

The ADVANTAGE Seeding Trial: A Review of Internal Documents

Kevin P. Hill, MD, MHS; Joseph S. Ross, MD, MHS; David S. Egilman, MD, MPH; and Harlan M. Krumholz, MD, SM

Background: Seeding trials, clinical studies conducted by pharmaceutical companies that are designed to seem as if they answer a scientific question but primarily fulfill marketing objectives, have not been described in detail.

Purpose: To describe a known seeding trial, ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness), through documents of the trial sponsor, Merck & Co. (Whitehouse Station, New Jersey).

Data Sources: Merck internal and external correspondence, reports, and presentations elicited to inform legal proceedings of *Cona v Merck and Co., Inc.*, and *McDarby v Merck and Co., Inc.* The documents were created between 1998 and 2006.

Data Extraction: An iterative case-study process of review, discussion, and re-review of documents to identify themes relevant to the design and conduct of ADVANTAGE. To supplement the case-study review, the authors did a systematic review of the literature to identify published manuscripts focused on seeding trials and their conduct.

Data Synthesis: Review of the documents revealed 3 key themes: The trial was designed by Merck's marketing division to fulfill a marketing objective; Merck's marketing division handled both the scientific and the marketing data, including collection, analysis, and dissemination; and Merck hid the marketing nature of the trial from participants, physician investigators, and institutional review board members. Although the systematic review of the literature identified 6 articles that focused on the practice of seeding trials, none provided documentary evidence of their existence or conduct.

Limitations: The legal documents in these cases provide useful, but limited, information about the practices of the pharmaceutical industry. This description of 1 company's actions is incomplete and may have limited generalizability.

Conclusion: Documentary evidence shows that ADVANTAGE is an example of marketing framed as science. The documents indicate that ADVANTAGE was a seeding trial developed by Merck's marketing division to promote prescription of Vioxx (rofecoxib) when it became available on the market in 1999.

Ann Intern Med. 2008;149:251-258.

For author affiliations, see end of text.

www.annals.org

Although much has been written about the marketing tactics of the pharmaceutical industry (1, 2), seeding trials have not been characterized in depth. Seeding trials are clinical trials designed by pharmaceutical companies to promote the use of pharmacotherapies that were recently approved or are under review by the U.S. Food and Drug Administration (FDA). Seeding trials are designed to appear as if they answer a scientific question but primarily fulfill marketing objectives. Kessler and colleagues (3) portrayed seeding trials as "attempts to entice doctors to prescribe a new drug being marketed by the company" while the company puts its product in the hands of practicing physicians, hoping that the experience of treating patients with the study drug and a pleasant, even profitable, interaction with the company will result in more loyal physicians who prescribe the drug (4). Despite attempts to call attention to seeding trials (5, 6), limited information about them is available in the public domain.

Confidential internal communications made public as a result of recent litigation against Merck & Co. regarding the cardiovascular safety of Vioxx (rofecoxib; Merck & Co., Whitehouse Station, New Jersey) offer a view of the planning, implementation, and publication of a seeding trial from the pharmaceutical company's perspective. We examined the documents related to the ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) clinical trial, a seeding trial designed and conducted by Merck that was published in the peer-reviewed literature on 7 October 2003 (7).

METHODS

Review of the Litigation Documents

During *Cona v Merck and Co., Inc.*, and *McDarby v Merck and Co., Inc.*, documents produced by Merck in response to discovery requests were archived in an integrated database maintained by the plaintiff's attorneys. These documents were created between 1998 and 2006 and included Merck internal and external correspondence, reports, and presentations. As paid consultants to the attorneys representing the plaintiffs, we had access to all archived documents. We identified a subset of approximately 2000 relevant documents by using the following search terms: *seeding*, *marketing*, *ADVANTAGE*, and the names of Merck employees and academically affiliated authors known to be associated with the ADVANTAGE clinical trial. Document numbers are approximate because information within 1 document may overlap with another, making it difficult to determine the exact number of distinct documents.

See also:

Print

Editors' Notes 252
Editorial comment 279

Web-Only

Conversion of graphics into slides

Context

People have long suspected that drug companies use seeding trials to promote a new drug by getting physicians to use it as they follow the protocol of a clinical trial. Strong documentary evidence has been lacking.

Contribution

The authors obtained court-ordered documents, some of which were e-mailed messages, that showed that the marketing division of Merck & Co. (Whitehouse Station, New Jersey) conducted the ADVANTAGE (Assessment of Differences between Vioxx and Naproxen To Ascertain Gastrointestinal Tolerability and Effectiveness) randomized trial to promote the use of Vioxx (rofecoxib) by physicians—the drug prescribed to patients assigned to the active intervention. The company did not tell institutional review boards, physicians, or patients the true purpose of the trial.

Caution

The documents lack many details about ADVANTAGE.

Implication

Seeding trials deceive trial participants and their protectors.

—The Editors

One investigator read the identified documents to determine relevance to seeding trials. We identified approximately 100 relevant documents from the search, most of which were Merck internal correspondence and marketing reports, memos, and presentations.

Two investigators independently completed a line-by-line review of each identified document by using the “constant comparative method,” a systematic, verifiable technique (8, 9), to identify broad themes reflecting the design and conduct of a seeding trial. In this iterative process, segments of text are catalogued according to their essential concepts (8, 9). Similar methods have been used recently with court documents to examine tobacco marketing, pharmaceutical marketing, and ghostwriting for scientific papers (10–13). Next, all investigators reviewed pertinent documents again to identify and develop core themes. Then, 2 investigators reviewed all of the documents for additional evidence to support or refute the core themes. Each investigator re-reviewed a subset of pertinent documents to compare the content with the 3 core themes that emerged from our review. The team communicated regularly to resolve discordant views through negotiated consensus. Finally, the investigators completed another iteration of the negotiated consensus process after the initial manuscript review by *Annals*.

Systematic Review of the Literature

To better understand ADVANTAGE in the context of seeding trials, we conducted a systematic review of the literature and identified published manuscripts about seeding

trials. First, we searched MEDLINE (from 1950 to March 2008) for the exploded Medical Subject Heading term *clinical trials as topic* and identified 201 557 publications. Second, we searched for the exploded Medical Subject Heading term *drug industry* and found 27 210 publications. Third, we did a search that included the exploded Medical Subject Heading terms *prescriptions, drug, advertising as topic*, and *conflict of interest* and the keywords *marketing* and *seeding* and identified 58 242 publications. Finally, we combined these 3 searches and identified 466 articles, 61 of which we excluded for not being published in English. Two investigators independently reviewed the titles and abstracts of retrieved publications and selected relevant articles for possible inclusion in our review. On the basis of this review, we excluded 400 publications that did not focus on seeding trials. We included the remaining 5 publications in our review and searched bibliographies of these articles for additional relevant publications; 1 was identified.

Role of the Funding Source

This research was exempt from review by the Yale University Human Investigation Committee. Neither the Hartford Foundation nor the Robert Wood Johnson Foundation had any role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; and preparation, review, or approval of the manuscript.

All authors were compensated for their work as consultants to the plaintiff’s counsel in connection with suits against Merck related to Vioxx. This independent research was not sponsored by the plaintiffs or in any way related to the trial work.

RESULTS

In January 1999, before the launch of Vioxx, Merck’s marketing division conceived the ADVANTAGE clinical trial (14). However, Merck did not reveal the key role of the marketing division and marketing objectives of the study. Instead, physician-investigators, participants, and institutional review board members were told that the purpose of the trial was to measure the gastrointestinal safety of Vioxx (15). Six hundred investigators enrolled and randomly assigned 2785 patients with osteoarthritis to Vioxx and 2772 patients to naproxen, with a target of 6 participants per site, for a 3-month trial starting on 27 March 1999, approximately 2 months before the drug’s FDA approval on 22 May 1999 (16). A Merck marketing slide set used for the company’s internal purposes stated that a goal of ADVANTAGE was for investigators to “[g]ain experience with Vioxx prior to and during the critical launch phase” (14).

Review of the Vioxx documents revealed 3 key themes that were related to the design and marketing objectives of the ADVANTAGE trial: The trial emerged from the marketing division with a marketing objective; Merck’s mar-

keting division collected, analyzed, and disseminated both the scientific and the marketing data; and Merck did not reveal the marketing purposes of the trial to participants, physician-investigators, and institutional review board members.

A Marketing Trial with a Marketing Objective

The Merck marketing division designed and executed the ADVANTAGE trial. **Figure 1** shows an internal award nomination memo from Charlotte McKines, Executive Director of Marketing Communications at Merck, and Louis Sherwood, Senior Vice President for Medical and Scientific Affairs, that describes the influence of the marketing division (17).

The memo outlines 4 key Merck marketing principles: target the trial to a select group of customers—in this case, primary care physicians; use the trial to demonstrate the value of Vioxx to these physicians; integrate the marketing division and those responsible for trial-related operations in the field with the highest level of precision; and carefully track marketing-related results, that is, rates of Vioxx prescriptions written by study physicians.

According to an internal presentation on 16 March 1999 by Jan Weiner, Executive Director of Public Affairs at Merck, the responsibilities of the marketing division were to “[s]et objectives” and “[d]esign [the] protocol and oversee execution of [the] trial” (18) (**Figure 2**). In a memo, Merck explained why the company targeted primary care physicians (17) (**Figure 1**):

First, the trial was targeted to a select group of critical customers. The clinical trial program for VIOXX focused primarily on specialists. While they would be critical to the early uptake and advocacy for VIOXX, the large majority of prescriptions in the A&A [arthritis and analgesia] market (~60%) come from primary care physicians. The ADVANTAGE trial utilized this important group of prescribers as investigators. In addition to gaining experience with VIOXX, many of these physicians gained a highly coveted introduction to clinical research. Second, the design of the trial focused on demonstrating the value of VIOXX to this important audience.

The internal memo also noted the importance of ADVANTAGE in creating positive perceptions of Vioxx and Merck among primary care physicians (17) (**Figure 1**):

Feedback from the field has been overwhelmingly positive about their ability to access key customers and the influence that being involved in the trial has had on their perceptions of VIOXX and Merck.

We did not identify documents describing participation of the research division in the planning or implementation of ADVANTAGE from the database search. However, Dr. Edward Scolnick, the head of the research division at

Figure 1. Merck commends marketing division's ADVANTAGE Trial.

USHH MERCK MARKETING ANNUAL AWARDS

Nomination Memo

TO: MERCK MARKETING WP37C-236

FROM: Charlotte McKines 652-2675 Signed: _____
Lou Sherwood 652-3730 Signed: _____

DATE: 1/4/99

SUBJECT: Best Physician Program Award

PROJECT: VIOXX: ADVANTAGE Trial

NOMINEES: Caroline Yarbrough, Greg Geba, Mary Dixon, Leo Mendez, Greg Bell

DESCRIPTION and RATIONALE:

The ADVANTAGE (Assessment of the Differences Between VIOXX and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness) trial is the largest ever initiated prior to the launch of a Merck product. The objectives were to provide product trial among a key physician group to accelerate uptake of VIOXX as the second entrant in a highly competitive new class and gather data important to this customer group. The trial was designed and executed in the spirit of the Merck marketing principles, as described below.

First, the trial was targeted to a select group of critical customers. The clinical trial program for VIOXX focused primarily on specialists. While they would be critical to early uptake and advocacy for VIOXX, the large majority of prescriptions in the A&A market (~60%) come from primary care physicians. The ADVANTAGE trial utilized this important group of prescribers as investigators. In addition to gaining experience with VIOXX, many of these physicians gained a highly coveted introduction to clinical research.

Second, the design of the trial focused on demonstrating the value of VIOXX to this important audience. The design was the result of a close collaboration between CDP and Marketing and again focused on a gap not filled by the pivotal clinical program. While the clinical trials gathered data on efficacy and safety of VIOXX vs. NSAID comparators, they did not provide extensive data on tolerability, perceived by many physicians to be as important for patient satisfaction as other more serious adverse events. Also, the comparators for the OA program did not include naproxen, a commonly prescribed and generically available NSAID. The ADVANTAGE trial encompassed these important criteria in an elegantly simple design that would be possible to execute with a very large pool of investigators.

Third, execution of the trial was of the highest level, involving integration of the field, marketing and CDP. The trial was completed in record time, from conception in January 1999 to first patient in by March 1999. The sales force nominated potential investigators and completed intake forms, allowing a very large number of sites to be evaluated and enrolled and ensuring equal distribution of investigators across the business groups. Weekly meetings were held with the team members throughout the first half of the year to allow any issues (such as slow investigator or patient recruitment) to be rapidly identified and resolved. The team has collaborated on mechanisms for continuing to interact with the investigator population, including a special sample program, interim investigator meetings and newsletters.

Finally, the results of the trial are being carefully tracked. An analysis performed at 6 months post launch demonstrated a significantly higher level of prescribing for VIOXX among primary care ADVANTAGE investigators compared to a control group of VIOXX 99 prescribers (see attached). Feedback from the field has been overwhelmingly positive about their ability to access key customers and the influence that being involved in the trial has had on their perceptions of VIOXX and Merck. Preparations are now underway for analysis and publication of the data, which will utilize key investigators as authors and advisors.

(Revised 12/1999)

Merck executives nominate those responsible for the design and execution of ADVANTAGE for an internal marketing award. A&A = arthritis and analgesia; CDP = clinical development program; NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis. USHS = United States Human Health.

Figure 2. Merck slide defining the role of the marketing division in the ADVANTAGE Trial.

ADVANTAGE	CDP
<ul style="list-style-type: none"> • Design protocol and oversee execution of trial • Select investigator sites • Run investigator meetings • Choose and manage CRO • Perform data analyses • Prepare publications 	

CDP = Clinical Development Program; CRO = Clinical Research Organization.

Merck Research Laboratories, wrote that ADVANTAGE and other “large marketing clinical studies” are “intellectually redundant” (19). In an e-mail on 4 April 2001 to a colleague about the impact of ADVANTAGE’s cardiovascular safety data on Vioxx’s status with the FDA, Scolnick wrote (typographical errors corrected and explanations of acronyms provided) (19):

[T]he reason we have resisted doing large marketing clinical studies is just this. It opens a lot of data to FDA that compromises the large clinically meaningful trials. Small marketing studies which are intellectually redundant are extremely dangerous and the PAC [Products Advisory Committee] system with the marketing emphasis in CDP [Clinical Development Program, a part of Merck’s Marketing Division] on all their studies opens Pandora’s box which we have urged against from

the beginning of time. Their budget is now 179 million for CDP—as much as our phase 2/3 new chemical entities used to be. I have told [another Merck colleague] I think it is wasteful.

Marketing Division Handles Scientific and Marketing Data

Merck’s marketing division, as illustrated by Jan Weiner’s internal presentation, handled the scientific and marketing data, including collection, analysis, and dissemination (18) (Figure 2). The first author of the primary publication resulting from ADVANTAGE, Dr. Jeffrey R. Lisse, an academic physician not employed by Merck, told *The New York Times* that he did not have a role in data collection or analysis (20):

Merck designed the trial, paid for the trial, ran the trial. Merck came to me after the study was completed and said, “We want your help to work on the paper.” The initial paper was written at Merck, and then it was sent to me for editing.

Merck collected detailed information about the prescribing habits of participating physicians, including the numbers of prescriptions written for Vioxx versus those written for a competing drug during the portion of the ADVANTAGE trial that took place after approval of Vioxx (21) (Figure 3). Merck summarized changes in prescribing habits that it believed to have occurred as a result of ADVANTAGE (17) (Figure 1):

An analysis performed at 6 months post launch demonstrated a significantly higher level of prescribing for

Figure 3. Merck document tracking the average number of new prescriptions written by rheumatologists who were ADVANTAGE study group investigators.

RHU ADVANTAGE INVESTIGATOR NRX AVG								
Arth CR	JUNE	JULY	AUGUST	SEPTEMBER	JUNE	JULY	AUGUST	SEPTEMBER
9907	VIOXX	VIOXX	VIOXX	VIOXX	CELEBREX	CELEBREX	CELEBREX	CELEBREX
A+	5	10	10	9	15	13	13	12
A	19	27	26	26	39	33	35	33
A-	2	4	6	5	6	5	8	6
B	1	3	2	3	4	6	6	5
C	0	3	2	2	2	5	3	1
D	1	2	1	1	0	2	2	0
Given Meded's RHU								
(316 records)								

Merck tracked new prescriptions written for both Vioxx and Celebrex (celecoxib; Pfizer, New York, New York) by ADVANTAGE investigators in the months after the trial. Investigators were given a portfolio profile grade of A+ to D on the basis of their prescription history of using Merck products. Arth CR = Arthritis Clinical Report no. 9907; AVG = average; Meded = medical education branch of the Institute for Internal Research; NRX = new prescriptions; RHU = rheumatologists.

VIOXX among primary care ADVANTAGE investigators compared to a control group of VIOXX 99 prescribers [primary care physicians not chosen to participate in ADVANTAGE].

Merck and its public relations corporation, Ogilvy, trained ADVANTAGE investigators for interaction with the media after the trial results were published. Investigators were given an information package that included a “sample pitch letter” (22):

Marketing Communications package: To help local physicians market their involvement with the trial as well as their expertise in the field, we would design an ADVANTAGE communications kit to be distributed to all investigators involved in the trial.

Merck emphasized the importance of having all aspects of their marketing program ready when the FDA approved Vioxx in order to help accomplish objective “AAA,” or “Announce ADVANTAGE at Approval” (22).

Purpose of Trial Hidden from Participants, Investigators, and Institutional Review Board Members

Although ADVANTAGE was called a seeding trial in many internal documents (22, 23), the marketing objectives of the trial were not described on the informed consent form (16). Charlotte McKines, Executive Director of Marketing Communications at Merck, and Louis Sherwood, Senior Vice President for Medical and Scientific Affairs, focused on primary care physicians as the target customer group and nominated the marketing personnel in charge of ADVANTAGE for the “Best Physician Program Award” in an internal memo (17) (Figure 1):

The objectives were to provide [a] product trial among a key physician group to accelerate uptake of VIOXX as the

second entrant in a highly competitive new class and gather data important to this customer group.

Similarly, Merck did not refer to the marketing objectives of the trial in submissions to the FDA. The Merck clinical study report describing the trial stated the primary objective of ADVANTAGE: “To compare the gastrointestinal (GI) tolerability of rofecoxib 25 mg q.d. and naproxen 500 mg b.i.d. in the treatment of osteoarthritis (OA) during a 12-week treatment period” (16).

However, Pharmaceutical Product Development, a contract research organization that assisted with the trial, was briefed by Merck’s public affairs department in a slide presentation before the launch of ADVANTAGE. Separate bullet points described the “market dynamics [and] highly competitive situation” surrounding the ADVANTAGE trial and the “importance of investigators as key customers of Merck” (18). Merck officials were careful about references to the seeding objectives of the trial. In an e-mail to Kyra Lindemann and others in the division, Rebecca Higbee, an employee in the Merck marketing division, attempted to convince others to avoid using this term in describing ADVANTAGE: “It may be a seeding study, but let’s not call it that in our internal documents” (22).

Systematic Review

Our systematic review identified 6 publications about seeding trials and their conduct (Table): 4 were editorials or commentaries, 2 discussed seeding trials within the context of the discussion of original research, and none directly referenced internal industry documents. In 1993, Stephens (5) characterized seeding trials as 1 of several theoretical marketing tactics used by pharmaceutical companies in postmarketing surveillance studies. Fretheim and Oxman (24) examined whether differences in prescribing patterns between the United Kingdom and Norway were caused in

Table. Scholarly Articles about Seeding Trials

Study, Year (Reference)	Article Type	Summary
Kessler et al., 1994 (3)	Editorial	Described promotional tactics, including seeding trials, used by drug companies. Adequate and well-controlled trials are the hallmark of the FDA’s drug approval process, and inappropriate promotional efforts, such as seeding trials, undermine the FDA’s standards.
Andersen et al., 2006 (4)	Observational cohort	Although participation in company-sponsored studies did not affect physicians’ adherence to international treatment guidelines, use of the sponsoring companies’ drugs increased.
Stephens, 2003 (5)	Editorial	Described marketing properties of postmarketing surveillance studies and pointed out factors that could be used to identify seeding studies.
Fretheim and Oxman, 2005 (24)	Cross-sectional survey	Considerable prescribing variation exists between the United Kingdom and Norway, perhaps caused in part by the promotion of less expensive drugs by pharmaceutical advisors in the United Kingdom and the presence of seeding trials of more expensive drugs in Norway.
Psaty and Rennie, 2006 (25)	Editorial	A brief review of the history of seeding trials and their evolving sophistication. The authors advocate for well-designed, large, long-term clinical trials as opposed to small, short-term, seeding studies.
Greenland and Lloyd-Jones, 2008 (26)	Editorial	Cautioned that marketing studies should not be conducted. Examined the ENHANCE trial as a possible marketing study.

ENHANCE = Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery; FDA = U.S. Food and Drug Administration.

part by the presence of publicly funded pharmaceutical advisors in the United Kingdom as opposed to increased use of seeding trials in Norway. On the basis of communication with academic physicians, drug regulatory agencies, and medical directors of drug companies in these countries, they hypothesized that promotion of less expensive drugs by pharmaceutical advisors in the United Kingdom and the prevalence of seeding trials in Norway could help explain this disparity, although they did not provide documentary evidence. Psaty and Rennie (25) described a randomized, open-label trial of asthma medication (also a seeding trial) that used Danish national health care prescribing data (4), and represented an improvement over the nonrandomized trials described earlier by Kessler and colleagues (3). More recently, when commenting on the ENHANCE (Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery) trial, Greenland and Lloyd-Jones (26) wrote that, "Trials designed for marketing purposes should not be conducted." They raised the concern that ENHANCE may have been a seeding trial for 3 primary reasons: The trial started at approximately the same time that the FDA approved ezetimibe; it was not conducted to earn a new drug indication with the FDA; and initial reporting of results of the trial occurred almost 2 years after the trial was completed, reinforcing the lack of scientific significance. In summary, these articles call attention to the practice of seeding trials, although they do not provide documentary evidence of the existence of seeding trials.

DISCUSSION

Merck conducted a seeding trial to promote the prescription of Vioxx. The trial coincided with the FDA's approval and the availability of the product on the market in 1999. Although billed as a gastrointestinal safety study, ADVANTAGE was actually a sophisticated marketing tool designed to allow optimal "seeding" of positive experiences with Vioxx among customers—primary care physicians—before its approval. As a result, 5557 participants received Vioxx and 600 investigators prescribed it just before it became available on the market, which generated positive publicity and anecdotes from physicians and patients (7, 22). Sales of Vioxx could then benefit from a "2-step flow" of media influence, with Merck's marketing enlisting ADVANTAGE investigators as advocates who in turn influenced many other physicians and patients (27).

To our knowledge, the confidential internal communications we examined provide the first strong documentary evidence of how a pharmaceutical company framed a marketing effort as a clinical trial. The ADVANTAGE trial was a seeding trial that was published in a major medical journal (7). Although seeding trials may have some positive aspects, such as education of community physicians and early access to medications for patients, the undisclosed use of research by corporate marketing divisions threatens the

integrity of the relationship of industry, academia, patients, and society.

At least 3 elements of seeding trials are harmful to science and society. First, full informed consent is not possible without disclosing the full purpose of the trial. Physicians and patients participating in ADVANTAGE were informed of the scientific objectives of the study, but the research protocol and informed consent templates indicate that they were not told about the key role of Merck's marketing division in the trial or the true purpose of the trial (16). Second, good research practice is at risk when the marketing division designs and conducts a study. In a seeding trial, in order to fulfill strong marketing objectives, the recruitment of several research sites with fewer patients per site may result in less quality control from investigators and use of sites that have less research experience than academic centers or community physicians' offices, which may be more accustomed to hosting clinical trials. Quality control and rigorous research conduct may not receive adequate attention when marketing is the primary purpose of the study. Third, the study may have little scientific merit. Around the same time as ADVANTAGE, Merck launched the VIGOR (Vioxx Gastrointestinal Outcomes Research) trial to be the definitive study of gastrointestinal toxicity (28). The FDA required Merck to conduct VIGOR before putting claims of improved gastrointestinal safety on the Vioxx label. Thus, the purpose of ADVANTAGE was neither to seek a new indication nor to perform postmarketing surveillance.

Failure to disclose the primary purpose of a trial has ethical ramifications for patients, physicians, and the design of clinical trials. Seeding trials like ADVANTAGE, in which the study medication has yet to receive FDA approval, may cause patient injury for marketing purposes. Such trials may provide incremental scientific benefit: ADVANTAGE affirmed the increased cardiac risk for Vioxx compared with naproxen (29), which was originally seen in the VIGOR trial (30), although the number of cardiovascular events was misreported in the original publication (31). However, the primary marketing objectives of seeding trials are hidden from the public, the medical profession, and institutional review board members, preventing them from making a fully informed decision about the balance of benefits and harms to themselves and society.

Identification of seeding trials is likely to be difficult. Without access to internal documents, the intent of pharmaceutical companies in conducting clinical trials is nearly impossible to prove. Even with access to internal documents, study intent may be hard to prove. Seeding trials are a moral offense because the sponsor does not disclose the true purpose of the trials, but there are no reliable ways to identify, prevent, or punish them. Increasing awareness of this practice is only a small, initial step toward its prevention. Nevertheless, greater transparency into the clinical trial process, including public clinical trial registration and requirements for study protocols to be included with insti-

tutional review board submissions, may help to better illuminate this practice. Physicians and patients should be fully informed of all trial objectives as part of the consent process. Laws and regulations may be necessary to promote the disclosure of the true intent of research conducted with human participants.

Our review has several limitations. First, the use of litigation documents from 1 company provides a useful perspective on the practices of the pharmaceutical industry but may not be generalizable to other companies (32). We do not know how common these practices are. Second, our search may have missed relevant documents—for example, documents demonstrating that Merck disclosed some of the marketing objectives of the study to patients, physicians, or institutional review board members. We used comprehensive search terms to minimize this possibility. Third, those who wrote or produced documents we referenced did not have an opportunity to comment on the documents or explain their context. Finally, although the documents provide insight into how Merck planned to execute ADVANTAGE, they do not describe some aspects of the planning and execution of the trial, so we cannot verify important details of what actually transpired. For example, we did not identify, despite an exhaustive and systematic search strategy, documents detailing discussions between the marketing and research divisions, nor could we identify documents describing contracts between Merck and collaborating companies. However, we identified a statement by the head of the research division indicating that he did not believe in the value of ADVANTAGE.

This study reveals key themes in the design and conduct of a seeding trial and raises questions about embedding research within marketing divisions and using research methods to achieve marketing objectives. The absence of novel study questions; the quest to engage future prescribers; the execution of the study by the marketing division of a company; and, most important, the failure to disclose the true objectives of the trial to patients, investigators, or institutional review board members is not in the best interests of patients, the profession, or society.

From McLean Hospital, Belmont, Massachusetts; Mount Sinai School of Medicine, New York, New York; Brown University, Providence, Rhode Island; and Yale University School of Medicine and Yale-New Haven Hospital, New Haven, Connecticut.

Note: All legal documents used in the article are available at <http://dida.library.ucsf.edu>.

Acknowledgment: The authors thank Leslie Curry, PhD, for her advice on our methods for review of the litigation documents and Greg Mulvey for his help in organizing the documents.

Grant Support: Dr. Hill was a Scholar in the Robert Wood Johnson Clinical Scholars Program sponsored by the Robert Wood Johnson Foundation while working on this project. Dr. Ross is currently supported by the Hartford Foundation.

Potential Financial Conflicts of Interest: All authors were compensated for participation in litigation against Merck at the request of plaintiffs.

Reproducible Research Statement: *Study protocol and statistical code:* None. *Data set:* Available at <http://dida.library.ucsf.edu>.

Requests for Single Reprints: Kevin P. Hill, MD, MHS, McLean Hospital, 115 Mill Street, Belmont, MA 02478; e-mail, kphill@partners.org.

Current author addresses and author contributions are available at www.annals.org.

References

- Weber LJ. Profits Before People?: Ethical Standards and the Marketing of Prescription Drugs. Bloomington, IN: Indiana Univ Pr; 2006:168.
- Avorn J. Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs. New York: Vintage; 2005:480.
- Kessler DA, Rose JL, Temple RJ, Schapiro R, Griffin JP. Therapeutic-class wars—drug promotion in a competitive marketplace. *N Engl J Med*. 1994;331:1350-3. [PMID: 7935706]
- Andersen M, Kragstrup J, Søndergaard J. How conducting a clinical trial affects physicians' guideline adherence and drug preferences. *JAMA*. 2006;295:2759-64. [PMID: 16788131]
- Stephens MD. Marketing aspects of company-sponsored postmarketing surveillance studies. *Drug Saf*. 2003;8:1-8. [PMID: 8471183]
- Guidelines on postmarketing surveillance. Joint committee of ABPI, BMA, CSM, and RCGP. *Br Med J (Clin Res Ed)*. 1988;296:399-400. [PMID: 3125920]
- Lisse JR, Perlman M, Johansson G, Shoemaker JR, Schechtman J, Skalky CS, et al. ADVANTAGE Study Group. Gastrointestinal tolerability and effectiveness of rofecoxib versus naproxen in the treatment of osteoarthritis: a randomized, controlled trial. *Ann Intern Med*. 2003;139:539-46. [PMID: 14530224]
- Glaser B, Strauss A. *The Discovery of Grounded Theory: Strategies for Qualitative Research*. Chicago: Aldine; 1967.
- Miles MB, Huberman AM. *Qualitative Data Analysis: An Expanded Sourcebook*. 2nd ed. Thousand Oaks, CA: Sage; 1997.
- Anderson SJ, Dewhirst T, Ling PM. Every document and picture tells a story: using internal corporate document reviews, semiotics, and content analysis to assess tobacco advertising. *Tob Control*. 2006;15:254-61. [PMID: 16728758]
- Wayne GF, Connolly GN. How cigarette design can affect youth initiation into smoking: Camel cigarettes 1983-93. *Tob Control*. 2002;11 Suppl 1:132-9. [PMID: 11893812]
- Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin: an analysis of internal industry documents. *Ann Intern Med*. 2006;145:284-93. [PMID: 16908919]
- Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA*. 2008;299:1800-12. [PMID: 18413874]
- Yarbrough C. E-mail to Dixon M, Geba G. ADVANTAGE presentation. 14 July 1999. Bates Nos. MRK-AGV0131386 to MRK-AGV0131401. Accessed at <http://dida.library.ucsf.edu/tid/vio28x10> on 17 June 2008.
- Proceedings of the ADVANTAGE Study Investigators Meeting, Los Angeles, California, 25 March 1999. Bates Nos. MRK-APU0025051 to MRK-APU0025303. Accessed at <http://dida.library.ucsf.edu/tid/vio29x10> on 17 June 2008.
- Merck Clinical Study Report. Assessment of Differences Between Vioxx and Naproxen to Ascertain Gastrointestinal Tolerability and Effectiveness (ADVANTAGE). 29 March 2001. Bates Nos. MRK-NJ0221292 to MRK-NJ0221423. Accessed at <http://dida.library.ucsf.edu/tid/vio20x10> on 17 June 2008.
- McKines C, Sherwood L. Memo to Merck Marketing. Best Physician Program Award. 4 January 1999. Bates No. MRK-ACJ0000495. Accessed at <http://dida.library.ucsf.edu/tid/vio21x10> on 17 June 2008.
- Weiner J. Merck Marketing PowerPoint on the ADVANTAGE Trial. 16 March 1999. Bates No. MRK-ADI0017766 to MRK-ADI0017776. Accessed at <http://dida.library.ucsf.edu/tid/vio24x10> on 17 June 2008.

19. **Scolnick E.** E-mail to Greene D. ADVANTAGE CV events tables. 7 April 2001. Bates No. MRK-ACR0009150. Accessed at <http://dida.library.ucsf.edu/tid/vio22x10> on 17 June 2008.
20. **Berenson A.** Evidence in Vioxx suits shows intervention by Merck officials. *New York Times*. 24 April 2005; A1.
21. **Poucket J.** E-mail to Yarbrough C. ADVANTAGE Investigators. 30 November 1999. Bates No. MRK-ACX0002964 to MRK-ACX0002968. Accessed at <http://dida.library.ucsf.edu/tid/vio23x10> on 17 June 2008.
22. **Higbee R.** E-mail to Lindemann K, Fanelle C, and Weiner J. ADVANTAGE ideas. 19 March 1999. Bates No. MRK-ADI0024344 to MRK-ADI0024346. Accessed at <http://dida.library.ucsf.edu/tid/vio26x10> on 17 June 2008.
23. **Webb J.** Communication to Smith B. Vioxx Seeding Study Selection. Bates No. MRK-AFB0001598. Accessed at <http://dida.library.ucsf.edu/tid/vio27x10> on 17 June 2008.
24. **Fretheim A, Oxman AD.** International variation in prescribing antihypertensive drugs: its extent and possible explanations. *BMC Health Serv Res*. 2005;5:21. [PMID: 15762983]
25. **Psaty BM, Rennie D.** Clinical trial investigators and their prescribing patterns: another dimension to the relationship between physician investigators and the pharmaceutical industry [Editorial]. *JAMA*. 2006;295:2787-90. [PMID: 16788134]
26. **Greenland P, Lloyd-Jones D.** Critical lessons from the ENHANCE trial. *JAMA*. 2008;299:953-5. [PMID: 18314439]
27. **Gladwell M.** *The Tipping Point: How Little Things Can Make a Big Difference*. Boston: Little, Brown; 2000:279.
28. **Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, et al. VIGOR Study Group.** Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med*. 2000;343:1520-8, 2 p following 1528. [PMID: 11087881]
29. **Braunstein N, Polis A.** Report of specific cardiovascular outcomes of the ADVANTAGE trial [Letter]. *Ann Intern Med*. 2005;143:158-9. [PMID: 15968005]
30. **Krumholz HM, Ross JS, Presler AH, Egilman DS.** What have we learnt from Vioxx? *BMJ*. 2007;334:120-3. [PMID: 17235089]
31. **Egilman DS, Presler AH.** Report of specific cardiovascular outcomes of the ADVANTAGE trial [Letter]. *Ann Intern Med*. 2006;144:781. [PMID: 16702599]
32. **Kesselheim AS, Avorn J.** The role of litigation in defining drug risks. *JAMA*. 2007;297:308-11. [PMID: 17227983]

READERS' COMMENTS

Readers wishing to comment on published articles should use the "Send comment/rapid response letter" option at www.annals.org. While this service is free to *Annals* subscribers, readers without subscriptions who wish to comment on articles may purchase temporary access.

Current Author Addresses: Dr. Hill: McLean Hospital, 115 Mill Street, Belmont, MA 02478.

Dr. Ross: Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY 10029.

Dr. Egilman: 8 North Main Street, Attleboro, MA 02703.

Dr. Krumholz: Yale School of Medicine, 333 Cedar Street, I-456, SHM, New Haven, CT 06510.

Author Contributions: Conception and design: K.P. Hill, J.S. Ross, D.S. Egilman, H.M. Krumholz.

Analysis and interpretation of the data: K.P. Hill, J.S. Ross, D.S. Egilman, H.M. Krumholz.

Drafting of the article: K.P. Hill.

Critical revision of the article for important intellectual content: K.P. Hill, J.S. Ross, D.S. Egilman, H.M. Krumholz.

Final approval of the article: K.P. Hill, J.S. Ross, D.S. Egilman, H.M. Krumholz.

Provision of study materials or patients: K.P. Hill, D.S. Egilman.

Administrative, technical, or logistic support: K.P. Hill.

Collection and assembly of data: K.P. Hill, D.S. Egilman.