CLINICAL INVESTIGATION

How can we effectively identify and report clinical research misconduct?

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Research conducted with the participation of human subjects requires strict adherence to the principles of good clinical practices (GCPs), including adequate human subject protection. As it is such a critical component of such research, many countries have adopted specific GCP principles as regulations or as law. In the United States, US FDA has had regulations for the conduct of clinical trials in effect since the 1960s, and these specifically address both GCP and human subject protection [1].

The FDA uses the terms "research fraud" and "misconduct" interchangeably. Misconduct in a research sense refers to falsification of data at any stage during the proposal, design, performance, recording, supervision, or review of research, or in the report of research results. Fraud is considered to include deliberate or repeated noncompliance with established protocol or GCP. Acts both of omission and of commission, be they knowingly not revealing all data, altering data, or fabricating results, are all considered fraudulent acts. Fraud does not, however, include honest mistakes or understandable errors [2].

The dangers of clinical research misconduct are very real. Falsification of data can potentially undermine the protection of clinical research subjects, which is the basis for the FDA's actions and regulations. The FDA discovers falsified data at both trial sites and in application submissions every year. Furthermore, falsification is not always an isolated incident; its' discovery may lead to uncovering fraudulent data at another site, or relating to other drugs being tested at the same site. It is therefore important that participants in product development assist the FDA in any way they can to aid in detection of falsified data [3].

In February of 2010, the Department of Health and Human Services in collaboration with the FDA proposed a rule (*Reporting Information Regarding Falsification of Data*) in the Federal Register, seeking to require sponsors to report any information they may have indicating that any person has, or may have, engaged in the falsification of data. This included fraud in the course of reporting study results, or during any stage of the study proposal, design, performance, recording, supervision or review, if the study involved human or animal subjects and was conducted by, on behalf of, or relied upon a sponsor. Although this rule has not been finalized, it offers some insight into the scale of the problem, and what specific actions the FDA has identified to help those involved in carrying out clinical studies understand what should be reported in cases of specific misconduct [4].

Sponsors would have been required to report information, such as confirmed or suspected falsification of data as a result of this proposed rule. The FDA also specified that falsification may be committed not only by individuals responsible for conducting studies but also by their subordinates or colleagues. Falsification of data such as the examples below would be reportable under the proposed rule:

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- Creation of data that was not obtained during the study (e.g., recording or reporting invented data or results, enrolling a fictional subject into a study, forging a signature on a subject's informed consent form);
- Alteration of data, specifically by replacing the original findings with information that does not reflect the study conduct or results accurately (e.g., modifying a laboratory measurement to indicate a less extreme variation);
- Obtaining or recording data from a test, sample, or specimen in a way that does not accurately reflect the data, or whose origins are not adequately disclosed [4].

How can we identify research misconduct? We must first understand that we should look for it. Assuming everyone engaged in clinical research is adhering to the highest ethical standards of conduct is part of the underlying problem. While the vast majority of research personnel are ethical in their work, there are some who are not. Front line professionals such as research coordinators, monitors and auditors are more likely to have direct access to the source data and may be in the best position to identify potentially fraudulent activities. Clinical Investigators overseeing the work of designees should also be involved enough to detect fraud being committed by those to whom study related duties have been delegated. Biostatistical support can be used to identify fraud, in fact several publications suggest that centralized monitoring techniques may better detect some data anomalies (e.g., fraud, data falsification, and other non-random data distributions) than on-site monitoring [2,5-7].

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Training and education are the most important first steps. Did you know that the risk of misconduct increases when there are added pressures such as financial reward, academic advancement, or time constraints? All research staff need to be trained on how to detect when there is greater risk for misconduct and educated on how to minimize those risks.

We must also move away from a check box mentality of data collection and study oversight/monitoring. Get technical, evaluate the ECG strips upon which reports have been provided, look closely at dates and subject identifiers. Other recommendations from the FDA include:

- Do not accept copies of reports – require originals to be submitted;
- All source or supporting documentation must be identified;
- Mistakes, changes, and inconsistencies should all be noted;
- The frequency of changes should be noted, and those who made them should be identified;
- It should be determined and documented if changes are justified;
- Suspicious data should be challenged;
- All information or data pertinent to the study should be requested (e.g., CRF, LAB, X-R and EKG) [2].

A standard operating procedure (SOP) is one highly recommended strategy for managing the potential for research misconduct. An SOP defines misconduct and outlines the roles and responsibilities for reporting suspicions. This is used to train employees, and to support them in their efforts to gather the appropriate level of supporting documentation and route this to the individuals with authority to pursue further investigation. A sample SOP for this purpose is available from the Department of Health and Human Services's Office of Research Integrity web site via the link noted in reference [8].

Reporting obligations for research professionals are more than a legal issue. A universally recognized critical requirement of research involving human subjects is that it be conducted ethically and we all play a role in this regard. Following procedures to identify, document and report misconduct should be pursued to conclusion as well. If the SOP or process you are to follow does not resolve the issue, or if you have no procedure, it is your duty to report suspected misconduct to your superiors, the IRB or the regulatory authority, in this case the FDA. The FDA's web site offers direct links for such reporting via the link noted in reference [9].

Conclusion

Instances of fraud and misconduct are reported to or discovered by the FDA every year. Research professionals must be aware of the added pressures that can contribute to higher instances of fraud. Awareness, training and support are the best tools we have to ensure that we each do our part to detect, report and end fraudulent activity whenever it is discovered.

Although the Proposed Rule discussed in this article has not been finalized, we still have an ethical standard to uphold in the conduct of our research activities. Reporting fraud according to standard operating procedures facilitates training and execution of the steps necessary for identification of fraud. The FDA accepts reports directly and follows up on all reports. It is our duty to conduct ourselves ethically and to ensure that our colleagues do as well.

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