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Research or Marketing? Ethical Considerations in Phase IV Research

Today Dr. O'Hara, who is a community-based physician, received two invitations to enroll patients in research.

Lotsapharma wants to "learn more about Ossalube," an expensive arthritis medication recently approved by the Food and Drug Administration (FDA). If Dr. O'Hara participates, his patients will receive free Ossalube for six months. After any office visit a study patient makes during that time, Dr. O'Hara will complete a one-page questionnaire concerning vital signs, range of motion, and other data. He will receive \$2,000 for each patient he enrolls, plus an additional \$5,000 if he recruits thirty patients in sixty days. Lotsapharma's invitation includes a journal article noting positive preliminary findings of Ossalube's efficacy and a final reminder that patients will receive the drug for free. A contract research organization (CRO) processes all paperwork; except for returning questionnaires, Dr. O'Hara will not submit any other documents.

The second invitation is from Mightymed. Its medication, Cardevac, lowers cholesterol and high blood pressure with a single pill taken once daily. Mightymed wants more information about patient adherence, tolerability, drug interactions, and incidence of side effects. Its letter summarizes Phase III (pre-approval) study results, including Cardevac's safety profile, and explains that, after signing a

consent form describing the study's purpose, and risks and benefits of study participation, patients will receive one month's supply of Cardevac. Each patient will visit Dr. O'Hara monthly, return the Cardevac bottle and any unused pills, and obtain another month's supply. At each visit a small amount of blood will be drawn and sent to an independent lab; both Dr. O'Hara and patients will complete questionnaires. Dr. O'Hara will summarize his exam, noting twelve specific clinical findings (weight, blood pressure, etc.). Patients will answer questions regarding physical activities and the ease or difficulty of taking Cardevac. A CRO manages the study, but Mightymed allows local IRB review. Dr. O'Hara will receive \$300 for each office visit to cover time spent with patients, the blood draw, and processing consent forms and questionnaires. The consent form advises patients that they should not be billed for office visits, lab work, questionnaires, or Cardevac since Mightymed covers all research-related expenses.

Both studies sound intriguing. How should Dr. O'Hara respond?

Discussion

Dr. O'Hara's interest in these projects is understandable. The importance of Phase IV research is well established. Sometimes referred to as post-marketing surveillance because it occurs after FDA approval, Phase IV research

provides opportunities to study dosage, drug interactions, and adverse events in larger populations over longer periods of time and in more natural settings than are typically available in Phase III research. Sometimes FDA approval is conditioned on Phase IV completion in order to confirm or change the safety profile of the drug (or medical device or procedure).

Phase IV studies represent part of an overall increase in industry-sponsored, office-based research. From 1991 to 1998 the proportion of pharmaceutical industry clinical research funding allocated to academic medical centers dropped from 80% to 40%, whereas the number of private physicians conducting clinical research tripled between 1990 and 1997.¹ It is therefore critical that Dr. O'Hara understand ethical issues in clinical research, especially those with particular importance for Phase IV studies.

The following questions should frame Dr. O'Hara's deliberations:

Is it research or marketing? All research, including Phase IV studies, requires a properly designed protocol with clear, obtainable objectives that can contribute to generalizable knowledge. Thus Mightymed has described how the Cardevac study will augment knowledge gained in previous studies. But some manufacturers call marketing strategies "research" in an effort to influence prescribing practices by means other than direct advertising and sales calls. While Mightymed identifies regular points

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when explicit data are collected from all subjects, Lotsapharma's "study" is completely open ended. In fact, Dr. O'Hara could give Ossalube to patients who make no follow-up office visits—and supply no data for the "research."

Are the incentives appropriate?

Propriety of physician incentives is determined less by their amount or value than by the purposes to which payment is applied and, in some cases, its form. If Dr. O'Hara enrolls thirty patients into the Lotsapharma study within two months, the \$65,000 he will make seems grossly disproportionate to the time and effort required. Mightymed's reimbursement appears much more in line with resources required to complete the protocol. Furthermore, Mightymed has anticipated the ethical problem of "double dipping," which would enable Dr. O'Hara to bill patients for research activities and be reimbursed by the sponsor. (Although not at issue in this case, compensation in the form of stock or stock options would be ethically problematic, as would Dr. O'Hara's holding a proprietary interest in Ossalube or Cardevac.)

Are subjects adequately informed and protected? Lotsapharma's omission of informed consent is serious. Patients could take Ossalube without knowing they are research subjects. The obligation to inform subjects of distinctions between research and clinical care, and of risks and benefits of study participation, is particularly important in office-based research because of the special trust patients place in their personal physicians. This obligation was noted by

an advisory committee that investigated thousands of radiation experiments conducted by the federal government between 1944 and 1974, and its importance was illustrated by excerpts from research subject interviews: "'[I]f you take the time to get yourself a good doctor and they're involved in research, they would never steer you wrong' . . . 'Oh, I love that man. He has kept me alive and I obey him and I do what he tells me to do.'"² The distinction between research and clinical care may be clear in Dr. O'Hara's mind, but he should take extra care to explain it to patients. Mightymed's study, unlike Lotsapharma's, requires informed consent to protect its subjects and includes local IRB review, which facilitates application of research protections to Dr. O'Hara's local patient population.

In sum, Lotsapharma's description of its "study" provides Dr. O'Hara ample ethical grounds to decline its invitation, while Mightymed's research appears sensibly designed, cognizant of subject rights and welfare, and free of inappropriate incentives.³

1. JE Klein and AR Fleischman, "The Private Practicing Physician-Investigator: Ethical Implications of Clinical Research in the Office Setting," *The Hastings Center Report* July-August 2002;32(4):22-26.

2. NE Kass, J Sugarman, R Faden, and M Schoch-Spanz, "Trust: The Fragile Foundation of Contemporary Biomedical Research," *The Hastings Center Report* September-October 1996;26(5):25-29.

3. The Advocate Ethics Integration Council's ethics advisory on Phase IV research can be found on the Advocate intranet "Clinical Resources" page.

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