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ELEMENTS OF A REGULATORY INSPECTION: WHAT YOU NEED TO KNOW

For purposes of readability, FDA investigators will be referred to as inspectors while clinical investigators will be referred to as investigators.

In 2015, there were 822 inspections of clinical investigator sites under the Food and Drug Administration's (FDA) BioResearch Monitoring Program (BIMO) (1). Site audits are triggered by numerous factors and can occur at any time. Routine BIMO inspections can result from sponsor submission of a marketing application to FDA, as one example. By evaluating trials of drugs or devices seeking marketing approval, FDA can further assess the sites, sponsor, and/or institutional review board (IRB) prior to making a decision on product approval.

While audits of studies with pending marketing applications are considered routine, FDA has recently shifted its focus toward an early intervention paradigm. Under this design, BIMO inspections occur prior to trial completion. This approach allows FDA the opportunity to affect proactive change and continuously improve clinical investigator compliance. Early intervention inspections can be more difficult to predict as the audits are not necessarily triggered by a sponsor regulatory submission.

A review of the most common findings cited during previous BIMO inspections can help sites avoid these mistakes and increase familiarity with the inspection process. The BIMO inspection metrics are released annually on the FDA website.

The top findings at clinical investigator sites have remained the same in each annual analysis from 2007 to 2015:

- **Failure to follow the investigational plan and/or regulations**
- **Protocol deviations**
- **Inadequate recordkeeping**
- **Inadequate accountability for the investigational product**
- **Inadequate subject protection – failure to report AEs and informed consent issues (1)**

The following finding was also among the most commonly cited between 2011 and 2015:

- **Inadequate communication with the IRB (1)**

FDA's Compliance Program Guidance Manual (CPGM)

The FDA's CPGM for Clinical Investigators and Sponsor-Investigators is available on the FDA website (7348.811) [2]. The compliance programs were designed to provide uniform guidance to FDA field inspectors and include specific instructions for conducting sponsor, clinical investigator, and IRB inspections.

When undergoing a BIMO inspection, it is important to understand the reasons why FDA inspects. The main objectives of the BIMO program are threefold:

- **To assess protection of human subjects rights, safety, and welfare in FDA-regulated clinical trials;**
- **To verify that the study data being collected reflects the clinical condition of subjects participating in the trials; and**
- **To assess compliance to the regulations governing clinical study conduct in the United States.**

CPGM 7348.811 evaluates clinical investigator procedures and practices to assess compliance in twelve areas (see Table 1).

Table 1: BIMO CPGM 7348.811 - PART III Inspectional

Clinical Investigator and Sponsor-Investigators:

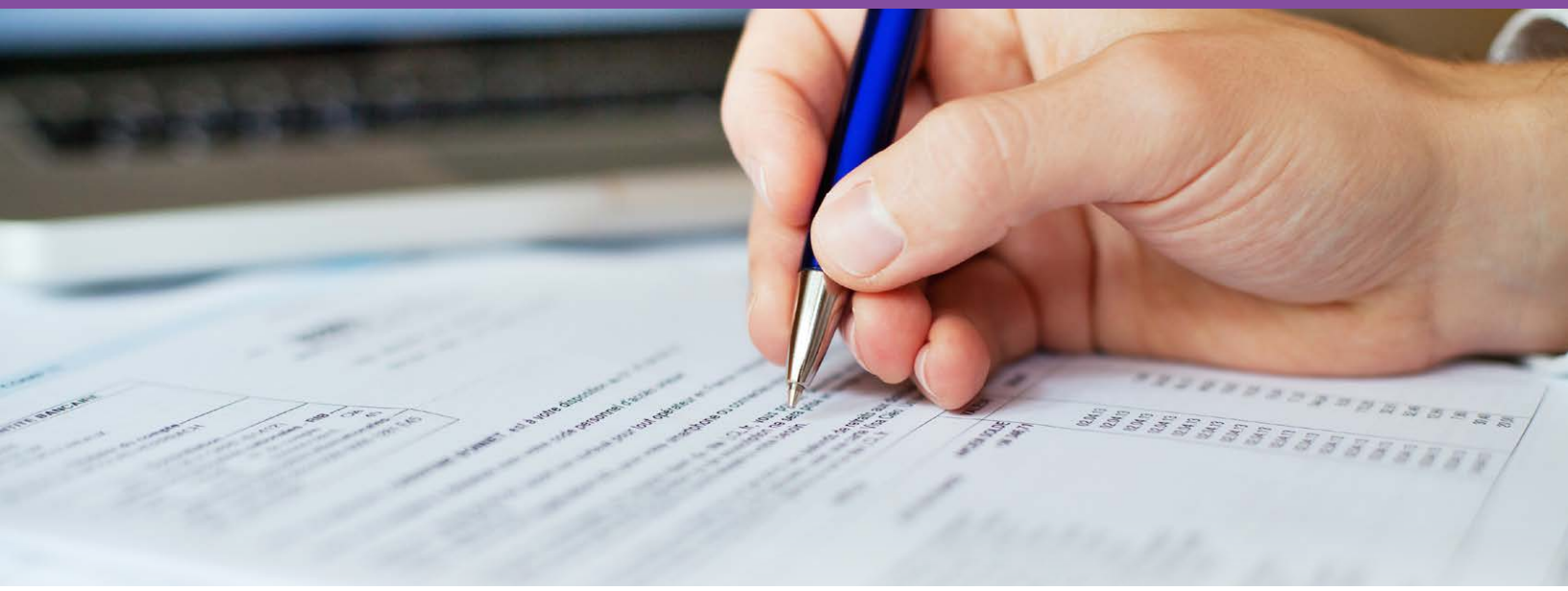
Review Areas for Studies involving Human Drugs, Biologics, or Devices

Authority and Administration	Electronic Records and Electronic Signatures
Protocol	Test Article Control
Institutional Review Board	Records Custody and Retention
Human Subjects' Records	Reports to Sponsor
Other Study Records	Monitoring
Financial Disclosure	Device Studies

In order to be prepared when FDA calls to schedule an inspection, familiarity with the questions that will be posed in each of these inspectional areas will provide a level of assurance to your clinical study sites. The following sections summarize the review areas and should be used when preparing sites. Even for sites that are prepared from Day 1, walking through the CPGM with the site to ensure the data is available will help the site (and the sponsor!) be confident that the site is inspection-ready.

Authority and Administration

The site must be familiar with the Investigator's Agreement/Form 1572 and should have a listing of all studies performed by the clinical investigator. There should be documentation of the following dates: initial IRB approval, signature of the Investigator Agreement/Form 1572, start of screening at the site, date when informed consent was first obtained, and the date when the first test article was administered. The enrollment log must be complete and up to date. In addition, certificates of qualifications should be on file for facilities performing laboratory or diagnostic tests required by the protocol. The site should review the process used to recruit subjects and ensure that IRB approval is on file for any materials used in the recruitment process.



Protocol

The inspectors will compare the versions of the protocol that have been released with those on file at the site. To prepare for this section, sites should ensure familiarity with study eligibility criteria, endpoints and measures, follow-up visit schedule, required assessments at each visit, and test article accountability. Questions will be directed at how subjects were selected, the number of subjects enrolled, randomization assignment procedure (if applicable), and administration of the test article according to manufacturer's directions. Other areas of review include the systematic implementation of protocol amendments, including IRB and FDA approvals and an assessment of protocol deviations and related documentation.

Institutional Review Board (IRB)

FDA relies on IRBs to be the eyes and ears at a clinical site. In assessing this area, the inspectors will collect information on the IRB and determine if IRB review and approval of the protocol, study informed consent document, and recruitment materials was obtained before initiation of study-specific procedures on subjects. Inspectors will also assess the nature and frequency of communication between the site and the IRB to evaluate if deaths, serious adverse events, or unanticipated problems involving risk to human subjects were reported in compliance with the protocol, applicable policies, and regulations.

Human Subjects' Records

The site should be prepared to give a description of the informed consent process and should have all signed informed consent documents available for review. The inspector may review all subject consent forms or may review a selected sample. In addition, source data will be verified with data entered in the case report forms and the data collection process will be evaluated in order to determine who obtained the data, its source, and whether corrections were made appropriately.

In order to ensure adequacy of source documents, sites should ensure that study documents meet ALCOA GCP Standards:

Attributable

- ☑ It should be obvious who created a record, and when it was created
- ☑ If a record was changed, it should be obvious who made the change, when the change was made, and why

Legible

- ☑ The research record should be easily read

Contemporaneous

- ☑ Study evidence/results should be recorded as they are observed
- ☑ All signatures/initials should be attached to a date indicating when the signature was added to the document

Original

- ☑ Study records should be originals, not photocopies

Accurate

- ☑ Study records should have a high level of integrity and honesty to what was truly observed; give a full accounting of the research process
- ☑ Study records should be thorough and correct; double check your work for unintentional errors

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The inspector will determine if there have been any drop-outs or subjects lost-to-follow-up and if those subjects have been reported to the study sponsor along with reasons for discontinuation.

Other Study Records

If any other study records are being maintained, i.e. administrative study files, correspondence files, master subject list, appointment books, etc., the inspector may review these other records to ascertain that all pertinent information has been reported to the sponsor.

Financial Disclosure

21 CRF Part 54 contains the regulations for disclosing financial interests to the sponsor. These disclosures extend to the clinical investigator, sub-investigators, and their spouses and dependent children. Financial disclosures are collected pre-study, during the study if changes occur, and within one year following completion of the study. Disclosures are closely evaluated since financial interests could introduce bias into the study.

Electronic Records and Electronic Signatures

The regulatory requirements for clinical research data do not change whether the data are recorded on paper, in an electronic database, or in hybrid systems. In evaluating the safety and efficacy of regulated products, the clinical trial data must be accurate and reliable. 21 CFR Part 11 regulations pertain to electronic data capture. The inspector will assess if electronic data collection methods are specified in the protocol and are being followed. Electronic records will be evaluated based on GCP-ALCOA requirements and the inspector may evaluate how records were reviewed during monitoring visits, which personnel were trained and authorized to enter and change study data in the electronic data capture system, and if appropriate security measures are employed to protect and maintain the integrity of the data.

Test Article Control

The regulations require 100% accountability for investigational products. This encompasses the receipt, use, and final disposition of all investigational products shipped to a clinical study site. Product logs and shipping records will be reviewed to reconcile product accountability. In addition, the inspector may determine how products were stored and if storage complies with instructions for use provided by the manufacturer. If product is stored on site, the inspector may request a tour to determine secure access to investigational product and will examine if the investigational product bears the required labeling.

Records Custody and Retention

Various regulations exist specifying the requirements for record retention. The inspector will assess compliance with the governing regulations and stipulations of record retention specified in the protocol.

Reports to Sponsor

There are required records and reports in clinical investigations. The inspector will assess compliance with the governing regulations and compliance with records and reports specified in the protocol. For example, the submission of protocol deviations, adverse events, completed case report forms or other study-related reports to the sponsor may be reviewed by the inspector.

Monitoring

Monitoring is a quality-control function required by the regulations. The frequency and nature of the monitoring visits will be assessed to determine if monitoring has been consistent with the monitoring plan and as specified in the protocol. The inspector will review the monitoring log and note if a follow-up letter was received by the site following each monitoring visit. Particular attention will be paid to action items in the monitoring follow-up letters to address deficiencies or recommendations noted by the monitor.

Device Studies

Investigational device regulations are detailed in 21 CFR Part 812. The inspector will determine whether the clinical investigator has been involved with other types of device studies; for example, Non-Significant risk (NSR) studies, Humanitarian Use Studies, or the use of custom devices. The inspector will also determine if the test article has been used in emergency or compassionate use cases and will review the documentation supporting these uses.

Additional Preparation Activities

IRB and Institutional Policies

In addition to becoming familiar with the BIMO checklist, further preparation should include a full understanding of the IRB and institutional policies by the clinical site team. It is critical to understand the requirements for obtaining informed consent as well as reporting of adverse events, unanticipated problems, protocol deviations, waivers, and other significant issues. In addition, relevant staff should be cognizant of any additional IRB/institutional requirements such as those regarding financial disclosure or personal health information. The following table can be used as a starting point for assessing knowledge of IRB/Institutional Policies in preparation for an Inspection:

Policy or Procedure	IRB Requirement	Federal Requirement
Informed Consent	• Legally Authorized Representatives • Re-consent • Non-English speaking subjects • Witnesses • Telephone consent • Vulnerable populations • Versioning and expiration • Required signatures	21 CFR Part 50 21 CFR Part 812 21 CFR Part 312
Adverse Event Reporting	• Types of events that require reporting • Reporting timelines	21 CFR Part 812 21 CFR Part 312
Protocol Deviations	• Types of deviations • Reporting timelines • Implementation of planned and unplanned deviations • Protocol waivers	21 CFR Part 812 21 CFR Part 312
IRB Communication	• Submission materials • Continuing review • Protocol amendments	21 CFR Part 56 21 CFR Part 812 21 CFR Part 312
Financial Disclosure	• Disclosure forms or methods of disclosure • Conflict management plans • Language present in ICF	21 CFR Part 54 21 CFR Part 812 21 CFR Part 312
Personal Health Information	• Consent • De-identification • Records release	Health Insurance Portability and Accountability Act (HIPAA)

Inspection Logistics

A successful audit outcome depends not only on the site's knowledge of policies and procedures, but also on careful consideration of inspection logistics. There should be a designated, reserved space for the FDA inspector for the duration of the inspection. This area should be separate from other employees and activities. Furthermore, there should be site staff specifically assigned to accommodate the audit. Roles and responsibilities of each staff member should be discussed and defined prior to the inspection. Functions to consider include greeting the inspector, giving a tour of the site, note-taking throughout the audit, providing requested copies while keeping records/copies of all requested items, answering questions or directing questions to the appropriate personnel, communicating with the clinical investigator(s), and communicating with the sponsor. The principal investigator will ideally be available throughout the inspection but, at a minimum, should have blocks of time reserved each day to check in with the inspector.

Once the site staff is comfortable with audit logistics, the tone of the inspection should be addressed. The desired tone for an inspection is calm, professional, and succinct. The inspector's questions should be answered completely and accurately, but responses should not include any information beyond what is needed to answer the question. In addition, if someone is asked a question to which they do not know the answer, it is perfectly acceptable for that individual to indicate the need to confirm the answer prior to responding. The key is not knowing all the answers, but knowing how to respond to the auditor and subsequently find the answers. It may be beneficial for site staff to participate in mock inspections in order to rehearse the desired tone and experience of the audit. Mock inspections can help build comfort in responding to difficult questions, managing emotions and feelings of nervousness, and dealing with varied personality types. It is also a useful way to become generally more comfortable with the audit process. It is important to utilize experienced professionals in the mock inspection as they can often provide insight and coaching on multiple aspects of audit responses and performance.

Conclusion

Regulatory inspections can happen at any time and occur for a variety of reasons. The recent shift toward early intervention inspections further warrants the need for improved audit preparation. There are several ways to increase audit readiness including review of recent inspection findings, evaluation of your site through the BIMO CPGM, ensuring familiarity with IRB and institutional policies, and audit planning and simulation. An understanding of how to use these resources to assure compliance will greatly improve inspection readiness. Audit preparation should start on the first day of the trial and, if done, will ensure all is ready when the FDA calls.

References

1. BIMO Inspection Metrics. (n.d.). Retrieved April 29, 2015
2. U.S. Food and Drug Administration. (n.d.). Retrieved April 29, 2015

Paul L. Cobb, MPH, CCRA, Clinical Auditor

Paul Cobb joined IMARC in 2013 and currently serves as a clinical auditor. Paul has monitored and audited studies investigating treatments for thoracic aneurysms, aortic dissection and transection, urinary incontinence, intracranial aneurysms, and robotic devices for percutaneous coronary intervention.

Paul's previous work experience includes time at the Centers for Disease Control and Prevention where he worked on multiple statistical surveillance projects analyzing the relationship between sodium intake, insulin resistance, and cardiovascular outcomes. He also developed an expertise in central nervous system, metabolic, and rheumatoid therapeutic areas during this time as a research coordinator.

Paul Cobb has a Masters of Public Health from Emory University and his Bachelor of Arts in Psychology from The University of Michigan. He is a Certified Clinical Research Associate through the Association of Clinical Research Professionals.

Mary Lewis, Senior Clinical Research Specialist

Having joined IMARC in 2012, Mary Lewis currently serves as a Senior Clinical Research Specialist. She has been involved in research since 1974, starting her career at Union Carbide Corporation as a Senior Research Technician performing carbon fiber technology patent work. Since then, Mary has held various positions including as a Decentralized Senior Clinical Research Associate at Parexel International, as a Manager of Clinical Studies at NeuroControl Corporation, as Director of Clinical Research at Fujirebio Diagnostics and as Senior Director of Clinical Research at Stryker Orthobiologics. Mary's clinical experience has covered various therapeutic areas including: spinal implant technology, biomarkers for epithelial ovarian cancer and malignant epitheloid and biphasic mesotheliomas, vertebroplasty in treatment of osteoporotic vertebral compression fractures, and post-stroke rehabilitation using functional electrode stimulation.

Mary received her Bachelor of Science Degree from Bowling Green State University. She is also a member of the Society of Clinical Research Associates (SoCRA).

Emily Haglund, Clinical Auditor

Emily joined IMARC in July 2014 as a Clinical Auditor, bringing with her experience in clinical quality assurance, technical writing, and research design in the medical device industry. Prior research experience has involved consumer product development, laboratory and preclinical work, and healthcare policy studies. Her most recent role before joining IMARC was as Project Manager, Clinical Quality Assurance at MicroPort Orthopedics.

Emily has been a member of the Society for Clinical Research Associates (SoCRA) since 2013 and earned her Certified Clinical Research Certification that same year. She has also been a member of Society for Quality Assurance (SQA) since 2012. Emily received her Master of Science degree in Biomedical Engineering from Purdue University and Bachelor of Science degree in Biomedical Engineering from Michigan Technological University.

For more information on how you can help prepare your sites for a better outcome, starting from Day One, please contact John Lehmann at 440.801.1540 or via e-mail at jlehmann@imarcresearch.com.

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22560 Lunn Road, Strongsville, Ohio 44149 • tel 440.801.1540 • fax 440.801.1542

info@imarcresearch.com • imarcresearch.com

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