

**CONFLICT OF INTEREST IN INDUSTRY-SPONSORED
ECONOMIC EVALUATIONS: REAL OR
IMAGINED?**

**Marco Barbieri
Research Fellow**

**Michael Drummond
Professor of Health Economics**

**Centre for Health Economics
University of York
UK**

Correspondence to:

Michael Drummond
Centre for Health Economics
University of York
Heslington, York YO10 5DD, UK
Tel: +44 1904 433709
Fax: +44 1904 433644
e-mail: chedir@york.ac.uk

Marco Barbieri
Centre for Health Economics
University of York
Heslington, York YO10 5DD, UK
Tel: +44 1904 434264
Fax: +44 1904 433644
e-mail: mb35@york.ac.uk

Abstract

As industry sponsorship of pharmacoeconomics studies has increased, concerns have been raised about potential biases, owing to the conflicts of interest that this sponsorship creates. A review of the literature indicates that there are some causes for concern, given the fact that most pharmacoeconomic studies report positive findings for the sponsor's drug. However, a more detailed analysis suggests that, while the methodological quality of some published studies may be poor, the main reason for positive results is that companies only sponsor economic studies where a positive outcome is likely. Therefore, it is concluded that the best way of dealing with perceptions of sponsorship bias is not increased rhetoric, but to increase public funding of economic evaluation of medicines, thereby creating a true mixed economy for research funding in this field.

Introduction

In recent years there has been a large increase in the publication of economic evaluations of medicines (often referred to as 'pharmacoeconomic studies'). Many of these studies are sponsored by the pharmaceutical companies whose products are the subjects of evaluation. This has led some commentators to question whether conflict of interest may cause some studies to be biased [1•, 2-7, 8•, 9,10]. In economic evaluations sponsored by companies, there is an obvious tension between the desire to undertake studies to show a marketing advantage and the desire to adhere to good scientific principles. This paper assesses the extent to which any bias is real or imagined, and makes recommendations for minimising the difficulties caused by conflict of interest in industry-sponsored studies.

Conflict of Interest - is it real?

Concerns about the potential bias in industry-sponsored research are neither new, nor confined to economic studies. Several authors have raised the issue of potential conflict of interest between physicians and their funding sources in company-sponsored clinical trials. In a recent study Stelfox et al [11] found that authors who had a financial relationship with manufacturers were much more likely (than those who did not) to support the use of calcium-channel antagonists for cardiovascular disorders. In a review of randomised control trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis, Rochon [12] et al found that in all trials associated with a pharmaceutical firm the manufacturer-associated drug was reported as comparable or superior to the comparison drug. In a retrospective analysis of randomised controlled trials published in 5 leading medical journals, Davidson et al. [13] found that studies supported by a pharmaceutical firms were much less likely to favour the traditional therapy over a new drug than studies not supported by manufacturers. Other reviews have confirmed this trend [14,15]. There are several ways through which sponsoring firms may bias the scientific evidence generated in a clinical study. Companies often control the research question, the selection of patients, the way of reporting drop-outs and side-effects and which data are reported in peer-reviewed publications [16].

The risk of bias is perhaps even greater in economic analyses of pharmaceuticals. While clinical trials are conducted using standardised designs and analytic techniques, often determined an external regulatory agency, economic analysis are generally less standardised and are exposed to subjective opinion and interpretation of the results. Investigators may thus be tempted to produce positive findings for pharmaceutical products in order to enhance future opportunities for collaboration and funding. Moreover positive findings are easier to publish and to attract public attention [17].

While the issue of financial conflict of interest in clinical trials supported by drug companies has been debated in the literature, less has been written about economic evaluations. In one study Azimi and Welch [18] reported that industry financed cost-effectiveness analyses were more likely to support additional expenditures on investigational drugs than standard treatments. In a more recent study, Friedberg et al [19] examined the published pharmacoeconomic literature for 3 areas in oncology. They addressed the question of whether pharmaceutical company-funded economic studies were more likely than nonprofit-funded studies to report favourable results and whether they were more likely to state qualitatively favourable conclusions, despite neutral or unfavourable quantitative results. They found that there was a statistically significant relationship between funding source and qualitative conclusion.

Unfavourable conclusions were reached by only 5% (1/20) of drug company-sponsored studies, compared with 38% (9/24) of non-profit sponsored studies. In addition, pharmaceutical-sponsored studies were more likely than non-profit-sponsored studies to overstate quantitative results (30% versus 13%), but this finding was not statistically significant.

Also, in a review of economic studies published between 1988 and 1994 Sacristan et al. [18] found that results favourable to the drug under study was reached by 92% of evaluations published in the journal *PharmacoEconomics*, where 83% of the studies were sponsored by drug companies. By contrast, the rate of positive findings was only 49% in studies published in general medical journals where 74% of the studies were financed by government agencies.

Conflict of interest – is it imagined?

From this evidence we can conclude that industry funding has an impact on research and that concerns about pharmaceutical sponsored studies remain, both in terms of financial considerations (that can influence both sponsors and analysts) and lack of methodological rigour in the studies themselves. Surveys of healthcare decision-makers have indicated that this potential bias is perceived by decision-makers as a barrier to the use of study results in practice (Drummond et al. [19]).

However, economic evaluation has a set of methodological principles that those sponsoring and undertaking studies are expected to follow [20] Therefore, are there any other explanations to these apparent biases?

Friedberg and colleagues themselves proposed some alternative explanations to the significant association they found between authors' stated qualitative conclusions regarding the cost-effectiveness of drugs and study sponsorship by pharmaceutical companies. They underlined the fact that retrospective methods had been used in 89% of the studies analysed. These methods allow investigators and drug companies to identify the clinical trials most likely to yield positive outcomes (looking at the early clinical data) and thus pharmaceutical firms can fund economic studies accordingly to these early results. The hypothesis of early screening is also supported by Gagnon [21]. He argues that drug companies often conduct internal economic evaluation throughout the development of a medicine, since the reimbursement for that drug is often dependent on positive economic findings. Therefore the drugs that are marketed are

less likely to be subjected of unfavourable economic evaluation. Moreover, because marketed product have demonstrated positive clinical findings during development and since these findings often lead to positive economic outcomes, it is not surprising that pharmaceutical-sponsored economic studies report favourable results.

Le Pen [22] raised another interesting issue. He addressed the fact that Friedberg and colleagues failed to find biases in the individual studies themselves, meaning that individual studies are in general reliable. Therefore they identified a publication bias rather than a study bias. Studies with unfavourable preliminary outcomes are less likely to be completed and submitted to peer review, regardless of funding sources. Investigators, journal editors and journal peer reviewers may all be responsible for the existence of publication bias [23, 24-27]. Obviously research sponsors might be responsible of this bias too, since it is difficult to force companies to support and publish studies showing that their products are not cost-effective. But again, this seems to be rational economic behaviour rather than a scientific bias in the pharmaceutical studies themselves. For example, Gazzaniga and Garattini [28] reviewed 7 pharmaco-economic studies on cholesterol-lowering agents and whilst they found lack of methodological rigour in some part of the analyses they failed to find a link with the source of funding. Also, although Friedberg and colleagues found an association between overstatement of quantitative results and companies-sponsorship of studies this association was not statistically significant. (A summary of the results of studies investigating conflict of interest in industry-funded research is given in Table 1.)

Conclusions and Recommendations

We can conclude that while the potential for bias in pharmaceutical-sponsored studies is both real and imagined, there might be other explanations rather than scientific bias. Pharmaceutical companies provide valuable resources to many areas of academic medicine and are a primary source of funding for pharmaco-economic studies. It is in the interest of drug companies themselves to assure credibility and scientific rigour to their studies. Nevertheless, the rhetoric about the potential bias in industry-sponsored research is likely to continue. However, to ban or restrict studies directly

sponsored by drug companies would not be practical and would deny companies the right to generate data about their products, possibly leading to economic claims for products based on even less research evidence than at present. Instead, activities such as the development of methodological standards and guidelines, improvement in the peer review process and clarification of the contractual relationship between sponsors and analysts should be increased in order to reduce this potential bias [8•].

The main problem is not that published pharmacoeconomic studies are subject to scientific bias. Rather, the problem is that, due to screening conducted by the companies, economic evaluations are only sponsored in situations where a positive result is likely.

This publication bias can only be addressed by increasing the funding for economic evaluations of medicines from other, mainly public, sources. In some jurisdictions, such as Canada and the United Kingdom, public agencies undertake and publish their own economic analyses of important new classes of pharmaceuticals. (See, for example, the reports of the Canadian Coordinating Office for Health Technology Assessment and the National Institute for Clinical Excellence) [29,30].

Thus, the best way of dealing with perceptions of sponsorship bias is not increased rhetoric, but a true mixed economy in research funding, accompanied by an adherence to explicit standards of good methodological practice.

Table 1. Main investigations on conflict of interest in drug company-sponsored studies

Authors	Type of study	Results
Stelfox et al. (1998)	Review of English-language medical literature (1995-1996) about the safety of calcium channel antagonists.	70 articles found: 30 supportive of calcium-channels antagonist, 17 neutral, 23 critical. 96% of the supportive authors had financial relationship with manufacturers of calcium-channel antagonists, as compared with 60% of neutral and 37 of the critical authors. The association was statistically significant.
Rochon et al. (1994)	Review of publications of manufactures-supported trial of NSAIDs (1987-1990)	52 publications representing 56 trials were found. In all 56 trials the manufacturer-associated drug was reported as comparable (71.4%) or superior (28.6%) to the comparison drug.
Davidson RA (1986)	Review of randomised clinical trials in different areas.	107 published trials were analysed. 71% of trials favoured new therapies; 43% of these were funded by pharmaceutical firms. Of 31% of trials favouring the traditional therapy, only four (13%) were supported by drug companies. There was a statistically significant association between the source of funding and the outcome of the study.
Cho and Bero (1996)	Comparison of drug studies published in symposium proceedings that are sponsored	The percentage in favour of the drug of interest was 98% for articles with drug companies support and 79% for articles without drug

	by drug companies with articles published in their parent medical journals.	companies support. The difference was statistically significant.
Friedberg et al. (1999)	Review of original English language (1988-1998) cost-effectiveness analyses of oncology drugs in 3 new drug categories (hematopoietic colony-stimulating factors, serotonin antagonist antiemetics, and taxanes).	44 eligible articles were found. Unfavourable conclusions were reached by 38% of non-profit sponsored studies (9/24) while only by 5% of pharmaceutical company-sponsored studies (1/20). There was a statistically significant association between funding source and qualitative conclusions. Favourable qualitative conclusion when quantitative results were neutral or unfavourable were present in 30% of studies sponsored by drug companies (6/20) versus 13% of non-profit sponsored studies (3/24). This association was not statistically significant.
Azimi and Welch (1998)	Comparison of cost-effectiveness analyses sponsored by drug companies with those sponsored by non-profit organisations	Industry-financed cost-effectiveness analyses were more likely to support additional expenditures with investigational drugs than standard treatments.
Drummond et al. (1997)	Survey of decision-makers' attitudes to economic evaluation conducted in the UK.	59% of responders cited the lack of credibility of industry-sponsored studies as an obstacle to the use of the study, with 8% of respondents identifying this as the most important obstacle. By contrast, the possibility that government studies were not credible was identified as a problem by only 9% of respondents, with less than 1% identifying this as the most important.
Sacristan et al. (1997)	Review of economic studies published over the period 1988 to 1994. Analysis of publication bias.	22 out of 24 studies (83%) published in <i>PharmacoEconomics</i> reported positive results, with 83% of them sponsored by drug companies. 34 out of 69 studies (49%) published in general medical journals reported positive findings, with 74% of them sponsored by government agencies. The difference in percentage of positive results between <i>PharmacoEconomics</i> and general medical journals was statistically significant.
Gazzaniga and Garattini (1992)	Review of 7 pharmaco-economic studies on cholesterol-lowering agents	Lack of methodological rigour in some part of the analyses, but this is not necessary linked to industrial sponsorship. The role of sponsor played by drug companies in 5 of the 7 studies did not seem to have significantly affected the quality of the results.

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