

## Pharmaceutical industry sponsorship and research outcome and quality: systematic review

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*This is an abridged version; the full version is on bmj.com*

### Abstract

**Objective** To investigate whether funding of drug studies by the pharmaceutical industry is associated with outcomes that are favourable to the funder and whether the methods of trials funded by pharmaceutical companies differ from the methods in trials with other sources of support.

**Methods** Medline (January 1966 to December 2002) and Embase (January 1980 to December 2002) searches were supplemented with material identified in the references and in the authors' personal files. Data were independently abstracted by three of the authors and disagreements were resolved by consensus.

**Results** 30 studies were included. Research funded by drug companies was less likely to be published than research funded by other sources. Studies sponsored by pharmaceutical companies were more likely to have outcomes favouring the sponsor than were studies with other sponsors (odds ratio 4.05; 95% confidence interval 2.98 to 5.51; 18 comparisons). None of the 13 studies that analysed methods reported that studies funded by industry was of poorer quality.

**Conclusion** Systematic bias favours products which are made by the company funding the research. Explanations include the selection of an inappropriate comparator to the product being investigated and publication bias.

### Introduction

Clinical research sponsored by the pharmaceutical industry affects how doctors practise medicine.<sup>1</sup> An increasing number of clinical trials at all stages in a product's life cycle are funded by the pharmaceutical industry,<sup>2,3</sup> probably reflecting the fact that the pharmaceutical industry now spends more on medical research than the National Institutes of Health in the United States.<sup>4</sup> Most pharmacoeconomic studies are either done in-house by the drug companies or externally by consultants who are paid for by the company.<sup>5,6</sup>

Results that are unfavourable to the sponsor—that is, trials that find a drug is less clinically effective or cost effective or less safe than other drugs used to treat the same condition—can pose considerable financial risks to companies. Pressure to show that the drug causes a

favourable outcome may result in biases in design, outcome, and reporting of industry sponsored research.<sup>7</sup> We reviewed the relation between the source of funding of the research and the reported outcomes and investigated the quality of the methods in trials funded by pharmaceutical companies compared with other studies.

### Methods

#### Study selection

We included only studies that specifically stated that they analysed research sponsored by a pharmaceutical company, compared methodological quality or outcomes with studies with other sources of funding, and reported the results in quantitative terms. Outcomes of interest were conclusions about differences in drug effectiveness, adverse effects, cost outcomes, or publication status between industry funded trials and other trials. Work published in any language was eligible for inclusion.

#### Search strategy

We searched Medline from January 1966 to December 2002 and Embase from January 1980 to December 2002 using a combination of terms as both MESH subject headings and key words (see [bmj.com](http://bmj.com)). We scanned the reference lists from each of the articles and searched the Cochrane methodology register. We placed messages on two email drug discussion groups, contacted content experts, and searched our libraries. In cases where the reported results were incomplete, the lead author was asked for further details.

#### Data collection

From each study, we extracted the study design, type of research assessed in the study, design of research assessed in the study, search strategy used to locate research, time period covered, drug or drug class, disease, number of industry and non-industry funded articles analysed in each study, how industry funding was defined, criteria used to assess methodological quality of the research, results with respect to methodological quality or outcome of the research, and primary purpose of study.

We provide a critical description of each included study on [bmj.com](http://bmj.com) (see table 1), but did not assess methods. Using a Mantel-Haenszel test, we constructed a pooled odds ratio.<sup>8</sup>

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## Results

### Search results

The combined searches and other data sources found 3351 potential titles. We scanned titles and abstracts (where available) for mention of the pharmaceutical industry in either the title or the abstract or any suggestion that the study would deal with industry funding. We read 103 articles in full (eight in languages other than English); we retained 30 articles for analysis (these are fully referenced on bmj.com).

### Characteristics of included studies

The characteristics of the 30 studies included in this analysis are given on bmj.com. Six were reviews of pharmaco-economic reports, two reviewed meta-analyses and systematic reviews, and the remaining 22 analysed groups of clinical trials. A total of 15 papers mentioned that some trials were funded by industry but offered no further definition of industry funding. In the other 15 papers the definition varied from a statement acknowledging industry funding in the article to a more comprehensive definition.

### Relationship between source of funding and outcome

A total of 26 of the 30 studies reported results on the association of the outcome of the research and the source of funding: six examined the effects on publication, five looked at the outcome of pharmaco-economic studies, and 16 analysed the outcome of

clinical trials and meta-analyses of clinical trials (see bmj.com).

### Funding source and publication status

Research funded by drug companies was less likely to be published or presented than research funded by other sources. Three studies looked at time to publication, and two of these found that company sponsored research took longer to be published than research with other sources of funding. Research funded by drug companies was also more likely to be published in the proceedings of symposiums than non-industry sponsored research.

### Funding source and economic outcomes

Pharmaco-economic studies sponsored by the drug industry were more likely to report results favouring the sponsor's product than studies with other sources of funding in all five articles that examined this question. In three cases, however, the bias in favour of industry funded research depended on the particular question being posed or on where the pharmaco-economic analyses were published.

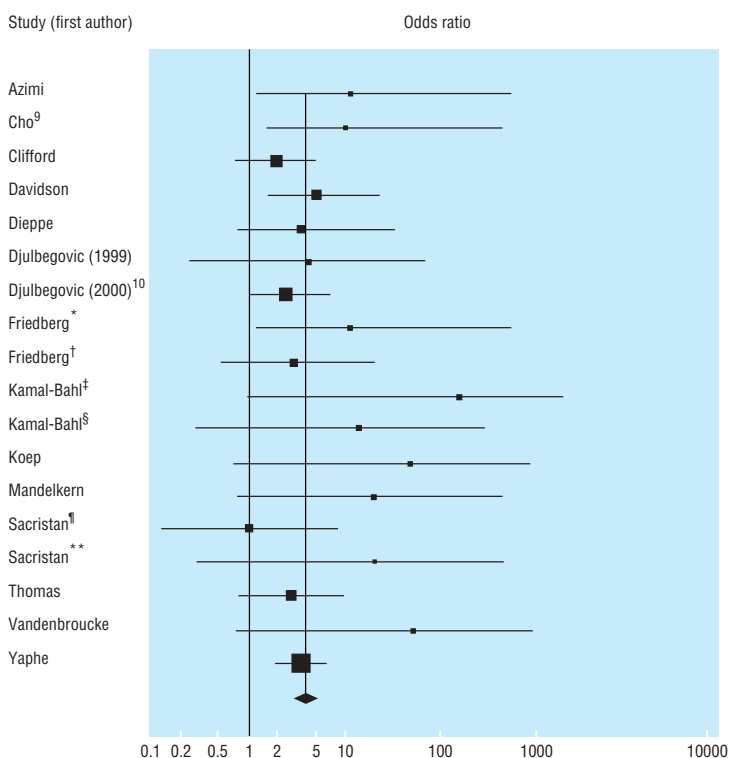
### Funding source and outcomes of clinical trials and meta-analyses

Sixteen studies investigated the relationship between funding source and the outcomes of clinical trials and meta-analyses. Of these, 13 found that clinical trials and meta-analyses sponsored by drug companies favoured the product produced by the funder. Statistical significance for this finding was reported in eight of the 13 studies and in another two there was a trend towards statistical significance. These studies covered a wide range of diseases, such as osteoarthritis of the knee, multiple myeloma, various psychiatric problems, Alzheimer's disease, and venous thromboembolism, and a wide range of drugs, such as tacrine, clozapine, third generation oral contraceptives, erythropoietin, antidepressants, and topical glucocorticosteroids. One study that found no difference looked at the outcome of trials of treatment for HIV and associated complications and in this case the trials were monitored by the National Institutes of Health. In one meta-analysis of third generation oral contraceptives, the risk of venous thromboembolism for non-industry funded research was higher than that for industry sponsored trials, although the increased risk for thromboembolic disease was significant in both cases. One study found no difference in outcomes in research published in five leading medical journals. The summary odds ratio for 18 different comparisons (15 studies) of the outcomes of industry and non-industry funded studies was 4.05 (95% confidence interval 2.98 to 5.51) (figure).

### Relationship between source of funding and methodologic quality

A total of 13 studies examined the relationship between the source of funding and the methodological quality of the research (table ). None of the 13 reported that industry funded studies had poorer methodological quality. Of the nine that provided statistical analyses, four found that drug company sponsored research had better quality scores.

Nine of the studies on clinical trials used well established methods of assessing quality. The single study



Source of funding and outcome in pharmaco-economic analyses, clinical trials, and meta-analyses of clinical trials of drug treatments; for references see bmj.com (\*Favourable qualitative results; †Overstatement of quantitative results; ‡Reporting possibility of cost effectiveness or cost savings of prophylaxis in entire high risk infant population either in point estimates or sensitivity analysis; §Reporting cost effectiveness or cost savings in either entire high risk populations or specific infant subgroups compared across studies; ¶Analyses reported in general medical journals; \*\*Analyses reported in *Pharmacoeconomics*)

## Relation between source of funding and methodological quality of research\*

Study (first author)	Criteria used to assess methodological quality of research	Results
Cho <sup>9</sup>	22 item validated scoring system	Study design in drug company sponsored clinical trials better than in research where no stated sponsorship (P=0.04)
Clifford	5 item validated scoring system (Jadad) plus component (individual items on Jadad scale and adequacy of concealment) approach	No difference by funding source for adequacy of allocation concealment (P=0.377); no difference by funding source for overall/composite score on Jadad scale (P=0.143)
Davidson	Sample size, blinding	For all trials higher rate of blinding for ones with industry sponsorship (67.5% v 41.8%, P=0.01); for trials investigating medications no difference in blinding (P=0.46); for sample size no difference between clinical trials supported by drug companies and those with other sources of funding or where funding not stated
Djulgovic (1999)	5 item validated scoring system (Jadad)	No difference in quality scores between randomised controlled trials funded solely by industry (mean 3.3 (SD 1.4); median: 3.5) and trials supported by public sources (mean 2 (SD 0.96); median: 2) (P=0.308)
Djulgovic (2000) <sup>10</sup>	5 item validated scoring system (Jadad)	Randomised controlled trials funded solely or partly by industry had trend towards higher quality scores (mean 2.94 (SD 1.3); median: 3) than trials supported by government or other non-profit organisations (mean 2.4 (SD 0.8); median: 2) (P=0.06)
Jadad	7 point validated scoring system (Guyatt and Oxman)	6/6 industry funded systematic reviews and meta-analyses had serious flaws versus 34/44 non-industry funded reviews
Kjaergard	5 point validated scale including: concealment of allocation, generation of allocation sequence, double blinding, dropouts/withdrawals, sample size	Clinical trials funded by either drug or device industry had higher quality than trials with no external funding (P<0.001); quality of publicly funded trials same as trials funded by drug or device industry (P=0.68)
Knox	9 item scale developed for this study, including clinical design, generalisable data sources, statistical tests of significance performed on appropriate outcomes, statement regarding perspective, description of costs of the main included resources, description of time horizon, description of source of total costs differences, discussion of limitations, comparisons with other published studies	Drug company sponsored pharmacoeconomic analyses less likely to formally report on study generalisability, but were more likely to provide information on the key components of the methods section than were non-profit sponsored analyses
Liebeskind	100 point scale addressing 5 aspects of trial design and reporting: randomisation, outcome, inclusion/exclusion criteria, description of therapeutic regimen, statistical analysis	Clinical trials with corporate support had better quality than trials with non-profit support (mean 73.1 (95% CI 3.9) v 53.4 (9.8); P<0.0001)
Mandelkern	Presence or absence of placebo control	5/16 industry funded clinical trials had placebo controls compared with 3/16 non-industry funded trials
Massie <sup>11</sup>	Not stated	Higher proportion of industry funded clinical trials were adequately controlled and designed than were trials with other sources of funding (71% v 33%, P<0.01)
Neumann <sup>12</sup>	Adherence to recommended protocols for cost effectiveness studies (adequate description of alternatives, study perspective clearly stated, discounted both costs and QALYs if needed, incremental analyses performed correctly) plus quality as judged by readers (scale of 1 to 7)	No difference between industry and non-industry funded studies on any measure: adequate description of alternatives P=0.30; study perspective clearly stated P=0.98; discounted both costs and QALYs P=0.65; incremental analyses performed correctly P=0.73; quality as judged by readers P=0.49
Rochon	Modified version of Chalmers score including 14 items: control appearance and/or regimen, randomisation, blinding, patients blinded, observers blinded to treatment and results, previous estimate of numbers, testing compliance, results of randomisation on pretreatment variables and inclusion in analysis, major end points, post-beta estimate, confidence limits, statistical analyses, withdrawals after randomisation, side effects discussion	No difference in quality score between industry only funded clinical trials and those funded by government or foundations (mean 36.9% (SD 17.6%) v 37.1% (17.8%), P=0.271)

QALY=quality adjusted life year.

\*References not cited here are on bmj.com

that reported on the methods of pharmacoeconomic analyses used commonly accepted criteria for assessing cost effectiveness.<sup>12</sup>

One study evaluated the appropriateness of the comparators in clinical trials and found that a greater proportion of industry sponsored studies compared innovative treatment to either placebo or no therapy than did studies sponsored by public resources (60% v 21%; P<0.001).

## Discussion

Research sponsored by the drug industry was more likely to produce results favouring the product made by the company sponsoring the research than studies funded by other sources. The results apply across a wide range of disease states, drugs, and drug classes, over at least two decades and regardless of the type of research being assessed—pharmacoeconomic studies, clinical trials, or meta-analyses of clinical trials. All the evidence reported in our meta-analysis of a subset of homogeneous studies suggests that there is some kind of systematic bias to the outcome of published research funded by the pharmaceutical industry.

## Other systematic reviews

Our results confirm and extend those reported by Bekelman et al.<sup>13</sup> They identified only five studies that compared outcomes in research funded by pharmaceutical companies and other sources and our study adds another 16 studies. We are also supported by Rochon and coworkers (we excluded this paper because all of the trials were sponsored by drug companies and were, therefore, not comparable with trials lacking company funding).<sup>14</sup> They found that trials supported by the manufacturers of non-steroidal anti-inflammatory agents almost always reported that the sponsor's drug was as effective or more and less toxic than the comparison drug.

## Possible explanations

At least four possible explanations exist for favourable results seen in industry sponsored research. Firstly, pharmaceutical companies may selectively fund trials on drugs that they consider to be superior to the competition. Data collected so far, however, indicate that researchers cannot predict results of trials in advance.<sup>15</sup>

Secondly, positive results could be the consequence of poor quality research conducted by industry. For

**What is already known on this topic**

When a pharmaceutical company funds research into drugs, studies are likely to produce results favourable to the sponsoring company's product

**What this study adds**

Research funded by drug companies was more likely to have outcomes that favour the sponsor's product than research funded by other sources

This cannot be explained by the reported quality of the methods in research sponsored by industry

The result may be due to inappropriate comparators or to publication bias

example, low quality trials exaggerate the benefits of treatment by an average of 34%.<sup>16 17</sup> We found that the research methods in research sponsored by drug companies are at least as good as the methods in non-industry funded research. This does not guarantee the absence of bias in studies sponsored by the industry since outcome could be influenced by factors left out of quality scores, such as the question asked or the conduct or reporting of the study.<sup>7 18</sup>

Thirdly, selecting an appropriate comparator is a key issue in planning a clinical trial.<sup>7 10 15</sup> In one study, when most cases in which the doses of the study and comparator drugs were not equivalent, the drug given at the higher dose was that of the supporting manufacturer. As the authors saw, higher doses may bias the results in favour of effectiveness of the manufacturer's product. Safer reports that in trials of psychiatric drugs the comparator drug is often given in doses outside the usual range or there is a rapid and substantial dose increase in the drug not manufactured by the sponsoring company.<sup>16</sup> In another instance, research funded by the company marketing fluconazole compared it to oral amphotericin B, a drug known to be poorly absorbed, thereby creating a bias in favour of fluconazole.<sup>17</sup> We did not consider who is finally responsible for the selection of the comparator—investigators, regulatory agencies, or sponsors.

Finally, our results suggest that publication bias may explain our finding of bias in favour of outcomes of research funded by industry. Although research sponsored by industry was less likely to be published than research with other sources of funding, the two studies with this finding did not specifically examine whether non-publication applied just to research with non-significant outcomes.<sup>18 19</sup> In the past few years, manufacturers have attempted to prevent studies which are unfavourable to their products from being published, in several high profile cases.<sup>20-22</sup>

Massie and colleagues raise another possible source of publication bias; research which was industry funded appears more often in symposiums.<sup>11</sup> Studies in symposiums are known to lack peer review and to favour the sponsor's product.<sup>9 23</sup> Although the methods of industry funded trials are at least equal to those in studies funded by other sources, the absence of peer review may result in an overly favourable interpretation of the results of a trial. Rochon and colleagues noted that claims of superiority for the sponsor's product were often not supported by the data.<sup>14</sup>

Leading medical journals recently decided to establish more rigorous criteria for the acceptance of research sponsored by industry; this is a step in the right direction towards increasing the credibility of studies paid for by drug companies.<sup>24</sup> The revised CONSORT statement should also help improve the quality of clinical research.<sup>25</sup> In addition, authors and editors should consider including a statement concerning prior beliefs of the investigators about the uncertainty of the treatments that are reported. Finally, all clinical trials should be registered prospectively as the only way to prevent publication bias.<sup>26</sup>

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