

# Patterns in Prescribing Behavior: The Potential Hidden Costs of Using CROs

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*Given the important role of contract research organizations (CROs) in conducting market support clinical trials, this analysis sought to answer the question of whether clinical investigators who participate in CRO-run market support studies subsequently prescribe the study drug differently than investigators in studies directly managed by sponsor companies. The phase 3b sample of investigator cases consisted of 679 randomly drawn clinical study sites, totaling 450 unique physicians. An additional*

*488 unique physicians, who had been involved as principle investigators at 534 phase 4 clinical trials sites, were randomly selected. Approximately 75% of the investigators came from sponsor company-run clinical trials, with the remaining 25% from CRO-run clinical trials. An analysis of covariance indicates that investigators in sponsor company-run clinical trials subsequently prescribe significantly more of the study drug, particularly in phase 3b trials.*

## Key Words

CRO; Clinical trials; Marketing; Investigator prescribing; Outsourcing

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## INTRODUCTION

Clinical trials perform a number of roles in the pharmaceutical industry and CROs play a significant function in conducting these studies for sponsor pharmaceutical companies. Phase 1–3a clinical trials are vital components in dossiers filed with the U.S. Food and Drug Administration (FDA) to secure regulatory approval for new drugs. In addition, the results from these studies add to the general medical knowledge base, as key results relating to a new drug's safety and efficacy appear in scholarly journals, and are presented at professional meetings.

Market support clinical studies, that is, phase 3b and phase 4, often provide information to the medical community on new and marketed drugs, and may be an integral component of 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 3b) provide competitive marketing advantages for that study drug. In addition, these studies can provide physicians with new or

added exposure to the study drug, enabling participating physicians to obtain a better understanding of how the study drug works in their specific practice and with their particular patients. Market support studies may provide evidence for a competitive marketing advantage, and equally importantly, allow physicians a controlled experience with the new medication.

A case and control study of 1846 physicians, half of whom participated in market support studies as principle investigators and half of whom had not participated in clinical trials, identified the incremental prescribing gain of the study drug among clinical investigators participating in market support clinical trials of that study drug, when compared to the control group of similar physicians who had not participated in clinical trials for the five-year period preceding the time frame of this study (1). In general physicians participating in either phase 3b or 4 clinical trials were more likely to prescribe the study drug once it came to market, in the case of the 3b compounds, or after the study was completed, in the case of phase 4 studies. However, the difference between the investigators and the controls was far more pronounced in phase 3b studies.

The value of understanding the prescribing behavior of these market support clinical trial physicians goes beyond the number of incre-

mental prescriptions these physicians may write, or the scientific papers they may publish. Many of these physicians, as peer opinion leaders, may ultimately play important roles in influencing the day-to-day prescribing patterns of other physicians who have not participated in the clinical trials (2–7). While the absolute number of incremental prescriptions written by these investigators may not be huge, what they say to their colleagues about the study drug may be very important in terms of a product's success in the market.

A large percentage of clinical trials are conducted by CROs for sponsor pharmaceutical companies, with total spending on CROs exceeding \$5 billion (8). The use of CROs to conduct clinical trials is, if anything, probably more pronounced among market support studies. When engaged to conduct a market support clinical trial the CRO no doubt has a strong interest in completing a well-executed study in a timely and cost effective manner. Critics of CRO usage argue though that even a well-done study by a CRO may have hidden costs to the sponsor company; the linkage between the sponsor company and clinical investigator may be weakened.

The sponsor company creates a greater distance between itself and its market when CROs run the clinical study. CROs may experience high turnover in their field force. These CRO field representatives may not be as knowledgeable about the study drug as their counterparts from the sponsor company. In addition, because the CRO representatives during the course of a year may work on numerous studies for multiple sponsor companies, CRO employees cannot represent the interests of any specific sponsor with the same fervor that a sponsor company study member would. In some cases, the CRO picks many of the investigators, trains them, negotiates the clinical grant amounts and payment structure, and even issues the grant payments to the investigators. These added communications steps may serve to distance the investigator from the sponsor company. Diminished contact with the market may be a hidden cost of conducting clinical trials through CROs.

Industry observers may differ on whether the

direct costs of using CROs are different from conducting the clinical trials in house. Whatever the differences in direct expenditures between CROs and sponsor companies to conduct clinical studies, critics of CRO usage assert that there is an opportunity cost in the use of CROs. Sponsor companies can lose contact with their own physician market when CROs assume the contact with investigators in clinical trials. Given the important role of CROs in conducting market support clinical trials, this analysis addresses the issue of any hidden opportunity costs of CRO usage by measuring the difference in subsequent prescribing behavior of the study drug between investigators in CRO-run and sponsor-run market support clinical trials. Specifically, the study answers the following question: Do clinical investigators who participate in CRO-run market support studies prescribe less of the study drug than those in studies run by sponsor companies?

## METHODS

### INVESTIGATOR SAMPLE

The original study constructed a case/control sample of phase 3b and phase 4 investigators with matching physicians who have not participated in clinical trials. This analysis does not include the control group since these control physicians had not participated in clinical trials of any type for at least five years prior to the time frames covered in the analysis. Study design details and results, comparing all investigators to the control physicians, are covered elsewhere (1). This study restricts its analysis to those physicians who have participated in market support clinical trials, concentrating on differences between investigators who have participated in CRO-run market support clinical trials and investigators who have taken part in sponsor company-run trials.

The phase 3b sample of investigator cases consisted of 679 randomly drawn clinical study sites, totaling 450 unique physicians, from a pharmaceutical industry database (9). For the years covered in this study, the database contained clinical study details from a large portion of studies undertaken by pharmaceutical com-

panies in the United States and Europe. The author worked with 46 companies participating in the database, including 8 of the 10 largest companies, and 26 of the 30 largest companies. Participating pharmaceutical companies supplied copies of their financial agreements with investigators (clinical grants) along with the corresponding clinical research protocols and study details.

An additional 488 unique physicians who had been involved as principle investigators at 534 phase 4 clinical trials sites were randomly selected from the same pharmaceutical industry database. The number of sites exceeded the number of unique investigators since an investigator could have been involved in multiple studies in both phase 3b and phase 4 population samples.

CRO study investigators constitute a minority of both the phase 3b and phase 4 study groups, 26% and 25% respectively, with sponsor trial investigators representing the remaining three quarters of the investigators in both clinical phases. All of the data came directly from the sponsor pharmaceutical companies and not the CROs. In some cases where the CROs have contracted with investigators, the CROs maintain the clinical grant information themselves. Hence, there is a potential bias in the sample in that it may exclude studies where CRO influence is the very greatest, and the distance between the sponsor company and the clinical investigators the most pronounced.

The clinical studies used in the analysis involved investigation of drugs for the outpatient treatment of asthma, allergic rhinitis, hypertension, osteoarthritis and rheumatoid arthritis, depression, and pneumonia (Table 1). Only outpatient treatments were used in the analysis because the IMS Health, Inc. 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 pre-

Percentage of Clinical Sites for Each Indication

Arthritis	19
Asthma	21
Allergic rhinitis	19
Depression	8
Hypertension	19
Pneumonia	14

TABLE 1

scribing data, the comprehensiveness of the prescribing data for each physician appearing in the study was more certain. CROs constituted between 13% and 35% of each indication group.

Phase 3b studies usually begin some time before drug approval, with a mean in this study of 1.6 years from the start of a phase 3b study until product launch for the drugs in this study. For the phase 3b 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 to 1998 were selected for the phase 4 studies. In the phase 4 study sample the drugs were already on the market so the study began tracking the relevant physician behavior immediately after the study's completion. In addition, for the phase 4 investigators, three months of the physician prestudy drug prescribing volume was extracted from the IMS Health, Inc. prescriptions database.

The study design did not stratify by whether a sponsor company or CRO had conducted the study. However, a sufficient number of CRO-conducted studies were available to compare the prescribing behavior of investigators in CRO-run studies with that of investigators in sponsor company studies (Table 2). The sponsor study and CRO study investigators are strikingly similar in many descriptive dimensions:

- The nature of their practices is similar. Most are office based (73%), with the next largest group coming from medical/teaching/research schools (16%),
- They spend roughly the same percentage of time in their primary and secondary hospitals, and

TABLE 2

Investigator Demographics by Investigator Type		
	Sponsor Investigators	CRO Investigators
<b>Nature of Practice</b>		
Hospital-based	8	9
Medical/Teaching/Research	16	16
Office-based	73	73
Other	3	2
Percent time spent in a hospital	44	40
1572s filed	8	9
<b>Physician Characteristics</b>		
Average age	53	52
% board certified	91	87
% male	92	93
<b>Region</b>		
Northeast	14	12
Mid-Atlantic	8	7
Southeast	15	15
North Central	17	16
South Central	19	22
Rocky Mountain	9	8
Pacific	18	20

- They do not significantly differ by age, board certification, gender, or number of 1572s filed.

We know their FDA audit activity, and here again there are no significant differences (Table 3). A somewhat higher percentage of sponsor trial investigators have been audited by the FDA, with a higher percentage of the sponsor investigators receiving an indication for voluntary action.

This study examines a number of prescribing activities both before and after the study began, along with the drug market share six months after product launch. Sponsor and CRO investigators do differ appreciably in some of their pre-study prescribing behavior (Table 4). Sponsor study investigators prescribe a substantially higher pre-study volume of the sponsor company drugs as a percentage of all the drugs they prescribe. Sponsor company drugs of all types rep-

TABLE 3

FDA Investigator Audit Results by Type of Investigator		
	Sponsor Investigators	CRO Investigators
No audit	64	68
Audit with No Action Indicated	7	7
Audit with Voluntary Action Indicated	28	24

TABLE 4

Investigator Prestudy Prescribing Behavior by Investigator Type			
	Prestudy Prescribing Volume*	Prestudy Sponsor Company Loyalty***	Prestudy USC Share (Phase 4 only)
Sponsor Investigators	632	4.2	9.9
CRO Investigators	698	1.8	11.8

\*.05 level of significance  
 \*\*\*.001 level of significance

resent 4.2% of the total prestudy prescribing of sponsor study investigators and only 1.8% of CRO study investigators.

From these data it appears that CROs are less likely to use investigators with prestudy prescribing loyalty to the sponsor company. CRO study investigators are generally higher prescribers than sponsor study investigators, writing 698 and 632 prescriptions, respectively, for the quarter before study initiation. However, these CRO investigators are not necessarily higher prescribers of the sponsor company drugs. CRO investigators averaged a higher share of the study drug before the phase 4 study began. However, the difference is not statistically significant.

Information on how the phase 3b compounds performed once they came to market, specifically, the market share ranking reached within the first six months of the product's marketing launch, was available for each of the drugs studied. On average, the sponsor investigator drugs had a market share ranking of 2.7 and the CRO investigator drugs had a market share ranking of 3.3, not a statistically significant difference. Consequently, any subsequent differences in subsequent study drug prescribing between CRO and sponsor company investigators are probably not due to the differential performance of the clinical drugs once they reached the market.

#### DEPENDENT VARIABLE: PRESCRIBING BEHAVIOR

The study's dependent variable was Uniform System of Classification (USC) share, that is, the percentage of a study drug's corresponding USC

code. The USC was created in 1975 by IMS Health, Inc. and pharmaceutical manufacturers. It uses five digits to standardize and categorize all United States pharmaceuticals based on product type. USCs are used in the United States and Canada. In Europe, the equivalent classification is referred to as ACT. USCs have four levels of hierarchy. USC2 is the broadest category and USC5, used in this analysis, 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 a specific drug by an individual physician is measured as the percentage of the physician's prescriptions of the corresponding drug class that is represented by that physician's number of prescriptions for 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 3b 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, Inc. For phase 4 studies, the 3-, 6-, and 18-month time frames began at the conclusion of the study itself. In addition, for phase 4 studies, the physician's USC share of the study drug three months before the investigator agreed to participate in the study was available.

TABLE 5

Analysis of Covariance Model					
	Sum of Squares	df	Mean Square	F	Significance
<b>Main Effects</b>					
(Combined)	250246.846	9	27805.205	35.030	.000
Indications	151097.374	4	37774.343	47.589	.000
Nature of practice	12557.884	3	4185.961	5.274	.001
Was a CRO utilized?	41907.414	1	41907.414	52.796	.000
<b>Covariates</b>					
(Combined)	34169.415	2	17084.708	21.524	.000
Prestudy sponsor company loyalty	16764.111	1	16764.111	21.120	.000
Rank in drug class first year	13340.986	1	13340.986	16.807	.000
<b>Model</b>	284416.262	11	25856.024	32.574	.000
<b>Residual</b>	815187.303	1027	793.756		
<b>Total</b>	1099603.565	1038	1059.348		

## RESULTS

### STUDY DRUG PRESCRIBING

An analysis of covariance (Table 5) demonstrates that a statistically significant difference exists between CRO and sponsor company investigators in their subsequent study drug prescribing behavior, when controlling for the role that other important variables might play. Since the CRO utilization is a dichotomized variable, either a CRO or sponsor company ran the trial, the variable had one degree of freedom. With an F score of 21.524, the variable is significant at a level stronger than .001. The other main effects, indications and nature of the physician's practice, are significant at the .001 level or stronger. In addition, the two covariates, prestudy sponsor company loyalty and the rank of each drug in its respective drug class at the end of the first

year the drug was launched, are both significant at a level stronger than .001.

Phase 3b trialists show distinctly different prescribing levels of the study drug 3, 6, and 18 months after the drug launch (Table 6). Sponsor company investigators' USC share of the study drug is 29.9% at 3 months, slowly declining to 26.4% at 18 months. In contrast, the CRO investigator share begins at 10.5%, gradually climbing to 12.9% at 18 months. All of the differences are significant, even when examined separately as an analysis of covariance model for phase 3b data alone.

Phase 4 results are less impressive, but again consistent (Table 7). Study drug prescriptions represent a USC share of 10% of the sponsor investigators' drug class prescribing three months before beginning their participation in the study. The figure climbs to 13.6% at 3 months

TABLE 6

Phase 3b Study Drug Prescribing by Investigator Type			
	Study Drug USC Share 3***	Study Drug USC Share 6***	Study Drug USC Share 18***
Sponsor investigators	29.9	29.9	26.4
CRO investigators	10.5	11.9	12.9

\*\*\*.0001 or stronger level of significance

TABLE 7

Phase 4 Study Drug Prescribing by Type of Study Investigator			
	Study Drug USC Share 3*	Study Drug USC Share 6*	Study Drug USC Share 18*
Sponsor investigators	13.6	13.3	13.3
CRO investigators	10.5	8.5	9.8

\*.05 level of significance

poststudy and remains stable over the 18-month period tracked by this study. CRO study investigators started with a prestudy drug class USC share of 11.8%, but this share quickly dropped to 8.5% three months after the phase 4 study concluded. The study drug USC share did climb to 9.8% at 18 months. Again, the use of a multiple analysis of variance model did not change the statistically significant difference between the two types of study investigators. Investigators who participate in CRO-run phase 4 studies are less likely to subsequently prescribe the study drug than are investigators who participate in sponsor company-run studies.

For all of the CRO-run phase 3b and phase 4 studies we know what activities the CRO had performed, ranging from monitoring only to five activities: monitoring, investigator selection, investigator training, grant negotiation, and grant payment. Although the differences were only statistically significant at the .10 level, they were instructive. When a CRO had performed only site monitoring, the difference between the sponsor study investigators was smaller than when a CRO had performed all five functions. It would appear that the less contact the sponsor company had with the investigator in the clinical trial, the greater the distance in the marketplace between the two was.

## LIMITATIONS

The study design has several limitations:

1. The data are restricted to several outpatient indication groups. The dynamics may be different for other outpatient indications, or for inpatient studies. Similarly, the dynamics may be different for phase 3a clinical trials.
2. The poststudy time frame is restricted to 18

months after drug launch. The study presents no conclusions about time frames beyond the 18th month. The investigator dataset comes chiefly from sponsor pharmaceutical companies. It may very well be that investigators used by CROs and for whom grant data are maintained by the CROs behave differently from CROs for whom the grant data are kept by the sponsor company. It is difficult though to see why this would be the case. One could more easily hypothesize that the CRO investigators, for whom the CROs maintain the data, are likely to be even more different from sponsor company investigators since these particular CRO investigators are, if anything, more removed from sponsor company contact. It may well be that the absence of data about these CRO maintained investigators only serves to diminish the strength of the findings in this analysis, and

3. The study deals with United States data only. The United States is the only major pharmaceutical market that currently allows individual physician prescribing behavior to be tracked and sold without explicit physician approval. Most countries prohibit the selling of these data under any condition. A few allow the data to be sold with the express agreement of the physician. It is impossible at present to replicate this study outside the United States because of the absence of widespread individual level physician prescribing data.

## DISCUSSION

A market support study is an important tool for pharmaceutical companies to provide physicians with early access to the study drug. Market support clinical research results are considered essential by many pharmaceutical marketing professionals, and will most likely continue to be conducted to provide scientific information for pharmaceutical product publishing strategies. Just as critically, a market support study repre-

sents a linkage between the sponsor company and the prescribing physician.

The literature points to the importance of peer opinion leaders in influencing other physician prescribing behavior. How investigators react to a study drug most likely reflects their subsequent prescribing behavior of the drug and what they may say about that drug to colleagues. Market support studies are a mechanism for pharmaceutical companies to remain connected to their market of prescribing physicians. It appears that the use of CROs to conduct market support studies may, in some cases, increase that distance and represent an additional cost, in the form of an appreciable opportunity cost, to the pharmaceutical company. The data in this study indicate that investigators in sponsor company-run clinical trials subsequently prescribe significantly more of the study drug, particularly in phase 3b trials. This constitutes an important challenge for marketing and clinical management.

CROs will remain an integral part of the drug development process. However, the attentive sponsor company will make every effort to minimize the potential opportunity costs of using CROs. Every effort should be made to strengthen the relationship between the investigator and the sponsor company when CROs are used to conduct the studies, for example, at investigator meetings and in subsequent correspondence with the sites, or even using the sponsor

company name, rather than CRO company name, on the clinical grant.

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