

Unreported Clinical Research Fraud and Misconduct

By JoAnn Jessen, Elizabeth Robinson, Suellen Bigaj,
Sherry Popiolek, and Norman M. Goldfarb

Clinical trial auditors occasionally discover very serious patterns of deviations from the study protocol or Good Clinical Practice (GCP) regulations. In some instances, the deviations appear to go beyond innocent error and may constitute fraud, willful misconduct, or gross negligence. In at least some cases, sponsors do not report them to the institutional review board (IRB) and/or the FDA.

Regulations and Guidances

According to the FDA, "there is presently no regulation or guidance..., but a proposed rule regarding reporting of instances of actual or suspected fraud is in clearance within the agency." ^{1,2}

According to the FDA Guideline for Industry (ICH E3) – Structure and Content of Clinical Study Reports, "there should also be a listing of all patients discontinued from the study after enrollment, broken down by center and treatment group, giving a patient identifier, the specific reason for discontinuation,..." (§ 10.1)

FDA's Compliance Program Guidance Manual states that during a site inspection, "if serious deviations occurred, obtain evidence that the sponsor obtained compliance or terminated the clinical investigator's participation in the investigation and reported it to FDA." (§ III.B.a.C.7) Unfortunately, this manual does not explicitly define the term "compliance." For example, does discarding tainted data constitute compliance?

According to the FDA, "FDA wants to know when issues of noncompliance and/or questionable data integrity arise for clinical studies, even if a sponsor is successful in obtaining compliance or discontinues use of a troublesome site. There are commonly both human subject safety concerns and data concerns that result. If a site or investigator is removed from a study, arrangements may need to be made to insure the safety of the subjects who have already been enrolled and treated at the site in question, particularly if they will not be continued as part of the official study. In addition, any and all data that is collected on an investigational product need to be shared with FDA, even if the data will not be usable to support marketing of the product. Such data need to be discussed in the next study progress report and a summary that includes a justification for rejecting the data if that is the case, [and] included in any marketing application/submission that uses the study's results. It would be beneficial to both the sponsor and FDA reviewers if there is a discussion, as soon as practical, of any such findings and their repercussions so both the sponsor and FDA can determine what needs to be done regarding human subject protection and the extent of information regarding the questionable data that might be needed." ¹

Case Study A

Site A enrolled 24 patients and was one of the highest recruiting sites in a clinical trial. After the 12th subject enrolled, the Study Coordinator resigned and the sub-investigator continued

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the study. An audit determined that the completed CRFs for the first 12 subject records were adequately supported by source documentation. However, for the last 12 subjects, although the CRFs had been completed, the source documentation was absent or deficient. When questioned, the sub-investigator stated that the information was on a diskette at his home. He agreed to provide it on the following day. The next day, when asked about the diskette, he stated that there was no diskette, but he had completed the CRFs based on his photographic memory of the subject visits. The Principal Investigator (PI) was unavailable for questioning by the auditor.

Outcomes:

- Three people from the sponsor's clinical team conducted an in-depth investigation.
- The sponsor did not include the non-verifiable data from last 12 subjects in the statistical analysis.
- The sponsor determined that it would no longer contract with the contract research organization (CRO) that monitored the site as they did not identify, rectify, or communicate the lack of adherence to GCP standards.
- The sponsor concluded that it would no longer invite the PI to participate in clinical trials.
- Payment to the PI for the last 12 subjects was withheld.
- To the best of the authors' knowledge, neither the FDA nor the IRB were advised of the audit findings.
- Twelve subjects wasted their time and risked their health to no purpose.

Case Study B

Approximately five of the 30 subjects that enrolled in this study at Site B completed the study then subsequently re-enrolled at Site B. The PI stated that he did not know this practice was unacceptable and that the subjects liked the investigational product so much, he did not see the harm.

Outcomes:

- The sponsor provided additional GCP training to the site staff, including the PI.
- The sponsor excluded the data from the re-enrolled subjects.
- When the problems were discovered, the sponsor notified neither the FDA nor the IRB. However, the sponsor reported the incident in the final report to the FDA.
- The investigator was not reimbursed for costs associated with the five re-enrolled subjects.
- The sponsor continued to use the investigational site for future studies.
- Five subjects wasted their time and risked their health to no purpose.

Case Study C

Dr. C operated Site C, a freestanding, dedicated research facility. He was also a partner in a separate and busy sub-specialty practice, Office X. Clinic X referred all of Site C's subjects in a Phase IV study. Site C did not have medical records from Office X, but the site monitor found potential evidence of subject ineligibility in the source documents. Dr. C strongly

resisted allowing access to the subjects' medical records at Office X. Eventually, after the Chairman of the central IRB intervened, the monitor was allowed to visit Office X. The monitor found evidence of multiple cases of ineligible subjects and unreported adverse events.

Outcomes:

- Site C was the top-enrolling site, so the sponsor terminated the study, as well as the development program for the expanded indication and the associated labeling change.
- Dr. C continues to operate in the same manner, having taken precautions to prevent access to medical records at Office X.
- To the best of the authors' knowledge, the FDA was not advised of the events that occurred.
- The sponsor concluded that it would no longer invite the PI to participate in clinical trials.
- All of the subjects in the study wasted their time and risked their health to no purpose.

Case Study D

Site D created source documents (worksheets) two years after the device implant procedures they documented. No contemporaneous supporting data were available for any subjects.

Outcomes:

- To the best of the authors' knowledge, the sponsor is currently deciding whether to use the data.
- Follow-up of enrolled subjects was transferred to another PI participating in the trial. Two subjects were lost to follow-up and put at risk in the transition.
- The sponsor notified the IRB but, to the best of the authors' knowledge, not the FDA.
- The IRB suspended the PI for three years and required him to obtain GCP training.
- The sponsor concluded that it would no longer invite the PI to participate in clinical trials.
- Four years later, the FDA inspected the site for another study, expanded the investigation to multiple studies, and issued a 483 and warning letter for lack of protocol adherence and other issues.

Case Study E

Protocol E required use of a prescription drug during the six months prior to the study and during the study. Site E had no documentation such as prescriptions or physician notes for use of the drug by over half of its approximately 20 subjects. The study coordinator stated that the subjects were poor and therefore could not afford to pay retail prices for prescription drugs. Therefore, they bought them at the local swap meet. The PI allowed their use.

Outcomes:

- The sponsor closed the study at Site E.
- The sponsor did not use any data from Site E.
- About half of the subjects did not have a permanent address and were lost to follow-up.
- Neither the FDA nor the IRB were advised of the findings.
- The subjects wasted their time and risked their health to no purpose.

Reporting Fraud or Misconduct

To report fraud, misconduct or gross negligence to the FDA, telephone the Division of Investigative Oversight (DIO) in the Office of Research Integrity (ORI) at 1.240.453.8800 or send an email to AskORI@hhs.gov. Alternatively, communicate anonymously through the First Clinical Research Anonymous Tip Line at <http://www.firstclinical.com/resources/tipline.html>.

Discussion

An auditor's primary task is to conduct a thorough investigation and provide all observations to the management of the study sponsor. Auditors may also provide recommendations and perform a root cause analysis to develop a corrective and preventive action (CAPA) plan. If regulatory compliance issues are found, the sponsor determines the course of action to be followed. In most cases when regulatory compliance issues are found, the sponsor informs the investigator of the deviation(s), explains the implications, and often provides training to prevent future occurrences.

Reporting incidents such as these to the FDA and IRB requires courage from the sponsor. When the IRB and FDA learn of such incidents, there may be serious consequences:

- The IRB may more critically evaluate the sponsor's future studies and the investigator's future study participation. It may impose strict guidelines or limitations on study conduct.
- The FDA may inspect the investigator's site "for cause" and disqualify or debar the investigator, with the potential for fines and imprisonment.
- When the sponsor submits the NDA, the FDA may question the integrity of other data from that site and from all the other sites, as well, causing delays in approval or a request for a study to be repeated.
- The FDA may impose serious sanctions on the sponsor, or more-critically review future applications
- The monitoring failure may have negative implications for the careers of the study manager and other sponsor and CRO personnel.

The FDA inspected 354 clinical research sites in 2005.³ From 1977 through 2004, it conducted 818 investigator-related (for cause) inspections, an average of 29 per year.⁴ With 25,642 investigators submitting 1572 forms in 2005, the chance of an FDA inspection was under 2%.⁴ Despite the low probability, sites comply with the regulations in part because of the potential concern of an inspection. This concern diminishes if sites believe it unlikely that the FDA will hear of their deviations, particularly after they experience no significant negative consequences for non-compliance.

If an investigator does not self-report his/her own serious deviations from GCP standards, he/she is then free to continue substandard work on future studies, potentially for even the same sponsor if its institutional memory is deficient.

Serious regulatory deviations significantly compromise data integrity, subject safety and welfare, and the nature of the relationship between site and sponsor. If the industry cannot police itself, onerous new regulations may be imposed.

The authors have audited only a microscopic fraction of clinical trials. The cases above raise a very serious question: How many similar cases have gone unreported?

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Authors

JoAnn Jessen is a principal consultant of Pharma Compliance Partners LLC, a provider of quality assurance, clinical research, and training services. Contact her at 1.847.363.4745 or jjessen@pharmacompliance.com.

Elizabeth Robinson is a clinical research and quality assurance consultant. Contact her at 1.847.328.1776 or bethrob@ix.netcom.com.

Suellen Bigaj is Vice President, Clinical Research at SMART CARE Life Sciences, LLC, a provider of clinical, analytical, and regulatory services. Contact her at 1.847.968.7500 or sbigaj@carebiopharma.com

Sherry Popiolek is a Quality Assurance Auditor III for PPD. Contact her at 1.609.528.8000 or sherry.popiolek@austin.ppd.com.

Norman M. Goldfarb is Managing Director of First Clinical Research LLC, a provider of clinical research best practices information, consulting and training services. Contact him at 1.650.465.0119 or ngoldfarb@firstclinical.com.