

Research in the Physician's Office: *Navigating the Ethical Minefield*

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Dr. Smith is an internist in private practice who works at an inner city clinic affiliated with a university hospital. He is also a member of the university faculty. Many of Dr. Smith's patients have type 2 diabetes mellitus and struggle with health care and other costs. Thinking about opportunities to better serve his patients and advance his career, Dr. Smith considers conducting clinical research in his office.

ACME is a respected pharmaceutical company that for decades has engaged in research, development, and production of widely used drugs. Several of ACME's oral agents for type 2 diabetes will soon go off patent. In an effort to retain its market share in this class of drugs, ACME wants to complete clinical trials expeditiously and obtain approval for its new oral hypoglycemic medicine. The company approaches Dr. Smith to be a coinvestigator in its multicenter clinical trial.

Cases like this are ever more common. At one time, the great majority of clinical researchers were affiliated with academic medical centers. But industry funding for academic medical center trials declined from 80 percent in 1991 to 40 percent in 1998, and in the last ten years the trend has continued.¹ Now, many industry-funded trials take place in physicians' offices and private testing centers through contract research organizations—private companies that design studies and provide assistance in running the trials. Drug companies find CROs attractive because they complete studies faster and generally more economically than academic

medical centers. CROs were involved in 64 percent of all phase I, II, and III clinical trials in 2003, up from 28 percent in 1993, with CRO annual industry revenues increasing to \$17.8 billion in 2007 from \$7 billion in 2001.²

Dr. Smith should carefully consider whether to get involved. Although this trial will be evaluated by an institutional review board, Dr. Smith should think about its ethics himself. Unfortunately, like many private physicians, he has had little training in evaluating potential studies, thinking about the ethical issues of clinical trials, and managing the implications for his relationships with patients and his practice. Gaps in such training were evident in a survey conducted by the American College of Physicians of its membership in 2005. For example, although 79 percent of respondents said that they had received training in informed consent, only 51 percent had received training in research misconduct. Being both a physician and an investigator may result in conflicts between what is best for Dr. Smith's patients and what is best for the study. Preventing such conflicts can be difficult because the lines between investigator and physician—and between patient and research subject—are not always clear.

The ethical guideposts for clinical research were established long before research moved from academic medical centers into physicians' offices. The National Research Act of 1974 mandated the establishment of institutional review boards for the independent review of research involving human subjects at institutions receiving federal support. It also created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, whose major achievement was the drafting of the *Belmont Report*, which has become the touchstone for the ethics of human research subjects.³ The report identifies three very general ethical principles that human subjects research must observe: respect for persons, beneficence, and justice. Respect for persons requires that research subjects be treated as autonomous agents with rights to self-determination. Beneficence requires that their well-being be secured. Justice requires that the burdens and benefits of research be fairly distributed—it would be unacceptable, for example, to conduct research largely on poor people if the therapy under investigation is likely to benefit only the privileged. The *Belmont Report* became the basis for the Common Rule, the federal regulations that IRBs employ when reviewing clinical trials.

A major challenge today is to ensure that research in doctors' offices is conducted in accordance with the *Belmont Report*. The case of Dr. Smith illustrates the ethical and practical issues that arise when clinical research moves from the academic medical center—with its IRBs, training, and staff resources—to the physician's office.

Before agreeing to help conduct the study, Dr. Smith should assess both its scientific validity (will it answer the questions asked?) and its value (are the questions worth answering—will the knowledge gained be important?). Studies cannot be justified if they do not generate scientifically valid and worthwhile knowledge—even if they involve minimal risk to those who participate in them. Proper study design is

Lois Snyder and Paul S. Mueller, "Research in the Physician's Office: Navigating the Ethical Minefield," *Hastings Center Report* 38, no. 2 (2008): 23-25.

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both a scientific and an ethical obligation. If the study design is not valid, Dr. Smith should end his review there. If the study's value is unclear, or if the agent being tested appears to be a "me-too" drug—a drug similar to an existing drug that serves mainly to help manufacturers carve out market share—then he should view the study with skepticism. At the very least, he should ask what the potential benefits of the new drug are, and for whom.

Weighing Pros and Cons

Dr. Smith believes the proposed research could bring much-needed attention and resources to his clinic. On the other hand, he also recalls that the university has had difficulty recruiting local patients for clinical trials. Some of his patients have expressed mistrust of the university and the health care system. Would asking them to participate in a trial jeopardize their trust in him?

Doctors might want to participate in a clinical trial for reasons other than the chance to make a general contribution to science. They might believe the research will improve the care and health of many of their patients by bringing resources to their clinics. But they should consider who will ultimately benefit from the research. For example, they should

be wary of a study that recruits potential subjects from a primarily poor population that probably would not be able afford the investigational drug if it is approved. Such a scenario could damage the already fragile relationship his patients have with the health care system.

Physicians will also need to be mindful of their dual roles as clinicians and researchers. The *Belmont Report* distinguishes the goals of clinical practice (to enhance patient well-being) and research (to test hypotheses and draw conclusions without necessarily benefiting research subjects). Patients should be informed that the primary goal of research is to gain new knowledge and that participating in a research study may or may not clinically benefit them. Physicians should disclose their financial conflicts of interest, including those involving the research. Finally, patients should be informed that participating in a research study is voluntary and not a requirement for continued clinical care.

Compensation and Conflicts of Interest

ACME wants Dr. Smith to recruit one hundred patients for the study and will pay him \$750 for each patient he recruits and cover all expenses associated with the study, including laboratory tests, personnel, and equipment. Patients will receive free health care and medication during the study, which is expected to last three years. Dr. Smith fears, however, that once the trial is over and the medication is put on the market (assuming it is approved), many of his patients will not be able to afford it. He also has questions about the integrity of the ethical review process in this case. ACME is using a CRO to design the study, provide data analysis, and perform other tasks, including IRB review.

These financial and administrative details raise several ethical issues. One concerns compensation to the physician. Compensation for participating in research should be commensurate with the work. The Office of the Inspector General of the Department of Health and Human Services requires that payments for research be fair market value for legitimate services.⁴ According to the American College of Physicians ethics manual, accepting a finder's fee for referring patients to a research study is an unethical conflict of interest.⁵

But physicians should be aware that any kind of financial gain can influence recruitment, data collection, and research conclusions.⁶ It can also influence treatment. A recent study in Denmark concluded that when general practitioners participated in a clinical trial, they were likelier to use the trial sponsor's drugs.⁷ Doctors should be particularly skeptical of offers to conduct postmarketing research, which, in the words of the Office of the Inspector General, are sometimes simply pretexts to generate prescriptions.

All of the ethical concerns described above should be assessed by an IRB as well as the physicians. But because this research is occurring outside an academic medical center, ACME is using the CRO to provide IRB review, and review by a CRO raises its own concerns. First, the CRO's efforts to please the study's sponsor could lead to conflicts of interest,

making an unbiased ethical evaluation of the study difficult. In addition, because most CROs are national or multinational corporations, they may not take local issues into consideration. Community-based research should benefit the community that participates in it.⁸ Review by a local IRB helps ensure that it does.

Finally, physicians must also attend to issues related to research misconduct—fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. Disputes over publication and related issues might also arise. Who will author articles resulting from the study? What if the sponsor attempts to restrict which results can be published? Such issues should be discussed and resolved up front.

Conducting clinical research can be very rewarding for the right reasons—contributing to knowledge to improve health and helping to translate research into medical advances that will benefit patients. But physician-investigators must be clinicians first and investigators second, putting patients first and making sure that the research they are involved in is valid, has value, and is ethical.

Acknowledgments

The authors thank Tony Mazzaschi and his staff at the Association of American Medical Colleges for their support of the American College of Physicians Center for Ethics and Professionalism in its implementation of an education and resource program on the responsible conduct of practice-based research under a grant from AAMC and the DHHS Office of Research Integrity.

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