



“Seeding” Sales and Science

By John E. Calfee

Clinical drug trials driven primarily by marketing intend to increase sales and profits for pharmaceutical companies. In fact, almost all of the most important drug trials have taken place for marketing purposes. Such clinical trials, called “seeding” trials, are performed to give the selected physicians experience with the drug being tested, in hopes that they will continue to prescribe the drug after the trial is over and that they will spread the word to other physicians. Regardless of the intentions, these clinical trials yield enormous benefits for patients and practitioners.

The August 19, 2008, issue of *Annals of Internal Medicine*, one of the most widely read medical journals anywhere, featured an article by Kevin Hill and three coauthors with the mysterious title, “The ADVANTAGE Seeding Trial: A Review of Internal Documents.” The article, which raises questions about the ethics of so-called seeding clinical trials, has ricocheted through the mainstream press. But what has received far too little attention is the extent to which marketing and R&D inevitably overlap in the pharmaceutical business.

ADVANTAGE was a randomized clinical trial, the “gold standard” research used to support new drug approvals and much else in health care practice. The trial showed that Vioxx, the arthritis pain reliever from Merck—later pulled from the market in 2004 because of cardiovascular side effects—had fewer gastrointestinal side effects than naproxen, an older pain reliever often sold over the counter under the name Aleve. ADVANTAGE was started before Vioxx was approved for marketing but after the clinical trials necessary to obtain Food and Drug Administration (FDA) approval had been successfully completed.

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The results were obviously of interest; they were published in 2003 in a leading journal, which happened to be the *Annals of Internal Medicine*.

After poring through internal Merck documents, the authors of the new *Annals* article concluded that ADVANTAGE was a “seeding” trial: a clinical trial that is mounted not to obtain valuable new scientific information but to give selected physicians experience with the drug being tested, in hopes that they will continue to prescribe it after the trial is over and will persuade others to do the same. The authors of the *Annals* article reached their conclusion working for plaintiff attorneys who were suing Merck over the health risks of Vioxx. They recognize that their perspective and the information they worked with were biased, but they think the facts speak for themselves. The ADVANTAGE trial was marketing, not science, the authors say, and it should be condemned because it exposed trial subjects to unnecessary risk without full disclosure of the circumstances. The *Annals* published an editorial to that effect, authored by its editor and the deputy editor of the *Journal of the American Medical Association*.

Merck executives, who had no knowledge of the critical study before it was published, immediately issued a statement that took issue with

nearly every essential point in the *Annals* article. They argued that ADVANTAGE differed from the trials required by the FDA in *useful* ways. Because it recruited general practice physicians rather than specialists and included patients with various conditions, the trial explored clinical circumstances quite different from the unrealistically purified, academic-run trials that typically generate new drug approvals. Most important, ADVANTAGE did not exclude patients on aspirin. This makes a difference because aspirin is widely used to prevent heart attacks and relieve arthritis pain—although it is not generally recommended for that—and also is a known cause of the upper-gastrointestinal problems that many patients experience while taking naproxen and other nonsteroidal anti-inflammatory drugs. Because Vioxx was designed to relieve pain while going easier on the gastrointestinal track, elucidating the differences between Vioxx and naproxen in a population of aspirin users would be of great interest to practitioners.

The *Annals* authors rest their case partly on the degree to which Merck's marketing folks were involved in the study and celebrated its results (including the fact that participating physicians prescribed Vioxx at modestly higher rates after the trial). But when the FDA approves a new drug, it is approved "for marketing." It is entirely appropriate for firms to run many of the most important trials with marketing goals in mind. When the trials are done, all that counts are the results.

History is decisive on this point. Merck's APPROVe trial demonstrated the expected result that Vioxx cuts the risk of prostate cancer, but it also revealed excess heart attacks. That led to Vioxx's withdrawal, massive litigation, and the hiring of numerous plaintiff experts, including the ones who wrote the *Annals* article.

Nearly all of the most valuable drug trials have been undertaken for marketing purposes. When Bristol-Myers Squibb (BMS) introduced its statin cholesterol-reducing drug Pravachol to compete with Merck's then-dominant Zocor, it mounted a huge and extremely expensive trial to show that Pravachol did something Zocor had never been shown to do: prevent heart attacks in patients who had high cholesterol but were otherwise healthy. The trial ended successfully, marketing measures were adjusted accordingly, and sales soared. The result was a triumph not only for marketing but also for patients.

Later, Pfizer introduced Lipitor, an even more powerful statin, with great success. BMS mounted another

hugely expensive trial, PROVE-IT, designed to show that Lipitor's extra power did not translate into better protection against heart attacks and deaths. But the trial unexpectedly showed that Lipitor was more effective, so much so that a celebratory *New England Journal of Medicine* editorial headline trumpeted intensive statin therapy as "A Sea Change in Cardiovascular Prevention." PROVE-IT is one of the most valuable clinical trials from the past two decades. Again, marketing-driven research was harnessed to the public benefit, in this case in a manner contrary to the intentions of the trial's sponsor.

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Now for a strange twist, which seems to have escaped the press's notice. The *Annals* editorial first praises Hill and his coauthors for revealing the existence of much-rumored seeding trials and condemns such trials because they deceive physicians and subjects. But then it thoughtfully confronts the simple truth that marketing and legitimate science often overlap; research undertaken to increase sales and profits can also benefit patients handsomely. "Perhaps," the editorial reasons, "physicians should focus less on intent and more on the scientific question." But then the editorial turns back to intent, ticking off certain characteristics of unjustifiable seeding trials, most of which happen to not apply to ADVANTAGE at all.

Annals published the ADVANTAGE trial—and is apparently without regret to this day—because it provided information of substantial value to practitioners. It shows—yet again—that what matters in a clinical trial is scientific value, not intentions, whether of the marketing sort or not. The article by Hill et al. is essentially irrelevant: it does not matter how close Merck's marketing department was to the ADVANTAGE trial or what they hoped to get out of it because scientific value trumps marketing intent.

Let us hope the rest of the world catches up with this reasoning so we do not do something foolish, like unduly regulate clinical trials, that would interfere with useful research.