Seeding Trials: Just Say "No"

The public has lacked convincing documentary evidence of a long-suspected drug company practice: promoting a new drug by sponsoring a randomized trial in which participating physicians use the drug as they follow the trial protocol. This practice—a seeding trial—is marketing in the guise of science. The apparent purpose is to test a hypothesis. The true purpose is to get physicians in the habit of prescribing a new drug.

Why would a drug company go to the expense and bother of conducting a trial involving hundreds of practitioners—each recruiting a few patients—when a study based at a few large medical centers could accomplish the same scientific purposes much more efficiently? The main point of the seeding trial is not to get high-quality scientific information: It is to change the prescribing habits of large numbers of physicians. A secondary purpose is to transform physicians into advocates for the sponsor's drug. The company flatters a physician by selecting him because he is "an opinion leader" and incorporates him in the research team with the title of "investigator." Then, it pays him good money: a consulting fee to advise the company on the drug's use and another fee for each patient he enrolls. The physician becomes invested in the drug's future and praises its good features to patients and colleagues. Unwittingly, the physician joins the sponsor's marketing team. Why do companies pursue this expensive tactic? Because it works (1, 2).

It works, but it may endanger the unwary physician. The tide is turning against the physician who accepts emoluments from drug companies. Academic institutions and professional organizations are issuing ethical guidelines that proscribe transactions in which drug companies pay physicians an amount that is disproportionate to the services that the physician provides (3, 4). The office of the U.S. Inspector General has issued guidance about which transactions are legal. Although its guidance focuses on gifts, it also states that payments for participation in research "should be fair market values for legitimate, reasonable, and necessary services" (5). Moreover—and most ominously for the future of seeding trials—"postmarketing research activities should be especially scrutinized to ensure that they are legitimate and not simply a pretext to generate prescriptions of a drug" (5).

Several years ago, *Annals* published a seeding trial (6). Merck & Co. (Whitehouse Station, New Jersey) sponsored ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness), a large, community-based, randomized comparison of a cyclooxygenase-2 inhibitor (Vioxx [rofecoxib]) and a nonselective cyclooxygenase inhibitor (naproxen). At the end of the 3-month follow-up, the proportion of patients who discontinued naproxen was larger (8.1% vs. 5.9%) than that of those who discontinued Vioxx. We published the study because we thought that physicians would be interested in the low discontinuation rates for both drugs and the small difference between them.

No one told *Annals* the true purpose of ADVANTAGE. We learned about it when we received a letter to the editor from Dr. David Egilman, who was a consultant to the plaintiffs' attorneys in the civil suits against Merck (7). He had access to publicly accessible trial documents, which included Merck employees' e-mail messages that disclosed the true intent of the ADVANTAGE trial. These messages are the meat of the article about seeding trials published in this issue by Hill and colleagues (8). To our knowledge, this article is the first to provide documentary evidence that proves the existence of seeding trials. Other than an excerpt from a single industry document cited in an article by Kessler and colleagues (9), we have not had "smoking gun" evidence, in which the perpetrators are on public record about why they conducted a trial like ADVANTAGE. The article provides clear evidence that the intent of ADVANTAGE was to increase prescriptions of Vioxx (the study outcome of greatest interest to Merck seems to have been Vioxx prescribing rates). However, despite the large body of documents searched by the authors, they discovered few details about exactly how Merck's marketing division carried out ADVANTAGE.

The documents do tell us that deception is the key to a successful seeding trial. That information—once it becomes general knowledge—could be the fatal blow for seeding trials. Institutional review boards, whose purpose is to protect humans who participate in research, would probably not likely approve an action that places patients in harms' way in order to influence physicians' prescribing habits. If they knew, few established clinical researchers would participate as coinvestigators. Few physicians would knowingly enroll their patients in a study that placed them at risk in order to provide a company with a marketing advantage, and few patients would agree to participate. Seeding trials can occur only because the company does not disclose their true purpose to anyone who could say "no."

It is also true that seeding trials exist only because physicians say "yes" to a deal that seems too good to be true. Academic physicians agree to be on the byline of an article that someone else wrote about a study that someone else designed and paid for because there is considerable prestige, little effort, and low risk (10). A practicing physician says, "Why not?" when he learns that he has been selected to participate in an important clinical trial and receives inducements designed to make it an offer he will not refuse. Our parents prepared us for this moment when they warned us to ask questions when someone offers us easy money. We owe it to them and especially our patients to ask if we are being recruited to participate in a seeding trial.

How can people with decisional responsibility—institutional review boards, researchers, physicians, and pa-

tients—identify a seeding trial? They could ask the about the intent of the trial. If the answer was "It's a seeding trial," most would say no, and seeding trials would soon fade away; but this scenario is a fairy tale, because sponsors would probably ascribe a scientific purpose to the trial and proving otherwise would be difficult. Nonetheless, institutional review boards could routinely ask, "Is this a seeding trial?" Sponsors would think twice about lying to an institutional review board, an institution that has so much legal and public support, especially in an era in which e-mail messages seem to live on forever, awaiting discovery by a curious someone.

Asking about intent may be the wrong approach. Does the goodness of a trial inhere in its intent or in something else? An adequately powered trial is good if it tries to answer an important scientific question on which patients should be in equipoise, even though participating physicians will become familiar with a new drug and be more likely to prescribe it. Is the same trial bad if its main purpose is to increase drug sales by habituating trial physicians to prescribing a new drug? Couldn't the answer to this question depend on the scientific importance of the question that it addresses? The trial would be bad if it addressed a question that lacked merit but good, despite its intent, if the question had intrinsic merit. Does the motivation for the trial make it wrong to participate in it, or does addressing an important, unsettled question make the study worthwhile, despite its intent? Perhaps physicians should focus less on intent and more on the scientific question. The ADVANTAGE physicians should have been asking whether the trial addressed an issue that previous trials had already answered—or should have answered.

This line of reasoning suggests that institutional review boards, researchers, physicians, and patients should be asking about the study hypothesis and whether it addresses a settled question. Physicians have a fiduciary obligation to ask these questions on behalf of their patients, as do institutional review boards and researchers, which have the skill set and personnel to judge whether a trial is asking an already-answered question. They could look for other clues, such as a study with an open-label design, no control group, a very large projected enrollment relative to the importance of the question, a short-term study of a chronic disease, a study of an already approved drug, and so forth (1, 8, 9). None of these clues is highly specific, but institutional review boards should start asking questions when a study has several of them.

A bureaucratic solution, such as relying on institutional review boards, could help to rid us of seeding trials, but simply shining a bright light on their existence may have already sown the seeds of their destruction. The next step would be a societal consensus that it is wrong to deceive institutional review boards and participants about the true purpose of a trial. Therein lies the importance of Hill and colleagues' article (8).

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