Research compliance: entering Phase II

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Conducting human subject research is a scary scenario for investigators, institutional review boards (IRBs), and institutions in light of increasing scrutiny from government entities. The scrutiny is due, in part, to recent media coverage of patients who were harmed while participating in research. Oversight of research activities has increased drastically; for those failing to comply with the vast and complex network of legal and regulatory requirements, the consequences are severe. In the past few years, the federal Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA) have suspended the authority to conduct research at a growing number of well-known institutions *(Table)*. In addition, noncompliance has resulted in the withdrawal of funding from investigators and, in at least one case, fines and a prison sentence (1).

The current environment has motivated organizations involved in human research to create and implement research compliance programs to reduce risks. Both institutions and investigators may benefit from these compliance efforts. An effective research compliance program is one that identifies legal and regulatory problems, corrects deficiencies, and assists in preventing future problems. For a research compliance program to be effective, certain basic elements must be in place, including established standards of conduct in research, training, disciplinary procedures, auditing, monitoring, and corrective action. With an effective compliance program, the risks for both human subjects and research personnel are greatly reduced.

IDENTIFYING THE RISKS

The primary risk factors in conducting both basic and clinical research are

- Lack of proper oversight by the institution and investigator
- Inadequate training
- Inappropriately handled conflicts of interest
- Improper expenditure of federal funds and residual funds
- Improper billing of research items

For institutions and investigators involved in human subject research, these issues may result in harm to human subjects.

Lack of oversight

The IRB is charged with overseeing the conduct of human subject research, and the investigator has ultimate responsibility for the conduct of the study. When either one fails to provide adequate supervision, compliance issues arise.

Table. Research operations suspended by the Office for Human Research Protection or Food and Drug Administration

West Los Angeles Veterans Affairs Medical Center
Duke University
Rush-Presbyterian Hospital
University of Illinois/Chicago
Virginia Commonwealth University
University of Colorado
University of Alabama/Birmingham
University of Pennsylvania
University of Oklahoma Health Sciences Center/Tulsa
Johns Hopkins School of Medicine

Most institutional suspensions of research have arisen from IRB oversight issues (2). If the IRB is not given the authority and the necessary resources to oversee research, the entire system is jeopardized. The basic requirements for the IRB are found in the Code of Federal Regulations (3); however, much in the way of interpretation is added by OHRP and FDA. Thus, a knowledgeable, experienced staff is required to provide guidance.

Despite the role of the IRB, investigators do not escape liability when research standards are violated. Recent problems at several institutions have resulted in the halting of an investigator's research, dismissals from employment, fines, and lawsuits. The investigator is responsible for carrying out a research study, including obtaining IRB approval; obtaining informed consent from each subject; keeping the IRB apprised of any changes, amendments, and adverse events; adhering to good clinical practices; and keeping adequate records. The investigator may delegate any of these responsibilities to qualified persons, but he or she is ultimately accountable.

Lack of training

Ignorance is no excuse in today's research world. Those involved in human research are obligated to be trained in its conduct. OHRP mandates that institutions and investigators know their responsibilities when conducting and overseeing research.

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This mandate is not easy in light of the thousands of pages of rules and regulations that govern human subject research. Because of the vast body of knowledge, a new "specialty" has developed known as research education. Nearly every research institution has recognized the need for education and has added personnel and resources to address it. Professional research administrative organizations have also risen to the challenge and are providing many excellent programs.

On October 1, 2000, the National Institutes of Health began requiring investigators and other key personnel in research studies to certify that they have received training on the protection of human research subjects. Investigators and key personnel are now required to describe the training prior to the award of funds.

The final Public Health Service Policy on Instruction in the Responsible Conduct of Research was released December 1, 2000. The policy outlines 9 core instructional areas of education but gives institutions flexibility in determining the length, method, and exact content of the instruction. Institutions must develop a written implementation plan by October 1, 2001, and must educate all research staff by October 1, 2003.

In addition, the new federal assurances call for the certification of training for the IRB chair, the IRB administrator, and the signatory official for the institution. The institution must provide education for the IRB members, staff, and investigators and indicate the number of full-time employees dedicated to research education.

Conflict of interest

Innuendoes of financial conflict in the conduct of research appeared in a series of articles published recently in the *Seattle Times,* exposing practices at the Fred Hutchinson Cancer Research Center (4). The articles revealed that several investigators at the center received stock and high-paid positions at companies that obtained exclusive commercial licenses for drugs these investigators tested. Patients are alleged to have died from the experimental treatments and were never told of the financial interests held in the experiments. This example illustrates the growing battle over conflicts of interest that may arise in research.

A draft interim guidance issued by OHRP in January 2001 is just one of the latest efforts to deal with the growing concern over conflicts (5). The FDA has already attempted to address the subject. When companies sponsoring clinical research trials submit marketing applications to the FDA, they are now required to disclose compensation and any equity interests held by principal investigators who are conducting clinical trials.

Financial conflicts are only one type of conflict that emerges in research. Perhaps the most obvious conflict issue arises when an IRB member is involved in the vote on a study in which he or she participates as an investigator. An IRB member involved in a study in any way should, in fact, be dismissed during the final discussion and vote.

Conflicts may also arise in the peer review of research grant applications, as well as other scenarios. Institutions must focus on detection of potential conflicts and must adopt and follow a written set of guidelines for their management. Dealing with this risk is a "work in progress," and much remains to be done.

Fund expenditures

Corporations and foundations usually place few restrictions on use of funds in studies they sponsor. An agreement or contract setting out the budget and use of funds is usually easy to modify and few regulatory restrictions intervene, although there is a specific work and delivery schedule for conducting the research. The main concern centers on the tax consequences of funds disbursement if a nonprofit research institute is involved with independent investigators. Proper accounting procedures address these issues.

However, when research is funded by the federal government, regulations govern the use of the funds, and the research is peer reviewed by the agency providing the funding. These regulations are found in the Code of Federal Regulations, the Federal Acquisition Regulation, and the Office of Management and Budget Circulars.

The National Institutes of Health requires periodic financial and progress reports as well as annual scientific misconduct, invention, lobbying, and audit reports. Failure to comply with the terms and conditions of the award may result in enforcement actions, including suspension or termination of the grant for cause.

Each federal agency may have specific requirements regarding the use of funds. An experienced staff and good communication between staff and investigators are essential in complying with the terms of each award.

Billing for research items

Since Medicare now covers some costs of clinical research trials (6), it may seem as if the billing compliance issues involved with research have disappeared. Do not be too hasty. The rule covers only 1) the routine costs of qualifying clinical trials, and 2) reasonable and necessary items and services used to diagnose and treat complications or prevent complications caused by participation in clinical trials. The items and services now covered by Medicare are those that are usually provided outside of participation in a research study—in other words, routine standard-of-care services. Previously, Medicare may have denied all payment if a clinical trial was involved. Other requirements to qualify for Medicare reimbursement of clinical trials include evaluation of a Medicare benefit, a therapeutic intent, enrollment of diagnosed beneficiaries, and inclusion of the characteristics stated in the policy.

These are just a few of the rules that may apply when billing for research-related costs. Fines, penalties, and sanctions still exist for Medicare fraud and abuse when research-related items and services are inappropriately billed. For example, violations of the False Claims Act may result in treble damages plus penalties. Proper billing and accounting of clinical research funds are critical in order to avoid these pitfalls. Research-related items and services must be accurately accounted for to avoid billing Medicare for things that have been paid for by the research sponsor. Even the items and services that are reimbursable by Medicare must be billed according to the new rules.

KEYS TO SUCCESSFUL COMPLIANCE

Through a thorough understanding of the regulations, ongoing monitoring, the correction of identified deficiencies, and

administrative support for compliance efforts, compliance in research conduct may be obtained. Coupled with quick responses to problems, research compliance efforts will be an affirmative move toward promoting a high level of ethical and lawful conduct in all aspects of research.

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3. Protection of human subjects. 21 CFR 50. Available at http://www4.law.cornell.edu/cfr/21p50.htm≠21p50s (accessed July 2001).
4. Wilson D, Heath D. Uninformed consent: what patients at "the Hutch" weren't told about the experiments in which they died [5-part series]. *Seattle Times*, March 11–15, 2001. Available at http://archives.seattletimes.nwsource.com/web/ (accessed July 2001).
5. Office of Human Research Protection. *Financial Relationships in Clinical Research: Issues for Institutions, Clinical Investigators, and IRBs to Consider When Dealing with Issues of Financial Interests and Human Subject Protection. Draft Interim Guidelines*. Washington, DC: OHRP, January 10, 2001. Available at http://ohrp.osophs.dhhs.gov/humansubjects/finreltn/finmain.htm (accessed July 2001).
6. Health Care Financing Administration. *Medicare Coverage Policy—Clinical Trials: Program Memorandum* (HCFA Pub. 6OAB, Trans. No. AB-00-89). Washington, DC: HCFA, September 19, 2000. Available at http://www.hcfa.gov/coverage/8d3.htm (accessed July 2001).