

Department of Health and Human Services

**OFFICE OF
INSPECTOR GENERAL**

**FDA Oversight of
Clinical Investigators**



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EXECUTIVE SUMMARY

PURPOSE

To examine the Food and Drug Administration's (FDA) selection of clinical investigators for inspection and FDA's discipline of those clinical investigators found in violation of FDA's regulations.

BACKGROUND

The FDA is responsible for monitoring and approving the development of new drugs, biologics and medical devices. Companies develop these products with the assistance of clinical investigators. Clinical investigators recruit the subjects, perform the studies and report the results. The FDA's bioresearch monitoring program inspects clinical investigators involved in clinical research to ensure the quality and integrity of data submitted to the agency and to protect the rights and welfare of human subjects. In most cases, these inspections occur after clinical work is complete.

The FDA is organized into Centers and the Office of Regulatory Affairs (ORA). Several of the Centers are involved in monitoring the development and testing of new human drugs, biologics and medical devices. The ORA staff conduct on-site inspections as part of the application review process for experimental products. The Centers assign the inspections, classify their results and decide what action to take.

We reviewed the universe of 184 official actions taken by FDA since Fiscal Year (FY) 1994. We interviewed the staff and managers in FDA's bioresearch monitoring programs. We also analyzed FDA's listing of clinical investigators, as well as performed a work flow analysis. We only examined FDA's bioresearch monitoring programs involved in the review of new human drugs, biologics and medical devices.

FINDINGS

Overall oversight of clinical investigators is limited

Sponsors, Institutional Review Boards and FDA oversee clinical investigators' research. Reviews by FDA have found serious problems with sponsors' monitoring of clinical investigators. Previous work by the Office of Inspector General found problems with Institutional Review Boards' oversight of clinical research. The FDA, in FY1999, non-randomly inspected only 468 clinical investigators of nearly 14,000 clinical investigators potentially involved in clinical trials. (The FDA could not provide the actual number of clinical investigators who submitted data in support of product applications.) We understand that the current FDA system is not intended to provide day to day oversight

of clinical trials. Rather, it provides a retrospective review of clinical trials. This report raises concerns about the assignment and classification of the current system of retrospective clinical investigator inspections.

Data integrity concerns, more than human subject protection, drive FDA's oversight of clinical investigators

Although respondents indicated that program goals are ensuring data integrity and protecting human subjects, FDA's monitoring of clinical investigators is more directly focused on verifying data. These inspections are application driven with number of subjects, data issues and inspection history driving the selection. While examining data integrity supports FDA's role of protecting consumers from unsafe or ineffective medical products, we did not find that this process protects human subjects during the research process. Other programs within and outside of FDA are more geared toward human subject protection.

Staff identified deliberate violations of the regulations and jeopardizing data integrity as the most frequent reasons to assign "official action indicated" to an inspection. Fraud and repeated violations will often merit disqualification. Review of official actions issued by FDA found the majority of official actions cited documentation and protocol violations. We also note that investigations are conducted after clinical research is completed, making oversight of human subjects protection retrospective rather than concurrent with clinical research.

The bioresearch monitoring program lacks clear and specific guidelines

The FDA regulations state that a clinical investigator may be disqualified from receiving investigational drugs, biologics or devices for repeatedly or deliberately failing to comply with the regulations. There is no required review of complaints or clinical investigator inspection histories as part of the clinical investigator selection process, although 70 percent of staff reported that they do check complaints or inspection histories. Staff receive little or no formal training on how to select clinical investigators for inspection or how to assess what action should be taken when violations are found. No written guidelines exist at a Center level for bioresearch monitoring staff on what "repeated or deliberate" violations mean. The FDA does not have agency-wide program measures for the bioresearch monitoring program.

RECOMMENDATIONS

This report does not make any recommendations regarding the weakness found with sponsor or institutional review board oversight of clinical investigators, since they have been addressed in other studies. Our recommendations focus on improving FDA's oversight of clinical investigators.

The FDA should define cross-Center goals for the bioresearch monitoring program and develop criteria to determine whether the program is achieving those goals

While respondents in all three Centers described similar program goals, there is currently no way to determine whether bioresearch monitoring is achieving those goals. The FDA, through the internal working group on bioresearch monitoring, should define what an effective bioresearch monitoring program should accomplish. As part of that definition, FDA should:

- clarify how long the process should take from the conclusion of the investigation and submission of the report until a decision is made on the results of the inspection and issuance of any Agency actions; and,
- clarify the criteria for selection of clinical investigators for inspection including looking at smaller sites and previous inspection history and compliance.

The FDA should also recognize the limitations of the current system's ability to protect human subjects during clinical trials. Currently, the vast majority of inspections are conducted after clinical trials are complete. Any human subject violations identified are found too late to protect the human subjects involved.

The FDA should develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products

The FDA's internal working group on bioresearch monitoring should develop guidance on the severity and number of violations needed to justify beginning disqualification proceedings. Cross-Center guidance would insure that each of the Centers handles the results of clinical investigator inspections consistently. We believe that having a written framework can provide structure for FDA reviewers.

AGENCY COMMENTS

We would like to thank the Food and Drug Administration for commenting on the draft of this report. Based on FDA's general and technical comments, some changes and clarifications were made in this final report.

The FDA commented that they are not responsible for providing patient care and that they are not currently equipped to monitor studies during the research process. We recognize this. We also understand that FDA attempts to protect human subjects and the general public through retrospective review of clinical investigators, research sponsors and institutional review boards. See Appendix B for the text of the Agency's comments.

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INTRODUCTION

PURPOSE

To examine the Food and Drug Administration's (FDA) selection of clinical investigators for inspection and FDA's discipline of those clinical investigators found in violation of FDA's regulations.

BACKGROUND

Agency structure

The FDA is responsible for enforcing the Federal Food, Drug and Cosmetic Act as well as other public health laws. To accomplish this mission, FDA is organized into Centers and the Office of Regulatory Affairs (ORA). Several of the Centers are involved in monitoring the development and testing of new drugs, biologics and medical devices. These Centers are the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER) and the Center for Devices and Radiological Health (CDRH), respectively. The ORA staff conduct on-site inspections as part of the application review process for new drugs, biologics and medical devices. These staff also conduct other inspections, such as food safety and mammography equipment.

Clinical Investigators

Clinical investigators perform the actual research used to support applications for new drugs, biologics and medical devices. A clinical investigator may be a professional researcher operating out of a research institution such as a research hospital or university, or may be a practicing physician who also conducts clinical research. A company developing a new product hires clinical investigators to recruit subjects, conduct the research and report the results back to the company.

Clinical investigators are monitored by several groups: the "sponsor" or company developing the product or a third party contracted by the sponsor; a local Institutional Review Board and FDA. Clinical investigators have several responsibilities in conducting clinical trials, including:

- documenting data collection and study procedures accurately and completely;
- reporting to the sponsor, Institutional Review Board and FDA;

- protecting the safety of participating subjects;
- following study protocols; and
- maintaining control of the investigational product.

Clinical investigators sign investigator agreements that attest to their knowledge of and agreement with their responsibilities under FDA regulations as researchers.

Clinical investigator inspections

Units within each Center review applications for new drugs, devices or biologics. Each application includes a list of all clinical investigators submitting research in support of the application. As part of the application process, FDA staff inspect a non-random sample of clinical investigators. In addition to clinical investigator inspections, bioresearch monitoring selects sponsors and Institutional Review Boards for on-site inspections.

Three quarters of inspections are initiated as part of FDA's application review process. The bioresearch monitoring team, in consultation with application review staff, select three or four clinical investigators per application for inspection. Clinical investigators are also investigated due to complaints received by FDA, observations noted during previous inspections of the clinical investigator or analysis of data submitted to FDA.

Once a clinical investigator is selected for an inspection, FDA bioresearch monitoring staff issues an inspection assignment to ORA. The ORA investigators conduct the inspection. Occasionally staff from the assigning Center will accompany the field investigator on their inspection.

The inspection involves interviews with the clinical investigator and study staff and a review of the clinical investigator's processes, records, data and documentation. Field investigators use a Form FDA-483 to record problems observed during the inspection. If problems are observed during an inspection, the clinical investigator receives a copy of the FDA-483 at the end of the inspection. The field staff sends a copy of the FDA-483 and the Establishment Inspection Report, which includes copies of all documents collected during the inspection, to the Center that issued the assignment.

Inspection classification

Using the information provided by the field investigator, Center staff classify the inspection as no action indicated, voluntary action indicated or official action indicated. The FDA would classify an inspection with few or no objectionable conditions or practices as no action indicated and the clinical investigator is not required to make any changes or respond to the FDA. When FDA classifies an inspection as voluntary action indicated, the clinical investigator is asked to make voluntary changes. A letter

requesting voluntary action does not necessarily require a response from the clinical investigator.

For inspections that result in an official action indicated classification, a Center can take a number of different official actions. However, two official actions appear to be used in the vast majority of cases. For those cases in which the violations appear less serious, a Center sends the clinical investigator a Warning Letter outlining violations and requesting a response. The response from the clinical investigator should include the specific steps the clinical investigator plans to take to correct the violations, as well as what steps will be taken to prevent a recurrence of similar violations. The FDA may also elect to not allow the clinical investigator's data to be included in the application. The FDA considers this decision one of their most significant controls over the activities of sponsors and ultimately clinical investigators.

Disqualification proceedings

For more serious violations, a Center can initiate the disqualification of the clinical investigator from future clinical research. A disqualified investigator may not receive investigational products, which in effect prohibits that clinical investigator from conducting clinical trials.

A Center issues the clinical investigator a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE). This notice offers the clinical investigator a chance to meet informally with the Center to discuss the violations found during the inspection. If the clinical investigator produces information that indicates he or she is taking corrective action or otherwise resolves the identified problems to the Center's satisfaction, this meeting may be the end of the process.

If FDA does not agree with information presented at the informal conference, the next step is to issue a Notice of Opportunity for Hearing. At this hearing, both the clinical investigator and FDA present their cases. The hearing records include the investigation results and the clinical investigator's explanation. Legal counsel may accompany the clinical investigator to the hearing. The hearing officer makes a recommendation to the Commissioner, who reviews the information and makes a decision. The process often takes several years, during which time the clinical investigator may continue to conduct clinical research.

At any point during the disqualification process, a clinical investigator can agree to be disqualified or restricted by signing a consent agreement. A restriction limits the ability of a clinical investigator to conduct clinical trials. A restriction can include a temporary disqualification for several years, specific restrictions on the type of studies a clinical investigator can conduct or supervision of the clinical investigator by another clinical investigator.

Impact and publicity of sanctions

The FDA maintains a list of disqualified or restricted clinical investigators on its Internet home page. The list identifies the person, city and state, FDA Center, nature of sanction, date of sanction and limited summary information, such as whether the sanction was applied after a hearing or through a consent agreement. As of January 2000, the FDA list included information on 133 clinical investigators. Although FDA can repeal a disqualification or restriction, the names of reinstated clinical investigators remain on the list with a note that their sanctions have been reversed.

The FDA's regulations require that the Center that disqualifies a clinical investigator review other studies to which the clinical investigator has contributed data. The goal is to investigate whether data provided by a disqualified clinical investigator in support of another drug, biologic or medical device application was also tainted and should be removed from that application.

The FDA makes Warning Letters available to the public by posting a redacted copy on its web site. The Centers have expressed the intention to post "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" letters on the FDA web site as well, although this has not yet happened. Currently, FDA does not list clinical investigators who have received a "Notice of Initiation of Disqualification Proceedings and Opportunity to Explain" on their web site.

Scope

We examined FDA's bioresearch monitoring programs involved in the approval of human drugs, biologics and medical devices. We did not examine FDA's bioresearch monitoring programs involved in approving animal drug or food products. We also did not examine how district offices conduct on-site inspections of clinical investigators.

METHODOLOGY

We reviewed the universe of 184 warning letters, NIDPOE letters and disqualification communications issued by FDA's Centers between Fiscal Years (FY) 1994 and 1999. We interviewed the staff (27) and managers (6) of the bioresearch monitoring programs at FDA's Center for Devices and Radiological Health, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Our respondents are responsible for assigning investigations of clinical investigators and classifying the results of those inspections. We discussed the role of bioresearch monitoring within the Centers, how clinical investigators are chosen for inspection and how decisions are made regarding case classification and disciplinary action.

We examined the lists of clinical investigators who have received warning letters or have been disqualified by FDA. In addition, we analyzed FDA's list of clinical investigators who have signed investigator agreements in conjunction with drug, device and biologics applications. We also conducted work flow analysis and examined how FDA's bioresearch monitoring program fits into overall human subjects protection structures.

We conducted our review in accordance with the *Quality Standards for Inspections* issued by the President's Council on Integrity and Efficiency.

FINDINGS

Overall oversight of clinical investigators is limited

The activities of clinical investigators who conduct research on investigational products regulated by FDA are supervised by several entities. Sponsors of clinical research are required to oversee the work of clinical investigators engaged in testing their products. Institutional Review Boards are required to review protocols and other research documents to make sure clinical investigators are protecting their research subjects from harm. Additionally, the FDA's bioresearch monitoring program investigates clinical investigators as part of application reviews and on the basis of complaints to the agency. Monitoring by these entities appears to provide limited oversight of clinical research and human subject protection.

Limited and problematic oversight of clinical investigators

Sponsor. A sponsor of clinical research is responsible for selecting qualified investigators, providing them with the information they need to conduct clinical trials and monitoring the clinical research. A sponsor can transfer any or all of its obligations, including the monitoring of clinical investigators, to a contract research organization.

As part of the monitoring process, sponsors try to ensure that clinical investigators conduct clinical research in accordance with approved protocols such as adhering to human subject protections. A sponsor who finds problems with an investigator should try to secure compliance or end the clinical investigator's participation in the investigation. The sponsor must notify FDA when a clinical investigator's participation is terminated for noncompliance. Sponsors who are reluctant to report misconduct may terminate an investigator for "administrative" reasons and are not required to report. The FDA is currently looking at a way to close this loophole in their regulations.

However, monitoring conducted by sponsors may be questionable. According to CDRH's bioresearch monitoring inspections of sponsors conducted in FY 1998, over 50 percent of sponsors failed to ensure the proper monitoring of their clinical investigators. In 1998, CDER examined recent problem clinical investigators and found significant problems with sponsor oversight. They found that serious misconduct was not reported by sponsors and that the majority of the objectionable problems should have been detected by adequate monitoring. In addition, CDER found that the Quality Assurance reports by sponsors were inaccessible and that monitoring plans and reports were not submitted. The CDER acknowledged that they have a limited knowledge of the nature and scope of industry monitoring practices.

Institutional Review Board. Since 1971, FDA has required that any study testing new drugs or biologics on human subjects within an institution receive review and approval by an Institutional Review Board (IRB). In 1976, FDA required IRB review for medical device studies. In 1981, FDA expanded the scope of its regulations to include a requirement for IRB review of any study conducted outside of an institution.

The FDA expects an IRB to conduct initial and continuing review of research involving human subjects. The initial review includes examining the research protocol, the informed consent process, advertisements used to recruit subjects and other relevant information. Continuing review involves examining a study at least once a year to ensure that the risk-benefit ratio has not changed. During continuing review, the IRB considers study amendments and reports of unexpected adverse events.

Questions have been raised about the effectiveness of IRB oversight of clinical investigator and clinical research. In April 1995, the Office of Inspector General (OIG) found inadequacies with IRB oversight. Problems included implantation of a device in three times the number of human subjects specified in the IRB approved research protocol and continuation of a research project for 6 weeks beyond when the IRB had suspended it. A 1998 OIG examination of Institutional Review Boards found problems with the IRBs' continuing review. This report found that continuing review by IRBs is of limited scope and significance.

FDA's Bioresearch Monitoring Program. The FDA carries out bioresearch monitoring inspections of clinical investigators. The goals of the program are to ensure the quality and integrity of data submitted to the agency and to protect the rights and welfare of human subjects. The inspections are conducted by FDA field staff with Center staff responsible for classifying the inspection results and identifying any needed FDA action.

According to FDA data, there were more than 21,000 investigator agreements received in FY 1998 from clinical investigators involved in clinical research although not all investigator agreements result in data being submitted to FDA. These applications represent nearly 14,000 individual clinical investigators located in more than 60 different countries. In FY 1999, FDA conducted 497 non-randomly selected inspections of clinical investigators for a total of 468 individual clinical investigators inspected. The number of clinical investigator inspections has remained fairly stable in recent years after dropping from a high of 627 in FY 1996.

Three-quarters of inspections conducted in FY 1999 were not due to any suspicion of wrong-doing. These were routine, or surveillance, inspections. Such inspections normally occur when FDA receives an application seeking approval for a new drug, biologic or device. The remaining 25 percent were directed (or compliance) inspections. A directed inspection is assigned when FDA receives information suggesting there may be a problem with a clinical investigator. This information could be from an analysis of

the data submitted by the clinical investigator in an application or other information that FDA may have received.

The following findings detail specific concerns about the selection and classification of clinical investigator inspections.

Data integrity concerns, more than human subject protection, drive FDA's selection of clinical investigators for inspection

Training given to FDA investigators conducting inspections of clinical investigators emphasize that the prime objective of a clinical investigator inspection is to verify the quality and integrity of significant study data in support of FDA's role of protecting consumers from unsafe or ineffective medical products. Information is collected and assessed based on this understanding. In the vast majority of cases, the bioresearch monitoring inspections occur after a clinical trial has been completed.

Bioresearch monitoring inspections of clinical investigators are application driven

Routine inspections focus on clinical investigators' efforts as representative of research conducted in support of an application. Clinical investigator inspections are primarily conducted to provide a sense of the data quality to the application review team responsible for approving an application for product approval.

Inspections based on site size, inspection history, data issues

Site size. Bioresearch monitoring staff at all three Centers agree that the primary consideration in selecting clinical investigators for inspection is the size of the subject population at the sites. Ninety-six percent of staff respondents (all but one) named site size as a major criteria in selecting sites, meaning the largest sites in an application are most likely to be chosen. The reason for selecting the largest site is to review the largest amount of data. One respondent stated that the goal in selecting large sites is ideally to cover 50 percent of the subject population, but that this goal is not realized currently. Staff at all Centers agreed that in general, three clinical investigators are inspected per application.

Respondents noted some concern that clinical investigators with small numbers of subjects never get visited. Under a data validation focus this is appropriate, as smaller sites contribute proportionally less to the overall data. This could be problematic in a

protocol or human subjects protection sense, as smaller sites may be no more or less likely to conduct studies correctly than sites with more subjects.

Inspection history. Respondents indicated that when information on the number of subjects at various sites is not enough to make selections, clinical investigator inspections histories will be considered. This may also be the case when review staff have not recommended sites they want reviewed, especially if multiple sites have similar subject populations.

There is some disagreement among staff as to how important inspection history is in the selection process. Although 70 percent of staff indicated that they review the inspections history of clinical investigators, remaining staff indicated that they did not review the inspections history of clinical investigators.

Clinical investigators may not get selected if they have had a recent inspection that found few problems, but may be selected if a previous inspection turned up violations. When asked about warning letter follow up, many staff indicated that they reinspect a clinical investigator who received a warning letter when they see that the clinical investigator is involved with a new application. However, this may not always happen. Forty-seven clinical investigators whose official actions we reviewed submitted investigator agreements after receiving FDA correspondence. Of these clinical investigators, only 17 percent were reinspected for any reason.

We understand that in some cases an investigator agreement may not lead to clinical trial data being submitted as part of the new product application. We did inquire whether it was possible to determine if the 47 clinical investigators submitted data as part of any product application. We were informed by FDA that this would be a very difficult and time consuming task.

Data issues. Twenty of 27 staff indicated that they consider data issues when selecting clinical investigators for inspection. Data issues include adverse events, unusual or suspicious data including results that look too good or bad.

Other factors. Almost half the staff respondents (48 percent) report working with the application review staff to some degree as they make their selections. The application review staff may recommend certain clinical investigators for inspection based on the size of sites or on data issues. Six of the 27 staff we interviewed indicated that they consider the workload or reputation of a district site before deciding whether to assign an inspection in that area. Some districts may have a lot of competing work which could delay completion of a clinical investigator inspection.

Fraud and jeopardizing data merit official action

Most respondents indicated that an inspection will be classified as “official action indicated” when the clinical investigator is found to have deliberately disregarded protocols or falsified data. While some respondents noted that multiple protocol violations due to sloppiness could lead to a warning letter if the volume of problems was large enough, this case was considered less likely than classification as official action indicated for deliberate falsification and fraud.

Intent is a key reason staff will recommend classifying a clinical investigator inspection as an “official action indicated.” Eighteen respondents indicated that whether violations result in a warning letter or disqualification proceedings depends in part on whether the investigator meant to violate the regulations. Respondents indicated that a clinical investigator who fails to get some required informed consents should be educated through a warning letter. Failure to get any consents signed may indicate a larger problem with the investigator’s disregard for human subject protection.

The decision to classify a case as an “official action indicated” also relies heavily on the impact violations have on study results. If violations call the data into question, staff are more likely to take stronger action than if the violations do not impact study results.

The severity and extent of violations impact whether staff recommend that a case receive a voluntary or official action. Protocol violations that may lead to “voluntary action indicated” if relatively few are found, might elicit an “official action indicated” response if the violations are numerous or show evidence of a serious disregard for study protocols. This is especially the case if the violations do not compromise the data or put subjects at direct risk. In such cases, a high volume of violations must be found for a warning letter to be issued to a clinical investigator.

Disqualification, the strongest type of official action, is usually the result of fraud and repeat violations

Respondents nearly unanimously reported that fraud was the main reason that disqualification proceedings are initiated against a clinical investigator. This includes data manipulation and falsification as well as protocol violations such as failing to collect required data or to record data in a specified manner. Some respondents noted that if the mistakes or problems do not affect the site’s data, the case will probably warrant a warning letter.

If violations first noted in an initial site visit are found again in a second inspection, the clinical investigator will likely have disqualification proceedings initiated against him. For example, when the first warning letter is written, the clinical investigator is required to respond to the Center indicating what steps the clinical investigator will take to correct

identified problems. If the same problems are found during a second site visit, the implication is that the clinical investigator's response to the initial letter was fraudulent. This proof of intent would be reason to initiate disqualification proceedings.

Review of official actions reveals that focus is primarily on data violations

We reviewed 189 official actions the three Centers sent to clinical investigators between fiscal years 1994 and 1999. The letters reviewed were warning letters, NIDPOE letters and letters documenting disqualifications. The majority (107 official actions) were written by CDRH. We reviewed 58 from CDER and 24 written by CBER.

The violations noted in the correspondence the Centers sent to clinical investigators fell into five main categories. Clinical investigators were routinely cited for problems with documentation, adherence to protocols, human subject protection, reporting and product (drug, device or biologic) control. The great majority of letters enumerated reporting, documentation and protocol violations. In addition, some other violations were noted, including promoting investigational products and failure to conduct work under federally required controls. See Appendix A for further details.

The FDA states that examining protocol criteria is the first line of defense in protecting human subjects. They believe that taking investigators to task on this issue during inspections and highlighting the issue as part of their outreach are two effective ways of enhancing human subject protection. While protocol violations can impact human subject protection issues, in most cases these reviews occur after a human subject completes a clinical trial. These retrospective reviews by FDA do not protect the human subjects that are currently enrolled.

Other programs more geared towards human subject protection

As previously noted, bioresearch monitoring staff tend to focus their attention more on data concerns than on direct review of human subjects issues. Other programs within FDA in general are more oriented towards human subject protection. In its 1996 report "Scientific Research: Continued Vigilance Critical to Protecting Human Subjects", the General Accounting Office notes that FDA monitors for compliance with human subject protections by inspecting Institutional Review Boards, reviewing researchers' and sponsors' reports and inspecting clinical studies and investigators. The General Accounting Office report indicates that FDA's inspection of Institutional Review Boards is its primary tool for human subject protection. While FDA does examine human subject protection issues during an inspection, the principal focus in such investigations is to verify that study data are accurate and complete and to ensure researchers' adherence to study protocols.

The bioresearch monitoring program lacks clear and specific guidelines

Review of complaints or inspection history is not a required part of the clinical investigator selection process

Complaints information is not connected to the routine inspection selection process. Most staff do not routinely use complaints made about clinical investigators as a factor in the selection process. Only CDER has recently instituted a complaints database. At the other Centers, when a complaint comes in but does not trigger an inspection, the complaint is often filed with the reviewer's correspondence files. However, staff at all centers agreed that all complaints are followed up to some extent.

Respondents at the three Centers said that they generally do not collect information about clinical investigators from the other Centers. Some staff pointed out that few clinical investigators work in more than one area of drug, biologics or device trials. Some clinical investigators do work in more than one area, however. In one example, a clinical investigator who received a warning letter from CBER was later disqualified from CDER without CDER knowing about the clinical investigator's previous inspection history.

Bioresearch monitoring staff are not formally trained in classifying violations

Most respondents indicate that they received little or no formal training on how to select clinical investigators for bioresearch monitoring inspections or how to assess whether violations necessitate voluntary action or a warning letter or the initiation of disqualification proceedings. Most respondents reported that they learned how to classify violations from other staff, that most training was informal "on the job" acculturation.

Repeated or deliberate violations: "You know it when you see it"

The FDA regulations state that a clinical investigator can be disqualified from receiving investigational drugs or devices when the Agency has evidence that he or she has repeatedly or deliberately failed to comply with the applicable requirements for the conduct of clinical trials. Disqualification proceedings can also be initiated if the clinical investigator has repeatedly or deliberately submitted false information.

While all respondents were familiar with the phrase "repeated or deliberate" with regard to violations noted in FDA inspections at clinical trial sites, many respondents were unable to give a specific definition of what constitutes "repeated" and "deliberate" violations or what the thresholds are for these terms. Some respondents indicated that the

definition depends on the case, that “you know it when you see it.” Staff responses to what “repeated or deliberate” means were fairly consistent, if somewhat vague.

Many respondents defined “repeated or deliberate” as violations about which the clinical investigator had received and ignored previous warnings. Several respondents said that a respondent with a warning letter has been told both what violations he needs to correct and what the consequences of noncompliance may be. A clinical investigator who does not fix the problems cited in the warning letter deliberately violates the rules. Other respondents indicated that deliberate action could be shown even if no previous warning letter had been issued. An IRB could have warned the clinical investigator to correct problems or the inspection may produce evidence that the clinical investigator knew he was violating the rules. Deliberate was also defined as fraudulent actions including falsification of data, forgery of consent forms or failure to report serious adverse events.

No Guidance on “Repeated or deliberate”

There is no Center-wide official definition of “repeated or deliberate” violations of FDA regulations for bioresearch monitoring staff. No written document outlines the meaning of the phrase and none of the Centers provide staff with formal training on what constitutes repeated or deliberate violations of the regulations. Staff members learn the working definition through on-the-job experience and informal discussions with more experienced staff.

The FDA Commissioner’s office does have some guidance on what “repeated or deliberate” means based on previous decisions. This information is used when reviewing disqualification cases. However, none of the staff involved in reviewing bioresearch monitoring inspections were aware of this information.

In 1976, GAO released a report entitled “Federal Control of New Drug Testing is Not Adequately Protecting Human Test Subjects and the Public.” The report noted that FDA officials offered differing interpretations of the term “repeatedly.” The report cited the Director of the Division of Scientific Investigations as saying that the meaning of the term is questioned because the regulation from which it comes is hard to interpret.

While FDA has not produced an official definition of “repeated or deliberate,” the Agency has produced a guidance document which outlines acceptable standards for clinical investigators. This information sheet, last revised in October 1995, provides standards of good clinical practice rather than legal requirements. The document is produced for use by clinical investigators and IRBs, but can be utilized by Center staff as a framework against which violations can be identified.

In 1997, a cross-Center bioresearch monitoring workgroup produced a draft memo on the thresholds for initiating disqualification of a clinical investigator. The memo indicates

that disqualification proceedings can be initiated against a clinical investigator who repeatedly or deliberately fails to comply with the requirements for the conduct of clinical trials or repeatedly or deliberately submits false information. While the memo outlines the categories of clinical investigator misconduct, it does not define what would constitute repeated or deliberate wrongdoing.

The workgroup that drafted the thresholds memo was established in 1997 to streamline the disqualification process. The workgroup includes Center managers and representatives from the bioresearch monitoring program's Office of Enforcement, the Office of Chief Counsel and the Office of Health Affairs. The group plans to clarify when and how staff should move to each step in the disciplinary process.

Bioresearch monitoring's time frames are external

The FDA conducts bioresearch monitoring inspections after the clinical research is completed and an application is submitted and before a decision on approval is made. Inspections are intended to provide information the application review staff need to make decisions on application approvals. The time frame for site selection, inspection and classification is short, especially for CDER and CBER. As these Centers are subject to the Prescription Drug User Fee Act, bioresearch monitoring work must be completed quickly so that the Centers can process a full review within the required 6-12 months. While deadlines are explicit for CDER and CBER, CDRH is also held to Center deadlines for application approvals.

Several respondents indicated that it is important for inspections to be timely, because if inspection classifications and other input are not seen before an approval decision is made, their work is essentially useless. In addition, faster classification of inspections and correspondence with clinical investigators allows the inspection to more fully act as an educational tool. Officially communicating violations can alert clinical investigators to the scope of their misdeeds and help set them on a path toward corrective action. The sooner the clinical investigator is told what is wrong and asked to respond with an improvement plan, the sooner he or she can make those improvements in ongoing clinical trial work.

Several staff had concerns about the bioresearch monitoring program's effectiveness with regards to the timing of their work in the application process as a whole. One respondent said, "BIMO comes in so late in the application process, [the Office of Device Evaluation] is afraid we will find something wrong. If BIMO finds something wrong [the Office of Device Evaluation] doesn't want to hear it unless it's really extreme." Respondents expressed concern that they only see information on the clinical investigators at the end of the application process. One respondent stated that they "aren't allowed to be involved soon enough to be fully useful."

Working within given time frames and the need to highlight the most serious problems , data validity is given priority. Poor data has an immediately recognizable impact on FDA's ability to validate study results. The effect of human subject protection problems or reporting violations on study results may not be as clear.

The bioresearch monitoring program does not have Agency-wide program measures

None of the bioresearch monitoring programs we reviewed have written goals nor are there any FDA-wide written goals. The majority of staff and supervisors believe that the programs are fulfilling their goals. However, there are no concrete criteria against which the programs can assess their success.

At the Center level, some performance measures are in the early stages of development. Since 1997, one of the Centers has used performance measures that look at timeliness, overall compliance rates and compliance with specific criteria. Another Center is using input measurements. However, neither of these Centers' measures are used by FDA to appraise the bioresearch monitoring program.

RECOMMENDATIONS

This report does not make any recommendations that address the weakness found with sponsor or institutional review board oversight of clinical investigators, since they have been addressed in other studies. Our recommendations focus on improving FDA's oversight of clinical investigators.

The FDA should define cross-Center goals for the Bioresearch Monitoring Program and develop criteria to determine whether the program is achieving those goals

While respondents in all three Centers described similar program goals, there is currently no way to determine whether bioresearch monitoring is achieving those goals. The FDA, through the internal working group on bioresearch monitoring, should define what an effective bioresearch monitoring program should accomplish. As part of that definition, FDA should:

- clarify how long the process should take from the conclusion of the investigation and submission of the report until a decision is made on the results of the inspection and issuance of any Agency actions and,
- clarify the criteria for selection of clinical investigators for inspection including looking at smaller sites and previous inspection history and compliance.

The FDA should also recognize the limitations of the current system's ability to protect human subjects. Currently, most inspections are conducted after clinical trials are complete. Any human subject violations identified are found too late to protect the human subjects involved.

The FDA should develop internal guidance on the thresholds that violations must meet to justify disqualifying a clinical investigator from receiving investigational products

The FDA's internal working group on bioresearch monitoring should develop guidance on the severity and number of violations needed to justify beginning disqualification proceedings. Cross-Center guidance would insure that each of the Centers handles the results of clinical investigator inspections consistently. We believe that having a framework can provide structure for FDA reviewers.

AGENCY COMMENTS

We would like to thank the Food and Drug Administration for commenting on the draft of this report. Based on FDA's general and technical comments, some changes and clarifications were made in this final report.

The FDA commented that they are not responsible for providing patient care and that they are not currently equipped to monitor studies during the research process. We recognize this. We also understand that FDA attempts to protect human subjects and the general public through retrospective review of clinical investigators, research sponsors and institutional review boards. See Appendix B for the text of the Agency's comments.

Review of FDA Official Actions

Table 1: Percentage of Official Actions Citing Various Types of Violations

Issue	Documentation	Protocol	Reporting	Human Subject Protection	Drug/Device/Biologic Control
CDRH 107 official actions	83 (78%)	83 (78%)	85 (79%)	69 (64%)	52 (49%)
CDER 58 official actions	57 (98%)	51 (88%)	35 (60%)	41 (71%)	21 (36%)
CBER 24 official actions	20 (83%)	21 (88%)	19 (79%)	16 (67%)	10 (42%)
Total 189 official actions	160 (85%)	155 (82%)	139 (74%)	126 (67%)	83 (44%)

Documentation violations. Eighty-five percent of all the official actions highlighted problems with documentation. Sixty percent of all warning letters mention missing documentation. Other documentation problems include missing data in submitted documents, discrepancies between documents, missing correspondence, documentation that has been altered, falsification of data and inconsistent or poor data collection.

Protocol violations. Protocol violations cited in official actions fall into four categories: enrollment violations, failure to follow protocol-required steps and instructions, problems with investigator agreements and authorizations and violations related to the use of a drug or device. While across the three Centers 82 percent of all official actions include discussion of protocol violations, this number is skewed somewhat because protocol violations appear in relatively fewer CDRH official actions (78 percent). As CDRH produced 107 official actions, this impacts the overall number. Both CDER and CBER noted protocol violations in 88 percent of their official actions to clinical investigators.

Protocol violations can significantly impact study data and human subject protection. Failure to follow required actions can invalidate the data collected on drug or device effectiveness and safety, not to mention result in death or serious injury to subjects of the research. Study protocols exist to ensure that all sites conduct the study in the same way, that treatments are uniform and that data is collected uniformly. While adherence to

protocols is the first line of defense in protecting human subjects from harm, in most cases FDA examines protocol violations after the human subject has been enrolled in the clinical trial.

Reporting violations. Overall, 74 percent of the official actions contained descriptions of a clinical investigator's failure to report to the appropriate IRB or study sponsor. Reporting violations include not submitting annual, final and other reports to the IRB or sponsor, not getting consent forms, protocols or advertisements approved by the IRB and not submitting data and substantiating documentation to the sponsor. Failure to report adverse events and deaths to IRBs and sponsors and late reporting of adverse events were also noted in warning letters to clinical investigators. While reporting violations usually refer to a failure to report to an IRB or sponsor, some official actions indicate that a clinical investigator also did not appropriately report to FDA.

While reporting violations appeared somewhat less often in CDER's official actions (60 percent), both CBER and CDRH cited these violations in 79 percent of their correspondence. Many of the CBER official actions focus on clinical investigators' failure to report adverse events to IRBs and sponsors. At CDRH, the most commonly cited reporting violations are failure to report adverse events and failure to submit progress, annual and final reports to the IRB or sponsor. Overall, while at least one reporting violation appears in 79 percent of all CDRH official actions we reviewed, there were generally fewer total reporting violations per action than there were protocol or documentation violations.

Human subjects protection violations. The most common human subjects protection violation cited was the use of a deficient consent form. Other letters noted a lack of signed informed consent forms, either because the subject never signed the consent or that the consents are missing full signatures or dates for subjects, witnesses and clinical investigators. Other clinical investigators were faulted for not getting subject consent until after performing a surgical or other procedure on the subject. Other violations noted include use of an unapproved consent form and failing to give a copy of the consent form to subjects. Additionally, a few clinical investigators were found to have allowed device or calibration equipment to malfunction despite the potential for harm to subjects.

Drug, device and biologic control violations. Many official actions cited clinical investigators' difficulties maintaining control of the receipt, use and disposition of investigational drugs, devices or biologics. Often no records existed to document when and how many such products came in and out of the investigator's control. Other warning letters note discrepancies in product control records. The Centers reported product control violations in 36 to almost 50 percent of their official actions; problems with product control are mentioned in 83 of the 184 actions we reviewed. This is the violation category that is mentioned the least in FDA official actions to clinical investigators.

Agency Comments



DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Food and Drug Administration

Date: APR 24 2000
From: Deputy Commissioner for Management and Systems, FDA
Subject: Office of Inspector General (OIG) Draft Report: *FDA Oversight of Clinical Investigators (OEI-05-99-00350)*
To: June Gibbs Brown
Inspector General

Thank you for the opportunity to review and comment on the OIG draft report, *FDA Oversight of Clinical Investigators*. The Agency prepared General and Technical Comments for your consideration.

Mary L. Balrock

Robert J. Byrd

Attachments

**AGENCY COMMENTS TO THE OFFICE OF INSPECTOR GENERAL DRAFT
REPORT, FDA OVERSIGHT OF CLINICAL INVESTIGATORS**

General Comments:

The Office of Inspector General (OIG) draft report concludes that the Food and Drug Administration (FDA) does not provide patient care or monitor studies at the time they are conducted and, thus, does not protect subjects during the research process. The system presently in place is not intended to provide - - and is not yet funded sufficiently to provide - - day-to-day oversight of all clinical studies. The system does contribute to one aspect of patient protection by providing evidence of informed consent and to overall better behavior by investigators and sponsor/monitors through assuring data integrity in a sample of studies. However, it does not *verify data but* assesses record consistency and completeness to evaluate study quality.

Caregivers/investigators are the major patient protectors during a study. The study monitor visits are infrequent and the Institutional Review Board (IRB), overseeing thousands of studies per institution, cannot possibly provide day-to-day assessments. On the other hand, the IRB can conceivably review reports provided by investigators and identify potential difficulties, but this action is more likely to be initiated by the investigators, sponsors, or FDA.