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Short Report

How pharmaceutical industry funding affects trial outcomes: Causal structures and responses☆

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Abstract

Three recent systematic reviews have shown that pharmaceutical industry funding of clinical trials is strongly associated with pro-industry results. This article builds on those analyses, situating funding's effects in the context of the ghost-management of research and publication by pharmaceutical companies, and the creation of social ties between those companies and researchers. There are multiple demonstrated causes of the association of funding and results, ranging from trial design bias to publication bias; these are all rooted in close contact between pharmaceutical companies and much clinical research. Given these points, most proposed measures to respond to this bias are too piecemeal to be adequate.

Keywords: Pharmaceuticals; Sponsorship; Funding; Conflict of interest; Clinical trials

Industry sponsorship influences published results

Pharmaceutical company funding of clinical trials is strongly associated with published results favoring those companies' interests. This is an important issue, as biases created by funding sources influence the medical literature, its representation in medical journalism (van Trigt et al., 1995), and its condensation in evidence-based medicine (De Vries & Lemmens, 2006). These results should leave us with questions about the histories, contexts, and causes of these associations. In this article, I focus on the causal routes by which funding has its effects.

Two meta-analyses provide quantitative estimates of the effects of funding (Bekelman, Li, & Gross, 2003; Lexchin, Bero, Djulbegovic, & Clark, 2003). On the basis of eight studies examining the relationship between funding and outcomes of clinical trials and meta-analyses, Bekelman et al. found that industry funding greatly increased the chances of pro-industry results, with an odds ratio of 3.60 (95% confidence interval 2.63–4.91). A wider analysis by Lexchin et al. found that 13 of 16 studies showed an association between industry funding and pro-industry outcomes, and a further 7 between funding and pharmacoeconomic analyses. Pooling data produced a summary odds ratio of 4.05 (95% confidence interval 2.98–5.51).

A recent qualitative review strongly corroborates those results (Sismondo, in press~~-a, in press-b~~). Twenty studies published between 2003 and 2006 found an association between industry support and published

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pro-industry results, typically a strong association; only two studies in those years failed to find such an association. The results are similar whether one is looking at presentations at professional meetings (Finucane & Boult, 2004; Fries & Krishnan, 2004) or the most prestigious journals in the field (Friedman & Richter, 2004; Ridker & Torres, 2006).

Direct and indirect actions

Regulatory changes, especially those giving longer monopolies for new drugs, have given the pharmaceutical industry more purchase in its interaction with medicine. Longer monopolies mean that the industry has more control over, and interest in, key medical tools. Simultaneously, the industry has developed new marketing strategies through what is called "publication planning." Although pharmaceutical companies have long used scientific data to convince physicians to prescribe their products, with the rise of publication planning in the past three decades, companies have treated data as an important resource to be managed and marshaled (Sismondo, ~~in press-a, in press-b~~). Since the 1970s, randomized, controlled clinical trials have come to be seen as the most reliable kind of medical information (Marks, 1997), and pharmaceutical companies have recognized this and produced trial results in quantity.

Publication planning is a form of "ghost-management" of clinical research and publication when pharmaceutical companies and their agents help to shape multiple steps in the research, analysis, writing, and publication of articles, in ways unseen by readers (Sismondo, ~~in press-a, in press-b~~). These companies not only fund clinical trials but also routinely design and shape them. In company-initiated trials, company statisticians usually perform statistical analyses, and are infrequently recognized by authorship (Gøtzsche et al., 2007). Hired medical writers produce first drafts or edit many papers (Mathews, 2005). Companies propose and design multiple manuscripts around studies, by lumping and splitting data (Melander, Ahlqvist-Rastad, Meijer, & Beermann, 2003). And, medical communication companies expertly shepherd manuscripts through the publication process (Healy & Cattell, 2003).

Dozens of firms advertise their services and skills in writing medical manuscripts, communicating with the formal authors of those manuscripts, submitting them to medical journals where they should have impact, and tracking their progress and effects (Sismondo, ~~in press-a, in press-b~~). These firms are successful. One document revealed in legal proceedings lists 85 manuscripts on sertraline (Zoloft) managed by a medical communications company. Those manuscripts, published between 1998 and 2001, became a substantial fraction of the published literature on sertraline, and were much more prominently published, authored, and cited than were the other articles on sertraline published in the same period (Healy & Cattell, 2003).

Contract research organizations (CRO) are important features of this landscape. Between 1992 and 2001, CRO revenues increased from US$1.0 billion to $7.9 billion, and the number of their enrolled research subjects increased from 7 to 20 million (Mirowski & van Horne, 2005). An increasing number of those subjects are in Asia and Eastern Europe (Petryna, 2006; Shah, 2006). In the same period, pharmaceutical companies shifted, approximately, half of their support of clinical trials from academic centers to CROs. Since CROs make no publication demands, they produce a wealth of data available for publication on the terms of its owners, and an equivalent wealth of opportunity for the ghost-management of medical publication. If academic researchers are competing with CROs for funding they may, consciously or not, feel pressure to cede more control over trials and publications to their sponsors.

Indirect actions by researchers that contribute to sponsorship bias are typically described as resulting from "conflicts of interest." This term is well established and is best retained, but is misleading. The term suggests that researchers act inappropriately to further their own interests. However, it is not clear that medical researchers often have material interests in particular results. Industry funding by itself does not give researchers material interests in the direction of results, though prospects of future funding are important. Physicians may not even have conflicting duties: the fact that industry-funded trials appear to be of equal or higher methodological quality than non-industry-funded trials (Bekelman et al., 2003; Brown et al., 2006; Lexchin et al., 2003; Montgomery et al., 2004; Perlis, Harwood, & Perlis, 2005; Procyshyn, Chau, Fortin, & Jenkins, 2004; Ridker & Torres, 2006) removes at least some of the conflict between funders' interests and researchers' duties.

When funding affects individual researchers' actions, we might interpret those actions in roughly behaviorist terms, rather than as calculated. This would be in line with industry perspectives, as companies do not aim to create conflicts, but to change dispositions (e.g. Moffatt & Elliott, 2007). If we see funding as a form of gift giving, its effects might stem from felt but unrecognized obligations (Katz, Caplan, & Merz,

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2003). A long anthropological tradition of studying gifts, beginning with Mauss (1967), argues that gifts create strong dispositions or obligations to reciprocate, especially if they involve extended relationships and more than mere economic transfers. Mather (2005) shows that physicians are subject to these obligations, and that through gift-giving pharmaceutical companies become accepted parts of physicians' social landscape; and gifts to physicians have measurable effects, even though most physicians believe themselves immune from influence (Wazana, 2000). Researchers may be similarly affected by relationships with pharmaceutical companies without having material interests in one or another research design or conclusion. Researchers who receive funding from a company are likely to have other relationships with that company, such as serving as a consultant or being on a speakers bureau (Chaudry & Love, 2005) these relationships can change researchers' attitudes and habits of thought toward the company and its products.

Besides the evidence from studies of gifts, there is evidence that medical experts on Food and Drug Administration (FDA) advisory committees tend to support the interests of firms that support their work (Lurie, Almeida, Stine, Stine, & Wolfe, 2006). Acute cases have made the news: at the 2005 FDA advisory committee meeting on COX-2 inhibitors, 93% of advisors who had received fees from Merck or Pfizer voted in favor of COX-2 drugs, compared with 56% of other members of the committee (Harris & Berenson, 2005).

Sponsorship, then, creates subtle influences through the building of relationships that lead researchers to see the pharmaceutical companies with which they interact, and their products, in a more favorable light than they would otherwise. Undoubtedly, this not only inclines researchers to promote those companies' interests, but also facilitates the companies' ghost-management of research and publication to produce and publish positive results.

A classification of causes

Many causal explanations can be given. What follows is one classification of those, and evidence that each type of account in this classification is right about at least some cases. This shows that the problem is complex, and suggests a need for radical solutions.

Design bias

Funding promotes study designs that are more likely to produce favorable results, such as designs involving: placebos or other poor comparators, inappropriate doses, carefully constructed experimental populations, poor surrogate endpoints, trial durations unlikely to show side effects, and definitions likely to show activity or unlikely to show side effects (Bekelman et al., 2003; Djulbegovic et al., 2000; Montori et al., 2004). Most researchers have little to say in research design, since the majority of the industry's spending on clinical trials goes to CROs, and even academic researchers are heavily influenced by sponsors' designs and requests (Abraham, 2005). Since, as mentioned above, industry-funded trials appear to be of higher quality than other trials, design biases do not stem from poor *general* methodological choices. We need to analyze the content of individual designs and protocols and the context-specific choices about such things as comparators, doses, and experimental populations made to produce them.

Multiple trials with predictable outcomes

Although this possibility is often dismissed (e.g. Lexchin et al., 2003) the majority of funded trials are performed after drugs are on the market, and many are designed more to "familiarize" physicians and patients of products than to produce novel knowledge (Berenson, 2005; CenterWatch, 2002). To accomplish that, trials would be designed to test an already-studied drug in a way known to be effective, on a population for which it is known to be effective.

As evidence, we might look at endpoints: why are there many hundreds of publications of small trials of blockbuster drugs—many funded by pharmaceutical companies—and very few on non-blockbusters? A Medline search found 560 articles on atorvastatin (Lipitor) published in core clinical journals, 1224 articles on omeprazole (Losec/Prilosec), and 305 on amlodipine (Norvasc) (keyword searches for scientific names, performed in July 2006). In contrast, there were only four articles on cevimeline, and only one on metaxalone, drugs of a similar age but with small patient populations. Does this only represent independent interest in statins, in proton pump inhibitors, in calcium channel blockers, or is it partly driven by marketing concerns?

Scientific misconduct

Misconduct is common in clinical trial research, though there is no evidence that it is more so in industry-funded trials (Gardner, Lidz, & Hartwig, 2005; Ranstam et al., 2000). However, 24% of surveyed medical specialists reported problematic behavior by

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sponsors in their experience of industry-sponsored studies (Henry et al., 2005). This included the company or CRO prematurely terminating studies, changing protocols while studies were in progress, and writing first drafts of reports (Henry et al., 2005). The researchers who conducted the survey considered 8.6% of respondents to be reporting serious breaches of integrity, such as unjustified failures to publish findings and concealment and alteration of data. We do not have comparable figures for independent research.

Interpretive and rhetorical effects

Funding affects the interpretation of data and the writing of articles. For trials included in Cochrane reviews the source of funding is a good predictor of the strength of published recommendations (Als-Nielsen, 2003). This finding is independent of treatment effect, in that stated conclusions are shaped as much or more by funding source as by data. In another study, reviewers evaluated the data and the claims of 52 funded publications on non-steroidal anti-inflammatory drugs (NSAIDS), and found that funders' drugs were almost always reported as superior, but that those claims, especially about side effects, were not always supported by the trial data (Rochon et al., 1994). This should not be surprising, as in general scientific articles are not neutral vehicles for the reporting of data, but are written for particular audiences and purposes (Myers, 1990), and when sponsors write or edit drafts we can expect interpretive and rhetorical choices to reflect their interests.

Publication bias

For industry-funded trials, positive data are over-reported relative to negative data. Melander et al. (2003) provide clear evidence of this in a study of trials of five selective serotonin reuptake inhibitors (SSRIs). Forty-two trials produced 38 articles, but the 21 positive trials produced 19 stand-alone articles, whereas the 21 negative trials produced only 6. Trials were also combined in various ways, some data were represented in publications five times, and some not at all, and the disparities favored positive results.

There may be other kinds of publication bias as well. Almost all journals earn considerable revenue from sales of reprints of articles sometimes selling hundreds of thousands of articles with high commercial value creating potential conflicts of interest that could affect publication patterns (Lexchin & Light, 2006). Many journals earn money from the publication of supplements, often based on symposia sponsored by pharmaceutical companies, and review standards applied to these supplements typically differ from those of normal issues of these journals (Bekelman et al., 2003). Research contracts often include provisions allowing for delays or even suppressions of publication for commercial reasons (Blumenthal, Campbell, Anderson, Causino, & Louis, 1997; Lexchin, 2005). Finally, biases of the literature toward positive results may accentuate the effects of pharmaceutical company funding (e.g. Carter, Griffin, & Carter, 2006).

Discussion

We are left with a number of questions and research projects, some mentioned above. Most important is, what policies might curb the effects of industry sponsorship?

Commonly proposed checks on clinical trials do not address the above pathways. *Peer review* mechanisms might address design bias and interpretive bias. However, peer review has not been shown to be an effective tool of quality control (e.g. Campanario, 1998; Jefferson, Rudin, Brodney, & Davidoff, 2006). *Trial markers and registries* allow for retrospective analysis of biases, but do not help to correct them, and certainly not when they are most important, in the period just before and after drug approval. There is conflicting evidence on whether *conflict of interest disclosure* increases or decreases credibility (Cain, Loewenstein, & Moore, 2005; Schroter, Morris, Chaudhry, Smith, & Barratt, 2004). Even were they followed, strong conflict of interest disclosure guidelines that accepted the status quo of funding regimes would not address any of the routes by which funding has its effects.

Instead of such post-hoc corrective attempts, we should find ways of eliminating biases. Because many problems with pharmaceutical research stem from a too-close interaction between industry and researchers, the two should be isolated from each other. Although politically difficult, this solution would dramatically reduce 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 and innovation, by nationalizing clinical trial planning and funding (e.g. Angell, 2004). Somewhat less directly, a proposal that would separate pharmaceutical research from marketing, and would have positive effects on the phenomenon at issue here, would replace monopoly licensing of drugs with a worldwide system of prizes for innovations (Hubbard & Love, 2004). But given the entrenchment of

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current patterns of research, many voices insist on maintaining close contact. Close contact is so much the norm that one recent article only has to catalogue different kinds of contact between industry and researchers in order to make a case for it; few medical researchers could imagine turning their world so inside-out that they could abandon all of these forms of contact (Chin-Dusting, Mizrahi, Jennings, & Fitzgerald, 2005).

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.

~~Uncited reference~~

~~Baird, 2003.~~

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