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Preparing For a BIMO FDA Inspection: *How to Answer The Call With Confidence*

It's the phone call no one wants to receive. The project manager hangs up the phone and freezes. She looks at her team members, who are scrambling to finish all the paperwork that needs to be completed before the trial data is submitted for approval. "The FDA is coming for a BIMO inspection," she tells them. "They'll be here first thing Monday morning."

It's 4:45 p.m. on a Friday. They return her look of panic with blank stares. Only one team member can remember the last time they experienced an inspection, and it was several years ago. There's so much to do, but no one knows where to start.

The project manager calls their department director, who is already packed for a weekend getaway. That makes two stressful phone calls.

Now the project manager needs to roll up her sleeves and determine how to feel prepared on Monday morning.

But where does she start?

FDA inspectors typically call to notify sponsors of their impending visit as a courtesy, not to ask permission.

However, it's important to remember the FDA's goal is the same goal of any reputable sponsor: to protect human subjects, ensure ethical guidelines are followed and ensure the integrity of clinical research data.

By taking a proactive approach to training and preparing for a potential FDA inspection from day one, study sponsors can greet inspectors with confidence and ensure the inspection has a favorable outcome.

In addition, sponsors should take the same approach by helping their site coordinators always be prepared for potential inspection.

While a BIMO inspection may feel like a pop quiz, the FDA's goal isn't for sponsors to fail, but to equip them to pass. That's why the FDA provides ample guidance — the equivalent of a study guide

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The Purpose Of The Bioresearch Monitoring (BIMO) Program

The FDA's Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections and data audits designed to inspect all aspects of clinical research.

As an important element of the FDA's preapproval process, the BIMO program assures the quality and integrity of study data and adequate protection of the rights and welfare of human subjects.

During a BIMO FDA inspection, the inspector will review study records and ask questions about the organization of the study team, monitoring, safety reporting, data collection and more.

The BIMO inspector's role is to determine if the sponsor, contract research organization or monitor's practices and procedures comply with regulations, NOT to attempt to scientifically evaluate the study data or protocol.

To help sponsors and research sites prepare for BIMO inspections, the FDA provides standard guidance to review, as well as BIMO Inspection Metrics detailing the most common findings by fiscal year.

How Sponsors Should Prepare For BIMO Inspections

Be Aware of Common Findings

The FDA conducted more than 1,600 domestic and international inspections in 2018, including 175 sponsor (including sponsor/investigator) inspections.[1] The most common findings for sponsors were:

- Failure to ensure proper monitoring
- Failure to ensure the investigation is conducted in accordance with the general investigational plan and protocol
- Failure to secure compliance or terminate an investigator's participation
- Failure to ensure FDA/IRB investigators are informed of significant new information or significant new adverse effects

Being aware of these findings can help sponsors educate their study teams about what to look for and take additional proactive measures if necessary. The findings change little from year to year. Having clearly defined protocols with proactive monitoring strategies will go a long way toward being prepared for regulatory inspection.

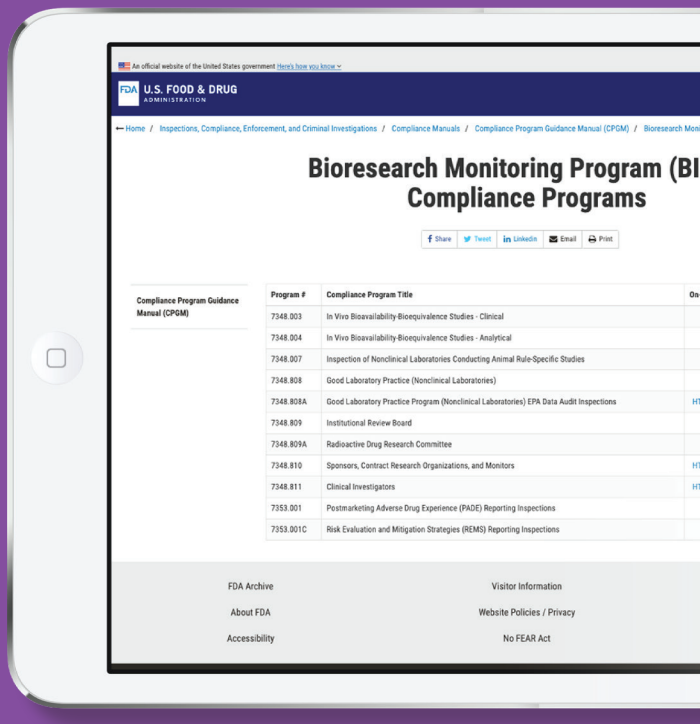
1. Bioresearch Monitoring (BIMO) Fiscal Year 2018 Metrics report. https://www.fda.gov/media/127110/download

Read The BIMO Guidance Manuals

To help sponsors and their research sites prepare for an inspection, the FDA provides guidance manuals detailing what inspectors will review.

For sponsors who want to prepare themselves and their sites, reviewing these is a good place to start — it's like having an open book test.

While individual inspectors may have special instructions for each assignment, the following is an overview of general BIMO sponsor inspection procedures.[2]



2. FDA Bioresearch Monitoring Compliance Programs. https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-program-guidance-manual-cpgm/bioresearch-monitoring-program-bimo-compliance-programs

An Overview of BIMO Inspections For Sponsors

Organization & Personnel

The inspector must determine the overall organization of clinical research activities and monitoring of the selected studies. To do so, they will:

- Obtain relevant organizational charts and responsibilities
- Obtain a list of all outside vendors and contractors, including CROs, monitors, labs and IRBs and their locations
- Obtain copies of any written agreement transferring responsibilities from a sponsor to a CRO (not applicable for medical device studies)
- Obtain a list of all monitors, along with their job descriptions and qualifications

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Clinical Study Registration

Applicable clinical trials must be registered on clinicaltrials.gov within 21 calendar days of enrolling the first subject. To verify registration, the inspector will:

- Determine whether the study is an applicable clinical trial
- Determine whether the study was registered within the required time frame
- Determine whether the sponsor has completed Form FDA 3674, Certification of Compliance

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Selection & Monitoring Of Clinical Investigators

The inspector will obtain a list of all investigators and determine if each has a signed investigator agreement in place. They will also:

- Determine the sponsor's criteria for selecting clinical investigators
- Determine if the sponsor/CRO provided investigators with all necessary information prior to the start of the trial, including clinical protocols and investigational plans
- Determine how the sponsor/CRO handles serious deviations from the approved investigational plan

Monitoring Procedures & Activities

Regulations do not prescribe a specific monitoring technique, simply stating that sponsors are required to select monitors qualified by training and experience to monitor the investigational study (21 CFR 312.53(d) and 812.43(d)). To evaluate monitoring, the inspector will:

- Review the procedures, frequency, scope and process used in monitoring
- Obtain a copy of the sponsor/CRO's written procedures for monitoring and determine if they were followed during the study
- Review pre-trial and periodic site visit monitoring reports
- Determine if the monitor documented the study in accordance with the investigational plan
- Review site records to determine if monitoring visits included a comparison of individual subject records and other source documents with case report forms (CRFs) and determine if all CRFs were verified during monitoring visits
- Determine if a form was used for data verification and obtain a copy
- Determine how the sponsor assured IRB approval is obtained prior to enrolling subjects in the study
- Determine how the sponsor/CRO assured informed consent was obtained

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Quality Assurance

Clinical trial quality assurance units (QAUs) are not required by regulation, but many sponsors obtain independent audits and data verifications to determine their compliance with clinical trial SOPs and FDA regulations. If a sponsor has a QAU, the inspector will:

- Obtain a copy of any written procedures and guidelines for QA audits
- Determine the separation of functions between QA auditing and monitoring

Safety & Adverse Event Reporting

To evaluate safety and adverse event reporting, the inspector will:

- Determine if adverse device effects were reported to FDA, to participating investigators and to reviewing IRBs (for device studies) as required by regulations
- Review the procedures (e.g., frequency, scope) the sponsor/CRO uses for the receipt, evaluation, and monitoring of safety information/unanticipated adverse device effects, as well as the process for updating the investigator brochure
- Review the composition and function of the safety team/committee (if applicable)
- Obtain copies of any notification to investigators relating to safety information or adverse device effects

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Data Collection & Handling

Sponsors are required to submit analyses of all clinical studies pertaining to a proposed drug or device used in any marketing application. They must also submit data tabulations on each subject in each trial. To evaluate data collection, the inspector will:

- Review the sponsor's written procedures (SOPs and guidelines) to assure the integrity of safety and efficacy data collected from clinical investigators
- Verify that the procedures were followed and document any deviations

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Record Retention

The inspector will verify that the sponsor maintained required records for the prescribed period of time, in accordance with 21 CFR 312.57(c) and 812.140(d).

Financial Disclosure

The inspector will determine if the sponsor obtained financial disclosure information from each investigator before his/her participation in the clinical trial.

Electronic Records & Signatures

The inspector will ensure the sponsor has complied with 21 CFR Part 11 pertaining to electronic records and signatures by:

- Validating the computer system used for electronic records
- Reviewing procedures used to create, modify and maintain electronic records
- Determining how the sponsor documents there are sufficient personnel with the necessary education, background, training and experience to manage electronic records

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Conduct a Trial Master File Audit Against The BIMO Checklist

A Trial Master File (TMF) tells the story of a study, documenting everything from the process for choosing sites and investigators to data analysis. Conducting a trial master file audit can help sponsors identify any gaps in documentation prior to a BIMO inspection.

A CRO can assist with conducting an independent audit and may even be able to do this remotely. The CRO should follow the BIMO Guidance Manual to ensure all regulatory requirements are met in accordance with FDA expectations.

Whether the audit is on-site or remote depends on the desired outcome of the audit. An on-site audit may be more advantageous near the end of the study, while a remote audit may be the better option midway through the study so that gaps can be identified.

An on-site trial master file audit can be time- and labor-intensive, typically requiring several study team members spending two to three days reviewing documents with the auditor(s). With travel costs factored in, these audits can be quite costly. However, the in-person interviews of the study team can prove valuable in allowing the study team to work out any kinks in the process for finding and presenting documentation, as well as how to communicate the “story” of their study to an auditor. In this way, the team will be better prepared when they receive the call from their inspector.

An electronic trial master file audit allows an auditor to review documents at his or her convenience via secure, read-only access to files. This eliminates travel expenses, potentially cutting the cost of an audit in half. In this scenario the documentation really stands for itself since direct communication with the study team may be more challenging. Gaps can be readily identified and sponsors can determine how to fill those gaps throughout the remainder of the study.

Prepare Sites for BIMO Inspections

Many sponsors take responsibility for ensuring sites are prepared when the FDA inspector announces a visit. Having a strong working knowledge of FDA regulations and using them to guide decisions during clinical trials is a good place to start. Regularly reviewing FDA warning letters to be aware of the most common violations will also help to ensure the sites included in their studies are not making the same mistakes.

Here are three other proactive steps sponsors can take to prepare their sites.

1

HOST A TRAINING REFRESHER COURSE

Most sites do not have research staff that have been through prior inspections. And even if they have, their experience is likely limited and/or in the distant past. Reviewing clinical study data as described in the BIMO Guidance Manual is not necessarily in line with day-to-day activities, which can lead to additional stress on sites to feel prepared at inspection time.

Refresher courses hosted on-site or online are a great way to supplement training for longtime veterans and new team members. When a sponsor is nearing submission to FDA, which may trigger site inspections, it is helpful to schedule webinars to provide an overview of the inspection procedures that will be followed should the site(s) be chosen for a routine inspection.

2

CONDUCT SITE AUDITS

Just as trial master file audits can help sponsors identify gaps in study documentation, site audits can identify specific challenges that can occur during a trial. Consider mid-study audits to assess compliance at sites and correct course midway through.

3

CONDUCT BIMO MOCK EXERCISES

One of the best ways to prepare for a BIMO inspection is to conduct a trial run before it happens.

Sponsors can help their sites prepare by hosting mock audits, asking the same questions and requesting the same documentation that an FDA inspector would request.

Like taxes, BIMO inspections are inevitable. However, with advanced preparation, they don't have to cause panic or dread. Taking these steps can help sponsors and their sites answer the call with confidence.

Brandy Chittester, MS, CCRA, President

Brandy Chittester is the President of IMARC Research. In this role, she assumes overall responsibility for all aspects of the company, including overseeing operations, maintaining the financial health of the company, establishing company culture, overseeing the quality management system, as well as attracting and retaining top talent.

Brandy joined IMARC as a Clinical Research Associate in 2007, building on her prior experience working in pre-clinical research. Throughout her tenure at IMARC, Brandy has grown with the company, taking on additional responsibilities in various service areas and advancing in responsibility. Prior to her position as company President, Brandy worked for four years as the Chief of Clinical Operations, primarily responsible for overseeing service delivery in all clinical departments.

About IMARC Research

As a global medical device CRO, IMARC Research provides expert third-party oversight throughout the clinical trial lifecycle to ensure study sponsors achieve approval from the FDA and international regulators. IMARC's services include monitoring, auditing, consulting, training, safety management, project planning, site support and more.

To learn more about how IMARC can help prepare your sites for a BIMO inspection, contact us today.

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