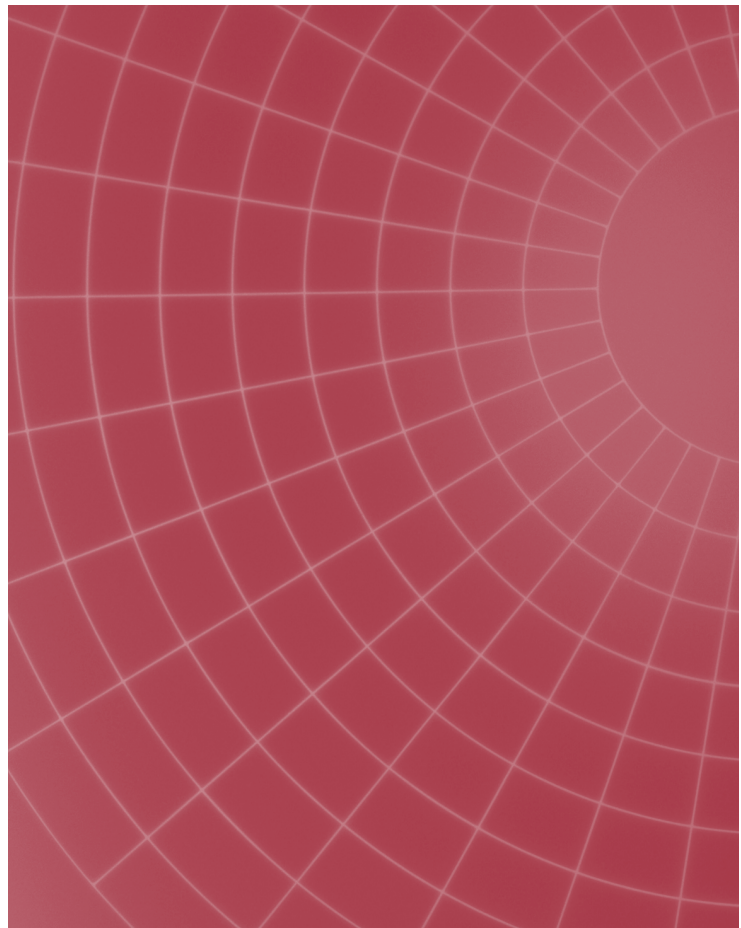


## **FDA GCP Inspection Preparation:**


**A Primer for Investigative Sites, Sponsors,  
CROs and IRBs**



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# **FDA GCP Inspection Preparation:**

## **A Primer for Investigative Sites, Sponsors, CROs and IRBs**

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## Introduction: Conducting Investigational Research

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Companies conduct investigational research for two main reasons. The first is to develop and investigate new treatments and products for use in the diagnosis, cure, mitigation and treatment of disease. The second is to improve the quality of life of patients. The companies that undertake research for these reasons also expect to reap some financial benefit from developing new products.

Companies that conduct investigational research must follow some important principles. While there are always risks in research, one of those principles is that companies must not expose subjects to any unreasonable and significant risk of illness or injury from the investigational product. It is critical that companies take steps to protect the subjects involved in clinical research.

Another principle is that companies also need to ensure that the anticipated benefits and the importance of the knowledge to be gained from the research are not outweighed by the risks to the study's subjects. Companies must ensure that the informed consent of subjects who participate in research projects is adequate and that their investigation is scientifically sound. They also must have reason to believe that the drug or device as used is effective.

A third principle is that companies must protect the safety of subjects participating in research studies.

Before a company can administer an investigational drug or biological product to humans, the FDA must give its approval, through the Investigational New Drug (IND) application process. The company must submit an IND request for authorization from the FDA. This is also true with investigational medical devices, where companies must request approval through the Investigational Device Exemption (IDE) process. In order to protect the subjects involved in clinical research, the FDA can put an investigation on hold.

It is up to sponsors to ensure that trial subjects understand the basis of the research project and, in doing so, freely agree to participate. Subjects should also understand if they might receive a placebo during a clinical trial; regardless, the subjects should also understand their participation is for the benefit of clinical research and may assist other people in the future. Companies should further make it clear to subjects that, at the trial's completion, they might be enrolled in an open label trial. If so, they would be given the particular product—if the results prove it could be beneficial for patients. In such a case, they would benefit from the product prior to its receiving FDA approval.

### **So what can go wrong?**

Most often, companies are able to develop products and move through the regulatory process with minimal issues. But there are times when things go wrong. Companies can face the following types of legal and regulatory problems:

- Breach of Contract;
- The rejection of the data in a marketing application;

- A loss of research funds;
- Inspectional observations and warning letters;
- Disqualification as an investigator;
- Debarment;
- Civil Penalties; and
- Criminal Penalties.

Take, for instance, what happens when companies face a breach-of-contract situation. Research agreements typically address issues such as using both best efforts and good clinical practices in the course of clinical trials. However, if researchers fail to follow the protocol, obtain informed consent from subjects, monitor the trial properly, keep track of the investigational product and so forth, these issues can give rise to a breach of contract. A breach of contract can be costly to companies. It can lead to the disqualification of a particular study, which would certainly impact the amount of time it takes to develop a particular product. Worse, it could lead the FDA to reject data submitted in a marketing application.

Indeed, many potentially significant issues can arise if companies fail to follow protocols and FDA requirements for conducting research.

Take the case of a company that monitored its own research investigations. When the FDA did an inspection prior to a pivotal trial, the agency found one investigator who had broken the blind of the trial. Another investigator did not follow the documentation protocol in compiling patient records. And a third investigator enrolled patients who didn't meet the inclusion/exclusion criteria for the study, simply because he thought they might benefit from the trial anyway.

Consequences can be severe. Companies can lose their research funds. At the conclusion of many FDA inspections, the inspector issues a list of inspectional observations. That FDA Form 483 notes any deviations from agency regulations. It is surprising the number of investigators who don't understand they need to respond to these observations and put in place a corrective and preventive action plan in order to continue to participate as an investigator in future clinical trials.

The FDA also issues warning letters to companies. Furthermore, the agency can disqualify investigators from conducting trials. Likewise, there exist debarment actions for the falsification of clinical data, as well as both civil and criminal penalties for the submission of false information to the government.

Given those consequences, it is easier for companies to follow the requirements.

### **More about warning letters**

When it finds violations, the FDA issues warning letters to companies. The FDA defines a warning letter as...

*“...written communication . . . notifying an individual that the agency considers one or more practices to be in violation of the Federal Food, Drug, and Cosmetic Act, or other acts, to the extent that failure of the responsible party to take appropriate and prompt action to correct the violation may be expected to result in enforcement (administrative and/or regulatory) action without further notice.”*

In plain English, the FDA is putting the company on notice that what it has done is inappropriate and that it must take action or face further enforcement action, such as a seizure or an injunction, without additional warning. It is the way the FDA warns companies of particular violations it has uncovered, either in the course of an inspection or through people coming forward with information, such as a whistleblower. All FDA warning letters are public.

## FDA Inspection Objectives

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The FDA designed its clinical investigator inspection program to monitor an investigator's adherence to federal regulations and to determine the validity of those studies or trials used to support applications for product approval. The inspection program also determines if companies are protecting patient rights and safety.

So companies can expect that the FDA will visit and its inspectors will evaluate the robustness of the data collection used to support the approval of new products. It is important that clinical investigators, hospitals and private sites doing investigational research understand this expectation.

So what needs to be known about these inspections? They are usually announced, but are typically conducted shortly after a company receives notice that the FDA plans to inspect.

Inspectors will ascertain whether clinicians can account for all test articles supplied to them. Companies need be sure they can account for these investigational products. Therefore, it is important to keep good records, written protocols and informed consent.

Inspectors will also check whether companies have a written protocol and whether they obtained informed consent from all participants, prior to entry into the trial.

Some practices represent a "red flag" for inspectors. For example, they will be suspicious if a company presents 150 informed consent forms, all signed in the same apparent hand on the same day, and all in the same color of ink. Were all patients really enrolled on the same day? Did they all start the study at the same time? If they were not, then how can a firm explain the similarities in penmanship and ink color? Inspectors will also look at whether existing records support case reports. Are the underlying source data supportive of the case reports? The FDA will check to see whether companies have reported all adverse reactions and other information to sponsors, as required by the regulations. Have companies reported adverse events and analyzed what happened? Inspectors want to look at these studies to know whether they have the correct information, which will ultimately go on the product label. It's critical that products are adequately labeled and safe for use by prescribers and patients.

### What the FDA finds in inspections

Some of what the FDA finds in inspections is disturbing. For instance, inspectors discover companies that failed to fulfill the general requirements of investigators, such as not documenting the qualifications of a study coordinator. The FDA also finds companies that have failed to put in place a signed investigational plan or to even follow the protocol.

Other findings include the failure to obtain informed consent, to maintain adequate records of the disposition of the investigational drug, to maintain adequate and accurate case histories and to notify the IRB of serious adverse events.

It is important companies communicate appropriately with the IRB and with the specific sponsor about adverse events. That way, they can review what is happening and decide whether to

change a study's design or some of its criteria. This also allows people to determine whether the study has brought to light certain characteristics of the drug product that affect a particular patient population.

FDA inspectors also find a fair amount of scientific misconduct, including the falsification and fabrication of data. That can include faking the dates of tests and examinations prior to study entry. Furthermore, inspectors find the fabrication of lab test results and dates. There is no excuse for this; companies must ensure it does not happen.

## **The distinction between research and medicine**

There is a big difference between investigational research and the practice of medicine. They are not the same thing. Research must be controlled and documented. Its purpose is to obtain knowledge about the safety and effectiveness of a particular drug or device. The practice of medicine is about the treatment of patients.

Nevertheless, individual investigators sometimes don't differentiate between medicine and research. There are some physicians who are used to treating patients and who want to apply the same types of principles to the conduct of research. In conducting research, companies must maintain a controlled situation, including the inclusion of subjects in clinical trials. Researchers focus on how a product is used. For example, with a drug product researchers must determine how to appropriately dose and administer it. Furthermore, researchers must determine what precautions, warnings and contraindications are necessary in the use of a particular drug.

In the practice of medicine, physicians treat patients. They are supposed to use drugs already established as safe and effective, even though there are products on the market that have not undergone FDA review and approval. Moreover, there are products used off-label that have become the standard of care.

Research oversight protects the rights and welfare of research subjects and ensures the integrity of the data collected during a clinical trial. This is true both at the local level, with the IRB and data safety monitoring boards, as well as at the sponsor level. This is why it is necessary to ensure companies and people comply with the requirements.

## **A look at the regulators**

Who regulates human research? There are four different organizations that oversee the conduct of research in the U.S.

The FDA oversees research that involves products it regulates. The agency established its Office for Good Clinical Practice (OGCP) in October 2001 to "improve the conduct and oversight of clinical research and to ensure the protection of participants in FDA-regulated clinical research."

The OGCP oversees coordination of the agency's Good Laboratory Practice (GCP) Bioresearch Monitoring. It coordinates human subject protection policy across the FDA, in collaboration with the National Institutes of Health (NIH) and the Office for Human Research Protections (OHRP), which is an office under the Department of Health and Human Services.



The FDA's Bioresearch Monitoring (BIMO) Program conducts on-site inspections and data audits designed to monitor all aspects of the conduct and reporting of FDA-regulated research.

Furthermore, there are oversight groups in the Center for Biologics Evaluation and Research (CBER), division of inspections and surveillance for the Bioresearch Monitoring Group; the Center for Drug Evaluation and Research (CDER), division of scientific investigations; and the Center for Devices and Radiological Health (CDRH), division of bioresearch monitoring. These offices monitor the conduct of trials within the purview of their respective centers; they perform many inspections on an annual basis. Domestic and international inspections total more than 1,000 annually.

The Department of Health and Human Services (HHS) also runs the Office for Human Research Protections (OHRP), formerly called the Office for Protection from Research Risks. This office regulates research when HHS funds are used to conduct or support research involving human subjects.

The Office of Human Subjects Research (OHSR) oversees compliance with NIH-conducted research funded through the Intramural Research Program through compliance with NIH Multiple Project Assurance (MPA).

Other federal agencies also fund research. Most have their own regulations, which adhere to the same federal policy (known as the "common rule") for the protection of human subjects, and are found in the Code of Federal Regulations, 45 CFR Part 46.

The CFR contains applicable regulations, including the following:

DHHS – 45 CFR Part 46 (Protection of Human Subjects)

FDA – 21 CFR Part 312 (Drugs) and 21 CFR Part 812 (Medical Devices)

FDA – 21 CFR Part 50 (Protection of Human Subjects)

FDA – 21 CFR Part 56 (Institutional Review Boards)

FDA – 21 CFR Part 54 (Financial Disclosures by Clinical Investigators)

Further information is available on the FDA website at [www.fda.gov](http://www.fda.gov), including information and guidances on actual requirements.

Note there are some differences between the OHRP and FDA when it comes to research. OHRP oversees government-funded research projects involving human subjects. This is governed by guidelines, rather than regulations. OHRP relies on project assurances made by grant recipients to enforce most of these guidelines. Failure to follow the guidelines can result in the withdrawal of a group's ability to do research under certain types of project situations.

FDA oversees research involving products that it oversees. The agency publishes very specific guidances and guidelines to help interpret those regulations. The FDA also conducts inspections; failure to follow the regulations can result in administrative, civil and criminal penalties, under the Federal Food, Drug and Cosmetic Act.

## An overview of clinical research regulations

FDA regulations require the following of clinical research:

- Protocol
- Informed consent
- Drug accountability
- Reporting requirements
- Record-keeping requirements

*Protocol.* A written, detailed protocol must address issues such as who can be part of a study and what is required for informed consent. It should describe expected adverse events. It should include characterizations given to clinical investigators, as well as the principal investigator and subinvestigators, which provide the framework and the outline for the conduct of the clinical research. It should detail the data collection forms to be completed during the course of the clinical investigation.

*Informed consent.* This is necessary to ensure subjects freely participate in the research. They need to understand and appreciate what's being undertaken in this research. Subjects must participate on their own accord and not be coerced in any way. It is surprising how many companies conduct research on their own employees or ask them to participate in studies. This is not a recommended practice.

*Drug accountability.* Investigational product accountability is a must. Ensure people know where these drugs are, where they go and ultimately how they are disposed of. If issues arise, reconciliation is required to ensure the product is controlled and it does not fall into the hands of the general population, where it should not be.

*Reporting requirements.* If a serious unexpected adverse event occurs during the course of the trial, such as a death or serious injury, it must be reported in a very short time frame. A full investigation must follow and action must be taken to ensure that no one else is hurt should there be an issue with a particular product.

*Record-keeping requirements.* These requirements are in place to make sure appropriate records are kept. Maintain documentation so they may be accessed freely, including for use supporting further study reports as well as the final audit to support approval of the drug.

## The Role of the Sponsor in FDA-Regulated Research

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There's an FDA maxim: If it isn't written down, it was not done. That includes spelling out the specific roles and responsibilities of each group involved in investigative research, whether it is the sponsor, principal investigator or IRB.

Let's first take a look at the role of the sponsor: The sponsor takes on numerous responsibilities in the research process.

The sponsor takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or a pharmaceutical company, government agency, academic institution, private organization or other organization. The sponsor does not actually conduct the investigation—unless the sponsor is a sponsor-investigator.

A word of caution: While sponsors can legally transfer their obligations to a contract research organization (CRO) to ensure all FDA requirements are met, it must be specified in a written agreement. These contractual obligations, if not met, can subject people to a particular liability. While some obligations are transferred from sponsor to CRO, that does not necessarily mean the sponsor has no responsibility. The sponsor must ensure the CRO does what it is supposed to do. Sponsors are still in a position, or should be in a position, to know what's going on at the CRO level. So sponsors must understand and appreciate that.

Sponsors are responsible for selecting qualified investigators and providing them with the information needed to properly conduct an investigation. The investigator actually conducts a clinical investigation; it is under the investigator's immediate direction that a drug is administered or dispensed to subjects.

The investigational brochure provides investigators with the information they need. That includes details of the particular product under investigation, any worldwide experience with the product, information from preclinical studies (as well as in human studies conducted both in the U.S. and abroad) and any safety concerns that merit highlighting.

Sponsors must ensure investigations are properly monitored and that someone reviews their conduct. Sponsors remain responsible for ensuring any investigation is conducted in accordance with the general investigational plan and protocols described in the IND/IDE. Anyone involved in the trial must receive copies of the protocol and any amendments—and must follow them. That also means making sure people are aware of any safety information to help ensure the product is used as safely as possible. Sponsors must also maintain an effective IND/IDE and make certain FDA investigators are promptly informed of significant new adverse events or risks.

Furthermore, the IND or IDE must be up-to-date and effective. That includes keeping people informed of any changes. The FDA can be asked to approve changes to the study protocol if, for instance, a sponsor learns of a particular subject who might benefit from participation in the trial. Sponsors may ask the FDA to make an exception, as long as it is appropriately documented.

These responsibilities are detailed under 21 CFR 312.50 and 21 CFR 812.40.

Another sponsor responsibility pertains to financial disclosures. This is important because the FDA wants to make sure an investigation is not biased by anyone with a financial stake in its outcome. Sponsors must obtain sufficient accurate information from investigators in order to file certification and financial disclosure statements.

Sponsors need to guard against potential bias. Does the clinical investigator have financial interest in the outcome of the study because of the way payment is arranged? It can be surprising how many investigators working on the development of a particular product have their compensation tied to its outcome. So it's critical to make sure people are either "blinded" or there are independent readers of any records, X-rays or other evidence. That can minimize any potential for bias that could be introduced by having some sort of financial interest in a study. These regulations are found under 21 CFR Part 54.

### **Conflicts of interest**

The regulations address conflicts of interest and require that companies conduct studies to minimize bias. 21 CFR Part 54 regulates financial disclosures by clinical investigators.

Regulations require an applicant to disclose certain financial arrangements between the sponsor and investigators. For each investigator of a covered study, the applicant must submit certification that no financial arrangement exists or otherwise disclose the nature of the arrangement.

The applicant must also disclose compensation affected by the outcome of a clinical study. The applicant must disclose significant equity interest in the sponsor of a covered study (if it exceeds \$50,000 and stays in effect for one year.) Regulations also require disclosure of any proprietary interest in a tested product, such as a patent, trademark, copyright or licensing agreement.

It is important that independent people conduct an investigation. That means finding people without anything invested in the outcome of the study or who do not have stock in the company.

## The Role of an IRB in FDA-Regulated Research

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IRBs provide oversight of the research conducted within a community. An IRB, also called an independent ethics committee or ethical review board, is a committee formally designated to approve, monitor and review biomedical and behavioral research involving humans. The aim is to protect the rights and welfare of research subjects.

The IRB's role is to approve or disapprove research—or require modifications needed to secure approval. An IRB typically consists of a group of diverse individuals who work together with medical, pharmacy and nursing professionals to look at a research project and make sure it conforms to standards, such as ensuring the balance between its potential risks and benefits is acceptable.

IRBs review informed consent documents. They want to ensure that the informed consent is intelligible to the subjects in that community. For example, the informed consent may have to be printed in multiple languages. IRBs will also check that the informed consent clearly communicates the nature of the study and its potential research benefits.

First and foremost, the IRB assures that the rights and welfare of subjects are protected. They look at protocols and can require changes or modifications, which then requires a company to submit an amended or modified protocol to the FDA. The FDA has a 30-day review period, so it is a good idea to alert the project manager of any particular reviewing division at the FDA before submitting a modification or amendment, as required by the IRB.

IRBs also make sure research undergoes continuing review, not less than once per year and perhaps more frequently, if issues crop up during the course of the study. For instance, IRBs can conduct a review if researchers see such tremendous results from a placebo trial that it would be unethical to continue it. Or IRBs can review a study if a safety concern emerges that makes it unreasonable to continue with the investigation of the product. Regulations governing IRBs are found in 21 CFR Part 56.

### Approval for new research

IRB approval for new research requires a determination that:

- Risks to subjects are minimized;
- Risks to subjects are reasonable in relation to anticipated benefits;
- Selection of subjects is equitable;
- Informed consent is adequate and appropriately documented;
- The research plan makes adequate provisions for monitoring data collected to ensure safety of the subjects;
- Adequate provisions are in place to protect the privacy of patients and confidentiality of data; and
- Appropriate safeguards are included to protect vulnerable subjects.

These regulations may be found at 21 CFR 56.111.

Different studies pose various challenges. For instance, a study's participants may be stroke victims admitted via the emergency room, where they are unable to give informed consent. What do you do in this situation? How do you contact a family member when time is of the essence and you have a very limited window of time to administer a drug that could benefit the patient? Can you forego informed consent within such a narrow time frame? In these kinds of cases, the IRB needs to work through the issues and come up with a method to make sure the rights of subjects are protected.

In another example, a company developed a new product for the military for use in germ warfare situations. Unsurprisingly, it chose to test it under battlefield conditions. The FDA waived the informed consent requirements in this case, but did require that soldiers before they went out into the field understood the risks associated with the product.

### **Continuing IRB review after study approval**

There is also continuing IRB review after study approval. FDA regulations require an IRB to develop and follow written procedures:

- For conducting continuing review of research at intervals appropriate to the degree of risk (but not less than once per year) (21 CFR 56.108 and 109).
- For determining which studies need verification from sources other than the investigator, and that no material changes in the research have occurred since the previous review (21 CFR 56.108 and 109).
- For ensuring that changes in research are promptly reported and approved by the IRB.
- For suspending or terminating approval of research that is not being conducted in accordance with the IRBs requirements (21 CFR 56.108 and 113).

Changes in research projects must be promptly reported. It is not always easy for investigators to meet the timeframe laid out in the requirements so the IRB can promptly review them. If the IRB doesn't meet on a frequent basis, the investigator must sometimes ask the IRB to call a special or emergency meeting to address a particular issue that arose during the course of a trial.

The process for conducting the continuing review of a study calls for submitting progress reports to the IRB, updating consent documents where necessary and terminating the study when necessary. There must be procedures in place at the IRB for suspending or terminating research approval.

### **Reviewing changes in ongoing research**

The IRB also needs to review changes in ongoing research. The IRB chairperson or a designee may approve minor changes, namely those that do not involve increased risk or discomfort to subjects. The IRB committee, however, must review and approve any non-minor changes before implementation.

So companies must have both the IRB and FDA review and approve parameters for changes in a study.

## **Required IRB records**

The IRB is required to keep multiple records, including:

- Copies of all research proposals reviewed;
- Minutes of IRB meetings;
- Records of continuing review activities;
- Copies of correspondence with investigators;
- A list of IRB members and their qualifications;
- Copies of written IRB procedures; and
- Statements of significant new findings provided to subjects (such as changes to informed consent).

IRBs need to retain these records for three years following completion of the research.

The regulations may be found at 21 CFR 56.115.

In some cases, hospitals and communities maintain their own IRBs. Indeed, the trend is toward more commercial IRBs. These are springing up to provide services to the regulated drug and device industries.

## **FDA IRB inspections**

The FDA's Bioresearch Monitoring Program conducts site visits for clinical investigators, research sponsors, CROs, animal laboratories and IRBs. Inspectors determine whether the IRB is operating in accordance with both its own written procedures and FDA regulations.

These regulations include:

- Informed consent (21 CFR Part 50)
- Standards for IRBs (21 CFR Part 56)
- Investigational new drugs (21 CFR Part 312)
- Investigational devices (21 CFR Part 812)

IRBs must have written procedures in place that parallel the regulatory requirements. They also have to make sure they follow those procedures. In too many cases, IRBs will create written procedures and then not follow them. Remember, IRBs must protect the safety of subjects who participate in research.

At the end of an inspection, FDA inspectors will conduct an exit interview. They will discuss any findings, clarify any misunderstandings and may issue a Form 483, or "Notice of Observations."

However, if and when FDA inspectors find problems during an inspection, firms sometimes can ask for an outline of some of those findings and thus begin addressing them immediately. If there's a break in the inspectional process, companies may be able to remedy some of the objectionable issues.

Sometimes, inspectors will take photographs to document their findings. If inspectors do so during an inspection, a sponsor can assign someone to take its own pictures of the same findings, which can help shed light on what issues are of apparent concern to the inspection team.

The arrival of investigators is stressful. Sponsors and others undergoing an inspection must cooperate with inspectors. However, if anything makes employees or others feel uncomfortable, it is appropriate to question what is happening. Sponsors, for instance, may choose to escort the FDA inspectors into a conference room and bring them any specific requested documents, rather than allow them to freely peruse the firm's files. That increases control over the conduct of the inspection.

If FDA inspectors do seek records, firms must copy them. Be cautious if the inspectors ask people within an organization to sign an affidavit. It is wise not to sign an affidavit, unless it is for the receipt of samples or to acknowledge the investigators have removed files or records. Sponsors and others undergoing an inspection should not allow FDA inspectors to read any affidavits to employees. They can state that it is policy not to sign affidavits or acknowledge them without first talking to legal counsel.

After the inspection, inspectors will submit a written report to FDA headquarters for evaluation. Headquarters then issues a letter.

There are three types of letters:

- A notice of no significant deviations from regulations.
- An informational letter that identifies deviations from regulations and good manufacturing practices (GMP), which may or may not require a response.
- A "warning letter" identifying serious deviations from regulations requiring prompt correction and response. This letter will give a contact person who may be contacted with questions.

Upon receipt of a warning letter, it should be shared with the sponsor and CRO. Plan to respond to those observations in a very timely manner. That means understanding the problems, doing a full investigation and putting a corrective and preventative plan in place to make sure issues don't reoccur in the future.

For serious violations, an IRB may be disqualified. These violations include a refusal or repeated failure to comply with regulations and noncompliance that adversely affects rights or welfare of subjects.



# The Role of the Clinical Investigator in FDA-Regulated Research

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Investigators also have clear responsibilities in any research project. Remember that investigators are the individuals who actually conduct a clinical investigation. Again, they are the individuals under whose immediate direction a drug is administered to a subject.

Investigators are responsible for ensuring that an investigation is conducted in accordance with a signed investigator statement, investigational plan and all pertinent regulations. They are also responsible for protecting the rights, safety and welfare of subjects under their control.

Investigators are responsible for controlling the drugs and devices that form part of the research study, as well as obtaining informed consent, keeping records, compiling required reports and assuring that the IRB is responsible for review of the study.

The regulations may be found at 21 CFR 312.60 and 21 CFR 812.100. These responsibilities should be integrated with the role of the IRB to ensure the research study is well controlled.

## Clinical investigation records

Investigators are responsible for many records, including case history records. Case histories must record all observations, and other data pertinent to the study, for each patient. They should include: basic identifying information, selection criteria, information to support data in the case report form, exposure to test article and copies of case report forms.

Every patient enrolled in the clinical trial must have a complete case history. It can be beneficial to keep some information about people screened for the trial but who did not meet entry criteria. This demonstrates that the process discriminated between people who did and did not meet study criteria.

Also, it may be helpful to maintain all information with respect to the study protocol and related documents. Make sure it is in an accessible place and that it includes:

- A statement of objectives and purpose;
- All investigator/IRB/facility information;
- Selection/exclusion criteria;
- Estimated number of subjects;
- Description of study design, controls and methods to minimize bias;
- Method of dosage, planned maximum dose (for devices, treatment parameters and exposure);
- Description of observations/measurements to be made; and
- Description of clinical procedures, laboratory tests and measures taken to minimize risk and to monitor the effects of the test/controls.

Take note that the investigator, and not the sponsor, remains responsible for the accuracy and completeness of study reports as well as for any discrepancies found in these records during an inspection. Also, the investigator cannot depend on the sponsor to monitor for compliance. The investigator cannot say, “Oh, the sponsor came in and said everything was OK.” That will not cut it with inspectors. Everyone has to participate and be a fully integrated member of the research team in order to comply with the requirements.

## **FDA inspection of clinical investigators**

Again, the FDA’s Bioresearch Monitoring Program conducts site visits, including of clinical investigators. The objectives are to ensure the quality and integrity of the data and other information submitted to the FDA and to protect research subjects.

There are three different types of inspections:

- Study-oriented
- Investigator-oriented
- Bioequivalence study

*Study-oriented inspections.* Study-oriented types of inspections can cover pivotal trials. Certain investigators may also be subject to audit if some of their data have come into question in the past. Bioequivalency studies for the support of new drug applications are also potentially subject to audit, depending on the nature of the product and the facility conducting the trial.

Study-oriented inspections consist of two basic parts. First, inspectors determine the facts surrounding the conduct of the study. They will determine who did what, how authority is delegated, where specific aspects of the study were performed, how and where data was recorded, how the test article accountability was maintained, how the monitor communicated with the clinical investigator and how the monitor evaluated the study’s progress.

The second part of the inspection involves auditing the study data. This means comparing investigator data to the data submitted to the agency or sponsor, along with all available records that might support the data. The inspectors will also look at follow-up records. The inspectors want to make sure that whatever lies in the automated database or has been transcribed from the actual clinical records is what’s in the actual database itself—and is supported by the raw data of the underlying patient records for that particular subject.

*Investigator-oriented inspections.* This type of inspection may be initiated where an investigator conducted a pivotal study in product approval or where the sponsor reports difficulty or concern.

Other reasons include inconsistent findings with other investigators, laboratory results outside of the range of expected biological variation or too many subjects enrolled with a specific disease given the locale of the investigation. If there are any questionable factors about the patients included in a trial, such a situation will likely give rise to some sort of inspection.

Procedures are the same as those in a study-oriented inspection but the inspection audit may go into greater depth and may cover more than one study.

The FDA has begun taking much more of a compliance and inspectional role. Expect this to continue, in terms of the frequency of inspections and an increase in for-cause inspections. The FDA has increased its focus on the inspectional process because of a perceived breakdown in the voluntary compliance process. The good manufacturing practices and quality systems requirements for both the drug and medical device industry are now subject to greater scrutiny, as are the clinical studies used to support those applications.

*Bioequivalence study inspections.* These are conducted where one study may be the sole basis for a drug's approval.

## **Clinical investigator regulatory sanctions**

Again, once FDA inspectors complete an inspection, they will submit a written report to headquarters for evaluation. Following that step, the agency issues its results. If inspectors identify serious deviations from the regulations, a warning letter will follow, requiring a prompt correction by the clinical investigator.

The clinical investigator is subject to regulatory sanctions, including disqualification. There are two reasons for disqualification: The FDA may disqualify clinical investigators from receiving investigational drugs if they have deliberately violated regulations or have submitted false information to the sponsor in a required report.

The FDA will send a warning letter describing the noncompliance and/or the false submission and allow for a response. If the FDA rejects the response, the agency will initiate a Notice of Opportunity for Hearing. An Office of Health Affairs (OHA) official will preside at the hearing.

Such hearings are informal and the rules of evidence do not apply. During the proceeding, the agency presents information and the investigator may respond. After the hearing, the official prepares a written report, including a recommendation. This is forwarded to the FDA commissioner, who issues a written decision. Criminal sanctions include violations of the Food, Drug and Cosmetic Act. More details may be found in the federal criminal and penal code, 18 USC § 1001 (false statements).

There aren't many excuses worth offering that would gain the agency's sympathy for failing to comply with the requirements. It's best to address the situation head-on and to take a responsible position. Acknowledge that the issues have occurred and put a plan in place describing what kind of controls and further assurances have been put in place to prevent similar problems occurring in the future. Note that the falsification of information ratchets up the situation to another level. There are significant civil and criminal sanctions for submission of false information to the government.

This goes to show that companies need to select clinical investigators on the basis of their qualifications and experience. They need to understand what the regulations require and appreciate that there are significant penalties for not following the rules.

## The Importance of Contractual Language

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There are certainly representations and warranties that can help demonstrate compliance with the Food, Drug and Cosmetic Act and all other laws and regulations pertinent to the FDA and any other relevant foreign regulatory authority. They can also help demonstrate that any studies are being conducted within generally accepted standards of good clinical practices and good medical practices.

It is wise to include language in any contracts making the expectation clear that companies should conduct any clinical study in conformance with these standards and regulations.

Contracts should also require the prompt disclosure of any discrepancies or errors, the free availability of all study documentation and the immediately notification of any serious or unexpected event that occurs during the clinical study. Contracts should require companies to retain all study documentation in conformance with the laws.

Writing these contracts involves many lawyers. This is the case to protect, for example, the sponsor or company underwriting the clinical research. The contracts provide assurance that whoever signs a contract understands the obligations and standards to which they will be held. They must know any breach of contract has legal consequences and liabilities.

Contract language also typically speaks to the standard of care customary in the industry. Anyone involved in clinical trials must understand their responsibilities and use procedures that comply with the regulatory requirements.

For instance, contract language may state that a CRO agrees to conduct its services in compliance with all applicable laws, rules and regulations, and within the standard of care customary in the CRO industry. Because of the range of transfers of obligation that are possible under the IND and IDE requirements, the contract should include language that ensures CROs are on the hook for the kinds of work they undertake.

Contract language may also speak to the fact that companies must render services in accordance with high professional standards. This is a vague term, but one that can be interpreted to include any number of actions. Actions such as failing to meeting the inclusion/exclusion criteria of a study or failing to give a subject informed consent can be interpreted as a breach of the contract requirement to meet high professional standards.

## Tips for Inspection Preparation

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A call from the FDA should not set a company atremble. If prepared, a company should not have to worry. Why? Because the inspection would consist of simply reviewing documentation related to clinical trial conduct maintained by the sponsor, investigator and IRB to ensure each party is compliance with each other and with the applicable regulations.

The FDA's purpose is to ensure the integrity of scientific testing. That means making sure the reliability of test data submitted to the FDA can be verified. In addition, the FDA is inspecting to ensure that the rights and safety of human study subjects are protected.

As previously discussed, sponsors, investigators and IRBs must be aware of their regulatory responsibilities. For more detailed information about these requirements, review the following regulations:

- 21 CFR Part 11 — Electronic Records; Electronic Signatures;
- 21 CFR Part 50 — Human Subject Protection (Informed Consent);
- 21 CFR Part 54 — Financial Disclosure by Clinical Investigators;
- 21 CFR Part 56 — Institutional Review Boards;
- 21 CFR Part 312 — Investigational New Drug Application;
- 21 CFR Part 314 — Applications for FDA Approval to Market a New Drug;
- 21 CFR Part 601 — Licensing (Biologics);
- 21 CFR Part 812 — Investigational Device Exemptions; and
- 21 CFR Part 814 — Premarket Approval of Medical Devices.

### Routine and Directed Inspections

The FDA conducts routine inspections of clinical investigators, sponsors, IRBs and nonclinical laboratories when approval is sought for a new medical product. The FDA may provide five to 10 days' prior notice of a routine inspection. It carries out directed inspections, or "for cause" inspections, after it identifies problems during the review process or when it receives complaints. If the complaints are egregious, the FDA is unlikely to provide advance notice of an inspection; at best, the FDA investigator might call on a Monday to give notice about a Tuesday inspection.

During the inspection, the agency seeks to confirm whether an investigator met the regulatory obligations. Is there evidence that subject rights and welfare were upheld and that the IRB upheld its regulatory obligations? The agency wants to see evidence that the sponsor met its regulatory obligations. Thus, the FDA will compare the practices and procedures to commitments made in an IND or IDE application.

## **Before the Inspection — Dress Rehearsal**

A dress rehearsal before any inspection is helpful. A practice run should involve everyone—clinical investigator, sponsor and IRB. It is important to interview responsible parties to make sure everyone is aware of the study. Also ensure the clinical investigator understands the reporting obligations to the sponsor and the IRB.

The dress rehearsal should include an inspection tour of the facility, to review procedures with responsible parties. Whenever FDA investigators escape the watchful eye of a sponsor, clinical investigator or IRB official, they might take the opportunity to talk to other employees. They also might give out business cards, telling employees to contact them with any questions or concerns. It can also be helpful during a dress rehearsal to go through the organization and make sure that the scale, blood pressure cuffs and all other equipment used in seeing subjects is operational.

In some situations, an inspection might come years after the fact. Thus, it is important to ensure that clinical investigators are familiar with all protocols relevant to them.

Sponsors and sites also must ensure that all files remain well organized. Some individuals have suggested that well-organized files can work against a sponsor, site or IRB in an investigation, since they make it easier to find violations. This is faulty logic.

“All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation, and verification,” according to “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.” It is essential to keep information organized and be honest about it. When an issue arises, the site should clarify it, report it properly and move on. The research team should not try to hide information in an attempt to make it harder for the FDA to inspect. Why? Because FDA investigators will notice if information is not well organized and then go on to find it regardless, after having spent only more time doing so. Hiding disorganized information will only make the site look bad—and will probably raise more questions for the FDA.

## **During the Inspection — Sites**

At the site, the FDA investigators will:

- Tour the facility.
- Review 100 percent of the informed consent documents. An informed consent form is a blank form submitted to the IRB for approval. For a site to obtain a fully effective informed consent document, the patient or a legally authorized representative must first sign the document.
- Assess the workload ratio. The FDA will ask for an unblinded listing of all the clinical trials with which the investigator has been involved, going back perhaps five years, including both the sponsor information and IND information. For that reason, those pieces of information should not be blinded. The site might want to blind it when submitting an investigator’s curriculum vitae to a sponsor, but the site needs to

otherwise maintain this listing because it forms part of the FDA’s inspectional approach.

- Review line listings of all the adverse events and serious adverse events reported, all the subjects that dropped out and any other issues that arose. The FDA will have information that the sponsor has provided, including case report forms, and can corroborate or verify at the site that this information is true and accurate.

“A line listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help regulatory authorities identify cases that they might wish to examine more completely by requesting full case reports,” according to the guidance “E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs.”

- Review subject records. If the site has only five or six subjects enrolled, then the FDA might look at all the records. But if the site has 50 or 60 subjects enrolled, it is then more likely that the FDA investigator will spot-check just one-third of those records.
- Review all of the regulatory documents. These documents are maintained before, during and after a clinical trial. They demonstrate compliance with good clinical practice (GCP) standards and regulatory requirements. They include the investigator’s brochure, case report forms, protocol, informed consent forms and source documents.
- Interview clinical research personnel. It is important that the site brief its employees about its requirements about speaking to FDA investigators during an inspection. It also should ensure that its employees are knowledgeable about the study. The site should ensure that the FDA is well informed as well, by making available someone who is able to provide accurate and relevant information.
- Request daily debriefings. The site and sponsor should make sure that the FDA investigator clarifies any information or issues as necessary as it arises, rather than wait to find out at the end of the inspection when the FDA investigator is preparing to issue a Form 483. Sites and sponsors should make two copies of requested documents—one to keep and one for the agency. Furthermore, it is important to look through the material to deduce what FDA investigators are looking at and why, and what they might be thinking.

The FDA investigator might ask the principal investigator questions, including:

- Were there any problems or protocol violations?
- How were protocol problems handled? Sites should define noncompliance and thresholds for keeping subjects in a study. For example, if a subject refuses to take the investigational drug three times in a row, then the site would likely drop the person from the trial. If subjects do not show up for follow-up visits three times in a row and the site did its due diligence—that is, it called, left messages, sent letters, did everything but physically drag the subjects into the office—then the site would likely reconsider keeping them on in the study, beyond these three missed visits, because

they are probably doing harm to themselves by not coming in and participating in a safety assessment of their progress;

- How did you recruit subjects? Advertisements to recruit subjects should be reviewed to ensure that the advertisement “is not unduly coercive and does not promise a certainty of cure beyond what is outlined in the consent and the protocol,” according to the FDA’s “Guidance for Institutional Review Boards and Clinical Investigators” information sheet;
- Can you explain the informed consent process? The requirements for informed consent are outlined in 21 CFR Part 50. Sponsors should make sure their clinical investigators—and not just the subinvestigators—are aware of and participating in the informed consent process;
- Who else worked with you on the study?
- How were you trained on the protocol? How did you train the subinvestigator after attending the principal investigator meeting? Sites should make sure to document the training;
- How is the study drug stored and dispensed? Who dispensed the investigational product? Proper storage and handling of the drug is essential so as not to jeopardize the quality and accuracy of the study;
- How often did the monitor visit the site? It is a two-way inspection, meaning it includes making sure the sponsor fulfilled its obligations, which includes monitoring;
- Were you audited by the sponsor?
- What IRB reviewed the study?
- Where is the investigator’s brochure (IB)? The purpose of the IB is “to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration, and safety monitoring procedures,” according to “Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance.” Furthermore, the “IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial.” The sponsor should make the IB available to the clinical investigator; and
- How many subjects were screened and enrolled? A master enrollment log should be maintained and provided to the FDA.

## Site Personnel

During an inspection, a site should name someone the FDA’s point of contact. It is important to be honest, fully answer the questions and provide data as requested. Sites should make two sets of copies of any documents the FDA requests, which allow officials to review the requested materials along with the FDA. Sites should also meet with the FDA investigator daily. In addi-



tion, sites should take the chance to note deficiencies and implement reasonable corrective action before the FDA investigator leaves the facility.

The principal investigator's fingerprints should be found throughout the study. There should be evidence of the principal investigator's prompt signature and dates. The bottom line is that the FDA wants confirmation that the principal investigator has provided oversight by:

- Enrolling eligible subjects and obtaining consent;
- Assessing adverse event causality; and
- Supervising the conducting of the trial—not over-delegating a degree of authority to other staff members.

### **During the Inspection — Sponsor**

Actions taken by FDA investigators include:

- Interviewing key individuals at the sponsor organization responsible for protocol development, site selection, statistical analysis, clinical supplies (how they were maintained and delivered), monitoring and quality assurance. The list of investigators also will be compared against the Form 1572;
- Reviewing contracted services and the selection process for monitors and investigators. The FDA investigators will spend a lot of time looking at the training files and reviewing the standard operating procedures (SOPs) for all of these activities, as they are critical; and
- Reviewing documentation on the selection of monitors and comparing monitoring procedures against the monitoring that was performed.

During a sponsor inspection, FDA investigators will also focus on specific sites, including those where compassionate use may be an issue, have been suspended or have high enrollments. They also will focus on randomly selected sites. Investigational product accountability, IRB approvals and reports to the IRB also will draw their attention. In particular, the investigators will concentrate on the following:

- Training records of all site personnel;
- Records and reports, including all correspondence between the site and the sponsor;
- Reports of unanticipated problems reported to the IRB and sponsor;
- Confirmation that the sponsor has refrained from commercialization of the investigational product;
- Confirmation that the investigational product is properly labeled;
- Evidence that the sponsor has provided the appropriate information to the investigators to conduct quality research; and
- Progress reports and final reports of the study.

In addition, the FDA investigator might ask the sponsor the following questions:

- How did you handle serious deviations from the protocol and FDA regulations? How do you stamp out noncompliance at the sites?
- How did you review and determine whether adverse events at the sites were reported to the FDA in accordance with regulations? What is your tracking method for adverse events and relaying information to investigators?
- How were corrections made on case report forms? How was confirmation and verification obtained from the clinical investigator? How were case report forms verified against the source documentation? How are you ensuring that corrections, confirmations and verifications actually occur?

### **During the Inspection — IRB**

When the FDA inspects the IRB, agency investigators will:

- Interview responsible IRB staff members;
- Conduct an in-depth review of the IRB's SOPs, files and records; and
- Examine active FDA-regulated studies to assess IRB operations and conformance with regulatory requirements for both initial and continuing review. That may trigger another inspection at the site.

The principal areas covered in the IRB inspection include IRB membership, written procedures, initial review and approval of studies, continuing review of research and how the IRB reporting occurred between the investigator and the IRB.

### **Inspection Closure**

At the end of the inspection, the FDA conducts an exit interview. During that discussion, the FDA investigator can clarify any observations.

If investigators find deviations from the regulations, then they will issue a Form 483 during the exit interview. The Form 483 is a written report of the objectionable conditions that agency investigators observed. It is important to treat a Form 483 as significant and to respond accordingly.

## A Review of Warning Letters and Violations

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Let's take a look at warning letters issued by the FDA in recent years. From 2008 through mid-2010, the FDA issued more than 50 warning letters related to the conduct of clinical trials. The FDA issued 14 of them directly to clinical investigators involved in medical device trials. It issued another 38 to investigators in drug or biological product trials. And it issued one letter to an IRB.

The nature of the violations has not changed over the years. However, the number of warning letters issued by the FDA to clinical investigators has increased of late.

So what are some of the issues the FDA cites in warning letters? The following summarizes the most common investigator and CRO violations cited in recent warning letters:

- Failure to retain complete, current and accurate records, such as missing or incomplete case histories or device disposition records; discrepancies between source documents and case report forms.
- Failure to ensure informed consent was obtained as required, with forms missing, not currently approved by IRB or incompletely documented; failure to meet/document requirements for emergency-use exemption from informed consent.
- Failure to conduct the investigation in accordance with the signed agreement, investigational plan/protocol, and/or applicable FDA regulations, such as enrolling subjects counter to inclusion/exclusion criteria; failure to perform/document required follow-up; failure to document IRB consent/correspondence; and unapproved deviations from protocol.
- Failure to timely report/adequately evaluate adverse events.
- Failure of principal investigator or CRO to adequately supervise conduct/ensure monitoring of trial.
- Failure to obtain required IND or IDE. Failure to make required records available for inspection.
- Other failure to protect patient safety/exposure to serious risk. Failure to submit/late submission of scheduled reports to sponsor, monitor. IRB Failure to submit/update conflict of interest information.

Consider the failure to obtain a required IND or IDE: There are exceptions to when a sponsor must submit an IND or IDE. However, some companies stretch the case. If exploiting an exception, look at whether doing so would subject participants to any particular risk. For example, take a trial on a legally marketed drug or device: The trial might keep within the dosing range or interval, but involve a different patient population. Consider carefully whether that patient population would be subject to any particular risk.

What is the nature of the trial being conducted? Is to support the approval of a particular product or is it a research study to provide additional information? There are certain instances where a physician can do studies to contribute to the knowledge base of medical science that can be

outside the IND or IDE process. Think carefully about the requirements—if anything, to avoid receiving a citation.

The real question is this: Are the rights, safety and welfare of subjects who are participating in those trials being protected? The FDA cites violations of these principles on a regular and routine basis.

The following is a summary of IRB-cited violations from warning letters:

- Failure to prepare, maintain and follow adequate written procedures for initial and continuing review of clinical investigations.
- Failure to review proposed research/amendments at convened meetings, which should include a majority of IRB members and at least one member whose primary concerns are in nonscientific areas.
- Failure to conduct continuing review at appropriate intervals.
- Failure to prepare and maintain adequate documentation of review activities.
- Failure to require adequate informed consent.

Other issues cited in recent warning letters include:

- Failure to follow the protocol
- Falsification
- Informed consent issues
- Failure to report adverse events
- Qualifications of persons performing physicals
- Inadequate records
- Failure to get IRB approval or report changes in research
- Failure to follow FDA regulations
- Charging for the test article
- Drug accountability
- No active IND
- Violations of good laboratory practice (GLP) regulations
- Misleading advertisements for subjects to participate in trials
- Blinding
- Failure to have an investigator statement, or Form FDA-1572
- Monitoring practices
- IRB shopping

Again, this list resembles those items the FDA has cited in the past, including shopping for IRBs. That practice occurs when a company seeks approval to conduct a trial elsewhere, after one IRB has turned down the study. The company will enlist a commercial sponsor or commercial IRB to review the study. When it comes to charging for test articles, this is not commonly allowed for drugs. In the medical device world, it is a little more common; still, companies must ensure they not going outside the bounds of the rules.

Some of the most serious items cited by the FDA involve informed consent issues, failure to follow the protocol and failure to report adverse events. These involve the rights and welfare of subjects participating in the trial.

Why does the FDA continue to see these citations? Frankly, the FDA is doing more data scrutiny. Funding cutbacks also contribute. Also, some companies seek to complete trials as quickly as possible or without sufficient monitoring systems. In these cases, there are not enough resources dedicated to routine monitoring to support the trial's proper conduct. And part of the problem lies with people who don't understand and appreciate their responsibilities in conducting these types of trials.


There are also concerns over the financial involvement of investigators in the outcome of these trials. Whistleblowers have reported that people put subjects at risk by doing things either outside the scope of the trial or not in accordance with the regulations. Whistleblower protection encourages people to report such grave problems. There is also a lack of training and understanding by investigators of what is expected in clinical trials.

So prepare for an FDA inspection by reviewing all the clinical investigator record-keeping and reporting responsibilities set forth in FDA regulations. Then review all present procedures for issues, such as IRB review, informed consent, investigation drug controls, clinical data record keeping and adverse reaction monitoring and reporting. Determine whether existing procedures are in compliance with the FDA's regulatory requirements.

Conduct an audit of all ongoing studies to evaluate whether existing procedures are being followed. There are a number of outside people well qualified to conduct these audits to ensure proper preparation in advance of an inspection, allowing studies to subsequently pass muster. Review the results of an audit with all personnel involved with the studies. If any issues are identified in the course of these audits, ensure there are appropriate corrective and preventative actions in place to remedy the situation and prevent those problems going forward. Document all changes that are initiated to bring the study into compliance.

Review procedures for handling an FDA inspection. An inspection can be a nerve-wracking experience. If not already in place, establish procedures to address such things as how to respond to questions from inspectors, who should interact with the inspectors, how to meet requests for documents and which records an inspector is entitled to review. It will make for a smoother inspection.

Then review procedures for following up to any FDA observations made during the inspection, as well as any post-inspection exit interview, FDA Form 483s and any potential warning letter. Be sure to communicate any observations from inspectors to the responsible parties. Establish a



plan for remedial action, if necessary, and to prepare and review documentation and response to issues raised by the FDA. Make sure of a response to any issues identified during an inspection and take appropriate steps to prevent such issues from reoccurring in the future.

Avoid violations by hiring and training adequate staff. Know the FDA and OHRP requirements and carefully monitor clinical studies. Keep adequate and complete records of all studies.

To avoid citations, organizations need to ratchet up the level of oversight in these investigations to ensure they are protecting the safety of the subjects participating in the studies and to get the best quality of clinical data to support innovation.

## FAQs

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*This Q&A section was taken from an audio conference led by David L. Rosen, BS, Pharm, JD, a partner in the Washington, D.C. law firm of Foley & Lardner, LLP. Rosen was an employee of the FDA for 14 years and held supervisory positions related to the drug approval process, combination products, jurisdictional issues and related compliance activities.*

**Q:** *Do you encourage the hiring of an independent, outside auditor to help prepare for an upcoming FDA inspection? If so, who should conduct this audit?*

**A:** I think anyone who's qualified by training and experience in the conduct of clinical trials can participate or audit a particular investigator or clinical trial site. He or she can ensure there is appropriate recordkeeping, proper monitoring and that source documentation agree with the case report forms.

Companies often have their own audit teams, whether it be the routine clinical auditors or clinical monitors that they use to ensure quality. There are third-party firms that have capabilities to audit sites and there are also some former FDA inspectors who do those types of investigations of clinical sites.

There's no study I've ever seen that has been conducted 100 percent perfectly. If you audit and take steps to identify issues and put in corrective plans voluntarily, you can certainly improve the quality of data from a clinical trial and increase the likelihood it will withstand an FDA audit. If the FDA raises questions, you can respond that you have put procedures in place to prevent recurrences in the future. This puts you in a better light than having the FDA find a problem you did not know about.

**Q:** *Our clinical trial software and its database are hosted by a vendor. What should be done, for example, regarding validation level or change control to ensure the data integrity? Is there any inspection observation and warning letter related to the software used in clinical trials?*

**A:** I've seen a lot of software-related issues come up. First, look at who has access and who has control over the database and the software used to create that database. Make sure that there's limited access for those people who are able to gain access to the underlying software architecture that controls the database.

Second, make sure that people have the most recent version of that software. If it's commercial software, use the most up-to-date version and make sure that it's installed appropriately. Verification and validation of that software is probably the biggest area that people have issues with. Test the software to be sure you cannot enter data that you shouldn't, such as data outside the scope of any particular limits or data in that would be outside the inclusion or exclusion criteria. Be certain if you have mechanisms in place in that software system that act as checks and balances or kick out an error code that they are working in an appropriate fashion. Be sure you check for data transcription errors.

Also, make sure that data is appropriately backed up and the software can be audited. You want

to see any audit trails where people have gone and tried to make modifications. Document that the appropriate administrator of the system has made modifications.

*Q: Do you have any data or list of warning letter numbers related specifically to medical device trials?*

**A:** If you go on to the FDA website ([www.fda.gov](http://www.fda.gov)) you can view warning letters based on who is the issuing agency. It's easy to pick out those issued by the Center for Drugs and the Center for Devices and Radiological Health. That's the easiest way I know to access the information.

*Q: Since more investigators are becoming further removed from direct personal conduct of trials, can you comment on where the FDA might draw the line between when an investigator is adequately supervising the conduct of a trial and when they are not?*

**A:** If the investigator is the principal investigator or has designated a sub-investigator, he or she is responsible for the conduct of that trial. No ifs, ands or buts. It's kind of like the case of a supermarket on the East Coast, which had a number of violations with respect to the cleanliness and the storage of foods and vegetables in the store. The president of the company, who was on the West Coast, was held responsible under FDA requirements, because he was in a position to know or should have known what was going on and was in a position to take appropriate action to prevent those issues from happening.

If you sign on as the principal investigator, you are taking responsibility for the conduct of that trial. The principal investigator needs to be involved and meet regularly with the sub-investigators. He or she needs to go through the conduct of the trial to make sure that it is being appropriately conducted. And the more he steps away, the more risk he takes for subordinates who are actually administering the investigational product to the subjects, as well as those people who are recording and completing the case report forms. So I think that, if you sign the FDA form 1572, you're on the hook.

*Q: Are there any regulations or guidance in place for the content of IRB approval letters?*

**A:** There are some IRB guidance sheets that are available on the Web. They give some guidance as to the kind of communication that needs to occur between an IRB and the principal investigator that documents the review and approval of a particular study or the comments that need to be changed in a particular protocol.

They certainly need to be very specific in terms of the name of the protocol, the protocol number, the date it was submitted, and specific comments. Approval letters need to document that yes, a study is approved and whether it is approved with certain conditions attached. Or if it is not approved, state the particular comments as to why. Be sure documentation is straightforward and detailed.

*Q: When would an IRB get audited by the FDA?*

**A:** If there's a safety concern. For instance, a safety issue has arisen in a study and people want to go back and look at the documentation to make sure it was actually reviewed and see whether or not there are any comments. This can occur whether or not there's a history of some



issues with that particular IRB. Frequently, there's a disgruntled person that has left an IRB and reports to the FDA that they haven't followed the proper procedures.

**Q:** *Is there any reason why the FDA would audit an exempted study?*

**A:** Only in the same type of situation. For instance, if a study was conducted and there was a rash of adverse events that occurred that put subjects at jeopardy or there were issues that arose during the course of that trial, that would be a pretty good trigger. That would likely give rise to an audit.

Any type of product complaint or product problem certainly gets the attention of the FDA. If someone steps up and raises a question, or alleges there is an issue, the FDA will frequently look into those situations.

**Q:** *When a clinical testing lab completes work for a clinical trial for an independent sponsor, what specific regulations should be followed outside of the Clinical Laboratory Improvement Amendments (CLIA)? For example, would CFR 21.820 still apply to firms that do not actually manufacture the device? What good clinical practices would apply? Can you specify which regulations we should be focusing on?*

**A:** That's a tough one, because this is a lab that's actually either conducting some sort of analysis or providing some sort of information to support the trial. So the question is whether or not quality systems and good clinical practice requirements need to be met.

The laboratory needs to be in compliance with good laboratory practices. This is certainly true if the lab is analyzing information or providing information that is being incorporated into a clinical study report or generating data that's going to be submitted as part of an FDA-regulated product. You would have to have appropriate training qualifications, experience, controls, recordkeeping and validations to demonstrate that the data that you're producing at that laboratory are valid. So I think it's a general proposition that you have to really be rigorous in conducting analyses that are being used for FDA-regulated products.