EDITORIAL

Reporting Research Misconduct in the Medical Literature

Robert Steinbrook, MD; Rita F. Redberg, MD, MSc

In this issue of *JAMA Internal Medicine*, we publish a report[1] that highlights an important area for improved public reporting of clinical trials and enhanced transparency at the US Food and Drug Administration (FDA). Seife[1] identifies numerous instances in which the FDA found evidence of apparent research misconduct serious enough to warrant regulatory action at clinical trial sites, but mention of these problems was largely missing from articles in medical journals. The specific examples cited by Seife[1] are disturbing: a foot amputation 2 weeks after a stem cell procedure, although the published trial states that all patients were aware of "major clinical improvements in the treated (more ischemic) leg"; an entire study deemed unreliable by the FDA but published without mention of the issue; a falsification of documents in a number of trials, in part because the falsifications led to the death of a subject in a chemotherapy trial (the researcher pled guilty to fraud and criminally negligent homicide); and a claim of a mortality benefit for a drug that included data from a trial site where patient records were allegedly altered.

Related article page 567

With the assistance of graduate students, Seife,[1] a journalism professor, used the methods of investigative journalism to ferret out information from FDA documents from 1998 to 2013. The FDA routinely inspects trial sites where research regulated by the agency is performed. When the agency finds apparent research misconduct serious enough to warrant regulatory action, it classifies its findings as "Official Action Indicated." Of 78 published reports from 57 clinical trials with an inspection classified as Official Action Indicated, Seife found that only 3 included any mention of the serious problems identified by the FDA.

Seife[1] obtained many of the documents, which were often heavily redacted, through Freedom of Information Act requests. For numerous documents, the redactions were so extensive that he learned that "it is usually extremely difficult—or impossible—to figure out which published clinical trials are implicated by FDA's allegations of research misconduct."

It is important to note that most FDA inspections are not classified as Official Action Indicated. Seife could not estimate the actual frequency of serious problems owing to the large number of records that were missing or unavailable. And he could not determine how often the violations found by the FDA could reasonably be expected to be acknowledged in an article or how often corrections or retractions were indicated. If the FDA documents had been more accessible and not heavily redacted, however, it is likely that Seife would have linked more published clinical trials to apparent research misconduct.

When the FDA identifies apparent research misconduct, it generally does not make a public announcement or, in the case of a published clinical trial, notify the journal that published the study. It is in the public interest for the agency to make available more information about its compliance and enforcement activities, and it has already begun to do so. In 2009, the FDA announced a transparency initiative; in 2010 and 2011 a task force issued draft proposals, including those to illuminate the agency's compliance and enforcement activities.[2]

In 2014, after Seife's study was completed and as part of its transparency initiative, the FDA released an "Inspections Classifications Database Search,"[3] covering inspections from March 1, 2008, to March 31, 2014. The database lists 113 005 records, 4143 (3.7%) of which are classified as Official Action Indicated. According to the agency's website, the data set includes "the final inspection classification for inspections conducted of clinical trial investigators, Institutional Review Boards (IRB) and facilities that manufacture, process, pack, or hold an FDA-regulated product that is currently marketed."[4] Information related to planned enforcement actions "may be withheld from posting until such action is taken."[4] Thus, the classification information in the database (ie, the name and location of an investigator or firm, the inspection end date, and the Official Action Indicated classification) could be used to request inspection documents from the FDA, but the database does not include documents.

In April 2014, the FDA also released a report about increasing public access to its compliance and enforcement data that includes specific initiatives and recommendations for their implementation.[5] It remains to be determined, however, if it is now easier to link alleged research misconduct to specific clinical trials. Seife's study[1] might be repeated, starting from the information in the FDA's inspections database.

Given the FDA's missions to protect research subjects and the public health, it should be made possible to link the agency's inspection documents to specific trials and publications. At present, many FDA documents that discuss or refer to clinical trials, including inspection reports, medical reviews, statistical reviews and even the public drug label, do not include the ClinicalTrials.gov Identifier, which is known as the National Clinical Trial, or NCT, number. It would be a great advance if the FDA included the NCT number of trials within all agency documents and reviews that refer to specific trials.

For inspections with findings classified as Official Action Indicated, it would be advantageous for the FDA to promptly notify ClinicalTrials.gov,[6] so that the trial registration listing can link directly to the inspection report, as Seife suggests.[1] Links in searchable public databases are also an efficient and

effective approach to informing medical journals and the medical and research communities.

The FDA should update the inspections database frequently; the agency should also consider adding a data field for the NCT number of clinical trials and enhancing the search capability to include searches by NCT number, product, and violation.[5] The agency should also release documents that are either not redacted or that are redacted to the minimum extent necessary to meet regulatory and legal requirements for the confidentiality of commercial information, to protect the privacy of research subjects, and to avoid interference with enforcement actions.

The ability to publicly link the FDA's compliance and enforcement data to specific trials and publications would also facilitate coordination with the Office of Research Integrity at the Department of Health and Human Services. The Office of Research Integrity oversees and directs research misconduct investigations, with the exception of the regulatory research integrity activities of the FDA. Better coordination within the federal government should help prevent further misconduct and promote the responsible conduct of research.

A central responsibility of medical journals is maintaining and improving trust in the medical literature.[7] Journals should expect that investigators and sponsors of clinical trials would promptly notify them of substantial findings from FDA and other regulatory agency inspections and modify their reports of clinical trials as needed, either before or after publication. As Seife points out,[1] the identification of a research violation by the FDA does not necessarily mean that this information should be included in an article or the article changed. Nonetheless, investigators should inform journal editors. Editors should review the inspection reports and related documents and reach decisions about what information should be communicated to readers based on a full understanding of the facts. Individual journals can provide guidance about the disclosure of findings through their instructions for authors, and the International Committee of Medical Journal Editors can provide guidance through its "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals."[8]

The report by Seife[1] describes the current reporting of research misconduct in the medical literature and offers important suggestions for improvement. We look forward to continued progress on transparency from the FDA, investigators, and sponsors to better protect research subjects and to better inform the medical and research communities, journal readers, and the public.

ARTICLE INFORMATION

Author Affiliations: Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut (Steinbrook); Department of Medicine, University of California, San Francisco (Redberg).

Corresponding Author: Robert Steinbrook, MD, Department of Internal Medicine, Yale School of Medicine, 333 Cedar St, I-456 SHM, PO Box 208008, New Haven, CT 06520 (robert.steinbrook@yale.edu).

Published Online: February 9, 2015. doi:10.1001/jamainternmed.2014.8052.

Conflict of Interest Disclosures: None reported.

Additional Contributions: Mitchell H. Katz, MD, and Joseph S. Ross, MD, MHS, contributed to this editorial.

Additional Information: Dr Steinbrook is a consultant to the FDA's Drug Safety and Risk Management Advisory Committee.

REFERENCES

1. Seife C. Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature [published online February 9, 2015]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2014.7774.

2. Asamoah AK, Sharfstein JM. Transparency at the Food and Drug Administration. *N Engl J Med*. 2010; 362(25):2341-2343.

3. Food and Drug Administration. Inspection classification database search. http://www.accessdata.fda.gov/scripts/inspsearch/. Accessed December 7, 2014.

4. Food and Drug Administration. Inspections database. http://www.fda.gov/ICECI/Inspections/ucm222557.htm. Accessed December 7, 2014.

5. Food and Drug Administration Transparency initiative. Increasing public access to FDA's compliance and enforcement data. http://www.fda.gov/AboutFDA/Transparency/TransparencyReports/ucm393798.htm. Accessed January 5, 2015.

6. ClinicalTrials.gov. https://clinicaltrials.gov/. Accessed December 7, 2014.

7. Steinbrook R, Redberg RF. Trust in the medical literature—and Viewpoints in *JAMA Internal Medicine*. *JAMA Intern Med*. 2013;173(12):1047-1048.

8. International Committee of Medical Journal Editors. Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals (December 2013). http://www.icmje.org/recommendations/. Accessed January 5, 2015.