Research Compliance: Preventing, Identifying and Addressing Misconduct in Human Subject Research

By Lauren Sullivan

In 1999, 18-year old Jesse Gelsinger died after receiving a gene therapy agent in a clinical trial at the University of Pennsylvania Institute for Gene Therapy. The ensuing investigation revealed, among other things, that Jesse was not notified that the principal investigator was also founder of the company that held rights to the product being studied.

In 2001, healthy 24-year old Ellen Roche, a laboratory technician at Johns Hopkins University's Asthma and Allergy Center, agreed to take part in a federally funded asthma study. A month after inhaling the hexamethonium intended to induce asthmatic symptoms, she was dead. In the aftermath, Ellen's parents sued Johns Hopkins, and the federal government suspended Johns Hopkins's research funding while they reviewed Johns Hopkins's human subject protection and research policies and procedures.

The deaths of these two research subjects led to numerous calls for reform in the conduct of human clinical research, and for enforcement of existing laws. However, even prior to these high profile deaths, federal agencies with regulatory enforcement authority over human subject research had begun to question the current state of human research subject protections. A year before Jesse Gelsinger's death, the Office of Inspector General (OIG) had issued a report called *Institutional Review Boards: Time for Change* (June 1998). The report was highly critical, and concluded that the effectiveness of Institutional Review Boards (IRB) was in jeopardy.

The OIG and other governmental authorities have begun to focus even greater time and energy on research compliance. In its 2005 Work Plan, the OIG identified a variety of investigative initiatives concerning human subject research, including investigations into the nature of financial interests disclosed by clinical investigators in Federal Drug Adminstration (FDA) regulated studies, the extent to which adverse event reports to IRBs are used effectively to protect human subjects, whether IRB's have adequate procedures in place to allow appropriate consideration of adverse event reports in the clinical trial review process and compliance with privacy requirements in clinical trials funded by the National Institutes of Health (NIH) and other research. The OIG will also continue to focus on compliance with time and effort reporting requirements and will continue to pursue False Claims Act cases against institutions receiving federal grant funds.

This article discusses existing laws and regulations directing the conduct of human subject research, and provides examples of how research institutions and healthcare providers conducting human subject research can tailor their compliance programs to comply with the myriad regulations directing the conduct of clinical research.

Regulatory Landscape

Federally funded research and privately sponsored drug trials are subject to separate, but similar and sometimes overlapping rules. These rules, whether regulating federally funded research or research directed at obtaining FDA approval for a new drug, are aimed at protecting human subjects in research and ensuring the integrity of the data that comes from such research.

The rules and regulations governing the conduct of human subject research are largely the result of instances of serious research misconduct, particularly the Public Health Service (PHS) study of untreated syphilis in African American men from 1932 to 1970. During this study, despite available treatment, the research subjects' syphilis was left untreated, and the subjects were not warned of the risk of continuing sexual activity, leading to numerous cases of death and disability. The public outcry following disclosure of the study conduct resulted in the formation of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research in June 1974, and led to the first codification of human subject protection regulations. The Commission drafted the Belmont Report, which sets forth three main principles: respect for persons, beneficence, and justice. These principles form the ethical foundation of human subject research, and are the basis of human subject protection regulations in the United States.

Belmont Report provides ethical foundation for U.S. Human Subject Projection Regulations, which encompass ...

- **Respect for Persons**
- **Respect for Beneficence**
- **Respect for Justice**

Federally Sponsored Research

The Common Rule

Both the Department of Health and Human Services (DHHS) and the FDA issued regulations based on the Belmont Report. DHHS codified the protection of human subjects in 45 CFR Part 46 Subpart A, the provisions of which are also known as the "Common Rule." The FDA codified its version of the Common Rule, at 21 CFR Parts 50 (Human Subjects) and 56 (IRB). The Common Rule applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency, including the NIH. The Common Rule regulates such things as IRB membership, functions and operations, informed consent requirements, basic rules for the approval and conduct of research, and additional protections for vulnerable populations.

Research Misconduct

Most federal research funds for clinical research are granted through the NIH and therefore are subject to PHS regulation. All recipients of federal research funds, as part of their grant award, certify to the truth and accuracy of the claims they make to receive federal funding of their research. Further, all PHS grant recipients are required to have their own administrative procedures for identifying and addressing scientific misconduct. Each grantee must certify to PHS, as a condition of the grant, that it will comply with both PHS and its own administrative procedures.

Pursuant to federal regulations at 42 CFR Part 50, Subpart A, the Office of Research Integrity (ORI) handles allegations of misconduct that involve research supported by PHS and that fit within the definition of "misconduct" or "misconduct in science." "Misconduct" or "misconduct in science" means the fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. Allegations of scientific misconduct involving NIH-specific grants may be referred to NIH's Office of Management Assessment, which is authorized to investigate misuse of NIH grant and contract funds, as well as NIH grantee and contractor conflicts of interest. If the researcher is found to have committed scientific misconduct, pursuant to 42 CFR Part 50, PHS may impose sanctions, including debarment from receiving federal research funding for some period of time or the case may be referred to the OIG and the United States Attorney's Office for prosecution under the False Claims Act or other federal law. The Office for Human Research Protections (OHRP) is responsible for responding to allegations of misuse of humans in research supported by PHS.

Recently, OHRP cited the University of Washington for significant problems in the oversight of human subject research. In its letter to the University dated April 1, 2005, OHRP cited the University IRB for frequently approving research contingent upon substantive modifications or clarifications, such as the receipt of additional information or changes to the informed consent form, without requiring additional review by the convened IRB. Studies were approved on a contingent basis, with substantive questions concerning the risk/benefit determination still outstanding. OHRP noted that IRB meetings failed to sufficiently detail actions taken by the IRB, the basis for requiring changes or disapproving research and a summary of discussions concerning controverted issues. OHRP also found numerous instances where the IRB failed to conduct continuing review of research at least once per year. As a result of ORHP's findings, the University is implementing changes to improve its human research subject protection programs, but any changes come too late for subjects who were not adequately protected in the past, and don't forestall any private causes of action.

As mentioned above, alternatively, or in addition to sanctions imposed by PHS and ORI, allegations of scientific misconduct may be addressed through the federal False Claims Act. The False Claims Act prohibits knowingly submitting or causing to be submitted a false or fraudulent claim for payment to the federal government, including filing false or fraudulent data in support of grant applications. Violations of the False Claims Act are subject to treble damages, plus penalties of $5,500 to $11,000 per claim. Both the institution and its researchers are potentially liable under the False Claims Act for the integrity of research conducted under a grant funded by PHS.

Some examples of recent False Claims Act actions based on research misconduct are:

- In a case against Thomas Jefferson University, the government alleged research fraud relating to NIH and National Cancer Institute grants, including submission of false research data to obtain grant funds, and using false or fabricated research data in several publications that were then used to obtain grant monies. The DOJ settled the case for $2.6 million in an unpublished settlement.

- In a case against the University of Alabama at Birmingham, a court ordered the University to pay nearly $2 million to the federal government and to a former graduate student who had conducted research at the University, because the University violated the federal False Claims Act by failing to credit the graduate student with the work and failing to accurately report her work in grant applications to the NIH.

- In a qui tam action against the University of California and the University of Utah, a researcher at the institutions was found to have fabricated and falsified data on a burn trauma research report in grant applications, leading to a $1,575,000 settlement.

FDA Regulations and Guidance

Human subject research involving the testing of drugs, biologics, and medical devices is subject to oversight by the FDA. Regulations promulgated under the Federal Food, Drug and Cosmetic Act direct the conduct of IRBs (21 CFR Part 50), informed consent (21 CFR Part 56) and the research itself (21 CFR Part 312).

While the ultimate responsibility for the Investigational New Drug Application (IND) under Part 312 is the responsibility of the sponsoring organization, much of the responsibility for the conduct of the research is placed on the clinical investigators. Each clinical investigator must sign an "investigator statement" also known as FDA form 1572, under which the investigator agrees to:

- Conduct the study in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

- Personally conduct or supervise the investigation.

- Inform any patients or any persons used as controls, that the drugs are being used for investigational purposes and ensure that the requirements relating to informed consent and IRB review and approval are met.
- Report to the sponsor adverse experiences that occur in the course of the investigation.
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.
- Maintain accurate records and to make those records available for inspection.
- Ensure that an IRB that complies with 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the study, report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others, and not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

FDA Bioresearch Monitoring Program

Under the FDA's Bioresearch Monitoring Program, the FDA monitors and audits clinical research records of clinical investigators, institutions, and IRBs involved the conduct of human subject research for drugs, biologics, and medical devices. The FDA conducts two kinds of audits. The first, "study-oriented inspections," are conducted by the FDA on studies that are important to the evaluation of the efficacy and safety of a product under review. The second kind of audit, a "for cause" audit, is directed at the behavior or a particular investigator or institution, and may be triggered by a number of factors, including a report by the study's sponsor, data that is inconsistent with other investigative sites or unusual enrollment patterns.

The FDA frequently identifies scientific misconduct during these inspections. If the violations are more than de minimis, the FDA may seek to have the investigator or IRB debarred from conducting FDA regulated research in the future, or pursue criminal charges for violations of the Food, Drug, and Cosmetic Act. Instances of research misconduct by clinical investigators identified through these audits are too numerous and too varied to point out one exemplary case. Common findings include the failure of research subjects to meet inclusion or exclusion criteria, inadequate or no informed consent, inadequate informed consent process, no IRB approval or approval of a different version of the protocol, failure to obtain continuing review, inadequate adverse event reporting, inadequate, incorrect or falsified data, poor record keeping including undocumented changes to records, failure to follow the protocol and failure to store the investigational drug as directed. Frequently, an investigator is cited with most or all of the above violations, in addition to some more creative kinds of misconduct. What is noteworthy is the level of scrutiny required to ferret out many of the above violations, and that FDA directs that level of scrutiny to these inspections. Accordingly, for a research institution to avoid being cited by the FDA for research misconduct, its compliance program must direct the same level of scrutiny to its ongoing clinical research programs.

Addressing Research Misconduct

While covering all of the pitfalls that clinical researchers and research institutions are subject to is beyond the scope of this article, we discuss below methods to resolve research misconduct and ensure data integrity.

Institutions receiving PHS funding are required to have a research misconduct policy. The policy should include, as appropriate to the institution, procedures on: reporting allegations of scientific misconduct; pursuing the allegations; maintaining confidentiality; conflicts of interest; expertise of committee members conducting investigations of allegations; rights of respondents; how inquiry committee members are appointed; conduct of the inquiry; inquiry reports; sanctions; appeals; and the role of whistleblowers.

Once discrepant data is identified, through whatever means, the matter must be reported to the appropriate official responsible for research misconduct (all recipients of PHS funds are required to have such an official). The official determines whether further inquiry is required, and should consider whether the discrepancies are the result of honest error or carelessness or intentional fraud. If further inquiry is required, the institution may be required to notify the PHS or study sponsor.

There are numerous tools available from the NIH and FDA on their websites, (http://grants.nih.gov/grants/policy/policy.htm#guidance and www.fda.gov) including audit checklists and guidance documents on how the FDA conducts an inspection, to assist with conducting an inquiry into research misconduct. An institution's report on the results of its inquiry should state how the original discrepancies were identified, the allegations of research misconduct found in the inquiry, the process of the inquiry, including who was interviewed, and the findings of the inquiry. For additional assistance, PHS provides instructions and examples for preparing inquiry and investigation reports, in the *ORI Model Procedures for Responding to Allegations of Scientific Misconduct*, available on ORI's website (http://ori.dhhs.gov/).

Conclusion

Clinical research is highly regulated and is subject to a complex and broad array of governing statutes, regulations, guidance, and other regulations, guidance, and other rules making compliance especially challenging. The federal laws and regulations addressing research misconduct affect the risk of severe civil, and in some cases criminal, penalties for research misconduct. It is important for individual investigators, research sites and institutions, as well as the entities that sponsor them, to be aware of the how to prevent, identify and address research misconduct. ▪

Disclaimer: Nothing in this article constitutes legal advice, which can only be obtained as a result of personal consultation with an attorney. The information included in this article is believed to be accurate at the time of publication but is subject to change and does not purport to be a complete statement of all relevant factors.

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