Ethics case study

When are industry-sponsored trials a good match for community doctors?

This is the 26th in a series of case studies with commentaries by ACP-ASIM's Ethics and Human Rights Committee and Center for Ethics and Professionalism. The series uses hypothetical examples to elaborate on controversial or subtle aspects of issues not addressed in detail in the College's "Ethics Manual" or other position statements.

Case history

Drs. Smith and Jones, senior partners of Internal Medicine Associates, have never before done office-based industry-sponsored drug research. Recently, Dr. Brown from DrugCo invited them to serve as co-investigators in a randomized double-blind clinical trial of a new medication to treat type two diabetes. It is the last trial DrugCo needs to complete before applying for FDA review and approval of the drug.

Rather than going to University Hospital's Institutional Review Board, DrugCo has arranged for a contract research organization (CRO) to manage the whole trial, including institutional review board (IRB) review, study design, data analysis, article preparation and FDA applications.

Subjects who enroll will be randomly selected to receive either one or two doses of the new drug or a placebo for six months. The prospect that some of his patients will get the placebo—not treatment—for that length of time concerns Dr. Smith. Subjects cannot take any other oral drugs for diabetes.

DrugCo will pay the doctors $3,000 per enrolled subject and will pay for all study-related care. In addition, if Drs. Smith and Jones enroll 10 subjects in three months, they will receive an additional $5,000. (Dr. Jones is a bit surprised by the level of these fees and worries about the practice becoming dependent on this kind of income.) Finally, a number of papers will be published from the study and Drs. Smith and Jones are welcome to participate as co-authors.

After taking courses in evidence-based medicine and putting their practice database online, Drs. Smith and Jones are definitely interested in office-based clinical research. They serve an urban population that includes many chronically ill, elderly and low-income patients. They believe that better data is needed to substantiate best practices for this population.

Moreover, the trial is attractive because it promises free medication, and so many of their patients have been hard hit by drug costs. But they want to think through the ramifications before going forward.

Commentary

Drs. Smith and Jones are carefully considering participating in a study in order to advance sound, clinic-based effectiveness research. A decision to participate could affect them, their patients, their patient-physician relationships and their practice.

Physicians who do research involving their patients have a dual role and must be aware of potential conflicts between what is best for the patient-subject and what is optimal for the conduct of the research. However, the lines between clinician and researcher can become fuzzy, as can the lines between patient and subject (1, 2).

Nevertheless, physician-investigators must consider their role as physicians first, and as investigators second, and they should ensure that research they participate in is ethically conducted (3). Therefore, as they consider this opportunity, Drs. Smith and Jones should evaluate the validity and value of the research, the ethical and scientific review that it has undergone, and compensation and authorship issues. We discuss each of these below.

- **Validity.** Drs. Smith and Jones' first consideration should be the study's validity. A study is scientifically valid if it answers the questions that it asks (4).

The study in question would be considered valid if it has a large enough universe of subjects to provide statistically significant results, and if the intervention and measurement techniques are sufficient to settle a research hypothesis. For instance, the goal of the study could be to prove that the new medication is more effective than another similar product.

Validity is a threshold requirement for all research, because it is unethical to expose human subjects to risks in studies that peer reviewers agree cannot adequately answer a research question (5). Because of this peer-review element, assessing the study's validity might be beyond the scope of what Drs. Smith and Jones can answer independently.

If the study were funded by the NIH or another institution that requires careful peer review, Drs. Smith and Jones could rely on this process as an assessment of validity. But the study they are considering is privately funded, with no such process of external review. However, they might look at the reputations of the study's investigators and advisory panel. If they are still unsure of the study's scientific quality, they could seek permission to send the protocol for informal, independent review.

To find a reviewer, they can contact medical schools, which may be able to recommend a faculty member with relevant experience. If serious questions arise about the study's validity, further considerations are irrelevant. Drs. Smith and Jones should not participate.

- **Value.**If they believe the study meets initial validity criteria, they should next carefully consider the study's value. A study's scientific value is based on the relevance or importance of its results (4). Good research is designed to produce knowledge that ultimately proves "important"(6), "fruitful"(7) or "valuable"(8). Unlike assessments of validity, judging value does not yield a yes or no answer, but a ranking on a continuum.

  A useful test for Drs. Smith and Jones might be to ask whether a study's results have the potential to change their practice immediately or in the future. If the study seeks determine whether a new medication is superior to an existing one, for example, it may offer considerable value. On the other hand, if DrugCo is seeking to simply obtain approval for a "me-too" medication that offers no advantages over currently available therapies, its value is suspect.

  A study's value also depends upon who will benefit from the results. Drs. Smith and Jones believe their patients lack the resources to pay for medications. Therefore, it seems likely that they will also be unable to afford the study medication if and when it is approved. The study's value may not apply to them.

  A lack of value, unlike a lack of validity, should not necessarily cause Drs. Smith and Jones to reject the study. However, they should view it with muted enthusiasm.

- **Ethical review.** Drs. Smith and Jones should next consider carefully the processes of ethical review that the study has undergone. At a minimum, most research carried out in the United States must go through review by an interdisciplinary IRB or meet stringent criteria for exemption from review (6). IRBs evaluate several aspects of a proposed study, including its risks, benefits, consent process, confidentiality issues, recruitment practices and the importance of the knowledge to be gained (6).

  If an institution has an IRB, as University Hospital likely does, that IRB should review the protocol. Indeed, if University Hospital accepts federal money for research, it is required to adhere to regulations governing the conduct of research, including IRB review (6). Local review is important because a committee whose members are drawn from the institution and the community are best prepared to assess a study's risks and benefit in light of the unique needs and concerns of that institution's patient population.

  For all of these reasons, Drs. Smith and Jones should make sure that the protocol is reviewed by their hospital's IRB. "All proposed clinical research, regardless of the source of support, should be approved by the local IRB to assure that the research plans are reasonable and that the research participants are adequately protected"(3).

If clinicians are not affiliated with an institution that has an IRB, they must rely on the IRB affiliated with the CRO to provide ethical oversight. To expedite trials, industry has increasingly used CROs and site-management organizations, rather than academic medical centers. In fact, industry funding for trials in academic centers fell from 80% in 1991 to 40% in 1998 (9).

Although this CRO-based review process should be objective, it lacks understanding of the local patient population required for adequate review. An outside IRB may not scrutinize studies as carefully as a local IRB, which needs to maintain community relations and patient trust. Therefore, clinicians who participate in research should be aware that they will have to take on the role of the local IRB to some degree, particularly by ensuring that the consent information is appropriate for their patients. Clinicians without access to an IRB may wish to contract with a nearby academic medical center IRB that may be willing to review protocols for a fee which could then be billed to the CRO.

- **Compensation.** Drs. Smith and Jones should also seek advice from local or distant IRBs regarding their other concerns, particularly the compensation they have been offered. A reasonable rule of thumb is that payments should be commensurate with the time and effort spent and the expenses incurred in recruitment. Compensation above this level is pure profit, and constitutes—or could be perceived to constitute—a conflict of interest. Providing finder's fees to individual physicians for referring patient to a study "generates an unethical conflict of interest" (3). Drs. Smith and Jones should refuse the offer of a bonus for active recruitment.

  This recommendation reflects commonly accepted standards for referrals in clinical care. For instance, if a laboratory approached Drs. Smith and Jones and offered them payments for each patient they referred, they would no doubt refuse, citing guidelines about improper business relationships and fee-splitting (3, 10, 11, 12). The same is true for this study.

- Drs. Smith and Jones should seek advice from the IRB about the added expenses of trial recruitment and follow up (which may be substantial) and for advice about proper compensation. Not all IRBs consider recruitment practices and incentives to be within the scope of their review (13). Some do; some specify what is permissible and what is not; and some require investigators to disclose any potential conflicts of interest (1).

- **Placebo controls.** Another big concern Drs. Smith and Jones might have about the study is the use of placebo controls. The World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects exhorts researchers to test against the "best current prophylactic, diagnostic and therapeutic methods" and to use placebo or no treatment only in studies where no proven method exists (14). Human subject research advocates see this principle as a way to protect subjects' welfare, especially for research done in developing countries.

  Those who support the wider use of placebo-controlled trials cite the scientific necessity of such studies in certain circumstances. They contend that, as long as alternatives are fully disclosed, the ethical appropriateness of placebos should be determined based on whether the subject will be harmed by deferring therapy (15, 16).

- **Authorship.** This study raises other concerns beyond the purview of most IRBs, such as the CRO's offer of authorship opportunities. Although it is not, strictly speaking, an issue of research ethics, this offer involves broader issues of professionalism and scientific propriety.

  In general, subject recruitment alone does not warrant authorship. Instead, authorship requires involvement in developing a study's conception and design, analyzing and interpreting results, drafting or revising the article's intellectual content, and approving the final version (17).

Drs. Smith and Jones have not been involved in conception and design. Unless they are invited and agree to participate in interpreting and reporting the study results, their level of participation is unlikely to warrant authorship in many medical journals.

Making a decision

The ethical conduct of research, like the scientific conduct of research, requires careful consideration, planning and attention to detail. Clinicians who are interested in contributing to research should spend some time learning about the responsible conduct of research, perhaps through courses now required by the NIH at most academic medical centers. Clinicians should also identify resources like IRBs, ethics centers and experienced investigators that can advise them.

Acknowledgements: The Ethics and Human Rights Committee would like to thank David Cassarett, MD, Lois Snyder, JD, and Jason Karlawish, ACP-ASIM Member, authors of the case history and commentary.

References

1. Department of Health and Human Services, Office of the Inspector General. Recruiting Human Subjects: Sample Guidelines for Practice. 2000. Publication no. OEI-01-97-00196.

2. Appelbaum P, Roth L, Lidz C, Benson P, Winslade W. False hopes and best data: consent to research and the therapeutic misconception. Hastings Center Report. 1987;17:20-4.

3. American College of Physicians. American College of Physicians Ethics Manual 4th ed. Ann Intern Med. 1998;128:576-94.

4. Freedman B. Scientific value and validity as ethical requirements for research: a proposed explication. IRB. 1987;9:7-10.

5. Rutstein DR. The ethical design of human experiments. In: Freund PA, ed. Experimentation with Human Subjects. New York: George Braziller; 1970:383-401.

6. Department of Health and Human Services. Protection of Human Subjects. Title 45, Part 46: Revised. Code of Federal Regulation. 18 June 1991.

7. The Nuremberg Code. In: Brody H. The Ethics of Biomedical Research: An International Perspective. New York: Oxford Univ Pr.; 1947:213.

8. Freedman B. Placebo-controlled trials and the logic of clinical purpose. IRB. 1990;12:1-6.

9. Bodenheimer T. Uneasy alliance—clinical investigators and the pharmaceutical industry. N Engl J Med. 2000;342:1539-44.

10. Thompson DF. Understanding financial conflicts of interest. N Engl J Med. 1993;329:573-6.

11. Relman AS. Dealing with conflicts of interest. N Engl J Med. 1985;313:749-51.

12. American Medical Association. Conflicts of Interest. Council on Ethical and Judicial Affairs, Report A (I-86). Chicago: AMA; 1986.

13. Department of Health and Human Services, Office of the Inspector General. Recruiting Human Subjects: Pressures in Industry-Sponsored Clinical Research. 2000. Publication no. OEI-01-97-00195.

14. World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. JAMA. 2000;283:3043-5.

15. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 1: ethical and scientific issues. Ann Intern Med. 2000;133:455-630.

16. Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments. Part 2: practical issues and specific cases. Ann Intern Med. 2000;133:464-70.

17. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA. 1997;277:927-34.