Disclosure and ethical conduct of clinical research

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Am J Health-Syst Pharm. 2008; 65:1851-3

Recent national efforts to promote and enhance clinical research by the National Institutes of Health (NIH), including the Clinical and Translational Science Awards (CTSA) and Roadmap Initiative, present new and challenging opportunities for pharmacists who require an advanced knowledge of clinical research, regulatory affairs, and ethics. Lack of awareness and negligence may result in serious ethical controversies and scientific misconduct that receive substantial attention.

The central source for most education and training related to ethical conduct and the safety of research involving human subjects in academic health centers is the institutional review board (IRB). The IRB is a committee mandated by the National Research Act, Public Law 93–348, and established within a university or other institution that conducts biomedical or behavioral research involving human subjects. All research involving human subjects must be reviewed by the IRB before the research is conducted and during various stages of the research, depending on associated risks. Pharmacists conducting clinical research should be aware of federal regulations governing the research, including IRB review procedures, provision of full disclosure of conflicts of interest, and consequences of research misconduct. These important aspects of research integrity and ethical conduct of research will be discussed.

Disclosure of IRB review. The level of IRB review required for a research project depends largely on the risk-to-benefit ratio associated with the investigation. Full-board review is the highest level of IRB review and is often reserved for high-risk studies, such as Phase I pharmacokinetic evaluations of new chemical entities, studies in which limited information regarding the safety of a drug is available, or studies in which there are no prospects of benefits to the research subjects. Some low-risk projects may qualify for expedited review by an IRB chairperson or designee. For example, most research conducted with the Food and Drug Administration (FDA) in accordance with FDA-approved package labeling for dosage and indication may qualify for expedited review. Projects that are of minimal risk (i.e., the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests) may qualify for IRB exemption. Some examples of exempt research include surveys of teaching strategies and retrospective studies, such as traditional drug-use evaluations and medical chart reviews. If research conducted by pharmacy faculty in the academic health care setting either is retrospective in nature or involves minimal risk interventions such as surveys, it may qualify for either expedited review or exempt status, depending on the type of data being collected (e.g., protected health information [PHI]). Most pharmacy-based drug-use evaluations that are used for internal purposes, and not intended for publication, may qualify for either expedited review or IRB exemption. Some small retrospective reviews, such as case reports, may also be subject to IRB review. A case report is a medical and educational activity that does not qualify as research but is defined by the Federal Policy for the Protection of Human Subjects as “a systematic investigation, including research development, testing, and evaluation designed to develop or contribute to generalizable knowledge.” Case reports typically involve a retrospective analysis of one, two, or three clinical cases. If more than three cases are involved in the analytical activity, then the activity will likely qualify as research. However, some journals may require a letter or other acknowledgement from an

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IRB before the publication of a case report. It is recommended that authors provide a cover letter indicating whether IRB approval was obtained or was not required for the described case report. It is also important to note that the authors of a case report must comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) regulations related to disclosure of PHI.

Although a project may appear to qualify for exempt status by the IRB, it is important to understand that the IRB makes this designation of review status, not the investigator. The reason for this is that some research projects that may initially appear to be of minimal risk may involve the collection of PHI, such as subject identification, medical or drug history, or criminal record. The handling of such PHI by any member of the research team, including pharmacy student volunteers, may place the subject at risk for loss of confidentiality or privacy, and a consent form and HIPAA research authorization form may be required to inform the participant of these risks.

An increasing number of journals and editorial boards that publish clinical research are now requiring specific disclosure related to ethical approval of studies, such as proof of IRB review (including exemption) and details of the informed-consent process before accepting manuscript submissions. For example, the *New England Journal of Medicine* requires a statement noting that the research protocol was approved by the relevant IRBs or ethics committees and that only human participants who gave written informed consent are included in the manuscript. The *Journal of the American Medical Association* requires a description of the formal review and approval, or review and waiver, by an appropriate IRB or ethics committee in the methods section of the article. For some journals, a provision is made for investigators who do not have formal ethics review committees. A statement indicating that the research was conducted according to the World Medical Association’s Declaration of Helsinki, which is the international code of research conduct, is often required. It is also recommended that the manner in which informed consent was obtained from the study participants, either oral or written, be included in the methods section of the manuscript. However, such requirements vary widely among journals that publish articles related to clinical research. In the future, it is likely that inclusion of an IRB approval letter may be required as part of the manuscript submission process.

**Conflicts of interest.** Maintaining objectivity in research is a critical component of scientific research and is required to maintain public trust. Relationships between academic researchers and the pharmaceutical industry, while not inherently unacceptable, raise the concern that scientific discoveries will bring financial gain for the research scientist and his or her institution and that scientific integrity will be compromised. This topic has recently been addressed by federal agencies such as FDA and NIH, which are charged with developing and enforcing policies related to financial conflicts of interest for their intramural faculty, as well as extramural grant applicants. Institutions are required to disclose potential conflicts with their investigators during the grant application process and to develop plans for managing and avoiding potential conflicts.

The reporting of financial conflicts of interest is often required during the IRB review process (for investigators as well as reviewers), during the presentation of research findings, and during the manuscript submission process. The most common types of financial conflicts include stock ownership, honoraria for speaking engagements and advisory board activities, and payment from industry sponsors related to the investigator’s research. However, the limits of financial conflict are not well-defined, and some institutions have adopted the Public Health Service (PHS) definition of “significant financial interest,” in which the investigator, including spouse and dependent children, has equity interest that exceeds $10,000, has 5% ownership interest in a single entity, or has salary and royalties that exceed $10,000 over a 12-month period.

Many journals are developing progressive policies that relate to authorship declarations and financial disclosure by authors. For example, journals such as *Arthritis and Rheumatism* are adopting the International Committee of Medical Journal Editors’ policy of authorship credit based on the following: substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published. At the time of acceptance of a manuscript, each author is required to complete and sign an author disclosure form. In an effort to increase awareness of the roles that commercial sponsors play in each manuscript, all manuscripts with commercial support must also include a statement in the methods section describing the role of the sponsor. The consequences of failure to comply with this policy may include refusal to publish the article in question, retraction of a published paper, a statement of loss of confidence, notification of the author’s primary institution, or exclusion from publication in the journal for a specified time frame. It is important to be aware of financial disclosure policies associated with an institution or journal publisher, because the disclosure of such relationships may be required for IRB protocol submissions, publications, presentations, and consent forms.
The development of standardized policies regarding the resolution and management of financial conflicts is clearly needed.

**Research misconduct and ethics training.** Recent reports of ethical breaches and research misconduct have heightened the awareness of the magnitude and importance of consequence and compliance. For example, an article published in *Science* in 2005 by a stem cell pioneer in South Korea claimed that stem cells had been successfully obtained from cloned human embryos. Allegations of data falsification associated with this study, followed by a university panel investigation, led to the author’s resignation and two article retractions by the journal.

Scientific or research misconduct in the United States is handled by the Office of Research Integrity (ORI), which evaluates biomedical and behavioral research supported by PHS. The ORI is charged with monitoring institutional investigations of scientific misconduct and facilitating the responsible conduct of research. Misconduct is most often defined as the fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. For example, falsely indicating that a research study was IRB approved in a manuscript or failing to report a financial conflict of interest would be considered research misconduct. The implications of research misconduct may include the loss of federal funding, being restricted to supervised research, or job dismissal. Increased dialogue among journal readership, authors, and editors is also needed. For example, journals could provide a mechanism for online discussion forums in which readers could submit comments and questions related to the scientific merit of the research article. These comments could then be addressed by the authors or editors and posted to the journal’s website.

Previous approaches to mentoring pharmacy students, graduate students, residents, junior faculty, and postdoctoral researchers based on informal discussions of ethical behavior are no longer considered sufficient. For example, NIH now requires training in the responsible conduct of research as part of its National Research Service Awards training grants. Structured programs related to ethics and regulatory affairs are required components of CTSA applications. Although many graduate training programs now require research ethics courses in their curricula, many faculty are trained in science-based disciplines, not in teaching ethics. Coursework related to research ethics should cover topics such as conflicts of interest, integrity in science, and responsible data management. One-time completion of such courses is also not the end of the story; effective training in research ethics must be ongoing, pervasive, and part of the institutional culture. It is critical that all members of the research team, from principal investigator to pharmacy student volunteers and graduate students, be aware of the various types of research misconduct, their implications, and ways to prevent their occurrence.

**Summary.** Recent initiatives to expand the clinical research enterprise have resulted in new opportunities for pharmacists to become engaged in research activities. One of the most important aspects of conducting research is compliance with IRB regulations, and the disclosure of IRB review is required by many scientific journals at the time of manuscript submission. The disclosure of conflicts of interest is also required during the submission of protocols to an IRB, as well as manuscripts to journals. Training in the ethical conduct of research is becoming an integral part of the continuous learning process for students and pharmacists.

**References**