White paper

FDA Inspections of Clinical Investigators: Are You Ready?

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Introduction

Life science companies are developing cutting-edge medicines, medical devices, and therapies that entail increasingly complex clinical trials. As a result, regulators throughout the world have to step up their vigilance in overseeing clinical trials to ensure the safety of participants and the integrity of clinical research.

In the United States, the Food and Drug Administration (FDA) has a number of guidances that are meant to strengthen its oversight of clinical investigators and clinical trials. In Europe, tougher regulations for medical devices are being proposed by the European Commission, including stricter rules for notified bodies that conduct inspections during clinical trials.

The increased focus on clinical trials means sponsors and CROs can expect more stringent (if not more frequent) inspections. If your company is sponsoring a clinical trial or if it's a CRO conducting research on behalf of a sponsor, are you ready for an inspection?

Types of Inspections

In general, life science companies undergo or participate in any or all of these inspections: first-party Inspection (conducted internally by a company); second-party inspection (conducted by a customer); and third-party inspection (conducted by regulatory agencies such as the FDA or notified bodies in Europe).

This white paper will discuss inspections conducted by:

- **Regulatory bodies auditing CROs and organizations conducting clinical trials;**
- **Sponsors auditing CROs that are conducting clinical trials on their behalf.**

FDA's Concerns in Clinical Research

There are two major regulatory concerns in clinical research: patient safety and data integrity. Existing regulatory requirements almost always stem from those concerns. In the U.S., the FDA finalized a guidance in August 2013 called "Guidance for Industry: Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring."[1] It signaled the agency's intention to maximize its oversight of clinical trials. The guidance encourages the industry to use risk-based approach in monitoring clinical trials, as well as wider use of alternative monitoring approaches.

In addition, the following FDA guidances are an important part of the agency's effort to protect clinical trial patients and ensure the quality of clinical research data:

- **"Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: FDA Inspections of Clinical Investigators" (2010)[2]:** Provides that the FDA may conduct either announced or unannounced inspections of clinical trials for a number of reasons, such as to verify the accuracy of data submitted to the agency, or as a result of a complaint about the conduct of a study. The agency inspects clinical trials in the U.S. and overseas. The guidance applies to clinical trials for drugs, biologics, and medical devices.
- **"Guidance for Industry: Investigator Responsibilities—Protecting the Rights, Safety, and Welfare of Study Subjects" (2009)[3]:** Clarifies the responsibilities of clinical investigators and what the FDA expects from them. The guidance covers what is considered appropriate delegation of study-related tasks and adequate training for all staff members conducting the study. This guidance was triggered by a spate of warning letters within a nine-month period in 2009[4].

EU's Concerns in Clinical Research

In Europe, the medical device industry is bracing for tougher regulations proposed by the European Commission (EC). In 2012, the commission proposed amendments to current medical device directives, including stricter designation and oversight of notified bodies. It also sets out requirements for the national authorities responsible for the notified bodies. The proposed changes stemmed partly from harsh public criticism of the quality and depth of the conformity assessment performed by notified bodies, particularly their assessment of the manufacturers' clinical evaluation[5].

As for the European pharmaceutical industry, a revision to the EC's clinical trial directive was made in 2005 to ensure Good Clinical Practice (GCP) compliance in clinical research, including addressing concerns about inspections. The 2005 directive called for guidelines on inspection procedures and spelled out the minimum standards of the qualification of inspectors[6].

Common Issues during Inspections

An inspection during a clinical trial is meant to verify patient safety and clinical data integrity. It is meant to ensure that the research is being conducted according to the study protocol and complies with GCP standards and regulations. The issues faced by sponsors and CROs during inspection vary from one clinical study to another, but here are some examples of violations that have warranted FDA warning letters.

Violations Pertaining to Patients: When it comes to clinical trials, the FDA's foremost concern is the safety of patients who participate in them. Clinical investigators are responsible for protecting the rights, safety, and welfare of subjects during a clinical trial.

A warning letter sent by the FDA to a clinical investigator for Medtronic CoreValve U.S. Pivotal Trial cited violations illustrating the emphasis placed by the agency on patient safety. The FDA said that the clinical investigator failed to do the following: ensure that informed consent was obtained; ensure that the clinical trial is conducted in accordance with the signed agreement with the sponsor, the investigational plan, and the FDA regulations; notify the FDA and IRB of deviations from the investigational plan; and maintain an accurate, complete, and current records relating to the investigation[7].

Another FDA warning letter cited a clinical investigator's violations pertaining to inadequate records of disposition of drugs and failure to report to IRB a number of unanticipated problems involving risks to human subjects[8].

In a 2010 warning letter, the FDA cited a sponsor for its failure to monitor a clinical trial closely, which in turn resulted in a failure to detect dosing errors involving 40 subjects at multiple trial sites, including 20 subjects who exceeded the maximum protocol dose[9].

Violations Pertaining to Inadequate or Incomplete Data Collection

Data integrity is critical in proving product efficacy. It is no wonder that the FDA has expressed great concerns about a clinical investigator who violated regulations that affect data integrity. In a warning letter to an investigator conducting a clinical trial for a pharmaceutical company, the FDA noted inaccurate and inadequate case histories for patients, failure to obtain informed consent from a number of subjects, and failure to promptly inform the IRB about changes in the study[10].

Violations Pertaining to TMF

FDA regulations and ICH E6 guidance call for maintenance of the Trial Master File (TMF), which contains all essential documents throughout

the life of a clinical trial. It's not only necessary to generate the required documents, it's equally critical that the documents are accurate and reliable. An FDA warning letter cited a clinical investigator for ineffective management of essential documents. Among other things, the clinical investigator had kept inadequate and inaccurate case histories, filed duplicate records, while some documents showed discrepancies with handwritten notes[11].

In another FDA warning letter, a clinical investigator was cited for his failure to report subjects with positive HIV results to the state health department within seven days as required by state regulations. Such a timely report is an important part of TMF documentation[12].

How to Prepare for Third-Party Inspections during Clinical Research

An inspection is, by nature, unpredictable. As far as the FDA is concerned, most inspections of clinical trials are announced for the practical purpose of making sure that clinical investigators would be around to answer questions. Even when the inspection is announced, one cannot predict what the inspector would focus on, considering the breadth and depth of regulations that a sponsor or a CRO complies with.

When the FDA makes an unannounced visit, it is usually because of a serious complaint or a recall or some other problem. If an announced inspection can be unpredictable, a surprise inspection can be doubly so. If your organization happens to be the target of a surprise inspection, your underlying goal is to show the inspector (FDA inspectors are called investigators) that the organization is on top of the clinical trial.

To stay on top of your clinical research at all times, you have to maintain a state of inspection readiness and keep your processes, documents, and your quality system always efficient and effective.

While there are many ways to prepare for third-party inspections, this white paper will focus on issues discussed in the above mentioned FDA warning letters. Based on those examples, here are some ways to prepare for third-party inspections while a clinical trial is ongoing.

Patients Ensure Safety of Patients: Common issues cited in FDA warning letters under "Violations Pertaining to Patients" (above) fell under three areas: informed consent, protocol deviations, and drug disposition. In all three areas, an effective monitoring visit report will strengthen processes that help identify and track safety issues.

- **Informed Consent:** Clinical investigators can help ensure the safety of study participants by informing them properly about the study. Informed consent forms demonstrate to an inspector that study participants understand the goals and corresponding risks of the study. The FDA requires informed consent documents to be signed either by the subject or the subject's authorized representative. Without informed consent, subjects could potentially be abused. In the same vein, missing informed consent forms could be construed by an FDA inspector as a sign of inadequate subject protection.
- **Protocol Deviations:** Two warning letters mentioned above cited the clinical investigators for their failure to follow the investigational plan (also known as protocol) [13]. Serious protocol violations could be considered a failure to ensure patient safety because such noncompliance exposes them to risks. Clinical investigators should minimize those risks by adhering closely to the study protocol. Accurate and timely documentation and notification of stakeholders all contribute to ensuring patient safety.
- **Disposition of Drugs and Proper Monitoring:** Proper administration of investigational drugs to subjects has direct bearing on patient safety. The 2010 warning letter mentioned above showed that dosing errors were due to failure to ensure proper monitoring. "As a result of inadequate monitoring, widespread overdosing of study subjects at multiple study sites were neither corrected nor detected in a timely manner," according to the FDA[14].

Make Sure Documentation is Complete

During an inspection, the study's TMF will show the inspector whether patient rights were protected, GCP requirements were fulfilled, and whether the data collected and analyzed are accurate and reproducible.

FDA warning letters discussed above under "Violations Pertaining to Inadequate or Incomplete Data Collection" and "Violations Pertaining to TMF" all demonstrate the importance of vigilance in completing and maintaining essential documents gathered during a clinical trial such as case histories, case report form (CRF) and CRF corrections, subject log, drug accountability documents, and serious adverse events (SAE) documents. "Complete documentation" includes identifying any deviations and documenting how they were rectified.

The warning letters also cited failure to promptly inform the IRB about changes in the study and failure to report subjects with positive HIV results to the state health department in a timely manner[15]. In both cases, an electronic clinical quality management system (CQMS) would have automatically notified stakeholders (sponsors, CROs, principal investigators, clinical research associates, clinical research coordinators) about serious issues and therefore reported in a timely manner to the IRB and the state health department.

Establish and Maintain an Effective CQMS

The violations cited above could have been greatly mitigated with the help of an effective CQMS. Using a robust system for document management, TMF project management, audit, and other clinical trial processes is a fundamental way for sponsors and CROs to ensure regulatory compliance.

For those using paper-based or hybrid processes, switching to an electronic CQMS for managing the TMF, monitoring trial sites, and reporting of quality issues will greatly increase inspection preparedness. An electronic CQMS will help you attain the following:

- **Effective Clinical Trial Management:** Automates all clinical trial processes, including management of thousands of documents and streamlining the collaboration process (routing, review, and approval of documents). An automated CQMS will facilitate document exchange among investigators, trial site support staff, sponsor, CRO, and CMO. The system will increase efficiency in managing site-specific documents such as site qualification, protocol amendments, and study updates.
- **Timely Notification, Effective Monitoring:** Provides automatic and timely notification about deviations, SAEs, and other quality issues so they can be addressed promptly. Robust tools such as electronic checklists will support sponsors and CROs in conducting regular monitoring of trial sites, regardless of location. The checklists can also be utilized to monitor and track GCP deviations and violations.
- **Thorough Data Collection:** Electronic checklists, as well as reports and analytics, will make any missing documents (case histories, informed consent, CRF, etc.) transparent to the clinical trial staff and easier to track and gather.
- **Standardized Documents and Processes:** Standardizes all documents and clinical trial processes for easier reporting and

smoother communication. Clinical trial staff members can focus on the accuracy and the quality of the information they are gathering instead of spending too much time and effort formatting their documents and reporting the data properly. Study protocol changes, updates, and corrections will be easier to make because routing, review, and approval will be automated.

- **Inspection Readiness:** A CQMS will serve as a structure and a platform that will keep you always ready for inspection by making it easier for all stakeholders to participate in quality and compliance processes and also easier to manage those processes on a daily basis. All essential documents will reside in a centralized repository, greatly facilitating the inspector's review of documents and processes. Choose a CQMS that provides a training control process to make sure all clinical trial personnel are properly trained in GCP requirements, protocol changes and updates, and CAPAs and amended SOPs.

Conclusion

Maintaining inspection readiness and consistency of quality across clinical trial sites is easier with an electronic CQMS that can connect all stakeholders and sites regardless of location. When the sponsor and the CRO share a system, they can collaborate more closely throughout the life of a clinical trial. In case of deviations and other issues noted in monitoring reports, notifications will automatically go out to all affected clinical trial personnel. This is critical in rectifying deviations in a timely manner.

FDA warning letters offer many lessons; foremost is the importance of maintaining your processes in a perpetual state of readiness. By doing so, you will be able to focus on your core mission of conducting a safe and high-quality clinical trial.

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14. Supra note 9.

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