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Fraud, conflict of interest, and other enforcement issues in clinical research

ABSTRACT

Fraud in scientific research is a widespread problem. It can involve falsifying data or documents, or knowingly failing to comply with regulations protecting research participants. Fraud can be committed by individuals, institutions, or corporations; in the context of research, fraud often is motivated by considerations beyond financial gain. Institutional review boards (IRBs) are designed to ensure that researchers comply with human research subject protections, including conflict-of-interest controls, but IRBs may fail to do so if investigators avoid existing IRB processes or if IRB members do not take responsibility for addressing actual or potential conflicts of interest.

Most cases that I handle as an associate US attorney involve fraud or deception of some kind. The conflict of interest (or motivating factor for research misconduct) is sometimes financial. However, some research misconduct arises when a researcher hopes for professional recognition or simply believes intuitively in the "right" answer despite evidence to the contrary. Juries are most likely to hold an individual researcher responsible if they are convinced that he or she knowingly deceived others and had a plausible motivation to cheat.

This article discusses how fraud is defined in the courts and uses historical and recent cases to illustrate how fraud frequently manifests itself in scientific research. Guidance on the roles of institutional review boards (IRBs) in avoiding and detecting fraud is offered. This article expresses my personal opinions and is not official policy of the US Department of Justice.

THE FRAUD STANDARD

How is fraud defined and how does it apply to conflict-of-interest questions in medical research? The concept of "fraud" has existed in the common law since its beginnings. However, with the passage of the first mail fraud statute in the 19th century, the federal courts have been called upon to provide a definition. The definition I rely on is "the knowing breach of the standard of good faith and fair dealing as understood in the community, involving deception or breach of trust, for money."

Each part of this definition is worth analyzing:

"The knowing breach…" Knowledge of fraud, or whether the bad conduct was intentional, is the first concern when determining whether to prosecute a case.

"…of the standard of good faith and fair dealing…" Standards of fairness evolve over time and may differ depending on the point of view. Subjects participating in clinical trials may have different standards than investigators. If a case goes to trial, jurors think, "What if I signed up for a clinical trial? What would I expect? What would I rely upon? What is the standard of good faith and fair dealing with respect to me or my family?"

"… as understood in the community…" The community encompasses all of society, not just the research community. The jury, made up of people from all walks of life, determines whether community standards are met.

"…involving deception or a breach of trust …" Deception typically involves a lie or a false document, or actions undertaken with the intention of creating a false impression (for example, "Photoshopping" a document or borrowing a photo from another study in violation of a protocol and without clearly labeling it as manipulated or borrowed). Breach of trust arises from specific relationships, and depends not only on specific undertakings but on the expectations of those within the relationship. This can be problematic in a research context. After all, what exactly is the responsibility to research participants of a principal investigator who is also a treating physician?

"…for money." Many people cheat, lie, or steal for money. But in research, money may not be the prime motivator. Investigators may commit fraud for glory, for the desire to be first, or because they are certain that

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their conclusions are correct even if the data do not support them. Fraud cases require a victim. In recent years, some courts have expanded the concept of money to loss arising from fiduciary or agent relationships, including loss of benefit from economic relationships.

HISTORICAL CASES OF RESEARCH FRAUD ABOUND

Numerous examples of fraud occurred with prominent scientists in the past:

- Sigmund Freud fabricated cases studies.
- Isaac Newton altered records of lunar and solar sightings to fit his theories.
- Louis Pasteur made false statements about the first public trial of his anthrax vaccine.
- Gregor Mendel's plant breeding results were too good to be true.

What motivated these scientists to commit fraud? It is perhaps easiest to explain in Pasteur's case: he had a competitor with a vaccine that worked better. He publicized a study in which all his research subjects—sheep—survived anthrax exposure, but he had secretly used his competitor's vaccine.

RECENT FRAUD CASES

A few recent cases of scientific fraud demonstrate the varieties of scientific fraud, as well as the outcomes:

- Dr. Eric Poehlman of the University of Vermont was sentenced in June 2006 to 1 year in jail for falsifying and fabricating research data related to menopausal changes and metabolism.
- Professor Elizabeth Goodwin of the University of Wisconsin resigned in 2006 for making false statements in genetic research.
- Dr. Gary Kammer of Wake Forest University resigned in 2005 for fabricating two families in a National Institutes of Health (NIH) grant application.
- Professor Ali Sultan, a malaria expert at Harvard University, resigned in 2004 after falsifying a grant application.

The Office of Research Integrity in the US Department of Health and Human Services received one third more misconduct allegations in 2005 than in the previous year. The increase can be explained, in part, by a change in the regulatory process as well as by greater awareness of potential problems.

DEFINING AND PROVING RESEARCH FRAUD

Scientific or research fraud, defined as intentional misconduct, can take many forms, including fabricating or falsifying data, plagiarism, overstating or misreporting results, or misrepresenting credentials. But key to proving criminal or civil fraud is determining the role of a conflict of interest: a jury must be convinced that a scientist would have a reason to cheat.

Related federal violations

Statutes other than those pertaining strictly to fraud are also relevant to cases concerning scientific research. One of the most important is section 1001 of title 18 of the US Code (18 USC §1001), which pertains to false records, statements, or documents (including billing records, statements to the US Food and Drug Administration [FDA] or the NIH related to approval of products or conduct of grants, written records of IRBs, and reports of results). The false documents need not have been submitted to the government to fall under this statute; they need only be part of the record created to obtain government approvals, or to be maintained at the institution to record and demonstrate work on a grant or an investigation covered by a New Drug Application to the FDA.

Fraud against the IRB

Defrauding an IRB is equivalent to defrauding a research grantor or sponsor, since virtually all grantors and sponsors make obtaining IRB approval a condition of the grant. Several problems that can lead to fraud occur commonly:

Knowing failure to request and obtain IRB approval. Sometimes institutions engage in research on patients but do not declare it as treatment. An article may result without an application ever having been submitted to the IRB or the IRB otherwise having been involved. Most major publications (at least in theory) now require compliance with human subject protections as a condition of publication.

Knowing failure to notify the IRB of protocol changes. Obtaining initial approval for research can be a long, difficult process. If changes are subsequently made to the protocol, some researchers forgo seeking the necessary approval again.

Knowing failure to comply with subject disclosures and protections, including conflict-of-interest protections. The IRB may require that certain disclosures be made, and investigators may not follow through. The IRB is not set up as an enforcement agency but rather relies on the good faith of investigators to assure compliance with study conditions.

Knowing failure to comply with third-party review entities or nongovernmental directives. Problems may arise if an investigator falsely represents that he or she complied with institutional guidelines or those of the Association of American Medical Colleges[1] that complement or implement government regulations or are

part of a condition precedent to grants (such as IRB approval). In such cases, the fact that a rule is not a government regulation is not the end of the discussion. If a grantor (including the NIH) testifies that a representation of compliance was relied upon or could be relied upon in connection with funding, then a knowing false statement of compliance may be considered fraud.

Violation of 'good faith and fair dealing.' A lawyer might ask the following questions when determining whether "good faith and fair dealing" was violated in a research project:

- Did the investigator ignore warning signs?
- Did the investigator decide not to consult guidance?
- Did the investigator seek advice and not follow it?

Knowing failure to comply with FDA guidance. FDA guidance is not, by itself, binding. An alternative approach may be used if it satisfies the requirements—and the spirit—of an applicable statute or regulation.[2] However, in determining whether a researcher's and an institution's conduct was consistent with the community standard of good faith and fair dealing, lawyers will ask why the decision was made to ignore or contradict the guidance.

Billing issues

A common financial conflict-of-interest scenario involves researchers who obtain grants and use the funds to meet other departmental goals. For example, services might be billed that are already paid by the study sponsor, services other than routine costs might be billed, or services might be billed that were meant to have been provided free as part of subject consent. These kinds of problems can be avoided by having adequate central billing controls and a system that can mediate such conflicts.

Failure to meet reporting requirements

Often we find resistance to compliance with reporting requirements that are mandated by law. Significant adverse events that occur during clinical trials must be reported to the FDA. Sometimes deaths of study participants are listed as the participant being "lost to follow-up," which may be true technically but is intended to deceive. In other cases, we see study participants allegedly being followed up with contacts or telephone calls years after their deaths.

IRBs also require reporting of adverse events, and many states do as well. Within the past few years, more than 30 states have enacted legislation requiring the reporting of medical errors that occur inside medical facilities and result in death or injury.

Deaths must also be reported to the coroner. Reports from the US Inspector General comparing death records with nursing home reports have found that up to one third of nursing home deaths were never reported. Dr. Adil Shamoo of the University of Maryland has suggested that a study comparing death records of research subjects with the reported death rates in clinical trials during the study period may reveal even more striking discrepancies.[3]

CASE STUDIES IN RESEARCH FRAUD

The following examples illustrate cases of research fraud committed by individuals, institutions, and corporations.

Data fabrication

As mentioned previously, Eric Poehlman, professor of medicine at the University of Vermont, fabricated research data in studies of menopause and aging, involving false grant applications and papers. After pleading guilty under 18 USC §1001, he was permanently excluded from all federal health programs.

In a similar case, BioCryst Pharmaceuticals, together with researchers from the University of Alabama at Birmingham, reported false results from a lymphoma study. The incident resulted in the conviction of a nurse and a scientist. Both the university and researchers involved in the study had financial interests in the outcome.

In cases like these, the IRB may receive warning signs suggestive of fraud or conflict of interest and should not hesitate to take a second look at the research results and other relevant documents.

Failure to disclose risks and report adverse events

In September 1999, 18-year-old Jesse Gelsinger died as a result of a participating in a gene therapy study at the University of Pennsylvania. The research team did not stop the study after learning of serious toxicities and failed to disclose risks to participants. James Wilson, lead investigator of the study at Penn, was barred from performing research on humans until 2010.

The conflict of interest in this case allegedly included significant financial interests in the outcome of the study by some of those involved in it. However, a contributing factor to the research team's failure to halt the study was eagerness to be the first to achieve success in genetic therapy of a particular rare disease.

Modern-day Martin Arrowsmiths

Another common motivator is the desire for simple professional advancement: graduate students covet their PhD and job placement in a hot field, postdoctoral fellows hope to be hired at a better institution, and principal investigators want to conclude a study successfully and move on to the next one. Sinclair Lewis' novel *Arrowsmith* describes medical research 80

years ago, but the personalities are similar today; the character of Martin Arrowsmith wanted to save the world and felt intuitively that he was on the right track even when the evidence was inconclusive or contradictory. The same qualities of intuition and persistence that characterize good scientists have on occasion led some to suppress or ignore contradictory evidence, or to ignore warning signs of risks to subjects.

In the Gelsinger case, the Department of Justice attempted to create a corporate integrity agreement model with the NIH to ensure that what happened at the University of Pennsylvania does not occur again. Documents relating to this case illustrate how the Department of Justice and the NIH approach these issues.[4]

Technology-fueled fraud through data manipulation

In the 1970s, William Summerlin used black felt-tipped pens to make it appear he had successfully grafted tissue from black mice to white mice. Today, powerful image-processing software has made fabrication of research data easier and more convincing.

Recent cases of data manipulation involve Charles Rudick, a Northwestern University graduate student who falsified illustrations of electrophysiologic recordings using imaging software; T.S. Ramalingam of the California Institute of Technology, who plagiarized and electronically manipulated images; Dr. Regina Horvat, a Northwestern University postdoctoral fellow who falsely labeled a Western blot result to support her results in an NIH grant; and Dr. Hans Geisler, a physician at an Indianapolis hospital who solicited a false report from a pathologist and submitted it to justify enrollment in an NIH protocol.

Mike Rossner, editor of *The Journal of Cell Biology*, found 8 cases of major improper digital image manipulation in a survey of 800 manuscripts.[5]

FRAUD APPEARS TO BE WIDESPREAD

How extensive is the problem of fraud in medical research? Several studies have found that more than 40% of surveyed researchers were aware of misconduct but did not report it.[6,7] Gardner et al reported in 2005 that 17% of surveyed authors of clinical drug trials reported that they personally knew of fabrication in research occurring over the previous 10 years.[8] These kinds of sociological survey results may not be totally reliable, but the findings suggest that a substantial problem exists.

The Office of Research Integrity, which oversees research funded by the US Department of Health and Human Services, receives 265 reports of research fraud each year. The National Science Foundation receives 100 complaints of misconduct each year.

GOVERNMENT ENFORCEMENT OF RESEARCH STANDARDS

Researchers who are caught cheating are devastated, and often their lives are ruined. Pursuing these cases through legal and/or disciplinary means is still important, however, because crucial values are at stake: honesty and accuracy in research, as well as the public trust.

In identifying cases appropriate for investigation or prosecution as criminal or civil violations, as well as other cases appropriate for deference to an internal review, the Department of Justice strives to make institutions responsible for the conduct of their employees and researchers, to create a climate of high ethical standards, and to support robust internal efforts to achieve these goals. Researchers must also be held accountable for intentional misconduct and for undisclosed conflicts of interest that threaten their objectivity as researchers and protections for research subjects.

We also aim to empower patients and research subjects. Much of the research in the United States involves participants who have much less power than the researchers and institutions have. Because subjects often are not in a position to protect themselves, the IRB has the responsibility to do so. If the IRB repeatedly fails in providing needed protections, or if the researcher evades the protections in place, the government must on occasion intervene to assure that these protections are enforced.

TAKING RESPONSIBILITY IS KEY

Well-drafted language in contracts relating to research often tries to shift specific risky or costly responsibilities, including conflict-of-interest and patient protection obligations, onto another party. This is what good lawyers are trained to do, but in research it can mean that no one takes responsibility. A study sponsor may hire a contract research organization. The contract research organization might hire a site management organization and shift responsibility to it. In turn, the site management organization may claim that the principal investigator, university, or medical center is responsible, and that it was relying on the undertakings of those subcontractors. At the end of the process, however, the sponsor, the institution, the investigator, and the IRB all have compliance and oversight responsibilities that remain their obligations by law, whatever the language of their contracts.

Another way that some academic and research institutions have tended to manage conflict is by establishing committees. In fraud cases, I have often seen numerous committees set up in addition to the IRB, including compliance committees, institutional

conflict-of-interest committees, ad hoc committees to review allegations of research misconduct, and committees on privilege and tenure.

It is important that each party's responsibilities are understood so that when potential conflicts arise, someone will identify the problems, pay attention to them, and resolve them before they become real issues. We do not suggest that one individual do all the work but instead that someone be responsible for ensuring that problems are identified and addressed. Someone must guarantee that federal guidelines and institutional policies are adhered to, and someone must have the authority to inquire about the activities of researchers and their departments.

THE ROLE OF THE IRB—INTELLIGENT, INDEPENDENT OVERSIGHT

Most types of law (eg, tax law, immigration law) use a unitary body of statutes, regulations, and series of opinions upon which cases are based. Most questions that arise in these fields can be answered by searching the relevant body of law.

This is not the model used in setting up IRBs. Because of the belief that doctors and professional researchers know more than the government does about how best to protect research participants and patients, the IRB processes were designed so that overseers understood and assimilated the issues and applied their knowledge to protect the participants as well as the research system.

In some cases, IRBs are completely independent of an institution. Regardless of affiliation, an IRB is expected not merely to follow regulations blindly but to exercise independent professional judgment about how to protect the interests of research subjects. In many situations, there is no definitive right answer to an issue that arises.

THE ROLE OF REGULATORY AGENCIES

Regulatory bodies have expanded to include private and nonprofit agencies and the traditional government watchdogs, a trend that reflects society's expectations of high community standards **(Table 1)**. These organizations provide guidance on the community's expectations of the IRB and what potential jurors might expect in terms of conduct on the part of a researcher.

'Bad acts' draw attention

Lawyers are taught the maxim, "The guilty fleeth where no man pursueth," and are trained to look for cover-ups, obstruction, and alteration or destruction of records. We also investigate whether anyone has been told to lie or has been threatened, something that is more likely to occur if there is something important to hide.

TABLE 1
Agencies relevant to research fraud

Office for Human Research Protections* (www.hhs.gov/ohrp/)
Office of Research Integrity* (http://ori.dhhs.gov)
US Food and Drug Administration (www.fda.gov)
Office of Human Subjects Research, National Institutes of Health (see http://ohsr.od.nih.gov/guidelines for regulations and ethics guidelines)
Association for the Accreditation of Human Research Protection Programs, Inc. (private accrediting agency) (www.aahrpp.org)
Association of American Universities† (www.aau.edu)
Association of American Medical Colleges† (www.aamc.org)

* Part of the US Department of Health and Human Services

† Provides guidelines for researcher conduct

Other red flags for regulators include misleading or cheating sponsors, including the US government; fraud related to approval of a drug or medical device; the use of fake science; and undisclosed conflicts of interest.

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