

Physician Participation in Market Support Clinical Studies and Subsequent Prescribing Behavior

Harold E. Glass

ABSTRACT. This paper examines how physician participation in a market support clinical trial (i.e., Phase IIIb and IV) influences subsequent prescribing behavior. The study used a random matched sample of 1,876 physicians, half of whom had functioned as principal investigators in outpatient market support clinical trials and half of whom had not. The study found a stronger relationship in Phase IIIb studies than in Phase IV studies between participation in clinical trials and increased study drug prescribing and established no relationship between trial participation and additional sponsor company prescribing for other, nonstudy drugs. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2003 by The Haworth Press, Inc. All rights reserved.]*

Harold E. Glass, Ph.D., M.Sc.(Econ), is Director, Graduate Business Program, University of the Sciences in Philadelphia, and Senior Research Fellow, Centre for Evidence Based Policy, Queen Mary, University of London.

Address correspondence to Dr. Glass at University of the Sciences, 600 South 43rd Street, Philadelphia, PA 19104-4495 (E-mail: h.glass@usip.edu).

Journal of Pharmaceutical Marketing & Management, Vol. 15(4) 2003

<http://www.haworthpress.com/store/product.asp?sku=J058>

© 2003 by The Haworth Press, Inc. All rights reserved.

Digital Object Identifier: 10.1300/J058v15n04_02

KEYWORDS. Clinical trials, clinical investigators, prescribing, Phase IIIb, Phase IV

INTRODUCTION

Clinical trials play a number of functions in the pharmaceutical industry. Phase I-IIIa clinical trials are critical because they help secure regulatory approval for new drugs and add to general medical knowledge. The published results from these clinical studies are important in the diffusion of innovation, as key results relating to a new drug's safety and efficacy appear in scholarly journals and are presented at professional meetings. However, market support clinical studies (Phase IIIb and Phase IV) may also be an integral component in a new or existing product's success in the marketplace. Sometimes these market support studies are designed to show no more than that the study drug has a comparable efficacy, safety, or cost-effectiveness profile to other important drugs or therapies. Market support studies are often designed, though, to test whether the drug profiles of a specific drug (or compound in Phase IIIb) provide competitive marketing advantages for that study drug. In addition, these studies may provide physicians with exposure to the drug, enabling participating physicians to obtain a better understanding of how the study drug works in their specific practice and with their particular patients.

Scant quantitative research exists on how physician participation in market support studies influences subsequent prescribing behavior. This case and control study of 1,846 physicians raises questions about the prescribing gain obtained from Phase IV study physicians, but points to the significant relationship between a physician's participation in Phase IIIb studies and that physician's ensuing prescribing of the study drug. The value of understanding the prescribing behavior of these clinical trial physicians goes beyond the number of incremental prescriptions these physicians may write or the scientific papers they may publish. Many of these physicians, as peer opinion leaders, may play important roles in influencing the day-to-day prescribing patterns of other physicians who have not participated in the clinical trials.

THE ROLE OF THE PEER OPINION LEADER

For over 50 years, the literature has pointed to the function that medical peers play in influencing how physicians prescribe drugs. In the

early 1950s, the pivotal study of the diffusion of a new antibiotic described in the literature by the pseudonym “Gammanym” showed that peers were the most important factor in getting other physicians to prescribe Gammanym (1). The physicians who first prescribed Gammanym were, among other attributes, considered opinion leaders by their peers. What these peer opinion leaders thought about the drug proved to have a great influence on the willingness of other physicians to prescribe that drug. These peer opinion leaders were not internationally recognized experts, but rather practicing physicians whose opinions were valued by other practicing physicians.

Other studies show that, despite physicians’ perceptions, academic sources of information about new drugs are of limited importance in their prescribing behaviors (2-4). The study reported that physicians obtained much of their information about new drugs from senior colleagues practicing in comparable situations. Other studies have demonstrated the limited value physicians place on pharmaceutical marketing and continuing medical education (CME) as sources of information. For example Lexchin reviewed 36 published papers and concluded that “physicians do not have a very high opinion of the information from detailers or of company sponsored CME events” (5). More recent studies have asserted that pharmaceutical information sources, such as detailer and CME programs, may have a greater influence on actual prescribing behavior than many physicians wish to acknowledge. However, medical colleagues remain a vital information source in the decision to prescribe a drug (6, 7).

Clinical research physicians (hereafter referred to as investigators or trialists) may be important sources of information about new drugs entering the market or existing drugs already on the market. An analysis of U.S. investigator profiles shows that investigators are often older, more educated, and more medically experienced than other physicians who have not participated in clinical trials. The majority of these investigators are actively engaged in treating patients, with nearly three-fourths being office based. Only a minority are found at academic medical centers or are otherwise primarily engaged in research or teaching (8, 9).

What investigators think about a drug may be of particular importance in how other physicians evaluate and ultimately prescribe that same drug. While few of these investigators may have their names appear on journal articles or present study results at medical conferences, how an investigator subsequently prescribes a drug that he or she has tested in a market support study may be an important indicator of that

investigator's experience with the study drug and indicate how he or she may describe that drug to other physicians.

Few papers have measured how participation in clinical trials of any type may affect study drug prescribing. In one such case, a Dutch study determined that of the 53 semi-innovative drugs registered in the Netherlands over the course of the study, only 7 were studied in Phase II or III clinical trials at the specific hospital in question. All 7 of the drugs were later adopted into prescribing routines, whereas only 14 of the remaining 46 were adopted (10). Another study noted that the use of lansoprazole was higher in a teaching hospital that had undertaken clinical trials of lansoprazole (11). These papers referred to earlier phase studies used in the new drug development and approval process.

Even less empirical literature appears to exist about physician participation in market support clinical trials and subsequent investigator prescribing behavior. It seems more an article of faith than empirical analysis that investigator participation in market support studies influences subsequent prescribing behavior.

Given the absence of data about how individual physicians' prescribing behavior is influenced by participation in market support clinical trials, this analysis sought to answer to the following questions:

- What effect, if any, does physicians' involvement in market support clinical studies have on their subsequent prescribing behavior of the study drug?
- What effect, if any, does physicians' involvement in market support clinical studies have on their prescribing behavior for other drugs from the clinical trial sponsor pharmaceutical company?
- Are there differences in prescribing behavior for late Phase IIIb market support studies and Phase IV market support studies?

METHODS

Phase IIIb and Phase IV Clinical Trials

Phase IIIb studies are typically initiated before the sponsor pharmaceutical company receives approval from the appropriate regulatory body to market the study drug. These studies are performed to support the general marketing and product launch program of the new drug to improve the drug's success in the marketplace. Because the study is conducted before the regulatory approval is received for the tested com-

pound, the Phase IIIb clinical study must be designed with all the scientific rigor and emphasis on patient safety found in Phase III studies of any type. Phase IIIb study results are often not included in the original dossier submitted to the appropriate regulatory body, the Food and Drug Administration (FDA) in the case of the United States. However, the results from all Phase IIIb studies are submitted to the FDA before the final new drug approval is granted.

Phase IV clinical studies are conducted on drugs already on the market. While safety is always a major concern in any type of clinical trial, basic drug safety is not a major end point in most Phase IV studies. Because drugs in Phase IV studies are already marketed, their safety profile should be understood. Phase IV studies are more often used to examine a specific feature of a study drug's marketing profile, for example, the study drug's comparative side effects or efficacy against a major competitor.

Investigator Sample

The study constructed a case/control sample of Phase IIIb and Phase IV investigators with matching physicians who had not participated in clinical trials. The Phase IIIb sample consisted of 679 randomly drawn clinical study sites, totaling 450 unique physicians, from a pharmaceutical industry database named *Grantplan* for the purposes of this research.¹ For the years covered in this study, the database contained clinical study detail from a large portion of studies undertaken by pharmaceutical companies in the United States and Europe. Forty-six companies participated in the database, including 8 of the largest 10 companies and 26 of the largest 30 companies. Participating pharmaceutical companies supplied *Grantplan* with copies of their financial agreements with investigators (called clinical grants), along with the corresponding clinical research protocols and study detail.

An additional 488 unique physicians who had been involved as principal investigators at 534 Phase IV clinical trials sites were randomly selected from the same pharmaceutical industry database. The number of sites exceeded the number of unique investigators because an investigator could have been involved in multiple studies in both Phase IIIb and Phase IV population samples.

The clinical studies used in the analysis involved investigation of drugs for the outpatient treatment of asthma and allergic rhinitis, hypertension, osteoarthritis and rheumatoid arthritis, depression, pneumonia, hypercholesterolemia, and diabetes. Only outpatient treatments were

used in the analysis because the IMS Health database, which provided the individual physician prescribing data, relies heavily on prescribing data from retail outlets and pharmacy benefits management companies as its sources. Hospital dispensary information was not included in the study because it was often difficult to link a prescription with a particular physician. Therefore, by concentrating on outpatient indications and prescribing data, the comprehensiveness of the prescribing data for each physician appearing in the study was more certain.

Phase IIIb studies usually begin some time before drug approval, with a mean in this study of 2.1 years from the start of a Phase IIIb study until product launch for the drugs in this study. For the Phase IIIb analysis, the calendar years 1995 to 1996 were selected to provide adequate time for study completion and regulatory submission and review, as well as to provide data for 18 months of post-product launch prescribing behavior.

The calendar years 1997-1998 were selected for the Phase IV studies. In the Phase IV study sample, the drugs were already on the market, and we began to track the relevant physician behavior immediately after the study's completion. In addition, for the Phase IV investigators, three months of the physicians' pre-study drug prescribing volume was extracted from the IMS Health prescriptions database.

Control Sample

The IMS Health database contains the names and medical identification numbers of virtually all U.S. physicians in active practice and their prescribing volume by drug, by class, and by total prescriptions written. The Phase IIIb control population (450) and Phase IV controls (488) were drawn from this database. Several characteristics of each of the investigator physicians were matched with those of a control physician in the IMS Health database. These control physicians had not been involved as principal investigators in the conduct of a clinical study at their site or any other site.² The following characteristics were matched for both study samples: geographic area, AMA specialty, and pre-study prescribing behavior. This prescribing behavior data for each physician included the total number of prescriptions written, the number of prescriptions written for the study sponsor's drugs, and the number of prescriptions written in the therapeutic area of interest, and for Phase IV studies, the number of prescriptions written for the study drug three months prior to study start.³

A difference of means analysis of the prescribing levels for both the investigators and controls, by geographic and specialty variables, showed no statistically significant differences between the two samples, providing confidence that the control group selection process had, in fact, provided a matched set of physicians. For example, geographic areas were matched using United States Post Office ZIP Codes. Investigators and controls from all geographic regions in the continental United States were included, with the largest percentage of investigators coming from the South Central (19%) region, followed by the Pacific (18%), North Central (16%), South East (15%), North East (12%), Rocky Mountain (11%), and Mid-Atlantic (9%) regions. The control physician percentages were exactly comparable by region, state, and three-digit ZIP Code. We also examined differences between the two samples on demographic variables not specifically controlled for in the selection process. There were no statistically significant differences between the investigators and controls by age or gender.

There were some differences between the two samples. For example, more investigators than controls were board certified. Eighty-eight percent of the investigators were board certified compared to 78% of the control physicians. As with the overall U.S. pattern, a large majority of the investigators in this study were office based (Table 1). Compared to control physicians, there was a greater chance that the investigators selected were teachers or researchers or were located in medical schools. There was also a slightly greater likelihood that the investigators were based in nonteaching medical or research hospitals than the control physicians. Throughout the analysis, we statistically controlled for differences between the two samples in board certification and major professional activity because prescribing behavior could possibly be influenced by these factors.

Dependent Variable: Prescribing Behavior

The study dependent variable was USC share, that is, the percentage of a study drug's corresponding USC code. The Uniform System of Classification (USC) was created in 1975 by IMS Health and pharmaceutical manufacturers. It uses five digits to standardize and categorize all U.S. pharmaceuticals based on product type. The USC is used in the U.S. and Canada. In Europe, the equivalent classification is referred to as ACT. The USC has four levels of hierarchy. USC2 is the broadest category, and USC5 is the most detailed category, allowing for more specificity within a category. For example:

- USC2 Respiratory Therapy
- USC3 Bronchodilators General
- USC4 Beta Agonists
- USC5 Beta Agonists Aerosol
Beta Agonists Nebulizer Solution
Beta Agonists Oral Solid

Prescribing share percentage for an individual drug by an individual physician was measured as the percentage of the physician's prescriptions of the corresponding drug class that were represented by that physician's prescriptions of the study drug in question. For example, if a physician wrote 100 prescriptions in a given USC drug class, of which 12 prescriptions were the study drug, that physician's USC share would be 12%. In the Phase IIIb studies, USC share was tracked at 3, 6, and 18 months after the date of the drug launch as measured by the date of the first recorded prescription by IMS Health. For Phase IV studies, the 3-, 6-, and 18-month time frame began at the conclusion of the study itself. In addition, for Phase IV studies, we had the physician's USC share of the study drug three months before the investigator agreed to participate in the study. The prescribing periods for the control physicians in both Phase IIIb and Phase IV studies corresponded to the same dates as those used for the respective matching investigators.

Statistically significant differences were defined by a *p* value of 0.05 or stronger using Fisher's least significant difference method and multiple regression analyses.

RESULTS

Phase IV

Phase IV investigators prescribed more of the study drug than the control physicians at the three-month post-study point. The results are

TABLE 1. Type of Major Professional Activity. Percentage of Investigator and Control Samples.

	Hospital Based	Medical School/Teaching	Office Based	Other
Investigators	8	17	71	4
Controls	12	5	76	7

summarized in Table 2. The relevant study drug USC share at three months was statistically significantly higher for the investigators than for the matched control physicians, whereas three months before the study start, there were no statistically significant differences in study drug USC share. However, the post-study increase in Phase IV investigator prescribing behavior was fairly modest, especially when one takes into account comparable changes in the control prescribing behavior. Three months after the Phase IV study's conclusion, study drug prescribing increased among the trialists, from a pre-study USC share of 12% to 16%. From these results, it might be concluded that participation in Phase IV clinical trials has a fairly clear, if somewhat limited, impact on subsequent prescribing. However, we also examined the control group and found that control physicians' prescribing of the study drug also increased.

Control physicians' prescribing of the study drug increased from a pre-study level of 11% USC share to a 3-month post-study share of 13%. The control physician increase was nearly half that of the trialists in terms of USC share. It must be remembered that many Phase IV clinical trials are part of larger marketing efforts, involving increased study drug detailing, advertising, and related educational efforts. These other marketing efforts may have influenced the prescribing behavior of both sets of physicians. The control group increase raises the possibility that an appreciable portion of the increased prescribing among trialists is the result of considerations other than clinical trial participation. Study drug prescribing increased among *both* investigators and controls, suggesting the role of additional marketing variables in understanding the study drug prescribing behavior of the investigator physicians. There was a statistically significant difference between the investigators and

TABLE 2. USC Share by Investigator and Control Physician at 3, 6, and 18 Months for Phase IV Studies.

USC Share (%) at Time After Study Completion for Phase IV Studies					
3 Months		6 Months		18 Months	
Investigators	Controls	Investigators	Controls	Investigators	Controls
16*	13	16*	13	15**	11

*.05 level of significance

** .01 level of significance

***.001 level of significance

controls at the three-month point, but the difference was modest. Moreover, study drug prescribing levels increased from pre-study levels for both the investigators and their control physicians.

The same general relationship between the investigators and controls held over the 18-month period tracked in this study. At six months post study, investigator prescribing still exceeded that of control physicians (16% and 13%, respectively). Study drug prescribing share declined at the 18-month point among both investigators and controls, yet trialist prescribing levels continued to exceed the control group (15% and 11%, respectively). At 18 months, however, control group prescribing levels returned to pre-study levels and trialist prescribing shares remained above their pre-study levels. Because this study did not track prescribing behavior beyond the 18-month points, it was not possible to determine how long the incremental study drug prescribing continued for the investigators.

A subgroup analysis by medical indication showed no changes in the general finding, with the exception that depression showed virtually no statistically significant difference between the trialists and controls at any point covered in this analysis. A more elaborate multivariate model controlling for physician demographic variables—major professional activity, board certification, age, and gender—again provided the same general findings. There is some incremental prescribing associated with Phase IV studies, but the level is not particularly pronounced. The limited difference between the Phase IV investigators and the control physicians is made all the clearer when we contrast these data to the Phase IIIb results.

Phase IIIb

The prescribing differences between the case and control physicians were distinctly more pronounced in Phase IIIb studies than in Phase IV studies. The results are summarized in Table 3. At 3, 6, and 18 months after drug launch, investigators prescribed a notably higher USC share of the study drug than the corresponding control physicians. At 3 months, the figures were 26% and 16%, respectively. The difference between the investigators and the controls was ten USC share percentages at all three points.

The difference between investigators and controls is immediate, pronounced, and sustained for those participating in Phase IIIb trials. There is no reason to believe that trialists and control physicians are not receiving comparable levels of exposure to the sponsor company's prod-

TABLE 3. USC Share by Investigator and Control Physician at 3, 6, and 18 Months for Phase IIIb Studies.

USC Share (%) at Time After Product Launch for Phase IIIb Studies					
3 Months		6 Months		18 Months	
Investigators	Controls	Investigators	Controls	Investigators	Controls
26***	14	26***	14	25***	15

*.05 level of significance

**.01 level of significance

***.001 level of significance

uct launch marketing campaign. However, the two groups differed on one important dimension: participation in the study drug Phase IIIb clinical trials. There were no statistically significant changes when we controlled for board certification or major professional activity. Again, for all therapeutic areas except depression, investigators prescribed the Phase IIIb study drug more than controls.

Carryover to Other Sponsor Company Prescriptions

The study data provided no evidence that participation in clinical trials for one study drug carried over to incremental prescribing for other sponsor company drugs, whether the study drug was in a Phase IIIb or a Phase IV clinical trial. The IMS Health database provided a total company prescribing share variable. This variable measured the share of a physician's total prescribing represented by all prescriptions that a physician wrote for the sponsor company's products other than the study drug. This variable measured the extent to which a physician was a high prescriber of a sponsor company's other, nonstudy drugs.

Investigators in this study were no more likely to prescribe other sponsor products after completing the clinical study than were the controls. While there were incremental study drug prescriptions associated with participation in a market support clinical trial, especially for Phase IIIb studies, the data did not indicate that there was a carryover to other sponsor company products. There were no statistically significant differences between the trialists and the controls in total company market share at the 3-, 6-, or 18-month points. There may be a subset of investigators where participation in a clinical trial by a given sponsor company carries over to incremental prescribing by the investigators of other

drugs from that sponsor. Further analysis may be warranted. Trialists as a group, though, were no more or less likely than control physicians to prescribe the study sponsor company's other drugs at any point measured in this study.

The Responsive Prescriber

Among the trialists, some may be more likely than others to show increased USC share of the study drug. A preliminary analysis of the study data indicated, for instance, that trialists who had done multiple clinical studies for a given sponsoring pharmaceutical company were more likely to prescribe the study drug at the 3-, 6-, and 18-month points. For each study completed with a given sponsor company by an investigator, that investigator's study drug prescribing increased by three USC share or percentage points. These repeat trialists may have developed a loyalty to the specific sponsor company based on greater confidence in the sponsor's approach to clinical studies. The data do suggest that the more an investigator participates in a company's clinical trials, the more likely that physician is to prescribe the study drug once the study is completed. Increased understanding of the responsive investigator profile represents an important area for further analysis.

Other Factors

Other factors may explain some of the patterns found in post-study drug prescribing. For example, all investigators received a financial grant for conducting a clinical study at their site. In addition, not all physicians were paid the same amount to conduct the same trial at their specific site. If the existence of grant payments explained post-study prescribing, one could reasonably expect that the higher the relative grant amount contracted with the investigator, the higher the subsequent USC share for the study drug would be. Our grant database provides the details of how much each investigator was paid in absolute terms and relative to other, comparable studies.⁴ An analysis of these grant data did not show that investigators receiving higher grant payments were more likely to prescribe the study drug at any of the time points covered in the study.

DISCUSSION

Market support clinical studies are important components of a pharmaceutical company's marketing mix. The role of published scientific

results in influencing physicians' prescribing behavior has been the subject of extensive research, with some observers questioning and some emphasizing the direct value of these published studies. Market support clinical research results are considered important by many pharmaceutical marketing professionals and such studies will most likely continue to be conducted to provide scientific information for pharmaceutical product publishing strategies.

A market support study can also be an important tool for pharmaceutical companies to provide physicians early access to the study drug. The literature points to the importance of peer opinion leaders in influencing other physicians' prescribing behavior. How investigators react to a study drug most likely projects their subsequent prescribing behavior of the drug. It is not unreasonable to assume that the volume with which investigators prescribe the study drug is related to the opinions these investigators share with others about the drug. What the investigators subsequently prescribe and what they say about the study drug may have far greater marketing ramifications than the absolute number of study drug prescriptions they write, particularly in Phase IIIb trials, where the role of peer opinion leaders in new product innovation is more pronounced.

These results raise another question about the role of market support studies and their relationship to "seeding" studies, that is, studies supposedly used to seed the market with users. These study results would seem to indicate that the research component of market support studies is clearly more important than any seeding element might be. The incremental prescribing return from Phase IV studies is minimal. The incremental sales value of these studies is less related to an incremental increase in prescriptions from the study investigators than to the opinion-leader role these investigators might play in published studies and interactions with colleagues.

Little empirical research has been done to assess the added sales from the incremental prescribing of market support investigators or to separate out what role clinical trials themselves have in explaining that subsequent prescribing. In the absence of other empirical literature, this study raises questions about the incremental prescribing utility of Phase IV trials and highlights the broader value of Phase IIIb trials to the pharmaceutical marketer.

RECEIVED: August 28, 2002

REVIEWED: January 3, 2003

REVISED AND ACCEPTED: May 21, 2003

NOTES

1. For more details about the size, structure, and composition of the *Grantplan* database, see: Glass HE. Higher payments don't speed study completion. *Appl Clin Trials*. 1995; 4(Nov):40-4.

2. All investigator physicians appeared on one or more clinical grants in *Grantplan*. Control physicians' names did not appear anywhere in the database. The FDA maintains a comprehensive list of 1572 forms, which give the names of physicians who conduct IND studies at their sites. None of the control physicians' names or medical education numbers appeared in any 1572 listing, dating back to 1990.

3. This date is defined as the date on the clinical grant agreement between the investigator and the sponsor pharmaceutical company.

4. For each investigator in *Grantplan* we had a copy of the clinical grant indicating the date at which the investigator's participation in the study began, plus the details of the grant payment to that investigator for participating in the clinical trial.

REFERENCES

1. Coleman J, Katz E, Menzel H. The diffusion of an innovation among physicians. *Sociometry*. 1957; 20:253-70.
2. McKinney WP, Schiedermayer DL, Lurie N, Simpson DE, Goodman JL, Rich EC. Attitudes of internal medicine faculty and residents toward professional interactions with pharmaceutical sales representatives. *JAMA*. 1990; 264:1693-7.
3. Lichstein PR, Turner RC, O'Brien K. Impact of pharmaceutical company representatives on internal medicine residency programs. A survey of residency program directors. *Arch Intern Med*. 1992; 152:1009-13.
4. Wazanna A. Physicians and the pharmaceutical industry: Is a gift ever just a gift? *JAMA*. 2000; 283:373-80.
5. Lexchin J. Interactions between physicians and the pharmaceutical industry: What does the literature say? *CMAJ*. 1993; 149:1401-7.
6. Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *Am J Med*. 1982; 73:4-8.
7. Guldal D, Semin S. The influences of drug companies' advertising programs on physicians. *Int J Health Serv*. 2000; 30:585-95.
8. Glass HE. Why investigators take part in clinical trials. *Appl Clin Trials*. 2000; 9(Jun):46-54.
9. Hovde M, Seskin R. Selecting U.S. clinical investigators. *Appl Clin Trials*. 1997; 6(Feb):34-42.
10. Denig P, Haaijer-Ruskamp FM, Wesseling H, Versluis A. Impact of clinical trials on the adoption of new drugs within a university hospital. *Eur J Clin Pharmacol*. 1991; 41:325-8.
11. Jones MI, Greenfield SM, Jowett S, et al. Proton pump inhibitors: A study of GPs' prescribing. *Fam Pract*. 2001; 18:333-8.