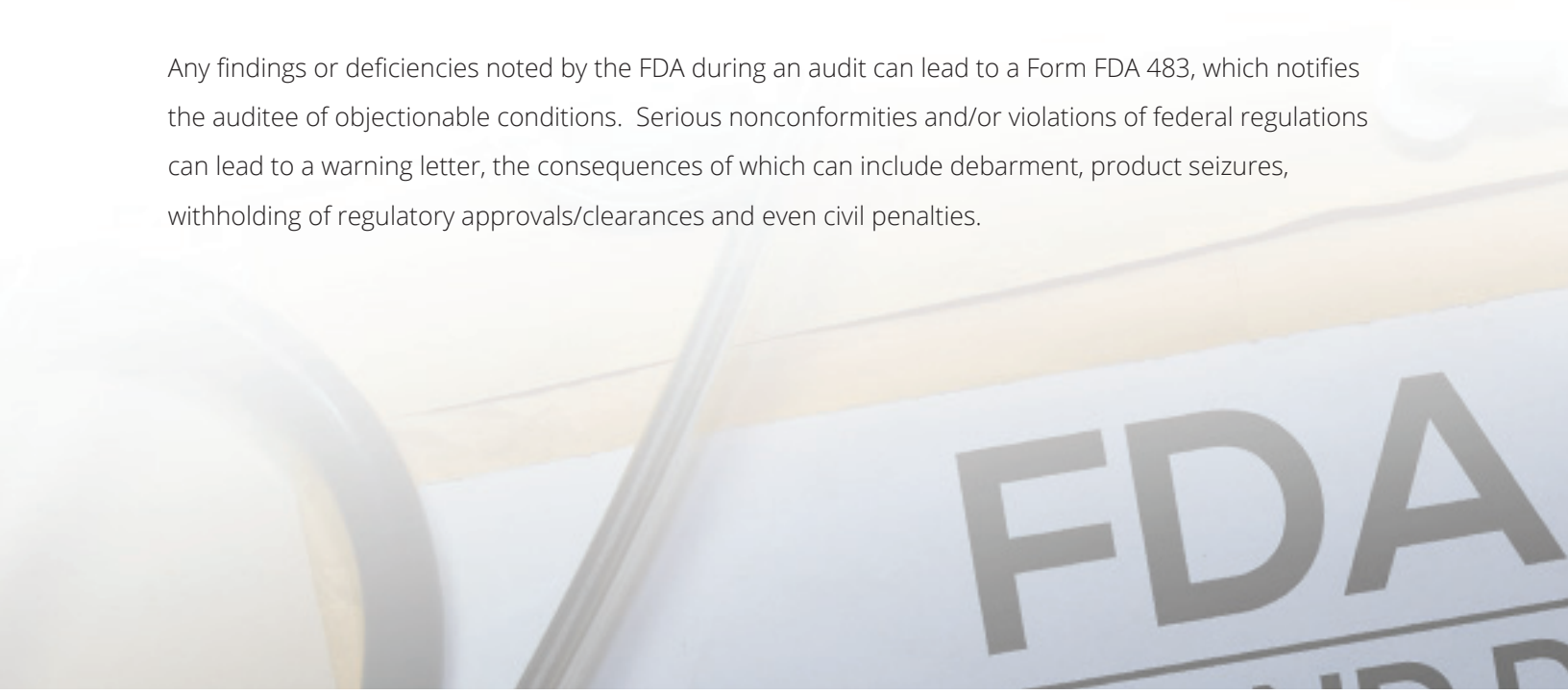
FDA Bioresearch Monitoring Program

The Food and Drug Administration's (FDA) Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections and data audits designed to support marketing applications and submissions to the agency.

FDA BIMO inspectors audit all aspects of clinical research, performing audits of sponsors, labs, IRBs, and, of course, study sites. In 2019, the FDA performed approximately 1,400 domestic and foreign BIMO inspections, with 113 geared toward sponsor/monitor/CRO inspections and 779 geared toward study sites.

FDA audits are classified as routine or for-cause. Routine audits are typically conducted following FDA's receipt and initial review of a sponsor's marketing application (Pre-Market Application (PMA) or New Drug Application (NDA)). For-cause audits are often based on a concern, complaint or allegation that was received by the agency. These claims can include allegations of fraud, concerns of patient safety, patient or staff complaints, or other specific problems that were brought to their attention.

Any findings or deficiencies noted by the FDA during an audit can lead to a Form FDA 483, which notifies the auditee of objectionable conditions. Serious nonconformities and/or violations of federal regulations can lead to a warning letter, the consequences of which can include debarment, product seizures, withholding of regulatory approvals/clearances and even civil penalties.



Answers to the Test

Fortunately, for FDA BIMO audits (and third-party pre-BIMO audits), there should be no surprises regarding what the inspector will be reviewing. FDA publishes Compliance Program Guidance Manuals (CPGMs) which identify the items the inspectors will be reviewing and give an overall sense of how the audit will be run.

Areas that will be covered are as follows:

Sponsor/CRO Audits	Investigational Site Audits
• Organization and Personnel	• Authority and Administration
• Registration on Clinicaltrials.gov	• Protocol
• Selection and Monitoring of Clinical Investigators	• Institutional Review Board
• Selection of Monitors	• Human Subject Records
• Monitoring Procedures	• Other Study Records
• Quality Assurance	• Financial Disclosure
• Safety/Adverse Event Reporting	• Electronic Records and Electronic Signatures
• Data Collection and Handling	• Test Article Control
• Record Retention	• Records Custody and Retention
• Financial Disclosure	• Reports to Sponsor
• Electronic Records and Electronic Signatures	• Monitoring
• Test Article	• Device Studies (if applicable)
• Devices (if applicable)	
• Emergency Research (if applicable)	
• International Data for Drugs and Biologics (if applicable)	

Common Inspectional Findings

Once the CPGMs are reviewed, looking at the common inspectional findings for the last few years is also a good idea. The FDA updates its most common findings every year.

The top findings typically include the same topics:

Sponsor Findings	Investigational Site Findings
• 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 maintain and/or retain adequate records in accordance with 21 CFR 312.57; accountability for the investigational product • Failure to bring non-compliant investigators into compliance	• Failure to follow the investigational plan; protocol deviations • Failure to comply with Form FDA 1572 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 56 (IRB) requirements

Armed with the knowledge of the most common findings, sponsors and sites can work to ensure a strong foundation to get their study started on the right track.

FOUR MAIN CONCEPTS FOR ENSURING READINESS

1. Know the Study

For both sponsors and sites, deep familiarity with the study is the most important part of ensuring compliance, and in turn, inspection readiness. It may sound a bit obvious, but as listed above, failure to ensure that the study is conducted in accordance with the protocol (sponsor/CRO) and failure to follow the investigational plan (Investigational site) are two common findings.

While "knowing" the following aspects of the study are important, rote memorization is not required. Instead, current study information could be made readily available to appropriate study team members using tools such as weekly reports or study dashboards.

Know the ins and outs of the protocol

By knowing the protocol and knowing it well, sponsors and sites will not only be able to conduct a well-controlled, compliant study, but they may improve overall patient safety, decrease the odds of protocol deviations, and decrease the likelihood of overall non-compliance. Knowing how many versions/amendments of the protocol occurred, what changes were made (especially significant changes like inclusion/exclusion criteria changes or follow-up requirements), when study staff were trained and when they were submitted/approved by the IRB are all important.

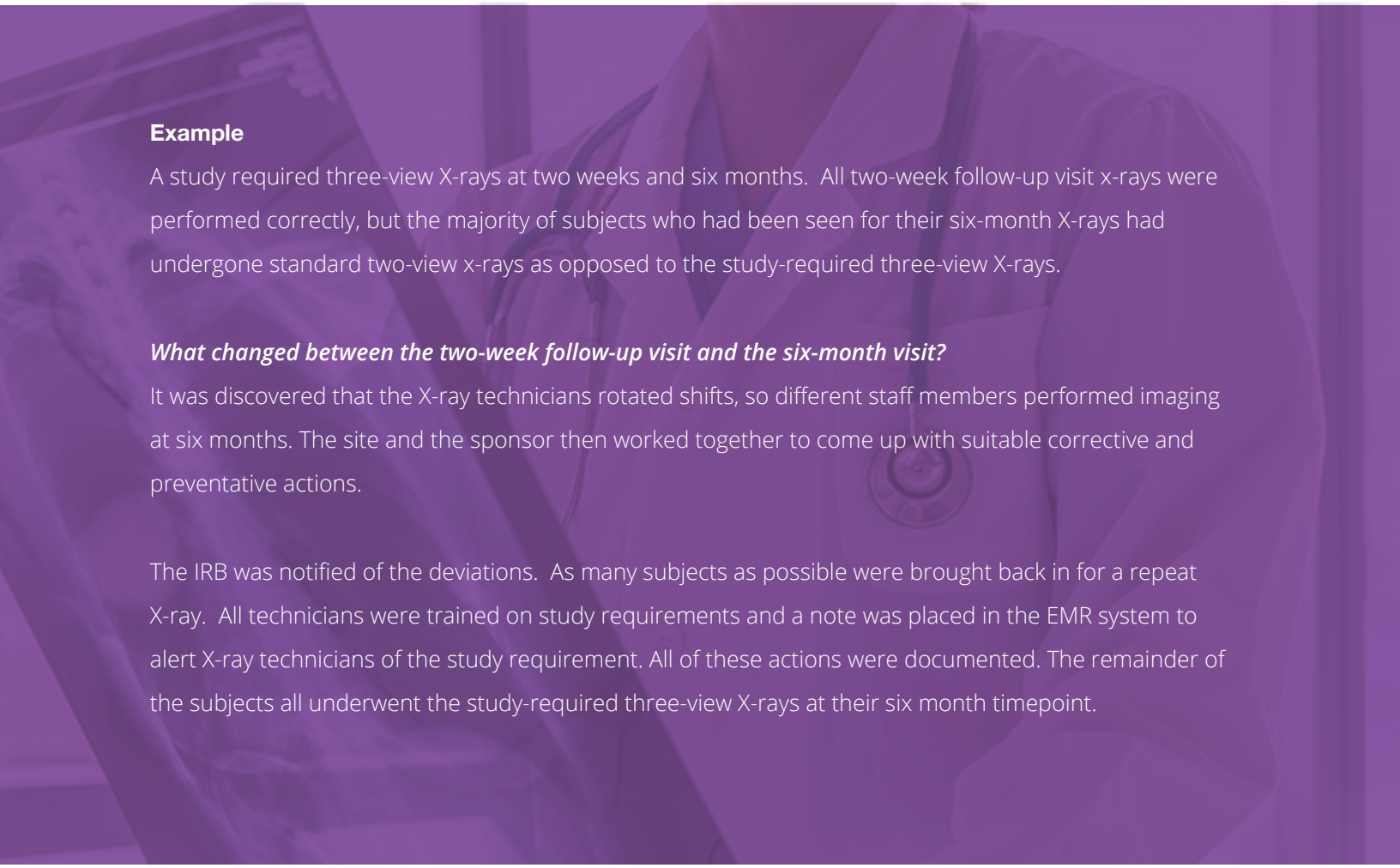
Know the study subjects

Know how many trial participants have been enrolled, withdrawn, lost-to-follow-up and completed the study. It is also helpful to know the details surrounding any withdrawals or lost-to-follow-ups that may have occurred along with documentation that supports the efforts that were made by the study team. If a subject is lost-to-follow-up, all attempts to contact the subject should be documented along with what steps were taken prior to exiting the patient.

Know the protocol deviations and adverse events

Protocol deviations and adverse events are inevitable. In fact, not having any protocol deviations or adverse events can raise questions. Knowing each protocol deviation that occurred and why it occurred is important. Likewise, being familiar with each adverse event that has occurred is critical. Sponsors and sites should consider customized reports that can be run from the database to stay current with this information. In addition, track other key pieces of information such as reporting timelines, IRB requirements, and any corrective and/or preventative actions taken, if applicable.

Using some type of dashboard like this can help sponsors and sites easily spot "one-off" situations or systemic issues and allow them to react accordingly.



Example

A study required three-view X-rays at two weeks and six months. All two-week follow-up visit x-rays were performed correctly, but the majority of subjects who had been seen for their six-month X-rays had undergone standard two-view x-rays as opposed to the study-required three-view X-rays.

What changed between the two-week follow-up visit and the six-month visit?

It was discovered that the X-ray technicians rotated shifts, so different staff members performed imaging at six months. The site and the sponsor then worked together to come up with suitable corrective and preventative actions.

The IRB was notified of the deviations. As many subjects as possible were brought back in for a repeat X-ray. All technicians were trained on study requirements and a note was placed in the EMR system to alert X-ray technicians of the study requirement. All of these actions were documented. The remainder of the subjects all underwent the study-required three-view X-rays at their six month timepoint.

Know the study records and study logs

Well-organized and accurate study files that accurately tell the story of the study is essential. A disciplined process of record keeping that is instituted at the beginning of the study will be helpful in ensuring adequate documentation is available to an inspector. Study staff should consider reviewing study records and performing periodic spot-checks of regulatory documents, logs, study worksheets, source documentation and EDC entries to ensure they align, and that all documentation is appropriately filed.

Know the IRB's expectations

Maintaining a copy of the current IRB policies, including their reporting requirements and timelines for protocol deviations, non-compliances and adverse events will help in audit preparations. Each IRB is different, and some may be stricter than others. Regardless, both the sponsor and site should frequently review IRB policies in detail and update the study team when policy updates have been made.

2. Principal Investigator (PI) Engagement

Whether at the site level or sponsor level, studies are much more effective with a group of engaged PIs who take their responsibility for running of a well-controlled study seriously. This level of engagement goes both ways. Sponsors sit in an ideal position to provide PIs with the information they need to adequately oversee the study at their institutions. This may include information such as number of enrolled subjects, protocol deviations, adverse events, general study issues, co-investigator concerns, research coordinator concerns, monitoring findings, and product accountability, among others.

Likewise, PIs are in a good position to set the culture and tone for how studies are run within their specific environment. By attending required trainings, ensuring staff availability for training, being available to the monitors during visits, knowing the regulations, knowing the protocol, and understanding their role as an active leader in the study, the PIs set a high bar for compliance at their sites. Research coordinators play a role in this as well. By setting regular meetings with the PIs, sending email updates, checking their schedule prior to scheduling monitoring visits, reviewing follow-up letters in order to come up with an action plan together, or other such actions, they help position the PI to effectively oversee the site operations.

3. FDA Inspection Day Plan

Long before an actual FDA inspection, sites and sponsors can be proactive in thinking through the logistics of inspection day. **Some considerations include the following:**

- **Establishing an Inspection SOP**

  An Inspection SOP can help ensure that the entire company and/or clinical site is operating under the same set of expectations about inspection conduct, from the first interaction with an inspector to the closing meeting. Requirements such as who to notify when an inspection is announced, who will participate in the inspection, how the inspection will be handled, etc., can be covered in an Inspection SOP.

- **Identifying a designated location**

  A conference room or independent office with enough space for the FDA inspector(s) and the facilitator(s) from the sponsor or site staff is essential. A designated space that is not in a patient care area and where the inspection can be conducted relatively free from interruptions is preferred.

- **Determining internal inspection roles**

  The sponsor and/or site should create a plan as to who will interact with the inspector, field questions, collect requested documents and take notes. Assigning subject matter experts to be available to speak to various topics can help ensure a smooth inspection process.

  At the sponsor level, the project manager generally assumes a key role in working with the FDA Inspector while the remaining study team assists in pulling requested documents, finding answers to questions, and keeping the study team informed of inspection progress. At the site level, the research coordinator tends to be the main liaison with the FDA Inspector and the PI checks in as frequently as is possible. When permitted and/or requested by the site, the sponsor sometimes supports a site inspection either remotely or onsite.

- **Practicing for Inspection Day**

  Just like any good team practices for the big game, so too should a study team who has so much on the line with this inspection. Consideration should be given at the sponsor and site levels to hire someone experienced in the conduct of FDA inspections to put them through a practice run. Putting the plans to the test will help a study team work out the kinks and determine areas that may need to be strengthened prior to inspection day.

4. Avoiding the Tendency to Over-Prepare

There is a fine line between being audit ready and being "too ready."

While a study team may be taking steps to ensure adequate documentation, they may be putting themselves in a worse position. An example of that comes from a very high performing site that had been notified of an impending FDA inspection. Upon hearing this, the study team re-reviewed the subject binders to ensure that they were in good shape for the inspection. One of the research coordinators decided that the adverse event worksheets were too messy, and she began to completely rewrite them to make them neater and more consistent from subject to subject. Upon hearing this, the sponsor advised the site to immediately cease this activity because while rewriting source worksheets might make them easier for an inspector to read, it can introduce potential for errors and eliminate actual source data. Their intentions were good; their approach was clearly not.

This also happens at the sponsor level, when, usually during a panic phase, study teams decide to write notes-to-file to explain every deficiency they see. Like a big red arrow pointing to each issue, notes-to-file are not always the best approach. What may be more appropriate is for the study team to understand each situation and figure out how to discuss it if asked by the inspector. For particularly complex issues, sponsors can put together "story boards" or "talk tracts" to help guide their thought process in preparation for explanations to an inspector. These are generally for internal use only and are not intended to be shared with inspectors.

Conclusion

Study teams that adequately prepare by understanding the purpose of audits, familiarizing themselves with FDA's roadmap for BIMO Inspections, and taking some key steps throughout the study can really situate themselves in an "audit ready" position from day one. Successful preparation for an FDA inspection requires that study teams know their stuff, choose the right people to engage with on the study, plan appropriately for logistics of an inspection, and avoid the tendency to make mistakes in the haste and panic that comes with inspections.

Conducting clinical research is an immense responsibility. Are you ready?

Amber Edler, Project Manager

Amber is a Project Manager with a previous background in hospital-based innovation, product development and commercialization. Prior to her Project Management position, Amber was an IMARC monitor routinely involved with difficult trials including study cleanup, identification and resolution of compliance issues, training, and audit preparedness for both sites and sponsors.

Her unique background and monitoring experience brings open-minded approaches and trouble-shooting techniques to study management and projects while maintaining high-functioning project teams.

James Moat, Director, Project Management Services

Jim has over 28 years of experience in the medical device industry. Throughout his career, he has held positions in premarket and post-market clinical research, clinical research consulting, and management of not only clinical research professionals, but groups as diverse as Quality Systems, Biological Safety, Microbiology/ Sterilization Validation, Biostatistics, Data Management, and Regulatory. His focus is on ensuring that clinical studies are completed with the highest quality, while staying on schedule and under budget.