**Pharmaceutical Company Sponsorship of Research: A Review**

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**Introduction**

Many studies have shown that pharmaceutical companies' funding of clinical trials is associated with pro-industry results. This article reviews the literature on that association, confirming its existence, and discusses its causes and potential responses. The mechanisms of industry influence are varied, more than is usually acknowledged. It is straightforward to identify a number of distinct kinds of such mechanism, each of which operates in at least some instances. As a result, most policy responses are either inadequate or politically infeasible.

1. *Pharmaceutical industry sponsorship influences published results: two systematic reviews*

1.1 Justin Bekelman, Yan Li, and Cary Gross (2003) systematically survey studies that quantitatively examined the relationship between financial conflicts of interest and medical research results. "Conflict of interest" in their case was a diverse category, potentially including "industry sponsorship, consultantship, employment, technology transfer, new venture formation, gifts, or personal funds." (455). The systematic nature of their review makes it a good baseline, in that it summarizes previous research on conflicts of interest in this area. Bekelman et al. found 23 studies published in English between 1980 (when the U.S. Bayh-Dole Act encouraged academic/industry partnerships) and 2002.

Eight of the studies they examined compared outcomes for trials funded by industry (not all pharmaceutical) and other sources. A meta-analysis of those eight showed that **industry-funded trials were much more likely to produce pro-**
industry results, with an odds ratio of 3.60 (95% confidence interval 2.63-4.91). That is, relative to the baseline of the results of non-industry trials, the industry-funded trials were three times as likely to be reporting a pro-industry result.

Bekelman et al. also report various other results relating funding source and outcomes. One study examined 61 industry-sponsored trials of NSAIDs, and found that 100% reported that the drug being investigated was as effective as or more effective than the comparison drug, a striking result. A study of financial consultantships (Stelfox et al, 1998) in a controversial area has similarly striking results: of pro-industry articles on calcium-channel antagonists, 96% were authored by people with financial relationships with manufacturers of the drugs, versus only 60% of neutral articles and 37% of negative ones.

Sponsorship has associations with particular methodological choices, in particular the use of non-active or less-active controls. However, it is unclear whether there is any association between sponsorship and methodological quality: using either blinded review or quality assessment measures, two found that industry-sponsored studies were of inferior quality, but five more studies found no differences.

And financial conflicts of interest may be associated with choices of subject matter, shifting research from more basic to more applied topics. On the basis of survey results, it appears that researchers with relationships to industry were more than twice as likely as others to consider commercial potential when choosing topics.

1.2 Joel Lexchin, Lisa A. Bero, Benjamin Djulbegovic, and Otavio Clark performed a similar systematic survey, also published in 2003. They searched for quantitative studies of the relationships between research funding and outcomes, methodology, or publication, for studies published after 1966, including letters and abstracts, attempting to supplement data by contacting authors.

16 of the articles that Lexchin et al. examined looked at the relationship between research funding and the outcomes of clinical trials and meta-analyses, and of these 13 showed an association between industry funding and pro-industry outcomes. A further seven looked at the relationship between funding and the outcomes of pharmacoeconomic analyses. Pooling the data of the 18 of these for which that was possible produced a summary odds ratio of 4.05 (95% confidence interval 2.98 to 5.11) — industry-funded studies were four times as likely to report pro-industry results. The direction of association was also consistent, as of this group only one study had found no association between funding and outcomes and the rest had all found positive associations. Thus Lexchin et al.’s results agree very closely
with those of Bekelman et al., which is perhaps unsurprising since there was some overlap in their data sets.

Interestingly, Lexchin et al. found that industry funding was not associated with lower methodological quality in any of the studies they examined, and was associated with higher methodological quality in four of nine studies for which statistics were available.

Between these two systematic studies, the central results are very clear: **industry funding is very positively associated with published pro-industry findings. It is also associated with higher methodological quality on standardized measures, and some methodological choices, such as inactive controls as comparators.** Other kinds of industry support, such as consultantships, appears to be associated with pro-industry results as strongly as is financial support for research, though there is less evidence for this.

**2. Research since 2003 continues to paint a similar picture.**

At a clinically-oriented professional meeting, Finucane and Boult (2004) classified all studies of drugs as either positive or negative, and as sponsored by pharmaceutical companies or not. **Of the 63% of sponsored trials, 100% presented positive results. Of the other trials, only 67% presented positive results.** Landefeld (2004) says that since acceptance and editorial standards are less strict at most professional meetings than in journals, these meetings represent "an unwitting vector of promotional information" (876). Finucane and Boult also demonstrate the importance of thoroughness. **Of the 30 industry-supported trials, only 3 acknowledged that support.** The others were counted as industry-supported because one or more of the authors were employees of the relevant pharmaceutical companies, or because funding came from an institution that itself received substantial financial support from the relevant companies.

Coming at the issue from a different direction, Fries and Krishnan (2004) looked out the outcomes reported in industry-supported abstracts presented at the 2001 meeting of the American College of Rheumatology. Their goal was to examine the ethical concept of "equipoise," under which clinical trials should be conducted if their outcomes are genuinely unpredictable. **In Fries and Krishnan’s sample of 45 abstracts, all 45 reported pro-industry results.** Equipoise is impossible in a setting in which support predicts outcomes, and thus ethical frameworks for research need to be rethought; we might note that in settings in which support predicts outcomes much about research needs to be rethought.
Lurie et al. (2006) looked at conflict of interest and voting patterns on FDA advisory committees and voting patterns, using FDA records from 2001 to 2004. This difficult analysis, which involved coding votes on multiple questions, and looking at various different measures of voting outcomes, showed that the exclusion of FDA advisors with conflicts would have resulted in committee votes less favorable to the drug in question, but would not have changed any majority votes — though as the authors point out it is possible that authors with conflicts influenced the voting patterns of those without. On their individual-focused analyses there were weak positive associations or non-statistically significant ones, except when all conflicts, including to competitor drugs were taken into account: in that case, advisors with conflicts were found to be significantly more likely to vote in favor of the drug at issue than were advisors without conflicts. This is consistent with some spectacular cases, such as the 2005 FDA advisory committee meeting on COX-2 inhibitors, at which 93% of advisors who had received fees from Merck or Pfizer, the makers of the COX-2 drugs, voted in their favor, compared with 56% of other members of the committee (Harris & Berenson 2005, Lurie et al. 2006).

Friedman and Richter (2004) look at the relationship between conflicts of interest (on different definitions) and outcomes of articles published in the New England Journal of Medicine and the Journal of the American Medical Association. They found strong associations, from an odds ratio of 2.35 to 7.32, depending on the breadth of the criteria for conflict. Those associations were even stronger for negative studies: "the odds are extremely small that a negative result would be published by authors with conflicts of interest."

Als-Nielsen et al. (2003) add another study of the effect of sponsorship, with similar results. On the basis of a grading of conclusions, they show in addition that the strength of the data is not a good predictor of strength of published conclusions. Studies have further investigated funding in particular fields and subfields. Heres et al. (2006) examined the association of sponsorship and funding outcome in head-to-head trials of second-generation antipsychotics. 90% of trials found that the sponsoring pharmaceutical company's drug was superior overall. The title of Heres et al.'s article, recalling a game of rock paper scissors, tells the story: "Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapin." Of course, the circular pattern is part of the rock paper scissors game, but medical researchers might rightly be resistant to thinking of antipsychotic research as a parallel game. (Pharmaceutical companies may be somewhat more content to treat this kind of research as a game, but not as a game with nearly the amount of randomness as rock paper scissors.) Montgomery et
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al. (2004) find a similar result comparing second- and first-generation antipsychotics. In a review and meta-analysis of trials of the antipsychotic drug clozapine, Moncrieff (2003) found that financial support from a drug company was a good predictor of the observed benefits of clozapine, a finding that is echoed by Procyshyn et al.’s (2004) study of trials of clozapine, risperidone, and olanzapine. Clearly, the effects of industry funding are well-studied and well-established in psychiatry.

In an aberrant result, Barden et al. (2006) find no significant association between industry-sponsorship and outcomes in a set of articles comparing pain relievers. Because of the very few non-industry sponsored trials in their samples — taken from systematic reviews on acute pain and migraines — they turn to the correlation of results with funding in head-to-head comparisons. Since Barden start from review articles, they are thereby identifying important studies, and the lack of non-industry funded trials is thus all the more interesting. Surprisingly, considering all of the other studies of funding, they find that drugs owned by the sponsoring companies do not fare better in trials. There are two important differences between the study by Barden et al. and most of the other studies mentioned here, or reviewed in Lexchin et al. (2003) and Bekelman et al. (2003), that may be partially responsible for their unusual results: first, a number of the drugs in this meta-analysis have long been available as generics, and so pharmaceutical companies have less financial incentive to show them superior; second, Barden et al. do not compare articles but rather reported data, making head-to-head comparisons. If that is the case, then it shows that rhetorical analysis of articles would help to elucidate ways in which the published literature is made to meet industry interests.

Perlis et al. (2005) look at double-blind, placebo-controlled trials reported in the four most cited psychiatry journals between 2001 and 2003, and find that papers acknowledging or displaying conflicts of interest have an odds ratio of 4.9 in favour of positive results, and papers acknowledging industry funding and displaying conflict of interest report positive results with an odds ratio of 8.4. However, there was no statistically significant association between industry support by itself and outcome. Perlis et al. also discovered that the rates of conflict of interest are higher in psychiatry than in general medicine, at 47% of papers in psychiatry, versus 34%-43% (Bekelman 2003, Gross 2003).

Other fields in which recent studies have examined sponsorship include cost effectiveness (Baker et al. 2003, Bell et al. 2006, Miners et al. 2005, Beutels 2004), surgical treatments (Bhandari et al. 2004, Shah et al. 2005), and dermatology (Perlis et al. 2005). With the exception of the one discussed above, all of the investigations of the relationship between industry sponsorship and research shows that articles on
industry-sponsored studies are very much more likely to report pro-industry results than are other articles. It is unequivocally the case that sponsorship influences published results.

**Do we need more research along this line? Clearly not,** contrary to Barden et al., who say that "it is time to establish whether industry sponsorship affects the actual results of clinical trials, and subsequent meta-analysis of clinical trials." (Barden et al. 2006, p.208). On the basis of a more modest review than the above, American Medical Association (2004) took the phenomenon of industry sponsorship affecting outcomes as well established. However, the phenomenon needs to be more widely known, and more widely explored. Such studies as the above leave us with questions about the histories, contexts, and causes of these associations. The causal questions have attracted the most attention: (a) Does industry support research that is most likely to be favorable to it? (b) Does industry shape research so that it will be favorable? (c) Does industry encourage the biasing of analysis, through selective interpretations of data. (d) Does industry create publication biases, by discouraging or suppressing publication of unfavorable results, and encouraging publication of favorable ones?

### 3. Some history and context

Interactions between the pharmaceutical industry and university-based medical researchers are not new. Rasmussen (2004, 2005) shows that many of the same features that we associate with today's medical research were present in the first part of the twentieth century. Rasmussen argues that attempts to make medicine more scientific applied to pharmaceutical firms as well as to academic researchers, and created new types of collaborations. In particular, the commercial clinical trial that is at the center of the above results, became common in the period between the two world wars. There was a spectrum between collaborations in which the industry was little more than a source of drugs, funding, or other resources, and collaborations in which pharmaceutical companies initiated and designed trials, and controlled publication of results. Issues about authors failing to disclose support already existed before World War II, and Rasmussen documents a case in which the sponsoring company preferred that the author not disclose that support. Moreover, people were concerned about disclosure because reprints of articles were circulated as promotional material for drugs.

**While the issues are old ones, they have acquired renewed importance in the past few decades.** There are clearly many factors that have encouraged academic-industry interaction. In the United States, the Bayh-Dole Act of 1980 is
often seen as creating an entrepreneurial climate in universities by changing assumptions about the scope, nature, and control of intellectual property (e.g. Fielder 2004, Mirowski & Van Horn 2005, Bekelman et al. 2003). Since the Act, industry has become an increasingly welcome participant in scientific research, sometimes even seen as a necessary one: According to David Blake, a former Vice Dean of Medicine at Johns Hopkins University, "No conflict, no interest" (quoted in Schafer 2004, 15). The Bayh-Dole Act, which was itself the result of a decade of work to create a network of interested university patent administrators (Berman 2006), is not itself very relevant to clinical research, or to trends outside the United States, but it is plausible it has been influential in the creation of a new climate for research.

Whatever the causes of that climate change, they have resulted in very high levels of interaction between the pharmaceutical industry and medical researchers. In the United States, 70% of funding for clinical trials comes from the pharmaceutical industry (American Medical Association 2004). Bekelman et al. report studies that show that a minimum of 23% of biomedical researchers receive research funding from pharmaceutical companies, and that 34% of articles published in medical journals have at least one author with a financial conflict of interest. One investigation found that at 55% of FDA advisory committee meetings, at least half of advisors had conflicts of interest (Cauchon 2000). Lurie et al's (2006) more recent investigation, looking at the FDA's own conflict of interest data, found that 28% of advisory committee members reported conflicts of interest.

In one study of industry-sponsored published clinical trials, 43% of authors who disclosed their relation to sponsors were employees, 32% were consultants, 26% had received grants, 10% had stock ownership and 10% had participated in a speaker's bureau (Gross et al. 2003). Almost none of these described the sponsor's role in the study in precise terms, as is required by the journals. It is clear that there are very high levels of interaction between clinical researchers and the pharmaceutical industry.

There is also a high level of interaction between medical specialists more generally and the pharmaceutical industry. In a survey of Australian specialists, Henry et al. (2005) found that a full 41% reported having engaged in pharmaceutical-industry sponsored research in the previous 12 months. Industry interest in research is making many specialists into part-time researchers.

Mirowski and Van Horn (2005) point to the rise of the contract research organization (CRO) as a important feature of the landscape of commercialized research. Between 1992 and 2001, CRO revenues increased from US$1.0 billion, to
$7.9 billion, and the number of enrolled research subjects increased from 7 million to 20 million (Mirowski & Van Horne 2005). In roughly that same period

**pharmaceutical companies have shifted approximately half of their support of clinical trials from academic health centers to CROs — thinking in economic terms, Mirowski and Van Horne say that academic health centers have lost this market share to CROs, from in the range of 65% to 35% in ten years.** They are thus finding themselves having to compete to maintain it.

This analysis suggests two ways in which academic publication may be affected. First, if academic researchers are competing with CROs for industry support, they may, consciously or not, feel increased pressure write articles that please their sponsors. Second, since CROs make no demands about the publications stemming from their research, there is a wealth of data available for publication, essentially on the terms of its owners. There is an equivalent wealth of opportunity, then, for ghost authorship.

**Ghost authorship is a phenomenon well established to exist**, even if it is by its nature kept hidden. Healy (2003) describes attempts to enroll him as an honorary author on articles he had not written. Barnett (2003) and Johnson (2003) provide journalistic accounts, interviewing writers who earn a living crafting articles which are then authored by recognized medical researchers. A survey by Flanagin et al. (1988) found evidence of ghostwriters in 11% of articles published in major medical journals, and evidence of honorary authorship — people given author status without having participated substantially in the research, analysis, or writing of the article — in 19% of articles. Clearly, **if ghost authorship by pharmaceutical companies and their representatives is common, avenues of influence on results are extremely direct.**

Pharmaceutical companies have long recognized the value to themselves of research, and have supported it for that value. However, some commentators have argued that **in the late 1980s those companies started better understanding that their marketing efforts could benefit greatly from research** (Critser 2005). For example, when in the early 1990s, Pfizer wanted to sell its selective serotonin reuptake inhibitor (SSRI) sertraline (Zoloft) in a market dominated by other early SSRIs, it used its CRAM ("Central Research Assists Marketing") program. The company commissioned research that showed that sertraline had a cleaner breakdown route, and was associated with higher quality of life, than its competitors (Healy 2003; Critser 2005). In short Pfizer looked for data that could be used at seminars, sales events, and in continuing medical education to mark distinctions between sertraline and other SSRIs. Meanwhile, the company created research
programs to educate physicians about depression. Interestingly, even unbranded disease awareness campaigns have effects on sales of particular brands, perhaps because of consilience between unbranded and branded information (‘t Jong et al. 2004).

We see, then, that the amount of interaction between the pharmaceutical industry and medical researchers has been increasing, the number of industry-controlled clinical trials has been increasing, and the industry use of clinical research has become more varied and self-conscious.

4. Explanations and Discussion

Many possible reasons for the strong association between funding and results have been offered. Below is one classification of these. These are not competing causal explanations because, first, any or all could in principle be right about a given association and could even apply to particular studies and papers, and second, they do not all operate at the same explanatory level: researcher bias, for example, requires one or more other causal factors to be present.

4.1 Researcher Bias.

Does industry fund researchers who it has reason to expect to produce positive results in studies? As mentioned above, Lurie et al. (2006) show that FDA advisors with reported conflicts of interest are more likely to vote consistent with their conflicted interests than are other FDA advisors. These results are not surprising when we remind ourselves of the nature of concern about conflict of interest: conflicts are important because they increase the chance that people will act against one or another of their duties. With that in mind, the surprising result of Lurie et al. is the small association between reported conflicts and voting patterns.

Although there are well-known cases of pharmaceutical companies attempting to intimidate researchers to prevent them from publishing their results — such as Apotex's attempt to keep Nancy Olivieri's results hidden, or Knoll's and Boots's attempts to keep Betty Dong's results hidden (e.g. Schafer 2004) — undoubtedly the bulk of control and influence over researchers involves more hidden and subtle techniques (Baird 2003). As with much of pharmaceutical representatives' work with doctors, sponsorship creates subtle conflicts through the building of relationships that allow researchers to further their own goals, such as research and publication.
In the case of pharmaceutical representatives and physicians, the results are well known. A widely-cited meta-analysis by Wazana (2000) shows that gifts to physicians have effects. Despite the fact that physicians understand that pharmaceutical companies' primary goal in gift-giving is to influence their prescribing behavior, and though most physicians believe that they themselves are relatively immune from influence (and the more gifts they receive the more apt they are to believe this — Hodges 1995), gift-giving works. Even small gifts create felt obligations which create conflicts of interest (Katz et al. 2003).

If we apply the reminder about conflicts of interest to the more general case of the funding of trials, it is very plausible that industry funds researchers who it has reason to expect will produce favourable results: The funding itself causes such an expectation, as would any earlier association between the company and the researcher. The latter is particularly important, given that pharmaceutical companies often establish relationships with researchers — sometimes multi-faceted relationships that involve funding research, consulting, speaking at meetings and continuing medical education, and collaborative publication projects (Chaudhry & Love 2005).

This argument, though, does not elucidate the mechanisms by which researcher bias operates. For that we turn to some of the below.

### 4.2 Design Bias.

**Does industry funding promote study designs more likely to produce favourable results?** It is a relatively straightforward matter to design research around desired outcomes. Trials pitting an experimental drug against a placebo or against a low dosage of a competitor are more likely to show positive results than trials pitting that drug against the most effective established competitor. Trials pitting an experimental drug against a competitor with known side effects are more likely to show positive safety profiles than trials pitting that drug against a placebo or a competitor with established record of few side effects.

There is evidence that industry-funded studies involve poor comparators. Djulbegovic et al. (2000) found that in one pool of 130 studies of multiple myeloma trials, 60% of industry-funded trials compared the experimental treatment to placebos or no treatment, versus 21% of publicly-funded trials. Montori et al. (2004) report other examples of this kind of association. In general, drug approval processes only require that new products be shown more
effective than placebo, so pharmaceutical companies should be interested in performing or supporting trials involving placebos.

Specification of experimental populations may also affect results, though there appear to have been no systematic studies of this. Drugs are often tested in populations considerably younger than their apparent target patient populations, which in many cases may reduce the number or severity of seen side-effects. Or experimental populations that are particularly healthy in one or another respect may be created, to reduce particular side-effects. To just take one example, the by now well-known study of rofecoxib (Vioxx) by Bombardier et al. (2000) excluded patients with some risk factors for heart disease, which — given rofecoxib's suspected negative effects — might have been thought to reduce the number of heart attacks in the experimental population (though it remains a possibility that that choice actually increased the difference between numbers of heart attacks in experimental and control populations).

Non-blinded, non-randomized trials have been shown to favour the experimental treatment, whether because of expectancy effects or more conscious forms of influence (Colditz et al. 1989). There is, however, no evidence that trials funded by drug companies are in general less likely to employ randomization or double-blinding. In fact, the secondary studies report that industry-funded trials are of equal (most of those reported in Bekelman et al. 2003) or higher (Perlis et al. 2005, Montgomery et al. 2004, Procyshyn et al. 2004, and most of those reported in Lexchin et al. 2003) methodological quality than non-industry funded trials. Pharmaceutical companies often have an interest in publication of good-looking results resulting from sound trials. We might speculate that pharmaceutical companies have the resources to create trials of high quality, to check that trials are of high quality, and to ensure that reports of trials display their quality. Thus when those companies want, the trials in which they invest are likely to appear stronger than independent trials.

When there is design bias, then, it appears to stem more from local choices about comparators and populations than from more generalizable methodological choices. Some such local design bias has been found, though a full understanding of it and its scope would depend upon detailed examination of trials by knowledgeable independent experts.
4.3 *Multiple Trials with Predictable Outcomes*

**Does industry fund studies that, independent of their design, it has reason to expect to be positive?** The majority of studies it funds are of drugs that have already been extensively tested, and so it is possible that likely outcomes have already been established.

This possible cause is routinely acknowledged, and frequently dismissed: According to Lexchin et al. (2003), evidence suggests that researchers cannot predict results in advance. Hirsch (2004), writing for Merck, acknowledges that studies deemed more likely to succeed are supported, but also claims, citing some cases, that researchers cannot in general predict the results of trials.

It may be made more plausible with the recognition that a substantial number, and perhaps the majority, of individual studies funded by the pharmaceutical industry are post-marketing studies. The goals served by those studies are various, but among them are the goals of better familiarizing doctors with products, and publishing results that promote products (CenterWatch 2002). "Seeding trials" pay physicians to prescribe specific drugs as part of trials, but are clearly aimed at increasing prescriptions. A U.S. Federal investigation revealed that in some of Schering-Plough's post-marketing trials of its hepatitis C treatment Intron A, liver specialists were paid between US$1000 and $1500 per patient enrolled in the trials (Harris 2004). There were, doctors claimed, few efforts to ensure that doctors would collect and forward data to the company. Such a trial can be a successful seeding trial because the Intron A was not provided for free, as it would be in a Phase III trial, but was paid for by patients and their insurers, at an annual cost of more than $20,000 (when packaged with Schering-Plough's ribavirin). In this case the best evidence that it was a seeding trial was that it was so poorly performed as to be unpublishable.

However, not all cases of post-marketing research for marketing are as blatant, and many promise publication. Some advertising firms now own contract research organizations (CROs) and medical education and communication firms, allowing them to provide a fully integrated service from research to publication, in the aid of marketing (Angell 2004). To see their effects, we might look at the endpoints: Why are there many hundreds of publications of small trials of blockbuster drugs? A Medline search (performed in July 2006) finds 560 articles on atorvastatin (Lipitor) published in core clinical journals, 1224 articles on omeprazole (Losec/Prilosec), and 305 on amlodipine (Norvasc). Does this only represent independent interest in statins, in proton pump inhibitors, in calcium channel blockers? It is noteworthy that non-blockbuster drugs are considerably less well represented in the literature.
Post-marketing studies are, of course, designed to be successful. Given that these goals are achieved by the reproduction of established results, however, we need not see the designs as in any way inappropriate in and of themselves: an already well-studied drug is tested, in a way in which it is known to be effective, on a population for which it is effective. This is the very epitome of what Thomas Kuhn (1962) called "normal science." The publication of post-marketing studies, though, has the effect of dramatically changing the shape of the literature!

4.4 Fraud or Scientific Misconduct.

Does industry funding promote fraudulent behavior in its favour? There is some evidence that fraud and scientific misconduct is common in clinical trial research, though no or very little evidence that such misconduct is tied to sources of funding.

Gardner et al. (2005) chose target articles reporting clinical trials and surveyed randomly selected authors of those articles about scientific misconduct, achieving a relatively high response rate (59%). Of those authors, 0.6% reported misconduct in the target study, 4.7% reported misconduct in another study in which they had participated over the previous 10 years, and 17% reported knowing, not through published reports, about a case of misconduct that had occurred in the previous 10 years. The events were more or less evenly distributed among a variety of types of misconduct: fabricated or falsified data, unjustified deletion of data, deceptive or misleading report of design, deceptive or misleading report of data, and seriously misleading interpretation.

An earlier survey, by Ranstam et al. (2000), had asked clinical biostatisticians about fraud (sharply distinguishing it from poor practice) in trials in which they had been involved, and found much higher reported numbers, though from a survey with a smaller response rate (37%, or 166 completed questionnaires). Of responders, 51% reported knowing about a study that involved fraud, 31% reported participation in a project in which fraud had taken place, and 13% reported having been asked to support fraud. Despite the low response rate, these figures should still be regarded as of concern, since they represent a large number of reports of having participated in fraud.

Henry et al. (2005) performed a survey specifically looking at academic-industry interaction. They mailed surveys to 2253 medical specialists in Australia, and had a response rate of 39% of those who received the questionnaire. 24% reported
potentially problematic events in their experience of industry-sponsored studies. For example, 14% reported premature termination of a study, 12% reported that the first draft of a report had been written by the company or a CRO, 5% reported a failure to publish findings, 3% reported that the report had been edited to produce a misleadingly positive impression, and 2% reported concealment of findings. Although it is impossible to use these figures to compare industry-sponsored and more independent research, the results suggest that misconduct in sponsored trials is common.

4.5 Interpretive and Rhetorical Effects.

Does industry funding promote favourable interpretations of data? A number of analyses of the effects of sponsorship either explicitly or implicitly consider rhetorical issues. Although Montori et al. (2004) focus the bulk of their attention on possible methodological weaknesses such as faulty comparators, composite endpoints, and subgroup analysis, they also recommend that readers skip discussion sections of journal articles, paying attention only to methods and results sections. Similarly, Scott & Greenberg (2005) tell readers to "[r]esist the temptation to only read the Introduction and Conclusion sections, and carefully read the Methods and Results sections as well," and to "beware subliminal messages [in] selective or obfuscating reporting." They caution readers to beware such tools as surrogate outcomes, reporting of borderline benefits, the use of composite end-points, results not consonant with stated objectives and methods, post-hoc analyses, etc. Scott & Greenberg also suggest putting more emphasis on independent sources such as Evidence-based Medicine, ACP Journal Club, the Cochrane Library, and the like.

Evidence from a study by Als-Nielsen et al. (2003) supports such recommendations. They found that the strength of the conclusion of articles on randomized, clinical trials was unrelated to treatment effect. For example, similar positive data could lead to the conclusion that the experimental treatment was highly preferred over the control, or was only possibly preferred, with more experiments needed. Source of funding, however, was a predictor of strength of conclusion. An earlier study (Rochon et al. 1994) came to the same conclusion on using different methods: reviewers evaluated the data and the claims of 52 drug company funded publications on NSAIDS, and found that funder's drug was almost always reported as superior, but that those claims, especially claims about side-effects were not always supported by the trial data.

The survey by Henry et al. (2005) mentioned above lends weight to the idea that sponsorship may promote rhetorical bias. When researchers report that first drafts of
articles are written by the sponsoring company, they are indicating that the first round of rhetorical control is the sponsor's, and some identified misleading impressions created by the sponsor's writing.

One possible explanation for Barden et al.’s (2006) negative results in their sponsorship study is that they examined not the conclusions of articles, but published data. So to the extent that industry sponsorship affects interpretive and rhetorical moves, looking at the published data alone would not have revealed any association. This hypothesis might be tested by assessing the effects of sponsorship on the conclusions of the articles included in the study of Barden et al.

Chan et al. (CMAJ 2004) looked at a group of randomized controlled trials funded by the Canadian Institutes of Health Research (CIHR), comparing protocols for 48 trials and their associated 68 publications. (An overlapping group of authors (Chan et al., JAMA 2004) performed a similar study on a less prestigious group of trials, and found similar results.) They found that in 96% of trials efficacy outcomes had been incompletely reported, and in 81% of trials harm outcomes had been incompletely reported. Nonetheless, 80% of principle investigators who responded to an initial questionnaire denied any unreported outcomes. When confronted with evidence to the contrary, they tended to justify their non-reporting on the basis of lack of clinical importance and/or lack of statistical significance. As Chan et al. point out, their sample "consisted of relatively large, government-funded trials whose protocols were subjected to rigorous per review." Nonetheless, they identified "major deficiencies" in outcome reporting. This study says little about pharmaceutical industry sponsorship, but it indicates that journal articles should be seen not as neutral vehicles for the reporting of data, but rather as texts written for particular audiences and purposes. This is entirely consistent with other rhetorical studies of scientific writing (for an overview see Sismondo 2004).

More study needs to be done of the rhetoric of journal articles, with attention to the portions of journal articles on which most readers focus: abstracts and discussion sections. As for the study of design bias, it would be most effectively done via focused examination and analysis of particular articles, rather than via statistical treatments; to understand medical writing, interpretive work on actual writing, with attention the rhetorical choices made, is important. We know that the design of trials, and the writing of articles is decision-laden and has effects; what is needed is work to examine the content of those decisions and their effects, to display techniques used to make the conclusions of published articles more positive.
4.6 Publication Bias.

Does industry funding promote publication of favourable results and discourage publication of unfavourable results? Undoubtedly. The most clear evidence of this is the investigation by Melander et al. (2003) of the publication of trials of five selective serotonin reuptake inhibitors (SSRIs) submitted to the Swedish drug regulatory agency.

Melander et al. were able to identify all of the 38 publications resulting from 42 studies' worth of trial data. Of the 42 studies, 21 had found the test drug to be more effective than placebo. 19 of those positive studies became "stand alone" articles — articles not pooling data. Only six of the negative studies became stand alone articles. Three of the studies were each published twice as stand alone publications.

But many of the articles on SSRIs involved pooled data from subsets of the trials, with some subsets being published as many as three times; and thus some of the data (from three studies) was represented in publications five times, and some of the data was unrepresented in publications. Few of the duplicate publications cited others of their overlapping cohort, and many of the publications did not acknowledge that they represented pooled data from several studies. Thus the publications probably gave the impression of considerably more trials than there had been.

All of the articles involving pooled data were more positive than they would have been had data from all comparable trials been pooled.

Moreover, published articles tended to present only one analysis, either the intent-to-treat or a less restrictive protocol, and generally whichever showed more effect, though the regulatory submissions presented results of two or more analyses. Melander et al. thus display the orchestration of publication to present a considerably more positive image of these drugs than would be warranted by the trials on their own.

Dickersin and Rennie claim that approximately one million randomized, clinical trials have been carried out, and that only half that number has been published. Especially when one considers phenomena of multiple publication and pooling, this leaves ample room for quite extreme publication bias. The published literature should not be seen as a neutral representative of research, but of the research that authors, editors, sponsors, and controllers of data want to publish.
Lexchin and Light (2006) raise the issue of publication bias that has origins in the conflicts of interest faced by journals and journal editors. Only nine of 30 peer reviewed major medical journals surveyed had an explicit policy for dealing with journal editors' financial conflicts of interest. Almost all journals earn considerable revenue from sales of reprints of articles, occasionally by the hundreds of thousands for articles with high commercial value. Many major journals earn substantial advertising revenue: In the late 1990s the Journal of the American Medical Association earned approximately 10% of its total revenue from advertisements, and the New England Journal of Medicine approximately 20%. Thus there are clear conflicts of interest that could be expected to affect publication patterns. Perhaps much more importantly, many journals earn money from the publication of supplements, often based on symposia sponsored by pharmaceutical companies; the review standards applied to these supplements are not always the same as for normal issues of these journals.

There may be other kinds of publication bias as well. Healy (2004) observes that **ghost-written (or at least ghost-controlled) articles on sertraline (Zoloft) were published in journals with higher impact factors than were apparently non-ghost written articles, and were cited more than five times as often.** Since pharmaceutical companies have the resources to ensure that (when desired) trials have the best possible methodological controls (see above), and since they have the resources to know how to work on publication, articles they attempt to publish are likely to appear in more widely read and highly regarded journals than are articles by fully independent authors.

Pharmaceutical funding often comes with contracts that include provisions allowing for delays or suppressions of publication for commercial reasons. There is evidence that these provisions are applied (e.g. Lexchin 2005). Even if contracts are not invoked, pharmaceutical companies may delay publication simply through their control over data or over stages in the process of writing and publishing articles; thus 6.7% of survey respondents claimed to have experience publication delay (Henry et al. 2005). Obviously the suppression of results can have important effects on the literature, but so can delays, as they may make negative results invisible until later in the commercial life of a drug, affecting all the different decision-makers and analysts who pay attention to the medical literature. And where there is publication delay, we might also imagine publication rushes, where commercially valuable results are pushed to appear in print more quickly than others.

It is well known that authors and editors are more likely to publish positive than negative results (e.g. Stern & Simes 1997, Hirsch 2004). That trend continues into
the secondary literature, which tends to discuss the more positive results of the primary literature (Carter et al. 2006). While neither of these publication biases explains associations of sponsorship and outcomes, they should amplify the effects of those associations on the shape of the literature.

5. Conclusion: Some Questions

We should be left with a number of questions. Clearly all of the above explanations for the effects of research sponsorship are right at least some of the time. But we should want to know much more precisely the mechanisms by which they operate. We should want to know more about the:

- operation of conflict of interest at the level of individuals and institutions,
- decisions that lead to design bias,
- ways that postmarketing trials are used
- ways that researchers and specialists are enrolled to participate in trials
- rhetorics of articles on clinical trials
- influence on publication that allows for publication bias

Probably the most important question with which we are left is: What policies might be effective in curbing the effects of industry sponsorship? The rest of this review addresses some responses to this question.

**Peer review is ineffective at checking this kind of effect, and modestly improved peer review would be unlikely to be more effective.** With the exception of design bias and rhetorical bias, the other sources of the association are invisible to readers of single articles. And even design and rhetorical bias are not straightforward to eliminate in peer review, since many trials incorporate less than ideal methodological choices and all articles involve rhetorical choices — the difference from sponsorship being a predictable effect. The results of pharmaceutical company sponsorship are often high quality articles reporting high quality research, and so they should survive peer review as that institution is currently understood.

Probably the most commonly mentioned policy suggestion is to increase openness in clinical research by creating a system of trial markers and a registry of trials, and to disallow publication of articles based on trials not identifiable on the registry (e.g. Wager 2004). While such a measure would allow better retrospective evaluation of the literature and results on particular drugs — it would make the work of critics easier and better — it would do little or nothing to guard against: researcher bias, design bias, a proliferation of trials with predictable outcomes, misconduct, articles
rhetorically crafted to support particular drugs, or publication bias. In other words, a trial registry would directly address none of the causes of the association between sponsorship and outcome. So a trial registry would make audits easier, but it would do little to change the way that the published literature reflects pharmaceutical company interests.

Other versions of the promotion of openness, for example about conflicts of interest among authors, fare similarly. Standard journal policies already require reporting conflicts of interest, which are then acknowledged in standardized ways. There are concerns that these conflicts are under-reported, and certainly there is no virtue in that. Nonetheless, by themselves acknowledgement of conflicts may accomplish little. Even though we have good reason to believe that conflicts affect reported outcomes, articles written by conflicted authors appear in journals in almost exactly the same form as do other articles. Though readers are apt to rate relevance, believability, importance, and validity lower if financial interest are declared (Schroter et al. 2004), there is no evidence that this affects long-term citation rates. At best, this is a factor that helps to balance others (Carter et al. 2006, Healy 2004) that will tend to increase the citation rates of sponsored research.

**Furthermore, a focus on conflicts of interest might distract from other features that shape the clinical literature.** As Melander et al. (2003) show, publication bias is a serious phenomenon. Pharmaceutical companies' control over data, their interest in publishing articles that reflect well on their products, journals' tendencies to preferentially publish positive findings, and medical researchers' strong interest in authoring articles, easily combine to create a literature in which positive findings are published multiple times in different configurations, and negative findings are published once or never. In the abstract, conflict of interest plays several roles in this result, but the more important issue is surely pharmaceutical company control over data and ability to set publication wheels in motion. Ghost authoring, which probably plays a role in some instances of multiple publication, is probably another issue here, and is only indirectly related to conflict of interest as we usually think of it.

**Slightly better is pressure on authors in the form of, for example, signed statements that they have had full access to all data, and accept full responsibility for the design and conduct of the trial** (Baird 2003), or perhaps a widespread and well-enforced form of medical authorship that would make explicit the roles played by different authors, and demand a "guarantor" on articles responsible for overall integrity (e.g. Rennie et al. 1997). Of course, authors may not fully disclose roles played by sponsors (see Gross et al. 2003). To the extent
that authors comply, such measures would help prevent medical researchers being "dupes," acting as unwitting agents for pharmaceutical companies by authoring articles over which they have had limited control. Thus this kind of proposal probably reduces the amount of direct control pharmaceutical companies wield. However, it does not address the full range of causes of the association of sponsorship and outcomes.

Montori et al. (2004) recommend that physicians (and presumably others as well) read only the methods and results sections of articles; an extension of that recommendation is for journals not to publish discussion sections. In an oddly complementary proposal that might have a similar effect, Smith (2005) suggests that journals stop publishing clinical trials, but only criticisms of trials. At present, the majority of criticism of major trials, in the form of letters to the editor, has very little effect on subsequent use and evaluation of those trials (Horton 2002). Both of these suggestions run into the difficulty that current publications of clinical trials serve not just the interests of pharmaceutical companies, but also those of researchers, physicians, journalists, and others.

Adjusting publication styles is difficult, and yet it fails to get to the obvious root of the problem. Recognizing that many of the current problems with pharmaceutical research stem from a too-close interaction between industry and researchers, Schafer (2005) defends what he calls the "sequestration thesis," that industry and clinical research need to be isolated from each other. This politically infeasible solution is undoubtedly right. It would have the effect of dramatically reducing the influence of the pharmaceutical industry on the outcomes of trials and the shape of medical knowledge. Moreover, there are proposals for how to achieve this while maintaining current levels of funding. But given the huge costs of current research, many voices insist on maintaining close contact. Close contact is so much the norm that Chin-Dusting et al. (2005) merely have to catalogue different kinds of contact in order to make a case for it; few medical researchers could imagine turning their world so upside-down and inside-out that they could abandon all of these forms of contact.

Therein lies the problem: Clinical research is so tightly tied to pharmaceutical interests that the knowledge it produces is highly responsive to them. And clinical research is so tightly tied to pharmaceutical interests that it is extremely difficult for it to remove itself from them while remaining what it is today.
Works Cited (and stable http addresses where available)


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