Editorials

Is Academic Medicine for Sale?

In 1984 the *Journal* became the first of the major medical journals to require authors of original research articles to disclose any financial ties with companies that make products discussed in papers submitted to us.[1] We were aware that such ties were becoming fairly common, and we thought it reasonable to disclose them to readers. Although we came to this issue early, no one could have foreseen at the time just how ubiquitous and manifold such financial associations would become. The article by Keller et al.[2] in this issue of the *Journal* provides a striking example. The authors' ties with companies that make antidepressant drugs were so extensive that it would have used too much space to disclose them fully in the *Journal*. We decided merely to summarize them and to provide the details on our Web site.

Finding an editorialist to write about the article presented another problem. Our conflict-of-interest policy for editorialists, established in 1990,[3] is stricter than that for authors of original research papers. Since editorialists do not provide data, but instead selectively review the literature and offer their judgments, we require that they have no important financial ties to companies that make products related to the issues they discuss. We do not believe disclosure is enough to deal with the problem of possible bias. This policy is analogous to the requirement that judges recuse themselves from hearing cases if they have financial ties to a litigant. Just as a judge's disclosure would not be sufficiently reassuring to the other side in a court case, so we believe that a policy of caveat emptor is not enough for readers who depend on the opinion of editorialists.

But as we spoke with research psychiatrists about writing an editorial on the treatment of depression, we found very few who did not have financial ties to drug companies that make antidepressants. (Fortunately, Dr. Jan Scott, who is eminently qualified to write the editorial,[4] met our standards with respect to conflicts of interest.) The problem is by no means unique to psychiatry. We routinely encounter similar difficulties in finding editorialists in other specialties, particularly those that involve the heavy use of expensive drugs and devices.

In this editorial, I wish to discuss the extent to which academic medicine has become intertwined with the pharmaceutical and biotechnology industries, and the benefits and risks of this state of affairs. Bodenheimer, in his Health Policy Report elsewhere in this issue of the *Journal*,[5] provides a detailed view of an overlapping issue — the relations between clinical investigators and the pharmaceutical industry.

The ties between clinical researchers and industry include not only grant support, but also a host of other financial arrangements. Researchers serve as consultants to companies whose products they are studying, join advisory boards and speakers' bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings. Many also have equity interest in the companies.

Although most medical schools have guidelines to regulate financial ties between their faculty members and industry, the rules are generally quite relaxed and are likely to become even more so. For some years, Harvard Medical School prided itself on having unusually strict guidelines. For example, Harvard has prohibited researchers from having more than $20,000 worth of stock in companies whose products they are studying.[6] But now the medical school is in the process of softening its guidelines. Those reviewing the Harvard policy claim that the guidelines need to be modified to prevent the loss of star faculty members to other schools. The executive dean for academic programs was reported to say, "I'm not sure what will come of the proposal. But the impetus is to make sure our faculty has reasonable opportunities."[7]

Academic medical institutions are themselves growing increasingly beholden to industry. How can they justify rigorous conflict-of-interest policies for individual researchers when their own ties are so extensive? Some academic institutions have entered into partnerships with drug companies to set up research centers and teaching programs in which students and faculty members essentially carry out industry research. Both sides see great benefit in this arrangement. For financially struggling medical centers, it means cash. For the companies that make the drugs and devices, it means access to research talent, as well as affiliation with a prestigious "brand." The time-honored custom of drug companies' gaining entry into teaching hospitals by bestowing small gifts on house officers has reached new levels of munificence. Trainees now receive free meals and other substantial favors from drug companies virtually daily, and they are often invited to opulent dinners and other quasi-social events to hear lectures on various medical topics. All of this is done with the acquiescence of the teaching hospitals.

What is the justification for this large-scale breaching of the boundaries between academic medicine and for-profit industry? Two reasons are usually offered, one emphasized more than the other. The first is that ties to industry are necessary to facilitate technology transfer — that is, the movement of new drugs and devices from the laboratory to the marketplace. The term "technology transfer" entered the lexicon in 1980, with the passage of federal legislation, called the Bayh–Dole Act,[8] that encouraged academic in-

stitutions supported by federal grants to patent and license new products developed by their faculty members and to share royalties with the researchers. The Bayh–Dole Act is now frequently invoked to justify the ubiquitous ties between academia and industry. It is argued that the more contacts there are between academia and industry, the better it is for clinical medicine; the fact that money changes hands is considered merely the way of the world.

A second rationale, less often invoked explicitly, is simply that academic medical centers need the money. Many of the most prestigious institutions in the country are bleeding red ink as a result of the reductions in Medicare reimbursements contained in the 1997 Balanced Budget Act and the hard bargaining of other third-party payers to keep hospital costs down. Deals with drug companies can help make up for the shortfall, so that academic medical centers can continue to carry out their crucial missions of education, research, and the provision of clinical care for the sickest and neediest. Under the circumstances, it is not surprising that institutions feel justified in accepting help from any source.

I believe the claim that extensive ties between academic researchers and industry are necessary for technology transfer is greatly exaggerated, particularly with regard to clinical research. There may be some merit to the claim for basic research, but in most clinical research, including clinical trials, the "technology" is essentially already developed. Researchers are simply testing it. Furthermore, whether financial arrangements facilitate technology transfer depends crucially on what those arrangements are. Certainly grant support is constructive, if administered properly. But it is highly doubtful whether many of the other financial arrangements facilitate technology transfer or confer any other social benefit. For example, there is no conceivable social benefit in researchers' having equity interest in companies whose products they are studying. Traveling around the world to appear at industry-sponsored symposiums has much more to do with marketing than with technology transfer. Consulting arrangements may be more likely to further the development of useful products, but even this is arguable. Industry may ask clinical researchers to become consultants more to obtain their goodwill than to benefit from their expertise. The goodwill of academic researchers is a very valuable commodity for drug and device manufacturers. Finally, it is by no means necessary for technology transfer that researchers be personally rewarded. One could imagine a different system for accomplishing the same purpose. For example, income from consulting might go to a pool earmarked to support research or any other mission of the medical center.

What is wrong with the current situation? Why shouldn't clinical researchers have close ties to industry? One obvious concern is that these ties will bias research, both the kind of work that is done and the way it is reported. Researchers might undertake studies on the basis of whether they can get industry funding, not whether the studies are scientifically important. That would mean more research on drugs and devices and less designed to gain insights into the causes and mechanisms of disease. It would also skew research toward finding trivial differences between drugs, because those differences can be exploited for marketing. Of even greater concern is the possibility that financial ties may influence the outcome of research studies.

As summarized by Bodenheimer,[5] there is now considerable evidence that researchers with ties to drug companies are indeed more likely to report results that are favorable to the products of those companies than researchers without such ties. That does not conclusively prove that researchers are influenced by their financial ties to industry. Conceivably, drug companies seek out researchers who happen to be getting positive results. But I believe bias is the most likely explanation, and in either case, it is clear that the more enthusiastic researchers are, the more assured they can be of industry funding.

Many researchers profess that they are outraged by the very notion that their financial ties to industry could affect their work. They insist that, as scientists, they can remain objective, no matter what the blandishments. In short, they cannot be bought. What is at issue is not whether researchers can be "bought," in the sense of a quid pro quo. It is that close and remunerative collaboration with a company naturally creates goodwill on the part of researchers and the hope that the largesse will continue. This attitude can subtly influence scientific judgment in ways that may be difficult to discern. Can we really believe that clinical researchers are more immune to self-interest than other people?

When the boundaries between industry and academic medicine become as blurred as they now are, the business goals of industry influence the mission of the medical schools in multiple ways. In terms of education, medical students and house officers, under the constant tutelage of industry representatives, learn to rely on drugs and devices more than they probably should. As the critics of medicine so often charge, young physicians learn that for every problem, there is a pill (and a drug company representative to explain it). They also become accustomed to receiving gifts and favors from an industry that uses these courtesies to influence their continuing education. The academic medical centers, in allowing themselves to become research outposts for industry, contribute to the overemphasis on drugs and devices. Finally, there is the issue of conflicts of commitment. Faculty members who do extensive work for industry may be distracted from their commitment to the school's educational mission.

All of this is not to gainsay the importance of the spectacular advances in therapy and diagnosis made possible by new drugs and devices. Nor is it to deny the value of cooperation between academia and industry. But that cooperation should be at arm's length, with both sides maintaining their own standards and ethical norms. The incentives of the marketplace should not become woven into the fabric of academic medicine. We need to remember that for-profit businesses are pledged to increase the value of their investors' stock. That is a very different goal from the mission of medical schools.

What needs to be done — or undone? Softening its conflict-of-interest guidelines is exactly the wrong thing for Harvard Medical School to do. Instead, it should seek to encourage other institutions to adopt stronger ones. If there were general agreement among the major medical schools on uniform and rigorous rules, the concern about losing faculty to more lax schools — and the consequent race to the bottom — would end. Certain financial ties should be prohibited altogether, including equity interest and many of the writing and speaking arrangements. Rules regarding conflicts of commitment should also be enforced. It is difficult to believe that full-time faculty members can generate outside income greater than their salaries without shortchanging their institutions and students.

As Rothman urges, teaching hospitals should forbid drug-company representatives from coming into the hospital to promote their wares and offer gifts to students and house officers.[9] House officers should buy their own pizza, and hospitals should pay them enough to do so. To the argument that these gifts are too inconsequential to constitute bribes, the answer is that the drug companies are not engaging in charity. These gifts are intended to buy the goodwill of young physicians with long prescribing lives ahead of them. Similarly, academic medical centers should be wary of partnerships in which they make available their precious resources of talent and prestige to carry out research that serves primarily the interests of the companies. That is ultimately a Faustian bargain.

It is well to remember that the costs of the industry-sponsored trips, meals, gifts, conferences, and symposiums and the honorariums, consulting fees, and research grants are simply added to the prices of drugs and devices. The Clinton administration and Congress are now grappling with the serious problem of escalating drug prices in this country. In these difficult times, academic medicine depends more than ever on the public's trust and goodwill. If the public begins to perceive academic medical institutions and clinical researchers as gaining inappropriately from cozy relations with industry — relations that create conflicts of interest and contribute to rising drug prices — there will be little sympathy for their difficulties. Academic institutions and their clinical faculty members must take care not to be open to the charge that they are for sale.

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REFERENCES

1. Relman AS. Dealing with conflicts of interest. N Engl J Med 1984;310: 1182-3.
2. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000; 342:1462-70.
3. Relman AS. New "Information for Authors" — and readers. N Engl J Med 1990;323:56.
4. Scott J. Treatment of chronic depression. N Engl J Med 2000;342: 1518-20.
5. Bodenheimer T. Uneasy alliance — clinical investigators and the pharmaceutical industry. N Engl J Med 2000;342:1539-44.
6. Faculty policies on integrity in science. Cambridge, Mass.: Harvard University, February 1996.
7. Abel D. Harvard mulls easing rules on research. Boston Globe. February 10, 2000:A1.
8. University and Small Business Patent Procedures Act of 1980.
9. Rothman DJ. Medical professionalism — focusing on the real issues. N Engl J Med 2000;342:1284-6.

TREATMENT OF CHRONIC DEPRESSION

THE majority of persons who have an acute episode of a major depressive disorder will have a response to the first or second treatment tried.[1] In patients with mild or moderately severe episodes, treatment with antidepressant drugs and brief psychotherapies are equally effective; in those with severe episodes, medication is usually recommended.[2] The treatment of chronic depression is more problematic, since in 20 to 30 percent of initial episodes, there is incomplete remission after two years.[3,4] Patients with chronic depression have marked impairments in psychosocial function, poor responses to single therapies, and very high rates of use of health care resources.[3] Furthermore, even if they have a partial remission, they have a risk of relapse of 50 to 80 percent.[4]

The poor response of patients with chronic depression to treatment with antidepressant drugs alone is not fully understood, but it cannot be explained solely on the basis of inadequate dosing or the failure of patients to take their medication.[1] Psychotherapy has been advocated as an alternative. Unfortunately, a review of nine studies of psychotherapy for chronic depression that were published before 1998 revealed that in only two trials were patients appropriately randomized, and the combined sample size was only 126 subjects.[5]

Given the lack of empirical data, establishing the relative efficacy of pharmacotherapy and psychotherapy for this disorder has been difficult.[6] Nonetheless, two trends in research results are apparent. First, there is a relatively low rate of response to placebo (about

Health Policy Report

UNEASY ALLIANCE

Clinical Investigators and the Pharmaceutical Industry

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CLINICAL practice is changing rapidly. New cardiovascular drugs, antiinflammatory drugs, cancer chemotherapy, and other pharmacologic weapons are being added to physicians' therapeutic armamentarium virtually daily. Most clinical studies that bring new drugs from bench to bedside are financed by pharmaceutical companies. Many of these drug trials are rigorously designed, employing the skills of outstanding clinical researchers at leading academic institutions.

But academic medical centers are no longer the sole citadels of clinical research. The past 10 years have seen the spectacular growth of a new research model. Commercially oriented networks of contract-research organizations (CROs) and site-management organizations (SMOs) have altered the drug-trial landscape, forcing academic medical centers to rethink their participation in industry-funded drug research.

The infusion of industry dollars into an industry–investigator partnership has clearly improved clinical practice. Yet the medical literature contains many articles expressing concern about industrial funding of clinical research. Stelfox et al. found that authors whose work supported the safety of calcium-channel antagonists had a higher frequency of financial relationships with the drugs' manufacturers than authors whose work did not support the safety of these medications.[1] Davidson reported that results favoring a new therapy over a traditional one were more likely if the study was funded by the new therapy's manufacturer.[2] Cho and Bero demonstrated that articles from symposiums sponsored by a single drug company were more likely than articles without company support to have outcomes favorable to the sponsor's drugs.[3] Friedberg et al. reported that 5 percent of industry-sponsored pharmacoeconomic studies of cancer drugs reached unfavorable conclusions about the company's products, as compared with 38 percent of studies with nonprofit funding that reached similar conclusions.[4]

How much influence does industry have over the work and products of the research community? Can practicing physicians trust the information they receive about the medications they are prescribing? Does the shift from the academic to the commercial research sector give industry too much control over clinical drug trials?

In this report, I discuss some of the problems raised by pharmaceutical-industry funding of drug trials, problems that may deepen as trials are increasingly conducted by commercial organizations. I interviewed 39 participants in the process: 6 pharmaceutical executives, 12 clinical investigators, 9 people from university research offices, 2 physicians with CROs, 8 people who have studied the process of clinical drug trials, and 2 professional medical writers. Each interview consisted of standard questions plus an opportunity for the interviewees to discuss the industry–investigator relationship in a general way. Several interviewees preferred not to allow the use of their names in the article.

THE CLINICAL-DRUG-TRIAL SYSTEM

The Food and Drug Administration (FDA) requires manufacturers to show that their products pass tests of efficacy and safety.[5,6] For such drugs as antibiotics for acute infections, large populations and long time lines are seldom needed to establish efficacy and safety. With the new emphasis on prevention and treatment of chronic diseases, however, clinical drug research has changed. Many people must take antihypertensive drugs and lipid-lowering drugs for many years in order to prevent relatively few undesired clinical end points.[7] To establish the efficacy and safety of preventive products and products designed to treat chronic disease, clinical trials must be large, lengthy, and conducted at multiple centers, because a single site cannot recruit enough patients to ensure statistical validity.

The average cost of developing one new drug is estimated to be $300 million to $600 million.[8] Of the $6 billion in industry-generated money for clinical trials worldwide yearly, about $3.3 billion goes to investigators in the United States.[9] Seventy percent of the money for clinical drug trials in the United States comes from industry rather than from the National Institutes of Health (NIH).

THE SHIFT TO COMMERCIAL DRUG NETWORKS

Until recently, the pharmaceutical industry needed academic physicians to perform drug trials for three reasons: companies did not have the in-house expertise to design trials themselves, academic medical centers provided patients as subjects for trials, and companies needed the prestige of academic publications to market their products. Lately, industry's dependence on academia has weakened: industry employs top-level research physicians to design and interpret drug trials, and community physicians have become a reliable source of patients.

Moreover, pharmaceutical firms are frustrated with academic medical centers. Most medical schools and teaching hospitals require that industry–investigator agreements be approved by an office of sponsored research. Slow review of industry proposals by academic research offices and institutional review boards (which must review all trials to protect patients' safety[10]) delays the starting dates of trials. Since academic physicians have multiple responsibilities in teaching, research, and patient care, trials may proceed more slowly than the pharmaceutical firms desire. For each day's delay in gaining FDA approval of a drug, the manufacturer loses, on average, $1.3 million. Speed is paramount for pharmaceutical firms.

To expedite trials, industry is turning from academic medical centers to a growing for-profit marketplace whose key players are CROs and SMOs.[11-13] In 1991, 80 percent of industry money for clinical trials went to academic medical centers; by 1998, the figure had dropped precipitously to 40 percent.[14] Evidence suggests that the commercial sector completes trials more rapidly and more cheaply than academic medical centers.[11]

Because multicenter trials may involve hundreds of sites and investigators, few pharmaceutical manufacturers choose to manage the trials themselves. CROs, which employ physician-scientists, pharmacists, biostatisticians, and managers, offer manufacturers a menu of services. Large drug companies often create their own study designs and contract with CROs to develop a network of sites, implement the trial protocol at those sites, and send report forms to the sponsoring company, which performs the data analysis. Smaller pharmaceutical firms may hire a CRO to manage the entire trial, including study design, data analysis, and preparation of FDA applications and journal articles. Several hundred CROs compete for the drug-trial business; the largest are Quintiles Transnational and Covance.

CROs may use both academic medical centers and community physicians to recruit patients for a trial. In the community arm of drug trials, yet another intermediary has entered the picture, the SMO. CROs may subcontract with for-profit SMOs to organize networks of community physicians, ensure rapid enrollment of patients, and deliver case-report forms to the CRO. Some trials have four layers (manufacturer, CRO, SMO, and physician–investigator), a situation reminiscent of the multitiered managed-care model (employer, health maintenance organization, independent practice association, and physician). Three of the largest SMOs are Clinical Studies Limited, Hill Top Research, and Affiliated Research Centers. SMOs provide community-physician investigators with administrative support and help market investigators' services to pharmaceutical companies.[15] They have been criticized for producing data of poor quality, inadequately training investigators, and costing more than a system of independent sites unassociated with an SMO.[13,15]

Competition for drug-trial money has stiffened as hundreds of CROs, SMOs, academic medical centers, and independent nonacademic sites scramble for a larger piece of the pie. According to Gregg Fromell of Covance, a leading CRO, "academic medical centers have a bad reputation in the industry because many overpromise and underdeliver." In contrast, critics, including Dr. Sidney Wolfe of Public Citizen, view CROs and the commercial drug-trial network as handmaidens of pharmaceutical companies, concerned with the approval and marketing of drugs rather than with true science. Whereas the academic and commercial drug-trial sectors can be seen as distinct networks with conflicting cultures, they also interlock, since CROs often act as intermediaries between drug companies and academic investigators.

Several academic medical centers are fighting to regain lost market share, transforming themselves into research networks to compete with the commercial drug-trial sector.[14,16] Columbia University, Cornell University, and New York Presbyterian Hospital have created a Clinical Trials Network as a joint venture. With funding from both industry and NIH sources, the network brings together academic researchers and community-based physicians in cardiology, hepatology, neurology, and oncology. The network has instituted required training for all participants and has centralized contracting, budgeting, and reimbursement systems. The network plans to be financially self-sufficient in a few years. Director Michael Leahey says, "Our goal is to take clinical research back from for-profit companies and place it where it rightfully belongs — in networks that are partnerships between academic medicine and community practice. We are trying to formulate a real alternative to the for-profit drug-trial entrepreneurs."

In 1997 the University of Pittsburgh Medical Center Health System chartered the Pittsburgh Clinical Research Network (PCRN), a single point of contact between industry and clinical researchers in academic and community sites. PCRN provides the administrative procedures associated with clinical trials in such areas as contracting, institutional-review-board approval, and project management. Academic research expertise and a large hospital and community-practice network give PCRN resources unavailable to most commercial SMOs. PCRN's medical director, David Watkins, feels that "academic medical centers are sleeping giants that are beginning to awaken and respond to industry's needs."

Duke University and the University of Rochester are also leaders in developing academic clinical-research networks. Some academic medical centers will probably succeed in revamping their drug-trial business; others will fail.

INDUSTRY–INVESTIGATOR RELATIONSHIPS

Trial Design

A company seeking FDA approval for a product often designs a clinical trial in its research division and circulates the proposed design to recognized investigators in that field. If the company has no in-house expertise, outside investigators are asked to design the trial. In some cases, company and academic investigators form a steering committee to discuss a trial protocol. In an interview, Dr. Thierry LeJemtel, of the Albert Einstein College of Medicine Division of Cardiology, said that 20 years ago outside investigators designed the studies, but that now companies write the protocols and bring in outside investigators pro forma, with little intention of changing the study design. In-house control is more likely in the commercial sector than in the academic sector, because of the limited expertise of many community-physician investigators.

Sometimes an investigator will propose a drug trial to the drug's manufacturer. Two investigators interviewed, including Steven Cummings, professor of medicine and epidemiology at the University of California at San Francisco, found that companies' marketing departments, which often rule on studies to be conducted after a drug has received FDA approval, declined to fund clinically important studies at least partly because the results might reduce sales of the drug.

Companies may design studies likely to favor their products. Bero and Rennie, in an article worth study by all physicians, catalogue the methods companies can use to produce desired results.[17]

If a drug is tested in a healthier population (younger, with fewer coexisting conditions and with milder disease) than the population that will actually receive the drug, a trial may find that the drug relieves symptoms and creates fewer adverse effects than will actually be the case.[17] Rochon et al. found that only 2.1 percent of subjects in trials of nonsteroidal antiinflammatory drugs were 65 years of age or older, even though these drugs are more commonly used and have a higher incidence of side effects in the elderly.[18]

If a new drug is compared with an insufficient dose of a competing product, the new drug will appear more efficacious.[17] Rochon et al. concluded that trials of nonsteroidal antiinflammatory drugs always found the sponsoring company's product superior or equal to the comparison product; in 48 percent of the trials, the dose of the sponsoring company's drug was higher than that of the comparison drug.[19] According to Johansen and Gotzsche, most trials comparing fluconazole with amphotericin B used oral, not intravenous, amphotericin B, thereby favoring fluconazole, because oral amphotericin B is poorly absorbed.[20]

Clinical trials often use surrogate end points that may not correlate with more important clinical end points. Companies may study many surrogate end points and publish results only for those that favor their product.[7,17,21]

Data Analysis

A study's raw data are generally stored centrally at the company or CRO. Investigators may receive only portions of the data. Some principal investigators have the capacity to analyze all the data from a large trial, but companies prefer to retain control over this process.

A physician-executive at one company explained, "We are reluctant to provide the data tape because some investigators want to take the data beyond where the data should go." Several investigators, including Dr. LeJemtel, countered that industry control over data allows companies to "provide the spin on the data that favors them." In the commercial sector, where most investigators are more concerned with reimbursement than with authorship, industry can easily control clinical-trial data.

Publishing the Results

For academic investigators, publication in peer-reviewed journals is the coin of the realm. For pharmaceutical firms, in contrast, the essential product is the new-drug application to the FDA. In the absence of FDA approval, no journal article is worth a cent to a drug company. Yet publication in prestigious journals is important, to persuade physicians to prescribe the company's products.

Some multicenter trials have publication committees, which may be dominated by in-house or outside investigators, that write up the results for publication. In other cases, the company or CRO writes the reports for publication, circulating draft manuscripts to the investigators who will be listed as authors. Authorship may be determined by such criteria as who participated in designing the study, who enrolled the most patients, and who has a prominent name in the field.

Control over Publication

Many academic medical centers review contracts between industry and investigators, insisting on the investigator's right to publish the trial's results and allowing the company prepublication review, with a time limit of 60 to 90 days. Nikki Zapol, head of the sponsored-research office of Massachusetts General Hospital, estimates that 30 to 50 percent of contracts submitted by companies have unacceptable publication clauses that must be renegotiated.

In a survey of life-science faculty members, 27 percent of those with industry funding experienced delays of more than six months in the publication of their study results.[22] Chalmers argues that the results of substantial numbers of clinical trials are never published at all.[23]

In 1996, Canadian investigator Nancy Olivieri and colleagues found that deferiprone, used to treat thal-

assemia major, could worsen hepatic fibrosis. Apotex, the sponsoring company, threatened legal action if Olivieri published the findings. The contract between Apotex and Olivieri forbade disclosure of results for three years after the study without the company's consent. An article was eventually published.[24,25]

In 1987, the manufacturer of Synthroid (levothyroxine) contracted with University of California researcher Betty Dong to study whether Synthroid was more effective than competing thyroid preparations. In 1990, Dong found Synthroid to be no more effective than other preparations, including generic preparations. The sponsoring company refused to allow the findings to be published; the contract with Dong stipulated that no information could be released without the consent of the manufacturer. An article was finally published in 1997.[26]

Six investigators interviewed for this report cited cases of articles whose publication was stopped or whose content was altered by the funding company. In one case, according to Dr. Cummings, the company held up the prepublication review process for over half a year, then requested pages of detailed revisions that would have made the manuscript more favorable to the company's official marketing position. During the delay, the company secretly wrote a competing article on the same topic, which was favorable to the company's viewpoint.

In another case, the drug being investigated did not work. The investigator argued that scientific integrity required publishing the findings. The company never refused to publish, but it stalled until the investigator lost interest.

Another investigator, most of whose relations with industry have been without problems, related the case of two trials of the same drug, one more favorable to the company. Despite a protest from the investigator, the results of the less favorable trial were never published.

A fourth investigator found that a drug he was studying caused adverse reactions. He sent his manuscript to the sponsoring company for review. The company vowed never to fund his work again and published a competing article with scant mention of the adverse effects.

Dr. Curt Furberg, professor of public health sciences at Wake Forest University School of Medicine and principal investigator in a study whose results were unfavorable to the sponsoring company, refused to place his name on the published results of the study, because the sponsor was "attempting to wield undue influence on the nature of the final paper. This effort was so oppressive that we felt it inhibited academic freedom."[27]

A sixth investigator recounted two examples of suppressed manuscripts regarding negative studies whose results were sufficiently important to publish.

In scenarios such as these, the frequency of which is unknown, companies repeatedly delay publication, eventually exhausting investigators who are busy with other projects. One industry executive explained that such cases result from priority setting within the company; with limited personnel to produce publications, certain trials take precedence over others. However, as one investigator described it, "when results favor the company, everything is great. But when results are disappointing, there is commonly an effort to spin, downplay, or change findings." A CRO executive added that "industry obstruction to publishing is a big problem. They are nervous if bad data comes out and gets into the mass media." Investigators in the commercial sector may be less concerned than those in academia with contract clauses guaranteeing their right to publish, thereby giving industry greater control over publications.

Authorship

In the past, publications were written by a study's principal investigator. More recently, a practice that one might call the nonwriting author–nonauthor writer syndrome has developed. Many interviews conducted for this report confirmed the wide prevalence of this syndrome in publications of drug-trial reports, editorials, and review articles. The syndrome has two features: a professional medical writer ("ghostwriter") employed by a drug company, CRO, or medical communications company, who is paid to write an article but is not named as an author; and a clinical investigator ("guest author"), who appears as an author but does not analyze the data or write the manuscript.[28-30] Ghostwriters typically receive a packet of materials from which they write the article; they may be instructed to insert a key paragraph favorable to the company's product.

The nonwriting author, who may be uninvolved in the research and have been requested to author the article to enhance its prestige, has final control over the manuscript. But many of these authors are busy and may not perform a thorough review. This guest–ghost syndrome[31,32] is a growing phenomenon, particularly in the commercial sector, where community-physician investigators have little interest in authorship.

In one study, 19 percent of the articles surveyed had named authors who did not contribute sufficiently to the articles to meet the criteria for authorship of the International Committee of Medical Journal Editors. Eleven percent had ghostwriters who contributed to the work but were not named as authors.[33,34] In justifying the nonwriting author–nonauthor writer syndrome, one industry executive explained that professional medical (ghost) writers are well trained, that investigators may be too busy to write, and that "nonwriting authors" are at fault if they do not carefully review ghostwritten manuscripts. An alternative view, articulated by Eric Campbell, of the Institute for Health Policy at Massachusetts General Hospital

and Harvard Medical School, holds that "a manuscript represents the accumulation of the intellectual and physical processes conducted under the aegis of a study and should be produced by the people who have actually been involved in the design, conduct, and supervision of the research." Tim Franson, Vice President for Clinical Research and Regulatory Affairs at Eli Lilly, believes that "any parties, be they industry staff, investigators, or others who contribute to the content of articles should have their names listed on the article."

CONCLUSIONS

Without industry funding, important advances in disease prevention and treatment would not have occurred. In the words of Lee Goldman, chairman of the Department of Medicine, University of California at San Francisco, "companies translate biologic advances into useable products for patients. They do it for a profit motive, but they do it, and it needs to be done." Investigators interviewed for this report confirmed that many collaborations with pharmaceutical companies were conducted on a high professional level.

But when results are disappointing for a company, conflicts may develop. Dr. Furberg, with years of experience in industry-funded drug trials, stated: "Companies can play hardball, and many investigators can't play hardball back. You send the paper to the company for comments, and that's the danger. Can you handle the changes the company wants? Will you give in a little, a little more, then capitulate? It's tricky for those who need money for more studies."

Although academic–industry drug trials have been tainted by the profit incentive, they do contain the potential for balance between the commercial interests of industry and the scientific goals of investigators. In contrast, trials conducted in the commercial sector are heavily tipped toward industry interests, since for-profit CROs and SMOs, contracting with industry in a competitive market, will fail if they offend their funding sources. The pharmaceutical industry must appreciate the risks inherent in its partnership with the commercial drug-trial sector: potential public and physician skepticism about the results of clinical drug trials and a devaluation of the insights provided through close relationships with academic scientists.

A number of authors have recommended changes to resolve the problems of clinical drug trials.[11,35-37] An essential ingredient of any solution is increasing the independence of investigators to conduct and publish their research. Some investigators interviewed for this article felt that drug trials should be funded by industry but that design, implementation, data analysis, and publication should be controlled entirely by academic medical centers and investigators. The rise of the commercial sector — which reduces rather than enhances the independence of investigators — appears to be moving drug trials in the opposite direction.

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REFERENCES

1. Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. N Engl J Med 1998;338: 101-6.
2. Davidson RA. Source of funding and outcome of clinical trials. J Gen Intern Med 1986;1:155-8.
3. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. Ann Intern Med 1996;124:485-9.
4. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. JAMA 1999;282:1453-7.
5. Chow S-C, Liu J-P. Design and analysis of clinical trials. New York: John Wiley, 1998.
6. Spilker BA. The drug development and approval process. (See: http://www.phrma.org.)
7. Psaty BM, Weiss NS, Furberg CD, et al. Surrogate end points, health outcomes, and the drug-approval process for the treatment of risk factors for cardiovascular disease. JAMA 1999;282:786-90.
8. Mathieu MP, ed. Parexel's pharmaceutical R & D statistical sourcebook 1998. Waltham, Mass.: Parexel International Corporation, 1999.
9. An industry in evolution. Boston: Centerwatch, 1999.
10. Woodward B. Challenges to human subject protections in US medical research. JAMA 1999;282:1947-52.
11. From bench to bedside: preserving the research mission of academic health centers. New York: Commonwealth Fund, 1999.
12. CRO mergers bring mixed results. Centerwatch 1997;4(6):1, 9-16.
13. Henderson L. The ups and downs of SMO usage. Centerwatch 1999; 6(5):1, 4-8.
14. Getz KA. AMCs rekindling clinical research partnerships with industry. Boston: Centerwatch, 1999.
15. Vogel JR. Maximizing the benefits of SMOs. Appl Clin Trials 1999; 8(11):56-62.
16. Academic medical centers: slowly turning the tide. Centerwatch 1997; 4(6):1-8.
17. Bero LA, Rennie D. Influences on the quality of published drug studies. Int J Technol Assess Health Care 1996;12(2):209-37.
18. Rochon PA, Berger PB, Gordon M. The evolution of clinical trials: inclusion and representation. CMAJ 1998;159:1373-4.
19. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. Arch Intern Med 1994;154:157-63.
20. Johansen HK, Gotzsche PC. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. JAMA 1999; 282:1752-9.
21. Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA 1999;282:790-5.
22. Blumenthal D, Campbell EG, Anderson MS, Causino N, Louis KS. Withholding research results in academic life science: evidence from a national survey of faculty. JAMA 1997;277:1224-8.
23. Chalmers I. Underreporting research is scientific misconduct. JAMA 1990;263:1405-8.
24. Olivieri NF, Brittenham GM, McLaren CE, et al. Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. N Engl J Med 1998;339:417-23.
25. Phillips RA, Hoey J. Constraints of interest: lessons at the Hospital for Sick Children. CMAJ 1998;159:955-7. [Erratum, CMAJ 1998;159: 1244.]
26. Rennie D. Thyroid storm. JAMA 1997;277:1238-43.
27. Applegate WB, Furberg CD, Byington RP, Grimm R Jr. The Multicenter Isradipine Diuretic Atherosclerosis Study. JAMA 1997;277:297.
28. Levy D. Ghostwriters a hidden resource for drug makers. USA Today. September 25, 1996.
29. Larkin M. Whose article is it anyway? Lancet 1999;354:136.
30. Ghost with a chance in publishing undergrowth. Lancet 1993;342: 1498-9.
31. Rennie D, Flanagin A. Authorship! Authorship! Guests, ghosts, grafters, and the two-sided coin. JAMA 1994;271:469-71.
32. Brennan TA. Buying editorials. N Engl J Med 1994;331:673-5.
33. Flanagin A, Carey LA, Fontanarosa PB, et al. Prevalence of articles

with honorary authors and ghost authors in peer-reviewed medical journals. JAMA 1998;280:222-4.
34. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. JAMA 1997; 277:927-34. [Erratum, JAMA 1998;279:510.]
35. Wood AJJ, Stein CM, Woosley R. Making medicines safer — the need for an independent drug safety board. N Engl J Med 1998;339:1851-4.
36. Kunin CM. Clinical investigators and the pharmaceutical industry. Ann Intern Med 1978;89:Suppl:842-5.
37. Shine KI. Some imperatives for clinical research. JAMA 1997;278: 245-6.

Roadside View, Southwestern Ontario

RUPERT KAUL, M.D.

Relationships Between Authors of Clinical Practice Guidelines and the Pharmaceutical Industry

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Context Increasing contact has been reported between physicians and the pharmaceutical industry, although no data exist in the literature regarding potential financial conflicts of interest for authors of clinical practice guidelines (CPGs). These interactions may be particularly relevant since CPGs are designed to influence the practice of a large number of physicians.

Objective To quantify the extent and nature of interactions between authors of CPGs and the pharmaceutical industry.

Design, Setting, and Participants Cross-sectional survey of 192 authors of 44 CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. One hundred authors (52%) provided usable responses representing 37 of 44 different CPGs that we identified.

Main Outcome Measures Nature and extent of interactions of authors with drug manufacturers; disclosure of relationships in published guidelines; prior discussion among authors regarding relationships; beliefs regarding whether authors' own relationships or those of their colleagues influenced treatment recommendations in guidelines.

Results Eighty-seven percent of authors had some form of interaction with the pharmaceutical industry. Fifty-eight percent had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company. On average, CPG authors interacted with 10.5 different companies. Overall, an average of 81% (95% confidence interval, 70%-92%) of authors per CPG had interactions. Similarly, all of the CPGs for 7 of the 10 diseases included in our study had at least 1 author who had some interaction. Fifty-nine percent had relationships with companies whose drugs were considered in the guideline they authored, and of these authors, 96% had relationships that predated the guideline creation process. Fifty-five percent of respondents indicated that the guideline process with which they were involved had no formal process for declaring these relationships. In published versions of the CPGs, specific declarations regarding the personal financial interactions of individual authors with the pharmaceutical industry were made in only 2 cases. Seven percent thought that their own relationships with the pharmaceutical industry influenced the recommendations and 19% thought that their coauthors' recommendations were influenced by their relationships.

Conclusions Although the response rate for this survey was low, there appears to be considerable interaction between CPG authors and the pharmaceutical industry. Our study highlights the need for appropriate disclosure of financial conflicts of interest for authors of CPGs and a formal process for discussing these conflicts prior to CPG development.

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INTERACTIONS BETWEEN PHYSICIANS and the pharmaceutical industry have received increasing amounts of attention over the last several years. Several authors have described significant contact between the pharmaceutical industry and academic researchers,[1] faculty physicians,[2] community physicians,[3] residents,[4] and medical students.[5] More importantly, these types of interactions have been shown to influence prescribing patterns,[6] stimulate requests for addition of drugs to hospital formularies,[2] result in favorable publications[7] and research articles,[8,9] and be related to the lack of publication of unfavorable articles.[10]

Clinical practice guidelines (CPGs) are intended to present a synthesis of current evidence and recommendations preformed by expert clinicians and may affect the practice of large numbers of physicians. As a result, any influence that the authors of CPGs experience from their interactions with pharmaceutical companies may be transmitted many times over to the readers of CPGs. Consequently, if individual authors have relationships that pose a potential conflict of interest, readers of these CPGs may wish to know about them to evaluate the merit of those guidelines.

To date, no published data exists regarding the extent to which the au-

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thors of CPGs interact with the pharmaceutical industry. This study seeks to provide empirical evidence concerning this issue to improve the process of CPG development in the future.

METHODS

Study Questions

We attempted to compare the amount of financial interaction that authors of CPGs had with the pharmaceutical industry with the amount of interaction that was disclosed in the published guidelines that they had authored. We also sought to assess the nature of these interactions and the authors' perceptions of the impact of interactions on recommendations made by the guideline committee. We asked 4 specific questions: (1) How much interaction do authors of clinical practice guidelines have with drug manufacturers and what is the nature of this interaction (ie, do the relationships predate or postdate the guideline writing process)? (2) What physician-pharmaceutical interactions are disclosed in the published guidelines? (3) Prior to beginning the guideline creation process, was there a discussion among the guideline authors regarding relationships with the pharmaceutical industry? and (4) Do guideline authors believe that their relationships or those of their colleagues influence the treatment recommendations that were put forth in the guidelines?

Selection and Review of Articles

Authors were identified by reviewing CPGs endorsed by North American and European societies on common adult diseases published between 1991 and July 1999. The list of medical conditions to be included was created using the 20 most commonly prescribed drugs that are paid for by the Ontario Drug Benefit Program. Drugs that are used symptomatically to treat many potentially nonspecific conditions were excluded (eg, acetaminophen with codeine, lorazepam). If not already included, we added conditions that accounted for the 5 most common admission diagnoses to the internal medicine services at our hospitals (ie, pneumonia, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease/asthma, and gastrointestinal bleeding). Finally, we excluded diseases for which CPGs did not exist.

Pertinent CPGs were identified through the MEDLINE database, reference lists from published articles, and interviews with expert clinicians. We restricted our sample to CPGs that had been endorsed by a recognized North American or European society and had identifiable authors. We selected the principal authors and, when indicated, those who participated in drafting the guideline to be surveyed.

The CPGs were reviewed and specific declarations of potential financial conflict of interest were recorded. Declarations regarding the guideline creation process and individual authors were classified as no specific declaration made, declaration that no financial interaction existed, declaration that funding was received from a pharmaceutical company, or declaration that funding was received from a nonindustry source (eg, government agency, professional society/association). Statements indicating that the guidelines had been prepared or approved by the endorsing professional association without explicitly indicating from where funds had been received were coded as having no specific declaration made.

Survey Instrument and Data Collection

Two surveys were used in this study. First, a survey instrument based on that of Chren and Landefeld[2] and used by Stelfox et al[7] was developed to examine authors' financial interactions with pharmaceutical companies. Manufacturers of drugs used to manage diabetes, chronic obstructive pulmonary disease/asthma, hypertension, pneumonia, coronary artery disease, congestive heart failure, hyperlipidemia, osteoarthritis, depression, and peptic ulcer disease were identified. For each of these manufacturers, authors were asked whether they had any of 6 types of financial interactions, including support for attendance at a symposium (eg, funds for travel expenses), honorarium for speaking at a symposium, support for organization of an educational program, support for research, employment by or consultancy for the company, and equity in the company.

The addresses of the corresponding authors were obtained from the articles, a citation index, and other articles published by the same authors. All authors were mailed the survey questionnaire with a cover letter explaining the purpose of the study. Reminder letters and questionnaires were mailed to authors who did not respond to the first mailing within 12 weeks.

Second, respondents to the first survey were resurveyed to characterize the nature of relationships and the disclosure process. Authors were asked whether their relationships specifically involved companies whose drugs were considered or included in the guideline they authored, whether these relationships predated or postdated the guideline process, whether they believed their own relationships or those of their coparticipants influenced the recommendations that were put forward, whether there was discussion among the participants prior to beginning the guideline process regarding any relationships and whether this process was formalized, and how potential conflicts of interest were managed.

Data Analysis

Descriptive statistics were used to examine the results of both quantitative surveys. The results are reported as proportions and means with 95% confidence intervals (CIs). The rate of response to the surveys was similarly analyzed. Analyses were conducted using STATA, version 7 (STATA Corp, College Station, Tex).

RESULTS

One hundred twenty CPGs were identified by our search strategy, of which 35 were excluded because a major North American or European society

Table 1. Type of Relationship With Pharmaceutical Manufacturers and No. of Companies With Which Authors Had Relationships

Relationship	% of Authors (95% Confidence Interval) (n = 100)	Mean No. of Companies (Range) (n = 87)
Any relationship	87 (80-94)	10.5 (1-37)
Travel funding/honorarium	53 (43-63)	5.4 (1-16)
Speaker honorarium	64 (54-74)	7.3 (1-20)
Educational program support	51 (41-61)	4.7 (1-36)
Research support	58 (48-68)	6.7 (1-26)
Employee/consultant	38 (28-48)	5.7 (1-21)
Equity	6 (1-11)	1.8 (1-4)

did not endorse the CPG and 38 were excluded because they were editorials about CPGs or comparisons of different CPGs. Therefore, 47 CPGs were initially included.[11-57] Subsequently, 1 CPG was excluded because the authors could not be identified[55] and 2 CPGs were excluded after the authors had been surveyed since these were evaluations of CPGs rather than actual CPGs.[56,57] Therefore, 44 CPGs with 192 authors were included in the study.

Current addresses of 13 authors could not be located and 3 authors had died, resulting in a total of 176 potentially contactable authors. Of these, 107 authors (61%) responded representing 37 of the 44 CPGs included in our study. Therefore, 7 guidelines were not represented in our final sample.[11,24,32,39,40,42,54] Despite this, all of the disease states that were initially included in our study protocol were still represented by at least 2 CPGs, with the exception of depression, for which there was only 1 CPG included in the sample and for which we received a response. Seven respondents refused to participate, all of whom were involved with different guidelines. Three of these 7 authors were from Europe, 2 were from the United States, and 2 were from Canada. This left 100 completed surveys, which form the basis of our results. Overall, the response rate was 57% of potentially contactable authors and 52% of all authors initially included in our sample. The distribution of sex and disease to which the guidelines pertained was similar for respondents and nonrespondents; however, the distribution of current country of residence was not. Sixty-three percent of authors currently residing in the United States did not respond whereas 29% of authors living in Canada did not respond ($P=.001$).

Twenty-eight (26%) of 107 authors responded with a letter attached to their survey. These letters could be interpreted as being supportive (21%), neutral (57%), or critical (21%) of our study.

Of the 100 authors who completed the first survey, 1 had died and 1 had moved and was unreachable, leaving 98 potentially contactable authors for the second survey. Of these, 82 (83%) responded. One of these authors refused to participate and 1 could not recall the nature of the disclosure process and, therefore, left the survey blank. Consequently, the response rate for the second survey was 82%.

CPG Author-Pharmaceutical Manufacturer Interactions

The nature of the authors' relationships with pharmaceutical companies is shown in TABLE 1. Eighty-seven percent of the responding authors had some form of interaction with the pharmaceutical industry. Fifty-eight percent had received financial support to perform research and 38% had served as employees or consultants for a pharmaceutical company.

The mean number of companies with which authors who did have financial relationships interacted is shown in Table 1. On average, CPG authors interacted with 10.5 different companies. Authors who received support for research received this funding from a mean of 6.7 companies and those who served as employees or consultants for pharmaceutical companies did so for a mean of 5.7 companies.

TABLE 2 shows response rates and interactions categorized by the diseases to which the CPGs included in our sample pertained. All of the CPGs for 7 of the 10 disease states had at least 1 author who had some level of interaction. Similarly, the average percentage of authors per CPG who had interactions was 100% for 6 of the 10 disease states. Overall, an average of 81% (95% CI, 70%-92%) of authors per guideline had interactions with the pharmaceutical industry.

Fifty-nine percent of authors had relationships with companies whose products were specifically considered or included in the guideline they authored (TABLE 3). Of these, 96% and 53% had relationships that predated and postdated the guideline process, respectively.

Only 7% believed that their own relationships influenced the treatment recommendations (Table 3). Nineteen percent believed that their coauthors' recommendations were influenced by relationships with the pharmaceutical industry.

Guideline Conflict of Interest Declarations

Forty-five percent of authors reported that prior to beginning the guideline process, discussion occurred among the guideline authors regarding their relationships with the pharmaceutical industry. Of these, 61% reported that there was a formal process for this discussion and 75% indicated that all members of the guideline committee participated.

In the published versions of the 44 CPGs included in the study, authors declared that they had personal financial interactions with the pharmaceutical industry in only 1 guideline[51] (TABLE 4). Similarly, only 1 guideline declared that the authors had no conflicts of interest.[15] In the majority of cases (42 of 44 guidelines), no declarations were made with respect to the authors' potential conflicts of interest.

Table 2. Response Status and Relationship With Pharmaceutical Manufacturers by Disease

Disease	No. of Guidelines Included	No. of Guidelines With at Least 1 Respondent (%)	Authors Responding/ Authors Surveyed (%)*	No. of Guidelines in Which at Least 1 Respondent Had Any Interaction (%)	No. of Authors With Any Interaction (%)	Average % of Authors per Guideline With Any Interaction	Mean No. of Companies With Which Authors Had Relationships†
Asthma/chronic obstructive pulmonary disease	6	5 (83.3)	6/11 (54.5)	3 (60)	4 (66.7)	60	8.5
Coronary artery disease	6	5 (83.3)	20/37 (54.1)	4 (80)	15 (75)	65	13.1
Heart failure	4	2 (50)	8/16 (50)	2 (100)	7 (87.5)	100	8.3
Depression	1	1 (100)	1/5 (20)	1 (100)	1 (100)	100	11.0
Diabetes	5	4 (80)	9/15 (60)	4 (100)	9 (100)	100	8.0
Peptic ulcer disease	3	3 (100)	3/5 (60)	3 (100)	3 (100)	100	11.7
Hypercholesterolemia	3	3 (100)	9/13 (69.2)	3 (100)	9 (100)	100	10.3
Hypertension	6	5 (83.3)	12/27 (44.4)	4 (80)	10 (83.3)	70	16.9
Osteoarthritis	2	2 (100)	3/87 (37.5)	2 (100)	3 (100)	100	4.0
Pneumonia	8	7 (87.5)	44/70 (62.9)	7 (100)	38 (86.4)	76	9.1

*The total number of authors responding equals 115 (not 100) and the total number of authors surveyed equals 207 (not 192) because several authors participated in more than 1 guideline.
†Among authors with relationships.

In 11 of the 44 CPGs, a declaration was made that a pharmaceutical company had sponsored the guideline creation and writing process.* Nonindustry organizations sponsored 9 CPGs.† Two of these guidelines were supported by both industry and governmental sources.[21,27]

Table 3. Nature and Author Perceptions of Relationship With Pharmaceutical Manufacturers

	No. of Authors (%) [95% Confidence Interval]
Had relationship with companies whose drugs were considered in the guideline process	47/80 (59) [48-70]
Relationship predated guideline process	45/47 (96) [92-100]
Relationship postdated guideline process	25/47 (53) [39-67]
Believed that relationships influenced personal recommendations	5/68 (7) [1-9]*
Believed that relationships influenced recommendations of colleagues	13/67 (19) [8-30]†

*Only 68 of the 80 respondents provided answers to these questions.
†Only 67 of the 80 respondents provided answers to these questions.

Table 4. Declarations Contained Within Published Guidelines

Type of Declaration	No. of Guidelines Making Declarations Regarding Authors' Financial Interactions (n = 44)	No. of Guidelines Making Declarations Regarding Guideline Creation Process (n = 44)*
No declaration made	42	26
Declared that no sponsorship received	1	0
Received nonpharmaceutical industry support	0	9
Received pharmaceutical industry support	1	11

*Column values total more than 44 because 2 guidelines received funding from both industry and government.

COMMENT

Although the results of this study must be interpreted cautiously in light of the relatively low response rate, our results appear to indicate that most CPG authors have interactions with pharmaceutical companies and that a significant proportion work as employees/consultants for drug manufacturers. Moreover, a majority of our respondents indicated that they had relationships with companies whose products were considered in the guideline that they authored, and of these, almost all had relationships that predated the guideline creation process.

The majority of responding authors believed that their relationships had no influence on the recommendations that they put forward. Ideally, we would have liked to have objectively assessed whether this was true by evaluating whether guidelines authored by individuals with relationships recommended use of different therapies than those guidelines authored by individuals without relationships. Unfortunately, most authors had relationships and virtually all guidelines permitted use of a wide range of drugs as first-line agents "if clinically indicated," thereby making any differentiation impossible.

Nevertheless, the authors' perceptions of the influence of their relationships are in stark contrast with the large body of literature that indicates that these types of relationships are indeed significant in other domains.[2-10] Moreover, almost 20% of the respondents believed that their colleagues' relationships influenced the recommendations that they put forward.

We wonder whether academicians and physicians underestimate the impact of relationships on their actions because the nature of their professions is the pursuit of objective unbiased information. Unfortunately, bias may occur both consciously and subconsciously, and therefore, its influence may go unrecognized. In fact, pharmaceutical marketing or "detailing" may

*References 14, 16, 21-24, 27, 32, 43, 46, 47.
†References 15, 17, 18, 21, 27, 30, 40, 41, 51.

rely on the impact of these more subtle forms of influence.[58] Concern about bias in interpretation of outcomes in randomized trials led to the practice of blinding subjects, their caregivers, and outcome assessors to the knowledge of which treatment the subject received. Is the situation regarding CPG authorship not analogous?

Unlike relationships that individual authors or physicians have with the pharmaceutical industry, financial conflicts of interest for authors of CPGs are of particular importance since they may not only influence the specific practice of these authors but also those of the physicians following the recommendations contained within the guidelines.

There are several possible explanations for our low response rate. First, physicians' interactions with the pharmaceutical industry have received increasing amounts of attention in the medical literature[1-10] and popular press. As a consequence, physicians may have been reluctant to disclose their relationships. Second, the cover letter that we sent to our survey participants made no promise of anonymity. Rather, we indicated that participation in our survey was voluntary. Although we have presented our results in aggregate and never intended to identify individual physicians, it is possible that some authors may have been concerned about being recognized and therefore preferred to not respond. Therefore, based on these factors, it is possible that nonrespondents actually had a higher degree of interaction with the pharmaceutical industry than respondents. Consequently, our low response rate may have actually biased our results by underestimating the already high degree of interaction that we observed.

To put our results in perspective without unduly biasing our respondents, we conducted semistructured interviews with 5 guideline authors after the second survey had been completed. These authors underscored the lack of formal process for CPG authors to declare potential conflicts of interest and to sensitize each other to subtle or subconscious influences, especially for CPGs that were authored more than 5 years ago. In contrast, the interviewees thought that it may be neither possible nor desirable to exclude authors who are involved with industry since the "experts" who write guidelines are the same individuals who are most likely to receive financial support to conduct research. Moreover, our interviewees suggested that an author's objectivity might actually be maintained by having multiple small relationships with different pharmaceutical companies as opposed to large relationships with a few companies. The authors also suggested that relationships with pharmaceutical industries are not the only type of potential conflicts of interest that exist. Concerns regarding obtaining continued funding from governmental agencies (eg, by ensuring that one's government-funded research is included in the studies cited by a CPG) or of individual academic promotion (eg, by ensuring that one's own research is included in the studies cited by a CPG) may also influence the guideline process and may serve as forms of "dual commitment."

Recommendations

Based on our results and the considerable debate that has taken place about the relationships between clinical researchers and the pharmaceutical industry, we propose the following recommendations for the management of potential financial conflicts of interest for authors of clinical practice guidelines.

First, the process whereby authors disclose their potential conflicts of interest must be made more formal. In particular, authors must disclose relationships with the pharmaceutical industry before guideline meetings are held. A full discussion must occur among the participants before the start of the writing process about each person's relationships and how significant relationships (eg, those that predate the guideline process, involve large sums of money, or involve equity positions in companies) will be managed. Participants should be sensitive to the possibility that the influence of these relationships may subconsciously affect their judgments.

Second, authors who have relationships with the pharmaceutical industry need not necessarily be excluded from participating in the guideline creation process. However, authors with significant conflicts of interest should likely be excluded. What level of conflict is significant is clearly a contentious issue. Is there a threshold below which authors will not perceive subconscious influences from their relationships with pharmaceutical companies? The only threshold that is not arbitrary is zero, implying that all authors with any relationships would be excluded. This standard, however, is both impractical and likely too strict. Thus, groups will have to decide on this issue for themselves. However, we do think that authors who hold equity in a company whose products are being considered in the guideline process should be disqualified. This is consistent with the current practices of most governmental granting agencies in North America and the editorial policies of most major medical journals.

Third, there must be complete disclosure to the readers of CPGs of individual authors' financial relationships with the pharmaceutical industry. Ideally, this should occur in the printed version of the guideline. However, if this is not feasible given the large number of authors who may participate in a CPG and practical limitations on space, alternative forms of disclosure, such as the journal's Web site, could be used.

Conclusions

In conclusion, there appears to be a high degree of interaction between authors of clinical practice guidelines and the pharmaceutical industry. These specific interactions may influence the practice of a very large number of physicians. We believe that our study highlights the need for appropriate disclosure of financial conflicts of interest for authors of CPGs and a formal process for discussing these conflicts prior to CPG development.

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Acquisition of data: Choudhry, Detsky.
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Drafting of the manuscript: Choudhry, Detsky.
Critical revision of the manuscript for important intellectual content: Choudhry, Stelfox, Detsky.
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REFERENCES

1. Bowd EA, Bero LA. Assessing faculty financial relationships with industry. *JAMA*. 2000;284:2209-2214.
2. Chren M, Landefeld C. Physicians' behavior and their interactions with drug companies: a controlled study of physicians who requested additions to a hospital drug formulary. *JAMA*. 1994;271:684-689.
3. Caudill TS, Johnson MS, Rich EC, McKinney WP. Physicians, pharmaceutical sales representatives and the cost of prescribing. *Arch Fam Med*. 1996;5:201-206.
4. Ziegler MG, Lew P, Singer BC. The accuracy of drug information from pharmaceutical sales representatives. *JAMA*. 1995;273:1296-1298.
5. Sandberg WS, Carlos R, Sandberg EH, Roizen MF. The effect of educational gifts from pharmaceutical firms on medical students' recall of company names of products. *Acad Med*. 1997;72:916-918.
6. Wazana A. Physicians and the pharmaceutical industry: is a gift ever just a gift? *JAMA*. 2000;283:373-380.
7. Cox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med*. 1998;338:101-106.
8. Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med*. 1986;1:155-158.
9. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med*. 1994;154:157-163.
10. Friedberg M, Saffran B, Stinson TJ, Nelson W, Bennett CL. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA*. 1999; 282:1453-1457.
11. Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol*. 1995;96: 707-870.
12. Guidelines for the diagnosis and management of asthma. *J Allergy Clin Immunol*. 1991;88:425-534.
13. Guidelines on the management of asthma. *Thorax*. 1993;48:S1-S24.
14. Beveridge RC, Grunfeld AF, Hoder RV, Verbeek PR. Guidelines for the emergency management of asthma in adults. *CMAJ*. 1996;155:25-37.
15. North of England Asthma Guideline Development Group. North of England evidence based guidelines development project: summary version of evidence based guideline for the primary care management of asthma in adults. *BMJ*. 1996;312:762-766.
16. Canadian Thoracic Society Workshop Group. Guidelines for the assessment and management of chronic obstructive pulmonary disease. *CMAJ*. 1992; 147:420-428.
17. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. *Arthritis Rheum*. 1995;38:1535-1540.
18. Holbrook AM, Sabharwal M, Trepanier EF. *Medical Treatment Guidelines for the Treatment of Osteoarthritis, Rheumatoid Arthritis, and Acute Musculoskeletal Injury*. Toronto: Queen's Printer for Ontario; 1999.
19. American Psychiatric Association. Practice guideline for major depressive disorder in adults. *Am J Psychiatry*. 1993;150:S1-S26.
20. British Diabetic Association, Royal College of Physicians, and Royal College of General Practitioners. Guidelines for good practice in the diagnosis and treatment of non-insulin-dependent diabetes mellitus. *J R Coll Physicians Lond*. 1993;27:259-266.
21. Expert Committee of the Canadian Diabetes Advisory Board. Clinical practice guidelines for treatment of diabetes mellitus. *CMAJ*. 1992;147:697-712.
22. Meltzer S, Leiter L, Daneman D, et al. 1998 Clinical practice guidelines for the management of diabetes in Canada. *CMAJ*. 1998;159:S1-S29.
23. European IDDM Policy Group 1993. Consensus guidelines for the management of insulin-dependent (type 1) diabetes. *Diabet Med*. 1993;10:990-1005.
24. AACE guidelines for the management of diabetes mellitus. *Endocr Pract*. 1995;1:149-157.
25. Soll AH, for the Practice Parameters Committee of the American College of Gastroenterology. Medical treatment of peptic ulcer disease. *JAMA*. 1996; 275:622-629.
26. DeVault KR, Castell DO. Guidelines for the diagnosis and treatment of gastroesophageal reflux disease. *Arch Intern Med*. 1995;155:2165-2173.
27. Hunt R, Thomson ABR. Canadian *Helicobacter pylori* consensus conference. *Can J Gastroenterol*. 1998;12:31-41.
28. Subcommittee of the WHO/ISH Mild Hypertension Liaison Committee. Summary of the 1993 World Health Organization–International Society of Hypertension guidelines for the management of mild hypertension. *BMJ*. 1993;307:1541-1546.
29. Sever P, Beevers G, Bulpitt C, et al. Management guidelines in essential hypertension: report of the second working party of the British Hypertension Society. *BMJ*. 1993;306:983-987.
30. Myers MG, Gryfe CI, Leenen FH, Haynes RB, Ogilvie RI. *Guidelines for the Treatment of Uncomplicated Hypertension*. Toronto: Queen's Printer for Ontario; 1995.
31. Ogilvie RI, Burgess ED, Cusson JR, Feldman RD, Leiter LA, Myers MG. Report of the Canadian Hypertensive Society Consensus Conference. *CMAJ*. 1993; 149:575-584.
32. Evans CE. *Canadian Consensus Conference on Hypertension Management, 1984-1992*. Montreal, Quebec: Canadian Hypertension Society; 1993.
33. Sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med*. 1997;157: 2413-2446.
34. Betteridge DJ, Dodson PM, Durrington PN, et al. Management of hyperlipidemia: guidelines of the British Hyperlipidemia Association. *Postgrad Med J*. 1993; 69:359-369.
35. Frohlich J, Fodor G, McPherson R, Genest J, Langner N. Rationale for and outline of the recommendations of the Working Group on Hypercholesterolemia and Other Dyslipidemias: interim report. *Can J Cardiol*. 1998;14(suppl A):17A-21A.
36. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA*. 1993; 269:3015-3023.
37. ASHP therapeutic guidelines on angiotensin-converting enzyme inhibitors in patients with left ventricular dysfunction. *Am J Health Syst Pharm*. 1997; 54:299-313.
38. ACC/AHA Task Force. Guidelines for the evaluation and management of heart failure. *Circulation*. 1995;92:2764-2784.
39. Johnstone DE, Abdulla A, Arnold JM, et al. Diagnosis and management of heart failure. *Can J Cardiol*. 1994;10:613-631.
40. Agency for Health Care Policy and Research. *Heart Failure: Evaluation and Care of Patients With Left-Ventricular Systolic Dysfunction*. Rockville, Md: US Dept of Health and Human Services; June 1994.
41. Ontario Anti-infective Review Panel. Anti-infective guidelines for community-acquired infections. 2nd ed. Toronto: Queen's Printer for Ontario; 1997.
42. British Thoracic Society. Guidelines for the management of community-acquired pneumonia in adults admitted to hospital. *Br J Hosp Med*. March 1993: 3-16.
43. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventative strategies. *Am J Respir Crit Care Med*. 1996;153:1711-1725.
44. European Study on Community-Acquired Pneumonia Committee. Guidelines for management of adult community-acquired lower respiratory tract infections. *Eur Respir J*. 1998;11:986-991.
45. American Thoracic Society. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis*. 1993; 148:1418-1426.
46. Mandell LA, Marrie TJ, Niederman MS. Initial antimicrobial treatment of hospital acquired pneumonia in adults. *Can J Infect Dis*. 1993;4:317-321.
47. Mandell LA, Niederman MS. Antimicrobial treatment of community acquired pneumonia in adults. *Can J Infect Dis*. 1993;4:25-28.
48. Bartlett JG, Breiman RF, Mandell LA, File TM. Community-acquired pneumonia in adults: guidelines for management. *Clin Infect Dis*. 1998;26:811-838.
49. Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. *Circulation*. 1996;94: 2341-2350.
50. Weston CF, Penny WJ, Julian DG. Guidelines for the early management of patients with myocardial infarction. *BMJ*. 1994;308:767-771.
51. North of England Stable Angina Guideline Development Group. North of England evidence based guidelines development project: summary version of evidence based guideline for the primary care management of stable angina. *BMJ*. 1996;312:827-832.
52. Gibbons RJ, Chatterjee K, Daley J, et al. ACC/AHA/ACP-ASIM guidelines for the management of patients with chronic stable angina. *J Am Coll Cardiol*. 1999;33:2092-2197.
53. De Bono DP, Hopkins A. The management of acute myocardial infarction: guidelines and audit standards. *J R Coll Physicians Lond*. 1994;28:312-317.
54. Agency for Health Care Policy and Research. *Unstable Angina: Diagnosis and Management*. Rockville, Md: US Dept of Health and Human Services; 1994.
55. BTS Guidelines for the management of chronic obstructive pulmonary disease. *Thorax*. 1997;52:S1-S28.
56. Fein AM, Niederman MS. Guidelines for the initial management of community-acquired pneumonia: savory recipe or cookbook for disaster? *Am J Respir Crit Care Med*. 1995;152:1149-1153.
57. Gleason PP, Kapoor WN, Stone RA, et al. Medical outcomes and antimicrobial costs with the use of the American Thoracic Society guidelines for outpatients with community-acquired pneumonia. *JAMA*. 1997;278:32-39.
58. Avorn J, Soumerai SB. Improving drug-therapy decisions through educational outreach: a randomized controlled trial of academically based "detailing." *N Engl J Med*. 1983;308:1457-1463.