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Conflicts of interest in biomedical publishing

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PhD thesis

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Preface

The work included in this thesis was conducted during my appointment as a PhD student from 2008 to 2012 at The Nordic Cochrane Centre and during a visiting fellowship from September to November 2010 at the San Francisco branch of The US Cochrane Centre.

My supervisors were Professor Peter C. Gøtzsche and Professor Lisa Bero.

The thesis is based on the following seven papers:

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Lundh A, Krogsbøll LT, Gøtzsche PC. Access to data in industry-sponsored trials. Lancet. 2011;378:1995-6.

Lundh A, Barbateskovic M, Hróbjartsson A, Gøtzsche PC. Conflicts of interest at medical journals: the influence of industry-supported randomised trials on journal impact factors and revenue - cohort study. PLoS Med. 2010;7:e1000354.

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Structure and acknowledgements

Structure of the thesis

The structure of the thesis follows the guidelines from the Faculty of Health and Medical Sciences, University of Copenhagen. First, I give an introduction to the context of the thesis and present the objectives. The next part of the thesis consists of seven papers. Finally, I present an overall discussion and conclusion.

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Abstract

The amount of medical information is overwhelming and every day thousands of research papers are published. To stay up to date, clinicians may read the latest trials published in high impact journals, search for updated systematic reviews and use clinical guidelines. These approaches are laudable, but the medical literature may not always be a trustworthy source of information, free from commercial interests of the drug and device industry.

The aim of this PhD was to investigate how conflicts of interest related to the drug and device industry affect the medical literature through influence on generation, interpretation and dissemination of evidence. This was done in six studies reported in seven papers.

In our first study, we undertook a Cochrane methodology review investigating whether sponsorship of drug or device studies was associated with outcomes favourable to the sponsor's products. We found that sponsorship of studies by the industry leads to more favourable results and conclusions than studies sponsored by other sources and suggest that industry bias is prevalent. One mechanism behind this bias could be explained by the findings from our second study. In this study, we investigated a sample of protocols and papers of industry trials published in The Lancet. We found that the sponsors had major involvement with data analysis and reporting of the results of the trials, and that the participating academic authors often did not try to confirm the sponsors' analyses using the raw data. In our third study, we investigated how publication of industry trials influenced impact factors and journal economy in a sample of six major general medical journals. We found that publication of industry trials may increase journal impact factors and that sales of reprints may provide a substantial income for the journals. In our fourth study, we investigated how reporting bias in industry drug trials affected results of meta-analyses. We found that the inclusion of unpublished trial data may affect the results, but that the effect varies by drug and outcome. In our fifth study, we investigated whether Danish medical textbooks were sometimes sponsored by drug or device companies, and whether the sponsors had tried to influence the content. We found that sponsorship of medical textbooks was fairly common and may lead to lack of academic freedom. In our sixth study, we investigated the prevalence and disclosure of conflicts of interest among authors of clinical guidelines by Danish medical specialty societies. We found that conflicts of interest were common, that disclosure of these conflicts was rare and that it was often unclear which evidence was behind specific treatment recommendations.

The conclusion is that the drug and device industry influences the results and conclusions of research studies and that this impacts on the evaluation of drug and device treatment effects. Additionally, conflicts of interest also exist for journal and textbook editors and authors of textbooks and clinical guidelines. This may in turn affect which studies are published in high impact journals and how the evidence is described and interpreted. Results from industry-sponsored research should be read with caution and journals should disclose their income from industry sources and give readers access to protocols and raw data from industry trials. In addition, conflicts of interest in medical textbooks and clinical guidelines should be disclosed and better managed, preferably by making them completely free from commercial influence.

Danish summary

Mængden af lægevidenskabelig information er overvældende, og hver dag publiceres tusindvis af forskningsartikler. For at holde sig opdateret kan klinikere læse de seneste randomiserede forsøg publiceret i anerkendte tidsskrifter, søge efter opdaterede systematiske oversigtsartikler og anvende kliniske retningslinjer. Disse strategier er prisværdige, men den lægevidenskabelige litteratur er ikke altid en troværdig informationskilde, fri for lægemiddel- og medikoindustriens kommercielle interesser.

Formålet med denne ph.d. var at undersøge, hvordan interessekonflikter i forbindelse med lægemidler og medikoudstyr påvirker den lægevidenskabelige litteratur gennem indflydelse på frembringelse, fortolkning og formidling af evidens. Dette blev gjort i seks studier rapporteret i syv artikler.

I vores første studie udførte vi et Cochrane review med henblik på at undersøge, om sponsorering af lægemiddel- eller medikoforsøg var forbundet med resultater der favoriserede sponsors produkter. Vi fandt, at forsøg sponsoreret af industrien havde mere favorable resultater og konklusioner i forhold til forsøg sponsoreret af andre kilder, og tyder på tilstedeværelsen af industribias. En årsag til denne bias kan forklares ud fra resultaterne af vores andet studie. I dette studie undersøgte vi en stikprøve af protokoller og artikler af industriens randomiserede forsøg publiceret i The Lancet. Vi fandt, at sponsorerne havde stor involvering i dataanalyse og rapportering af resultaterne fra forsøgene, og at de medvirkende akademiske forfattere ofte ikke forsøgte at bekræfte sponsorernes analyser ved hjælp af rådata. I vores tredje studie undersøgte vi, hvordan publicering af industriens randomiserede forsøg påvirkede impact factors og økonomien hos seks lægevidenskabelige toptidsskrifter. Vi fandt, at publicering af industriens randomiserede forsøg kan øge impact factors, og at salget af særtryk af artiker kan give en betydelig indtægt for tidsskrifterne. I vores fjerde studie undersøgte vi, hvordan rapporteringsbias i industriens lægemiddelforsøg påvirkede resultaterne af meta-analyser. Vi fandt, at medinddragelse af upublicerede forsøgsdata kan påvirke resultaterne, men at effekten varierer afhængigt af typen af lægemiddel og effektmål. I vores femte studie undersøgte vi, om danske lægevidenskabelige lærebøger nogle gange var sponsoreret af lægemiddel- eller medikoindustrien, og om sponsorerne havde forsøgt at påvirke indholdet i bøgerne. Vi fandt, at sponsorering af lægevidenskabelige lærebøger var forholdsvis almindelig og kan føre til mangel på akademisk frihed. I vores sjette studie undersøgte vi forekomsten og offentliggørelsen af interessekonflikter blandt forfatterne af kliniske retningslinjer udgivet af danske lægevidenskabelige selskaber. Vi fandt, at interessekonflikter var almindelige, at offentliggørelse af interessekonflikterne var sjælden, og at det ofte var uklart, hvilken evidens der stod bag konkrete anbefalinger.

Konklusionen er, at lægemiddel- og medikoindustrien påvirker resultaterne og konklusionerne i videnskabelige undersøgelser, og at dette påvirker bedømmelsen af behandlingseffekten af lægemidler og medikoudstyr. Derudover eksisterer der interessekonflikter for tidsskrifts- og lærebogsredaktører og forfattere til lærebøger og kliniske retningslinjer. Dette kan igen påvirke, hvilke undersøgelser der publiceres i anerkendte tidsskrifter, og hvordan evidensen fremlægges og fortolkes. Resultater fra industrisponsoreret forskning bør læses med forsigtighed, og tidsskrifter bør oplyse deres indkomst fra industrien og give læserne adgang til protokoller og rådata fra industriens

randomiserede forsøg. Desuden bør interessekonflikter i medicinske lærebøger og kliniske retningslinjer offentliggøres og håndteres bedre, helst ved helt at undgå kommerciel indflydelse.

Introduction

It is a prerequisite for delivering the best available healthcare for patients that decisions are based on updated evidence from valid research studies.[1] This is not an easy task, as the amount of medical information is enormous. The database PubMed alone includes more than 22 million biomedical records[2], and every day 75 trials and 11 systematic reviews are published.[1] It has been estimated that a clinician needs to read 4 to 6 papers daily just to keep up to date in his or her subspecialty[3] and more than 30 papers to keep up to date in internal medicine.[4] This is impossible and reading all papers would also be a waste of time, as much of the research is biased in design and conduct, answers the wrong clinical questions and is poorly reported.[5] A more focused strategy for obtaining valid information is therefore necessary.

Evidence-based medicine is one proposed solution to this problem. It aims at integrating the best research evidence with clinical expertise and patient values.[6] The cornerstone of evidence-based medicine and the gold standard for evaluating therapeutic and preventive interventions is the randomised clinical trial. Due to the randomisation procedure and other bias preventing principles in their methodology, trials provide more valid results than observational studies.[7] Results from individual trials can be synthesised in systematic reviews using meta-analysis.[8] However, as clinical decisions often involve choosing between various diagnostic tests and treatments, and as multiple systematic reviews may exist in the same area, this still present a challenge for clinicians in handling the information. The evidence is therefore often summarised further in medical textbooks and clinical guidelines.

Treatment decisions and industry influence

Clinical decision making is a complex process and patients may weigh the balance of benefits and harms of a treatment differently.[9] A prerequisite for informed decision making is that the physician provides the patient with balanced information. However, busy physicians may not have time to track down the evidence themselves and they sometimes rely on information provided by the industry, e.g. through meetings with sales representatives, advertisements, sponsored continuing medical education or sponsored conference participation.[10] The reliance on industry sources is not without consequences for patients and society, as it leads to irrational prescriptions of sponsor's drugs and higher costs.[11,12] In contrast, this interaction is highly profitable for the industry and it has been estimated that the drug industry spends twice as much money on promotion than on research.[13,14] Developing a new innovative treatment is expensive and the current patent model makes it more rewarding for companies to develop a large number of new drugs with few clinical advantages, if any, and spend money on persuading physicians to prescribe these drugs.[15]

Even physicians who do not interact with the industry have problems providing their patients with trustworthy information. Apart from the industry's focus on influencing the dissemination of evidence, the industry also has a major impact on how the evidence is generated and interpreted.[16] Commercial biases may be introduced at various steps of the pathway from the generation of data in clinical trials, through synthesis of trial results in systematic reviews, and to summarisation of the evidence in textbooks or clinical practice

guidelines. In this way, the industry may also influence individual decision making indirectly, even when a doctor tries to remain critical and fact-based.

Clinical trials

Drugs are the most commonly used treatments in health care and most clinical trials are of drug interventions.[17] The drug and device industry funds most biomedical research[18] and around half of clinical trials are industry funded.[17] In this way, the industry has a major impact on which treatments are being tested in clinical trials and how trials are conducted, which also results in a major influence on clinical decisions.[16] The influence on generation of evidence for drug treatments has had untoward consequences for patients. Recent cases include the antiarthritis COX-2 inhibitors rofexoxib (Vioxx) and celecoxib (Celebrex), and the antidiabetes drug, rosiglitazone (Avandia). For these drugs, the increased risk of myocardial infarction was selectively underreported in the industry-sponsored trials.[19] It has been estimated that rofecoxib resulted in about 10,000 deaths in the US alone, before it was pulled off market.[19]

Industry sponsors have influence on how patient symptoms and events are coded in trial databases, how data are analysed and which data end up in journal publications. For example, a company may selectively publish favourable outcomes and withhold negative outcomes of a trial (outcome reporting bias) or it may choose not to publish a negative trial (publication bias).[20,21] Furthermore, the industry may bias the trial design by using inferior comparators, wrong dose, short follow-up or inappropriate patient populations.[22] This is a likely explanation why industry trials on average show more favourable results than non-industry sponsored trials.[23,24]

Biomedical journals

The results from clinical trials are published in biomedical journals, and journals are an important information source for physicians.[25] Due to the enormous amount of medical information, many physicians only read papers published in the leading general and specialist medical journals. Because of their prestige, these journals are able to select the most clinically relevant and methodologically sound studies for publication, and clinical trials of novel therapies are often published in these journals.

Editors have to ensure that the results from the trials they publish are valid, but this is not an easy task as the industry, makes trial results appear more favourable than they actually are through selective reporting and spin.[20] Furthermore, by means of publication planning and hiring of medical writing agencies, the industry deliberately aims at publishing the most favourable trials in the top journals and the rest in less important journals or leaving them unpublished.[26,27] Publication of clinical trials is also a good business for top medical journals.[28] Trials, especially industry-sponsored ones, are often cited, which increases the prestige of the journal and its impact factor, and it may also lead to increases in revenue from advertising and subscriptions. Furthermore, companies may buy journal reprints of published trial articles, leading to incomes of up to a million dollars for publishing a single article.[28] This puts considerable pressure on editors when deciding between publishing an industry or a non-industry sponsored trial. Editors also run the risk that the company may chose to withdraw their trial report and publish it elsewhere, if they ask too many critical questions.[29]

Systematic reviews and meta-analyses

Reliance of results from single trials published in top journals is problematic, as they may give a distorted picture of the truth by spuriously overestimating treatment effects[30], by being too small to detect relevant harms or by bias in study design.[8] Instead, systematic reviews that include data from all trials, address biases in trial methodology and summarise the data by quantitative methods (i.e. meta-analysis), are preferred.[8]

While evidence from systematic reviews is regarded as being more reliable than individual trials, systematic reviews are not immune to bias. For example, industry-sponsored reviews tend to provide more favourable conclusions than non-industry-sponsored reviews, particularly compared to Cochrane reviews, which generally are regarded as the most reliable ones.[31,32]

Even well conducted Cochrane reviews may reach wrong conclusions, e.g. if they do not include data from unpublished outcomes or unpublished trials. This has recently been the case for a Cochrane review on the antiinfluenza drug, oseltamivir (Tamiflu).[33] An early version of the review, based on published data only, and a company sponsored meta-analysis of unpublished trials[34], concluded that Tamiflu prevented important complications of influenza, such as pneumonia. However, after the authors got access to some of the unpublished data they did not find that Tamiflu prevented important complications.[35] Similar overestimation of effects based on published data alone has been found for antidepressants and antipsychotics.[36,37]

Medical textbooks and clinical guidelines

Medical textbooks are one of the preferred information sources for clinicians[25] and clinical guidelines are being promoted as a way to optimise patient care.[38] Textbooks and guidelines provide an easy overview of diagnostic and therapeutic questions by summarising evidence from multiple sources. However, textbooks and guidelines are often based on expert opinion[39,40], and are therefore particularly susceptible to commercial biases and personal prejudices.

Authors of medical textbooks and guidelines are often key opinion leaders in their field and often have industry affiliations[41], for example as investigators in clinical trials, as hired speakers for conferences or continuing medical education events, or as members of the companies' advisory boards. Such relationships create conflicts of interest[42] and may influence the recommendations in textbooks and guidelines. Authors with conflicts of interest tend to overestimate the efficacy and underestimate the harms of the drugs produced by the companies with which they are affiliated.[43,44] In this way, physicians without industry affiliations may also be influenced by industry on their clinical decisions if they rely on information written by authors with conflicts of interest.

Objectives

For this thesis, I wanted to investigate how conflicts of interest, related to the drug and device industry, affect the medical literature through influence on generation, interpretation

and dissemination of evidence. The topic was explored through six studies, reported in seven papers, with the following aims:

1. To investigate whether sponsorship of drug and device studies is associated with outcomes favourable to the sponsor (Paper 1).

2. To investigate what influence the sponsors have on trial conduct and reporting of results in industry-sponsored trials (Paper 2) and what types of data the academic authors have access to and how they use them (Paper 3).

3. To investigate how publication of industry-supported trials influence impact factors and the economy of major general medical journals (Paper 4).

4. To investigate how reporting bias in industry-sponsored drug trials affect results of meta-analyses (Paper 5).

5. To investigate the number of Danish medical textbooks sponsored by drug or device companies, and whether the sponsors try to influence the content (Paper 6).

6. To investigate the prevalence and underreporting of conflicts of interest among authors of clinical practice guidelines of drug treatments by Danish specialty societies (Paper 7).

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Methods and results

Paper 1

Industry sponsorship and research outcome

Cochrane Database Syst Rev. 2012, Issue 12. Art. No.: MR000033.

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[Methodology Review]

Industry sponsorship and research outcome

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ABSTRACT

Background

Clinical research affecting how doctors practice medicine is increasingly sponsored by companies that make drugs and medical devices. Previous systematic reviews have found that pharmaceutical industry sponsored studies are more often favorable to the sponsor's product compared with studies with other sources of sponsorship. This review is an update using more stringent methodology and also investigating sponsorship of device studies.

Objectives

To investigate whether industry sponsored drug and device studies have more favorable outcomes and differ in risk of bias, compared with studies having other sources of sponsorship.

Search methods

We searched MEDLINE (1948 to September 2010), EMBASE (1980 to September 2010), the Cochrane Methodology Register (Issue 4, 2010) and Web of Science (August 2011). In addition, we searched reference lists of included papers, previous systematic reviews and author files.

Selection criteria

Cross-sectional studies, cohort studies, systematic reviews and meta-analyses that quantitatively compared primary research studies of drugs or medical devices sponsored by industry with studies with other sources of sponsorship. We had no language restrictions.

Data collection and analysis

Two assessors identified potentially relevant papers, and a decision about final inclusion was made by all authors. Two assessors extracted data, and we contacted authors of included papers for additional unpublished data. Outcomes included favorable results, favorable conclusions, effect size, risk of bias and whether the conclusions agreed with the study results. Two assessors assessed risk of bias of included papers. We calculated pooled risk ratios (RR) for dichotomous data (with 95% confidence intervals).

Main results

Forty-eight papers were included. Industry sponsored studies more often had favorable efficacy results, risk ratio (RR): 1.24 (95% confidence interval (CI): 1.14 to 1.35), harms results RR: 1.87 (95% CI: 1.54 to 2.27) and conclusions RR: 1.31 (95% CI: 1.20 to 1.44) compared with non-industry sponsored studies. Ten papers reported on sponsorship and effect size, but could not be pooled due to differences in their reporting of data. The results were heterogeneous; five papers found larger effect sizes in industry sponsored studies compared with non-industry sponsored studies and five papers did not find a difference in effect size. Only two papers (including 120 device studies) reported separate data for devices and we did not find a difference between drug and device studies on the association between sponsorship and conclusions (test for interaction, P = 0.23). Comparing industry and non-industry sponsored studies, we did not find a difference in risk of bias from sequence generation, allocation concealment and follow-up. However, industry sponsored studies more often had low risk of bias from blinding, RR: 1.32 (95% CI: 1.05 to 1.65), compared with non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.84 (95% CI: 0.70 to 1.01).

Authors' conclusions

Sponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.

PLAIN LANGUAGE SUMMARY

Industry sponsorship and research outcome

Results from clinical studies on drugs and medical devices affect how doctors practice medicine and thereby the treatments offered to patients. However, clinical research is increasingly sponsored by companies that make these products, either because the companies directly perform the studies, or fully or partially fund them. Previous research has found that pharmaceutical industry sponsored studies tend to favor the sponsors' drugs much more than studies with any other sources of sponsorship. This suggests that industry sponsored studies are biased in favor of the sponsor's products.

This review is an update of a previous review on this topic that looked only at drug studies. It uses more rigorous methodology and also investigates sponsorship of medical device studies. The primary aim of the review was to find out whether the published results and overall conclusions of industry sponsored drug and device studies were more likely to favor the sponsors' products, compared with studies with other sources of sponsorship. The secondary aim was to find out whether such industry sponsored studies used methods that increase the risk of bias, again compared with studies with other sources of sponsorship. We did a comprehensive search of all relevant papers published before September 2010 and included 48 papers in our review.

Industry sponsored drug and device studies more often had favorable efficacy results, (risk ratio (RR): 1.24, 95% confidence interval (CI): 1.14 to 1.35), harms results (RR: 1.87, 95% CI: 1.54 to 2.27) and overall conclusions (RR: 1.31, 95% CI: 1.20 to 1.44), compared with non-industry sponsored drug and device studies. We did not find a difference between industry and non-industry sponsored studies with respect to standard factors that may increase the risk of bias, except for blinding: industry sponsored studies reported satisfactory blinding more often than non-industry sponsored studies. We did not find a difference between drug and device studies on the association between sponsorship and conclusions. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.84 (95% CI: 0.70 to 1.01). Our analysis suggests that industry sponsored drug and device studies are more often favorable to the sponsor's products than non-industry sponsored drug and device studies due to biases that cannot be explained by standard 'Risk of bias' assessment tools.

BACKGROUND

Description of the problem or issue

Clinical research sponsored by the pharmaceutical industry affects how doctors practice medicine (PhRMA 2008; Wyatt 1991). An increasing number of clinical trials at all stages in a product's life cycle are funded by the pharmaceutical industry, and the industry now spends more on medical research than do the National Institutes of Health in the United States (Dorsey 2010). Results and conclusions that are unfavorable to the sponsor (i.e. studies that find an expensive drug similarly or less effective or more harmful than drugs used to treat the same condition) can pose considerable financial risks to companies.

Several systematic reviews have documented that pharmaceutical industry sponsorship of drug studies is associated with findings that are favorable to the sponsor's product (Bekelman 2003; Lexchin 2003; Schott 2010; Sismondo 2008a). There are several ways that industry can sponsor a study, including single-source sponsorship, shared sponsorship, and provision of free drugs or devices only. There are also several potential ways that industry sponsors can influence the outcome of a study, including the framing of the question, the design of the study, the conduct of the study, how data are analyzed, selective reporting of favorable results, and spin in reporting conclusions (Bero 1996; Lexchin 2011; Sismondo 2008b). Although some journals now require that the role of the sponsor in the design, conduct and publication of the study be described, this practice is not widespread (Tuech 2005).

Why it is important to do this review

This systematic review is the update of an original systematic review by two of the authors (Lexchin 2003), which investigated whether sponsorship by industry is associated with the publication of outcomes favorable to the sponsor. That review is now out of date and included pharmacoeconomic papers. We therefore updated it. Recent developments, such as the adoption of trial registration could lessen the bias associated with industry sponsorship, as publication bias can be more readily detected (DeAngelis 2004). On the other hand, the release of internal industry documents as a result of settlement agreements resulting from litigation against drug companies has revealed examples of industry manipulation of the conduct and publication of studies (Fugh-Berman 2010; Ross 2008; Steinman 2006; Vedula 2009). In addition, the scope of the review is now expanded to include device studies, as they are subject to the same biases as drug studies and are also often sponsored by companies with a financial interest in the outcome.

OBJECTIVES

The objectives were to investigate whether:

- sponsorship of drug and device studies by the pharmaceutical and device industries is associated with outcomes, including conclusions, that are favorable to the sponsor;

- drug and device studies sponsored by the pharmaceutical and device industries differ in their risk of bias compared with studies with other sources of sponsorship.

METHODS

Criteria for considering studies for this review

Types of studies

This review includes reports of studies that investigate samples of primary research studies. To avoid confusion we will use the terms 'studies' for the primary research studies and 'papers' for the reports of studies of primary research studies. We will use the term trials to describe studies of a randomized clinical trial design.

We included papers of cross-sectional studies, cohort studies, systematic reviews or meta-analyses that quantitatively compared primary research of drug or medical device studies sponsored by the pharmaceutical or device industry with studies that had other sources of sponsorship. Drugs were defined as medications that require approval by a regulatory authority as a prescription drug, recognizing that these approval standards vary worldwide. Devices were defined based on the Food and Drug Administration (FDA) definition as instruments intended for use in the diagnosis, treatment or prevention of disease.

We excluded papers without quantitative data. We excluded papers of the effects of sponsorship by non-pharmaceutical or non-device (e.g. tobacco, food or chemical) industries, and papers that evaluated the effectiveness of herbal supplements or medical procedures. Papers of mixed interventions (e.g. pharmaceuticals and educational interventions) were included if drug or device data were reported separately or could be obtained from the authors.

We excluded papers that quantitatively compared the association of sponsorship and results of syntheses of research studies (i.e. systematic reviews or meta-analyses) or pharmacoeconomic studies of drugs or devices. We also excluded analyses of pharmacokinetic studies.

Only papers published in full were included; we excluded letters to the editor and published conference presentations. We had no language restrictions.

Types of data

Drug and device papers including human research studies comparing drug to placebo, device to sham, drug to drug, drug to device, device to device, or mixed comparisons where the effectiveness, efficacy or harms of the drug or device were evaluated.

Types of methods

We defined sponsorship as funding or provision of free drug or devices. Drug or device studies with pharmaceutical or device industry funding versus those with other or undisclosed funding were included. We extracted the definition of industry funding verbatim from the included papers (see Data extraction and management) and reported this in the 'Characteristics of included studies' table. For analysis, we grouped the definitions into a variety of categories, including 100% pharmaceutical or device company funding, 100% non-profit funding, mixed funding (e.g. non-profit and industry collaboration), free provision of drug or device only, and undisclosed funding.

We included papers that compared industry sponsored studies with non-industry sponsored studies and also papers that compared studies of products by competing manufacturers (i.e. studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the control treatment); we analyzed the two types of papers separately.

Types of outcome measures

Primary outcomes

We included two primary outcomes:

1. Whether the results were favorable to the sponsor.
2. Whether the conclusions were favorable to the sponsor.

We used the definition of favorable results as described in the methods of the included papers. For efficacy results, most papers considered favorable results to be those that were statistically significant (e.g. $P < 0.05$ or 95% confidence interval excluding the possibility of no difference) in favor of the sponsor's product. Based on the previous review (Lexchin 2003), which found very few studies that reported results unfavorable to the sponsor, unfavorable results were combined with studies that reported results that were neutral or not statistically significant. For harms results, most papers regarded favorable results to be those where harms were not statistically significant (e.g. $P > 0.05$ or 95% confidence interval including the possibility of no difference) or results that had a statistically significant higher number of harms in the comparator group.

Conclusions in which the sponsor's product was preferred over the control treatment were considered favorable to the sponsor. For conclusions we did not distinguish between efficacy and harms, as conclusions are often overall qualitative judgements based on a benefit to harm balance.

Secondary outcomes

We included three secondary outcomes.

1. The size of the effect estimate in industry sponsored studies versus those with other sources of sponsorship.
2. The risk of bias in industry sponsored studies versus those with other sources of sponsorship.
3. The concordance between study results and conclusions, i.e. whether the conclusions agreed with the study results, in industry sponsored studies versus those with other sources of sponsorship.

We included papers that reported at least one of these secondary outcomes, even if it reported neither of the primary outcomes.

Search methods for identification of studies

Electronic searches

We searched Ovid MEDLINE (R) In-Process and other non-indexed citations and Ovid MEDLINE (R) (1948 to September 2010), Ovid EMBASE (1980 to September 2010) and the Cochrane Methodology Register (Issue 4, 2010) (Wiley InterScience Online). We searched the Web of Science (August 2011) for papers that cited any of the papers included in our review.

Search strategy

We used the strategy shown in Appendix 1 for Ovid MEDLINE and adapted it for the other databases.

Searching other resources

Other sources of data included author files, searches of reference lists of included papers and previous systematic reviews.

Data collection and analysis

Selection of studies

Two assessors (AL and OAB) screened the titles and abstracts, when available, of all retrieved records for obvious exclusions, and assessed the remaining papers based on full text. Potentially eligible papers were sent to the other assessors for final validation of the inclusion criteria. Any disagreements were resolved by consensus and reasons for exclusions of potentially eligible papers are described in the 'Characteristics of excluded studies' table. There was no need for translation of non-English papers.

Data extraction and management

Two assessors (AL and SS) independently extracted data from included papers; differences in data extraction were resolved by consensus.

We extracted data on the following.

- Year published.
- Country of corresponding author.
- Study objective.
- Study design used in the paper (cohort, cross-sectional, systematic review or meta-analysis, other).
- Study domain - descriptive (e.g. oncology drug trials).
- Study domain - category (drug/device class, specific disease, medical specialty/type of diseases, mixed).
- Type of studies (drug, device, drug and device, mixed).
- Type of comparisons (drug versus drug, drug versus placebo, device versus device, device versus sham, device versus drug, mixed, other).
- Sample strategy used to locate research studies (electronic search only, electronic plus other, sampling of journals, sampling by venue (e.g. conference abstracts)).
- Whether there were language restrictions on the search.
- Number of studies included in the sample.
- Time period covered by studies in the paper.
- Sponsorship categories coded in the paper. Categories were:
  - 100% pharmaceutical/device company funded;
  - 100% non-profit funded;
  - mixed funding - e.g. non-profit and industry collaboration;
  - provision of drug or device only; and
  - undisclosed funding.
- Sponsorship categories used in analysis in the paper (e.g. 100% industry funded grouped with mixed funding for industry category).
- Data on association between author conflicts of interest and outcomes.
- Description of role of the sponsor (if any). For example, definition of the sponsor's role in the design, implementation or reporting in the sample of studies.
- Criteria used to assess risk of bias of the studies included in the paper.
- Primary purpose of the study.
- Whether the paper commented on appropriateness of comparators.
- Data on sponsorship and results.
- Data on sponsorship and conclusions.
- Data on sponsorship and effect size.
- Data on sponsorship and risk of bias.
- Data on sponsorship and concordance between study results and conclusions.
- Additional relevant data.

Assessment of risk of bias in included studies

Since there are no validated criteria for assessing risk of bias in these types of papers, we developed our own criteria. We reviewed papers for high, low or unclear risk of bias for each of four criteria. If a criterion was met it was regarded as having low risk of bias, and high risk of bias otherwise. If we could not determine whether a criterion was met, we coded it as unclear. We used the following criteria:

- whether explicit and well defined criteria that could be replicated by others were used to select studies for inclusion/exclusion;
- whether there was an adequate study inclusion method, with two or more assessors selecting studies;
- whether the search for studies was comprehensive; and
- whether methodological differences and other characteristics that could introduce bias were controlled for or explored.

Measures of the effect of the methods

We performed a meta-analysis of the papers that reported the association of sponsorship with favorable study outcomes in cases where a pooled risk ratio (RR) and its 95% confidence interval could be computed.

The definition of a favorable outcome varied among papers. In some papers it was stated that favorable outcomes were outcomes favorable to the sponsor's product and in others favorable to the test treatment. This difference in terminology did not matter when the comparison was between active treatment and placebo, since the sponsor was related to the active treatment and not placebo. For head-to-head comparisons, however, the sponsor could be either the manufacturer of the test treatment or the control treatment. In these cases, when data were available, we recoded outcomes as to whether they were favorable to the sponsor's product.

We separately analyzed papers of industry sponsored head-to-head studies, comparing studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the comparator treatment. This was done by assigning the newest treatment (most recent FDA approval date) as the 'test' treatment and the older treatment as the 'comparator' treatment using similar methods as described by Bero et al. (Bero 2007) and comparing the number of studies favorable to the test treatment in the two groups (i.e. sponsor produces test treatment or sponsor produces comparator treatment).

At the time many of the papers were conducted, the approach was to assess the methodological quality of studies as opposed to an assessment of the risk of bias of studies. We therefore recoded the data on methodological quality into 'Risk of bias' categories. So, for example, a trial with adequate concealment of allocation was coded as low risk of bias and a trial with inadequate concealment of allocation as high risk of bias. Some papers assessed risk of bias by summarizing the information of individual domains in an

overall methodological quality score (i.e. a scale approach). There are substantial methodological problems related to quality scales (Jüni 1999) and their use is not recommended. We therefore did not combine the results obtained with these scales, but report the results descriptively.

Dealing with missing data

We contacted authors of the original papers in an attempt to obtain missing data. If papers included studies reporting conflicts of interest, but not the source of funding, we contacted the authors in order to obtain separate data for funding. In total we contacted authors of 36 papers and received additional data for 18 of these papers.

Assessment of heterogeneity

We assessed heterogeneity using I^2. In our initial protocol we intended to use a random-effects model when P was < 0.10 for the Chi^2 test. However, since this is not in line with current recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011a), we instead used a random-effects model when statistical heterogeneity was substantial, defined as an I^2 > 50%.

Data synthesis

We used Review Manager (RevMan 2011) to analyze data. For dichotomous data we used the Mantel-Haenszel fixed-effect model to create a pooled RR. However, when substantial heterogeneity was observed, we used a DerSimonian-Laird random-effects model.

Subgroup analysis and investigation of heterogeneity

We considered the following factors as potential explanations for heterogeneity and investigated them in separate subgroup analyses.

1. We hypothesized that the association of industry sponsorship and favorable outcomes may be larger in high risk of bias papers. We assessed overall risk of bias of the included papers using the criteria described in 'Assessment of risk of bias in included studies'. We regarded papers with adequate study inclusion, a comprehensive search and controlling for bias as having a low risk of bias; others as having a high risk. We compared low risk of bias papers with high risk of bias papers in a subgroup analysis.
2. We compared papers of drug studies with device studies, as the mechanisms of influencing study outcomes may differ between the industries. For example, drug trials are more regulated than device trials, which could have an influence on biases in the design, conduct and reporting of the trials. We compared this in a subgroup analysis.
3. As the study domain might contribute to heterogeneity, we compared papers on specific treatments or diseases with papers of mixed domains in another subgroup analysis.

Sensitivity analysis

We undertook the following sensitivity analyses to test the robustness of our findings.

1. The primary analyses compared the number of favorable results and conclusions in papers with industry sponsorship to those with other sources of sponsorship; 'industry sponsorship' included 100% pharmaceutical/device company funding, mixed funding and provision of drug or device only. 'Non-industry sponsorship' included 100% government funding, 100% non-profit funding and undisclosed funding. In a sensitivity analysis, we excluded those studies with mixed funding sources and those with funding consisting solely of free product from the 'industry sponsorship' category, and excluded studies with undisclosed funding from the category of 'non-industry sponsorship', to determine if these had an impact on the initial analysis. As noted under 'Data extraction and management' we were reliant on how the studies in our review defined 'funding'.
2. Originally we had intended a sensitivity analysis restricted to papers with a low risk of bias using estimates adjusted for confounders (e.g. adjusted for sample size and concealment of allocation using logistic regression). However, because few papers with low risk of bias reported adjusted estimates in a way that we could use in our analysis, we decided to base our analysis on both low and high risk of bias papers reporting adjusted estimates. We used the generic inverse variance method to pool adjusted odds ratios in a fixed-effect model.
3. Due to the variability in study characteristics and methodology between papers, a random-effects model may be preferred, even if no statistical heterogeneity is observed. We therefore also undertook a sensitivity analysis where all analyses were based on a random-effects model.

RESULTS

Description of studies

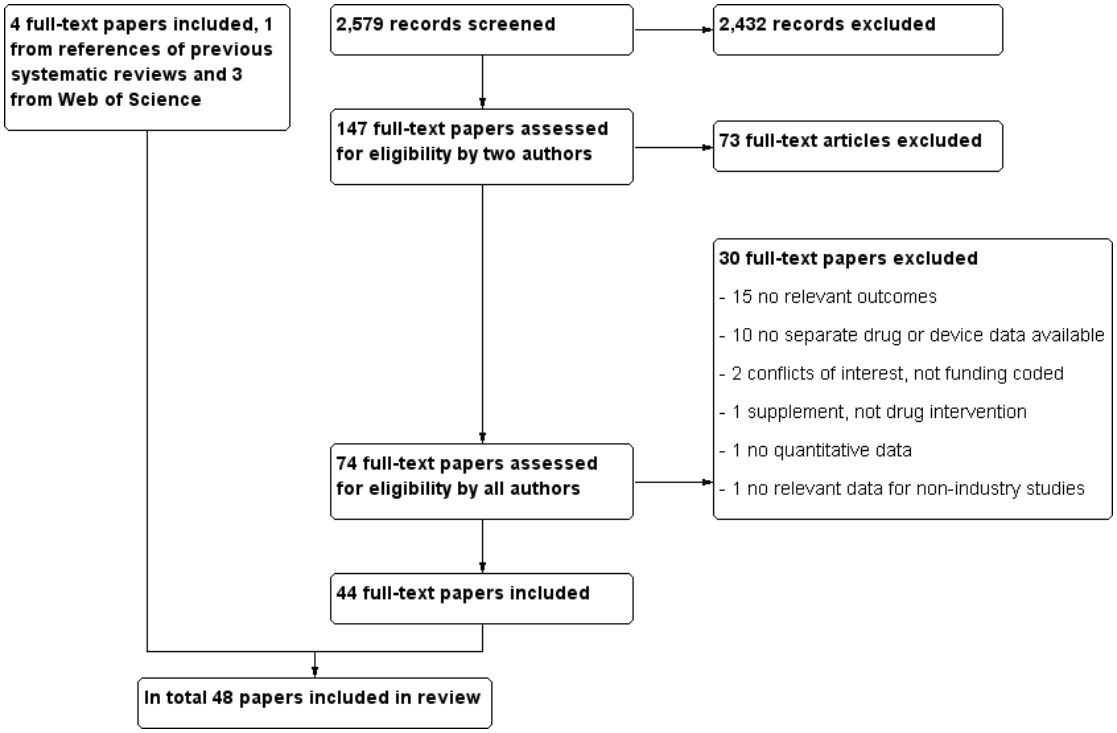
See: Characteristics of included studies; Characteristics of excluded studies.

See:Characteristics of included studies; Characteristics of excluded studies.

Results of the search

See: Figure 1

Figure 1. Study flow diagram.



After removal of duplicates, 2579 references were identified. From reading titles and abstracts, 2432 were eliminated as being not relevant to the review. Full-text papers were obtained for 147 references. From these 147 papers, 73 papers were excluded and 74 were retained for assessment by all assessors. Of these 74 papers, 30 were excluded (see Characteristics of excluded studies) and 44 included (see Characteristics of included studies). One additional paper (Chard 2000) was included as a result of searching reference lists of previous systematic reviews and three from searching Web of Science for papers citing any of the included papers (Jones 2010; Lubowitz 2007; Pengel 2009).

Included studies

See: Characteristics of included studies

The 48 papers were published between 1986 and 2010. Forty-six papers included mainly published studies, one included studies presented at a conference, and one included studies submitted to a medical journal. Thirty-seven papers included only drug studies, one only device studies, one drug and device studies and nine included different types of interventions (e.g. drugs, devices, behavioral interventions). Nineteen papers included studies related to specific drug classes, 13 related to specific medical specialties or types of diseases (e.g. endocrinology), six related to a specific disease, one related to a specific type of device, eight included all types of research studies and one did not state the domain. Various aspects of medicine were covered, but 10 (21%) papers were restricted to psychiatric diseases or drugs. Thirty-five papers included only clinical trials, two only observational studies, and 11 both clinical trials and observational studies. Eight papers included only drug versus drug comparisons, three only drug versus placebo, 34 mixed comparisons (e.g. drug versus drug, drug versus placebo) and three did not describe the kind of comparisons. The median number of included studies per paper was 137 (range: nine to 930). Of the 48 papers, 16 reported data on both favorable outcomes and risk of bias, 28 on favorable outcomes only and four on risk of bias only.

Risk of bias in included studies

See: Figure 2; Figure 3

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

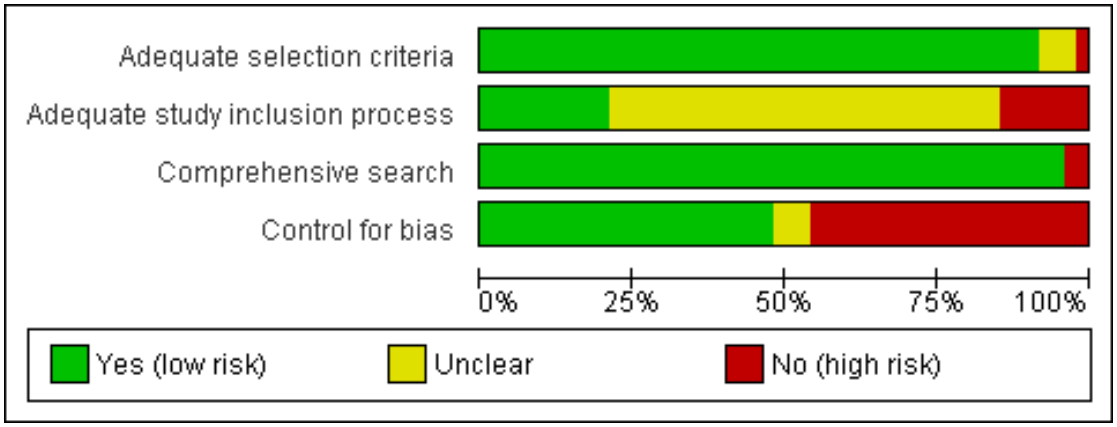
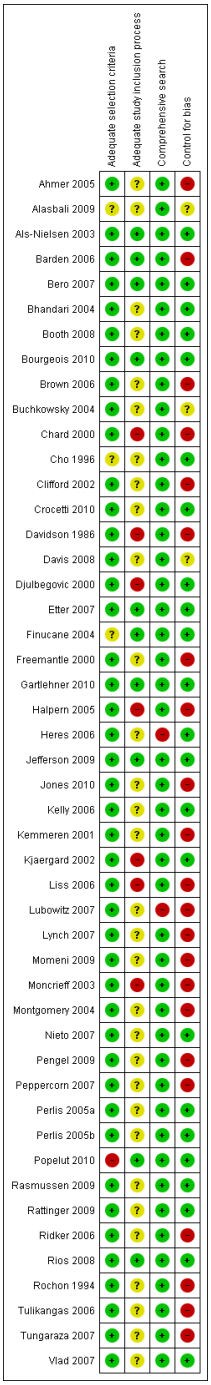


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Forty-four papers had low risk of bias for the selection criteria for inclusion of studies, three were unclear and one had high risk. Ten papers had low risk of bias for the study inclusion process, 31 were unclear and seven had high risk. Forty-six papers had low risk of bias from the search and two had high risk. Twenty-three papers had low risk of bias due to lack of control for bias in the studies, three were unclear and 22 had high risk. Nine papers were regarded as having an overall low risk of bias and 39 as a high risk of bias according to our criteria.

Effect of methods

Favorable results: industry sponsored versus non-industry sponsored studies

Fifteen papers, including 1746 studies (all drug studies), reported on sponsorship and efficacy results, and 14 could be combined in a pooled analysis. An analysis based on these 14 papers, including 1588 studies, found that industry sponsored studies more often had favorable efficacy results (e.g. those with significant P values) compared with non-industry sponsored studies, risk ratio (RR): 1.24 (95% confidence interval (CI): 1.14 to 1.35), I^2: 35% (Analysis 1.1). The paper that could not be included in the pooled analysis (Bhandari 2004), which had included 158 drug studies in general medicine, found similar results, odds ratio (OR): 1.6 (95% CI: 1.1 to 2.8).

Three papers, including 561 studies, found that industry sponsored studies more often had favorable harms results compared with non-industry sponsored studies, RR: 1.87 (95% CI: 1.54 to 2.27). No heterogeneity was observed (Analysis 1.2). The analysis was driven by one study (Nieto 2007) that contributed 97% of the weight in the analysis.

Favorable results: industry sponsorship by test treatment company versus industry sponsorship by comparator treatment company

Three papers, including 151 trials (all drug trials), compared efficacy results of trials sponsored by the manufacturer of the test treatment with trials sponsored by the manufacturer of the comparator treatment, and two could be combined in a pooled analysis. An analysis based on these two papers (Bero 2007; Rattinger 2009), which included 131 industry sponsored trials of statins and thiazolidinediones, found that trials were much more likely to favor the test treatment when they were sponsored by the manufacturer of the test treatment than when they were sponsored by the manufacturer of the comparator treatment, RR: 4.64 (95% CI: 2.08 to 10.32), I^2: 50% (Analysis 2.1). The paper that could not be included in the pooled analysis, which had included 20 selective serotonin reuptake inhibitor head-to-head trials, found that two trials favored the sponsor's drug, 18 had similar efficacy and none favored the comparator drug (Gartlehner 2010).

Favorable conclusions: industry sponsored versus non-industry sponsored studies

Twenty-four papers, including 4616 studies (4403 drug studies and 213 device studies), reported on sponsorship and conclusions, and 21 could be combined in a pooled analysis. An analysis based on these 21 papers, including 3941 studies (3821 drug studies and 120 device studies), found that industry sponsored studies more often had favorable conclusions than non-industry sponsored studies, RR: 1.31 (95% CI: 1.20 to 1.44), I^2: 83% (Analysis 3.1). Three papers could not be included in the pooled analysis. Of these, one paper of 301 psychiatric drug studies (Kelly 2006) found that industry sponsored studies more often had favorable conclusions than non-industry sponsored studies ($P < 0.001$) and similar findings were reported in a paper of 59 trials of antipsychotics ($P = 0.02$) (Montgomery 2004). A paper of 315 gastroenterology trials (222 drug trials and 93 device trials) did not find a difference in conclusions between industry sponsored trials and non-industry sponsored trials (industry: 86% favorable, non-industry: 83% favorable; $P = 0.57$) (Brown 2006).

Favorable conclusions: industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Five papers, including 348 drug trials, compared conclusions of studies sponsored by the manufacturer of the test treatment with studies sponsored by the manufacturer of the comparator treatment, and three could be combined in a pooled analysis. An analysis based on these three papers (Bero 2007; Heres 2006; Rattinger 2009) including 154 industry sponsored trials of statins, antipsychotics and thiazolidinediones, found that trials were much more likely to favor the test treatment when they were sponsored by the manufacturer of the test treatment than when they were sponsored by the manufacturer of the control treatment, RR: 5.90 (95% CI: 2.79 to 12.49). No heterogeneity was observed (Analysis 4.1). A paper of 138 psychiatric drug studies (Kelly 2006) had similar findings, RR 2.80 (95% CI: 2.02 to 3.88), and a paper of 56 non-steroidal anti-inflammatory drug (NSAID) trials (Rochon 1994) found that 16 trials favored the sponsor's drug, 40 concluded that the drugs had similar effect and none favored the comparator drug.

Effect size: industry sponsored versus non-industry sponsored studies

Ten papers, including 906 studies (865 drug studies and 41 device studies), reported on sponsorship and effect size, but could not be pooled due to differences in their reporting of data. The results were heterogeneous.

Five papers, including 798 drug studies, did not find a difference in effect size between industry sponsored studies and non-industry sponsored studies. One paper including 370 drug trials (Als-Nielsen 2003) found mean z-scores of -1.48 (95% CI: -1.19 to -1.77) in industry sponsored trials, -1.77 (95% CI: -1.35 to -2.28) in trials with mixed sponsorship and -1.20 (95% CI: -0.59 to -1.81) in non-industry sponsored trials, which were not statistically significantly different. Similarly, a paper of 176 trials of drugs for acute pain and migraine (Barden 2006) did not find a difference in number of patients with pain relief between industry sponsored trials and non-industry sponsored trials. A paper of 124 trials comparing second-generation antipsychotics with first-generation antipsychotics (Davis 2008) did not find a difference in effect size between industry sponsored trials and non-industry sponsored trials (P = 0.57). A paper of 105 trials comparing selective serotonin reuptake inhibitors with alternative antidepressants (Freemantle 2000) also did not find a difference in effect size between industry sponsored trials and non-industry sponsored trials. A paper of 23 studies of chondrocyte implantation (Lubowitz 2007) did not find a difference in effect size between industry sponsored studies and non-industry sponsored studies for various outcomes.

In contrast, four papers found higher effects in industry sponsored studies. A paper including nine trials comparing clozapine with conventional antipsychotics (Moncrieff 2003) found that the treatment effect was higher in industry sponsored trials than in non-industry sponsored trials, standardized mean difference (SMD): -0.83 (95% CI: -1.06 to -0.61) versus SMD: -0.21 (95% CI: -0.34 to -0.07) (P < 0.001). Similarly, a paper of 41 dental implant trials (Popelut 2010) found that the failure rates were lower in industry sponsored trials compared with non-industry sponsored trials, OR: 0.21 (95% CI: 0.12 to 0.38). A paper including 15 trials of glucosamine (Vlad 2007) found that the effect size was higher in industry sponsored trials than in non-industry sponsored trials, SMD: 0.47 (95% CI: 0.24 to 0.70) versus SMD: 0.05 (95% CI: -0.32 to 0.41) (P = 0.05). One paper including 34 nicotine replacement drug trials (Etter 2007) found higher effects in industry sponsored trials compared with non-industry sponsored trials, OR: 1.90 versus OR 1.61 (P = 0.06).

Only one paper assessed effect size of harms (Kemmeren 2001). It included nine observational studies that compared third generation with second-generation oral contraceptives and found that the risk of thrombosis was lower in industry sponsored studies compared with non-industry sponsored studies, OR: 1.3 (95% CI: 1.0 to 1.7) versus OR 2.3 (95% CI: 1.7 to 3.2).

Risk of bias: industry sponsored versus non-industry sponsored studies

Nine papers, including 1505 studies (1327 drug studies, 178 device studies), measured risk of bias using five different composite quality scales (Brown, Cho, Cochrane, Jadad or Sackett) and the results were heterogeneous. Four papers did not find a difference in risk of bias between industry sponsored and non-industry sponsored studies (Cho 1996; Jefferson 2009; Lynch 2007; Vlad 2007), whereas five papers found lower risk of bias (i.e. higher methodological quality scores) in industry sponsored studies (Brown 2006; Djulbegovic 2000; Montgomery 2004; Pengel 2009; Perlis 2005a).

Three papers, including 487 drug trials, did not find a difference in low risk of bias from sequence generation in industry sponsored trials compared with non-industry sponsored trials, RR: 0.85 (95% CI: 0.52 to 1.41), I^2: 86% (Analysis 5.1). Ten papers, including 1311 drug trials, did not find a difference in low risk of bias from concealment of allocation in industry sponsored trials compared with non-industry sponsored trials, RR: 1.09 (95% CI: 0.86 to 1.38), I^2: 54% (Analysis 5.2). Nine papers, including 1216 drug trials, found that industry sponsored trials more often had low risk of bias from blinding compared with non-industry sponsored trials, RR: 1.32 (95% CI: 1.05 to 1.65), I^2: 74% (Analysis 5.3). Two papers, including 118 drug trials, did not find a difference in low risk of bias from loss to follow-up in industry sponsored trials compared with non-industry sponsored trials, RR: 0.98 (95% CI: 0.84 to 1.16). No heterogeneity was observed (Analysis 5.4).

Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies

Five papers, including 667 drug studies, reported on concordance between study efficacy results (e.g. as judged by their P values) and conclusions. Industry sponsored studies were less concordant than non-industry sponsored studies, RR: 0.84 (95% CI: 0.70 to 1.01), I^2: 67% (Analysis 6.1). One paper (Alasbali 2009), including 39 drug studies, found markedly higher lack of concordance in industry studies than the other four papers, and this was the reason for the high heterogeneity between papers.

One paper, of 211 corticosteroid studies with statistically significant harms results, found that industry sponsored studies more often concluded that the drug was safe than non-industry sponsored studies, RR: 3.68 (95% CI: 2.14 to 6.33) (Nieto 2007).

Subgroup analysis and investigation of heterogeneity

Because only three papers with efficacy results data had low risk of bias (Bero 2007; Bourgeois 2010; Etter 2007) and only four with conclusions data had low risk of bias (Als-Nielsen 2003; Bero 2007; Finucane 2004; Jefferson 2009) our comparison of low and high risk of bias papers was limited. Nonetheless, the association between industry sponsorship and favorable results was stronger in the low risk of bias group than in the high risk of bias group, RR: 1.50 (95% CI: 1.30 to 1.74) versus 1.14 (95% CI: 1.03 to 1.25) (test for subgroup differences P = 0.002) (Analysis 7.1). For conclusions, the differences between the groups went in the same

direction, RR: 1.54 (95% CI: 1.24 to 1.91) versus 1.26 (95% CI: 1.14 to 1.39), (test for subgroup differences P = 0.10) (Analysis 7.2).

Similarly, as only two papers (Lynch 2007; Ridker 2006) had data on device studies, the comparison between drug and device studies was limited. We did not find a difference in the association between sponsorship and conclusions in drug studies compared with device studies (Analysis 7.3). Only two papers with results data (Bourgeois 2010; Clifford 2002) and four with conclusion data (Buchkowsky 2004; Cho 1996; Davidson 1986; Kjaergard 2002) were of mixed domain. We did not find a difference in the association between sponsorship and results or conclusion in studies limited to specific treatments or diseases compared with studies of mixed domains (Analysis 7.4; Analysis 7.5).

Sensitivity analysis

Our re-analyses of the outcomes using variations in definition of sponsorship categories gave similar results as our main analyses for results, conclusions, sequence generation, concealment of allocation and blinding (Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4; Analysis 8.5). Our analyses based on pooling adjusted odds ratios confirmed our findings that industry sponsored trials compared with non-industry sponsored trials more often had favorable results, OR: 3.86 (95% CI: 1.93 to 7.70) and favorable conclusions, OR: 4.15 (95% CI: 2.40 to 7.19). No heterogeneity was observed (Analysis 8.6; Analysis 8.7). Similarly, the change from a fixed-effect model to a random-effects model did not affect our analyses (Analysis 8.8; Analysis 8.9; Analysis 8.10; Analysis 8.11; Analysis 8.12).

DISCUSSION

Summary of main results

We found that drug and device studies sponsored by the manufacturing company more often had favorable results (e.g. those with significant P values) and conclusions than those that were sponsored by other sources. The findings were consistent across a wide range of diseases and treatments. We did not find any differences in risk of bias of drug and device trials sponsored by industry compared with non-industry sponsored trials, except in relation to blinding, where industry sponsored trials seemed to have lower risk of bias. The evidence from device studies was limited, but the association between sponsorship and outcomes was similar to drug studies.

Reasons for observed heterogeneity

For the association between sponsorship and favorable results of drug and device studies the data had acceptable heterogeneity, but heterogeneity for conclusions was substantial with an I^2 of 83%. One reason for this was likely that the coding of favorable results was similar across the different papers, using statistical significance as the cut-off, but coding varied for conclusions. Some papers did not describe what they considered a favorable conclusion and others used scales, but for similar scales the cut-off varied between papers. For example, on the same six-point scale one paper used four as cut-off (Djulbegovic 2000) and another six as cut-off (Als-Nielsen 2003).

Also, the proportion of studies with favorable conclusions in the non-industry sponsored group might have contributed to the size of the association and thereby the heterogeneity. For example, while the Chard and Liss papers (Chard 2000; Liss 2006) had a similar proportion of favorable industry sponsored studies (both 98%), they reported very different proportions of favorable non-industry sponsored studies (32% and 97%) and this explains why the risk ratios reported in the two studies were not the same: 3.03 in Liss and 1.01 in Chard. Variations in study domain or definition of favorable conclusions might explain why the risk ratios reported in the two papers were not similar. For example, in the Chard paper, a conclusion was coded as favorable if the study authors supported the use of the treatment, even in the absence of a statistical significant result. Our subgroup analysis to test for differences in the association of sponsorship and results or conclusions between studies of mixed domains and studies related to specific treatments or diseases did not show different results, though this was a simplistic comparison.

Our data for the relationship between sponsorship and effect size showed mixed results, with most not finding a difference. All but one of these papers were restricted to specific treatments, which may explain the different findings. A recent study of systematic reviews of nine different drugs found that the influence of reporting biases on effect sizes varied considerably between drugs (Hart 2012). Furthermore, one paper found that even when adjusting for effect size, industry sponsored studies more often had favorable conclusions, compared with non-industry sponsored studies (Als-Nielsen 2003). Therefore, while the direction of the relationship between sponsorship and favorable outcomes was consistent, the size of the effect likely varies depending on domains.

Reasons for favorable outcomes in industry sponsored studies

The pharmaceutical and medical device industries have strong interests in scientific publications that present their products positively, as publications are the basis of regulatory, purchasing, and medical decisions. These interests can influence the design, conduct and publication of studies in ways that make the sponsor's product appear better than the comparator product (Bero 1996).

Several possible factors can explain the relationship between industry sponsorship and favorable outcomes. It has been argued that since many industry sponsored studies are undertaken to fulfill regulatory requirements, industry sponsored studies could have a lower risk of bias than non-industry sponsored studies (Rosefsky 2003). Even if this were true, it would not explain the association of industry sponsorship and favorable results and conclusions. In addition, we did not find evidence for differences in risk of bias except in relation to blinding, where industry sponsored trials tended to have a lower risk of bias, even when restricted to head-to head trials (Bero 2007). The papers comparing blinding between trials with different sponsorship often used a description of double blinding as an indicator for low risk of bias. Double blinding is an inconsistent term and does not ensure that, for example, outcome assessors are blinded (Devereaux 2001). The more frequent use of double blinding may therefore be a reporting issue, with industry trials being better reported. This is further substantiated by the fact that nearly all the papers finding a higher methodological quality score in industry studies used the Jadad scale, a scale which has been criticized for having more focus on the quality of reporting than on methodological quality (Lundh 2008).

On the other hand, evidence suggests that for non-industry trials, companies may prevent proper blinding by restricting access to placebo drugs (Christensen 2012) and therefore differences in adequate blinding may be real. In addition, double blinding can be used as a proxy for low risk of bias and trials without double blinding are on average more likely to have favorable results (Pildal 2007). The effect of this bias is in the opposite direction of our findings, as it would lead to industry sponsored studies having less favorable results and conclusions, and our findings can therefore, not be explained by differences in risk of bias between industry and non-industry sponsored studies.

Another possible explanation for our findings could be that industry studies have larger sample sizes, and would have a higher chance of achieving statistically significant results. Although industry trials seem in general to be of larger size (Als-Nielsen 2003; Booth 2008; Bourgeois 2010; Etter 2007; Perlis 2005a), when we restricted our analysis to studies controlling for sample size and other confounders, the relationship between industry sponsorship and favorable results or conclusions was still present.

Industry argues that the trials they sponsor are more likely to have favorable results because they fund research that has a high chance of achieving success (Palmer 2003). However, when independent investigators conduct non-industry sponsored trials, they in most cases test treatments that have been approved based on favorable industry trial results. Non-industry sponsored trials would therefore also be expected to achieve successful results, unless they are designed to answer different questions than industry sponsored trials. For example testing a new treatment against a well-established treatment instead of against placebo or against an outdated, inferior treatment.

Accordingly, it seems most plausible that industry achieves overly positive results through a variety of biasing choices in the design, conduct and reporting of their studies. For example, industry protocols might include inferior comparators that will increase the chance of their product's success. Djulbegovic et al. (Djulbegovic 2003) have argued that industry sponsored studies violate equipoise by choosing inferior competing treatment alternatives. Previous studies have found that industry sponsored trials more often use placebo control (Als-Nielsen 2003; Djulbegovic 2000; Estellat 2012; Katz 2006; Lathyris 2010), active comparators in inferior doses (Rochon 1994; Safer 2002) or inappropriate administration of the drugs (Johansen 1999). Or, industry sponsored studies may be biased in the coding of events and their data analysis (Furukawa 2004; Psaty 2008; Psaty 2010). Industry and its sponsored investigators also may selectively report favorable outcomes, fail to publish whole studies with unfavorable results, or publish studies with favorable results multiple times (Chan 2004; Dwan 2008; Gøtzsche 2011; McGauran 2010; Melander 2003; Rising 2008; Vedula 2009). While such biases in analyses and reporting have been documented in a number of cases, the papers included in this review focused on comparisons of published studies. Therefore, we are unable to determine the extent to which selective analysis or reporting contribute to our findings.

The finding that industry sponsored studies are more likely to have favorable conclusions could be explained by use of spin in conclusions (Boutron 2010). It should also be noted that some studies in the non-industry group likely had authors with conflicts of interest, which may have influenced their interpretation of study results (Stelfox 1998; Wang 2010) thereby diluting the measured effect of industry bias on study conclusions. Also, we coded studies as non-industry sponsored if they did not state who sponsored the study. As some of these studies were likely industry sponsored, this misclassification will have led to similar bias towards the null. In our sensitivity analyses, we excluded studies without sponsorship statements and did not see a change in results, but the confidence intervals were wide and did not exclude a possible bias towards the null.

Further evidence for industry bias stems from our comparison of studies sponsored by the manufacturer of the test treatment with those sponsored by the manufacturer of the control treatment. These studies had the advantage of comparing like with like, as they are restricted to specific drug classes or types of devices and have similar methodologies. Though limited to only three papers on drug trials, the findings show associations that are stronger than the comparison between industry and non-industry sponsored studies. These comparisons are restricted to drugs competing for the same market, which may put pressure on companies to influence outcomes to a greater degree than what is needed in placebo controlled trials to present the drug in a good light.

In sum, the industry bias associated with favorable results and conclusions may be mediated by factors other than traditional measures of the risk of bias (e.g. lack of concealment of allocation, blinding and drop-out) and sample size. This industry bias may

be partially mediated by such factors as the choice of comparators, dosing and timing of comparisons, selective analysis, and selective reporting.

Quality of the evidence

The majority of included papers were regarded as having a high risk of bias. Many lacked information on study conduct and did not control for confounders that could influence the relationship. Nevertheless, we did identify nine papers with low risk of bias and analyses restricted to these papers actually strengthened the relationship between sponsorship and outcomes. In general, there is convincing and consistent evidence for the existence of an industry bias in studies; however, the evidence for device studies is not as strong as for drug studies. While papers, including studies of devices and other interventions, have been published in the surgical field (Cunningham 2007; Khan 2008; Leopold 2003; Roach 2008; Shah 2005; Yao 2007), the papers do not report separate data for device studies.

Potential biases in the review process

We did a comprehensive search, our methods were based on prespecified criteria in a protocol as outlined in *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Higgins 2011a) and our review has substantially increased the number of included papers from our previous review (Lexchin 2003). Nevertheless, there are some limitations. First, we decided only to include published papers. In our previous review (Lexchin 2003), we found problems with the completeness and quality of the data in conference abstracts and letters and therefore decided not to include them in this review. In our searches, we identified five conference abstracts and five letters that otherwise seemed to fit our inclusion criteria (Bond 2009; Djulbegovic 1999; Esquitin 2010; Higgins 2005; Koepp 1999; Mandelkern 1999; Thomas 2002; Vandenbroucke 2000; Wagena 2003; Wahlbeck 1999). Most were small (including a median of 30 studies, range 12 to 567 studies). Data from four papers could be included in a pooled analysis and gave similar findings for the association between sponsorship and study conclusions, RR: 1.57 (95% CI: 1.21 to 2.03), and RR: 1.32 (95% CI: 1.21 to 1.45) when they were added to the published papers (data available from authors on request). This makes publication bias unlikely to have influenced our results.

Second, our assessment of risk of bias in the included papers was not based on validated criteria similar to 'Risk of bias' assessment for clinical trials (Higgins 2011b). As no validated assessment tools exist for these type of papers, we developed our own criteria and included items similar to assessment tools for systematic reviews (Oxman 1991; Shea 2007).

Third, one item not included in our assessment of risk of bias in the papers was whether coders of outcomes were blinded to the sponsorship status of the studies. If these types of papers were undertaken by authors with a particular view on the drug industry, knowledge of sponsorship status could introduce bias in the assessment of whether outcomes were favorable, particularly for conclusions, as this is an outcome that is qualitative in nature. Some of the included papers were written by authors who had published multiple times in the area, and as such could be at increased risk of bias. These papers used coders who were both blinded and unblinded to the sponsorship status of the studies. The agreement in coding was high, suggesting a lack of bias (Als-Nielsen 2003; Bero 2007; Kjaergard 2002). Likewise, most of us (AL, JL, LB, SS) have published several times in the field and one of us (LB) is the author of four of the included papers (Bero 2007; Cho 1996; Rasmussen 2009; Rattinger 2009), which could have introduced bias. Because of the way data were presented in the papers, it was not possible to blind our data extraction process, so instead data extraction was undertaken by two of us with modest experience in the field and who were not authors of the original review or any of the included papers (AL, SS). Furthermore, our data extraction of outcomes did not involve any qualitative interpretation as we extracted actual numbers.

Fourth, if the papers included in this review included some of the same studies, their findings would not be independent. It was not possible to assess the potential overlap of studies as most papers did not provide a reference list of included studies. However, any overlap of included studies is likely to be very small and unimportant, as the disease and intervention topics of the included papers varied widely.

Agreements and disagreements with other studies or reviews

Our results are in agreement with previous systematic reviews (Bekelman 2003; Lexchin 2003; Schott 2010; Sismondo 2008a), though the risk ratios for the associations are less than previous quantitative estimates. Previous reviews did not distinguish between favorable results or conclusions, but looked at the association between sponsorship and outcomes. Bekelman found OR 3.60 (95% CI: 2.63 to 4.91) and Lexchin OR 4.05 (95% CI: 2.98 to 5.51). Translated to odds ratios, we found 2.15 (95% CI: 1.70 to 2.72) for results and 2.67 (95% CI 2.02 to 3.53) for conclusions in our review. This difference could be due to chance or it could be because the earlier reviews also included pharmacoeconomic analyses, non-drug studies, letters and conference presentations. It is also possible that the degree of industry bias has diminished over time, for example with a decrease in reporting bias due to trial registration. However, we do not find it likely. First, a recent study found that reporting bias is also prevalent in registered trials (Mathieu 2009). Second, one of the most recent papers (Bourgeois 2010) sampled drug trials registered at clinicaltrials.gov and conducted between 2000 and 2006 and found OR: 4.50 (95% CI:

2.60 to 7.80) for results, suggesting that industry bias has not changed over time.

AUTHORS' CONCLUSIONS

Implication for systematic reviews and evaluations of healthcare

Sponsorship of drug and device studies by the manufacturing company leads to more favorable results (e.g. those with significant P values) and conclusions than studies sponsored by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.

The findings resonate with current calls for access to full protocols and raw data when assessing drug and device interventions, for example while producing guidelines or systematic reviews, as relying on the published evidence of industry sponsored trials alone leads to too positive results, on average (Doshi 2012; Godlee 2009; Gøtzsche 2011; Krleza-Jeric 2005). To improve transparency, guidelines and systematic reviews should always report the source of sponsorship of trials, even when other risks of bias are assessed; this is currently not the case, neither in Cochrane reviews, nor elsewhere (Roseman 2011; Roseman 2012). We also suggest that the robustness of the results be assessed in a sensitivity analysis limited to non-industry sponsored studies with low risk of bias. Such requirements also necessitate proper reporting of funding in the original trial publications.

Journals should consider requiring independent statistical analysis, as is the case for JAMA (DeAngelis 2010), and that trial protocols and the raw data be posted on websites. Governments and non-commercial sponsors should also increase funds for independent drug and device trials and consider making submission of data from independent trials a mandatory requirement for gaining drug and device approval from regulatory agencies (Lexchin 2011). Independently sponsored trials should focus on testing innovative and essential treatments, as well as comparisons with existing effective treatments, thus shifting the resources spent on drug and device trials away from trials with a marketing purpose to those that are clinically important. Lastly, clinicians, guideline developers and others who rely on systematic reviews to aid decision-making should be aware of the influence of industry bias on research results and conclusions.

Implication for methodological research

Currently, the *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* acknowledges problems in relation to sponsorship, but does not recommend assessing industry sponsorship as a separate domain in the 'Risk of bias' assessment (Higgins 2011b). The assumption is that the influence of the sponsor will be mediated through the mechanisms of bias that are currently assessed, such as selective reporting of favorable outcomes. A Cochrane review that examined the association of sponsorship and selective outcome reporting bias (Dwan 2011) found uncertain evidence for the association; however, assessment of selective outcome reporting is complex and bias may be difficult to detect (Kirkham 2010). Some studies that have documented the extensive selective reporting of favorable outcomes have examined only industry sponsored studies (Rising 2008; Vedula 2009), thus making comparison with non-industry sponsored studies impossible.

Our data suggest that the more favorable outcomes in industry sponsored studies are mediated by factors other than those documented in the 'Risk of bias' assessment tool in Cochrane reviews. It has been suggested that industry bias should be regarded as a meta-bias, as industry sponsorship in itself is not a bias-producing process - as for example lack of concealment of allocation is - but a risk factor for bias (Goodman 2011). However, the characteristics currently assessed in the standard risk of bias approach in Cochrane reviews likely do not capture the additional risk of bias in industry sponsored studies. For example, the *Handbook* states that design issues, such as dosage of comparators are not issues of bias, but of generalizability. Yet, pharmacological interventions have dose-response curves, and testing drugs that are not in comparable places on their dose-response curves sets up a systematic, unfair and biased comparison (Safer 2002).

Consequently, our data suggest that industry sponsorship should be treated as bias-inducing and industry bias should be treated as a separate domain. There are many subtle mechanisms through which sponsorship may influence outcomes, and an assessment of sponsorship should therefore be used as a proxy for these mechanisms. Interestingly, the AMSTAR tool for methodological quality assessment of systematic reviews includes funding and conflicts of interest as a domain (Shea 2007). Methods for reporting, assessing and handling industry bias and other biases in future systematic reviews must be developed. Specifically, further methodological research should focus on how industry bias is handled in Cochrane reviews.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmer 2005

Methods	To study the association between study support and outcome in randomized controlled trials (RCTs) of psychotropic drugs. All RCTs published in *Acta Psychiatrica Scandinavica* (APS), *American Journal of Psychiatry* (AJP), *Archives of General Psychiatry* (AGP) and *British Journal of Psychiatry* (BJP) from July 1998 to June 2003.
Data	188 psychotropic drug RCTs (various comparators).
Comparisons	Manufacturer support and no support.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Database and handsearch.
Control for bias?	No	Subgroup analysis, but only of journal name.

Alasbali 2009

Methods	To investigate the relationship between industry vs non-industry funded publications comparing the efficacy of topical prostaglandin analogs by evaluating the correspondence between the statistical significance of the publication's main outcome measure and its abstract conclusions. Studies published from 1966 to November 2007
Data	39 reports of head-to-head comparisons of topical prostaglandins in ophthalmology (various study designs)
Comparisons	Industry and non-industry funding.
Outcomes	Study conclusions, study results and concordance between study results and conclusions
Notes	

Risk of bias

Alasbali 2009 (*Continued*)

Item	Authors' judgement	Description
Adequate selection criteria?	Unclear	Not clear which study designs and whether placebo controlled studies were included, cannot be replicated
Adequate study inclusion process?	Unclear	Three assessors for data extraction, but unclear in relation to study inclusion
Comprehensive search?	Yes	MEDLINE and handsearching.
Control for bias?	Unclear	Not described.

Als-Nielsen 2003

Methods	To explore whether the association between funding and conclusions in randomized drug trials reflects treatment effects or adverse events. All randomized trials included in eligible meta-analyses from a random sample of Cochrane reviews obtained in May 2001 (RCTs from 1971 to 2000)
Data	370 drug RCTs (mixed comparisons).
Comparisons	Funding from non-profit organizations, not reported, both non-profit and for-profit organizations, and for-profit organizations
Outcomes	Study conclusions, effect size and methodological quality (generation of randomization sequence, concealment of allocation and double blinding)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	One assessor screened and two involved in final inclusion.
Comprehensive search?	Yes	Identification via Cochrane reviews.
Control for bias?	Yes	Logistic regression adjusting for treatment effect, adverse events, and other potentially confounding trial variables (methodological quality, sample size, whether preset sample size was estimated and reached, meta-analysis, year of publication, and journal impact factor). Ad-

Als-Nielsen 2003 (*Continued*)

		justed for treatment effect and double blinding in final model

Barden 2006

Methods	To study if industry sponsored trials yield a better result than trials not sponsored by industry, and if a particular drug would perform better as the test drug in trials funded by its manufacturer and worse as the comparator drug in trials funded by a competitor. RCTs from published systematic reviews in acute pain and migraine (reviews from 1999 to 2004)
Data	176 acute pain or migraine drug RCTs (active comparator or placebo controlled)
Comparisons	Industry versus non-industry and manufacturer versus competitor funding
Outcomes	Effect size and methodological quality (Jadad score, 0-5 point scale)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	From Cochrane reviews, seems more than one assessor was used
Comprehensive search?	Yes	Identification via Cochrane reviews.
Control for bias?	No	No control for bias.

Bero 2007

Methods	To examine the associations between research funding source, study design characteristics aimed at reducing bias, and other factors that potentially influence results and conclusions in randomized controlled trials of statin-drug comparisons. All statin RCTs with active comparators from January 1999 to May 2005
Data	192 statin RCTs (active comparators).
Comparisons	Industry, none disclosed/no funding and government/private non-profit funding
Outcomes	Study results, study conclusions, methodological quality (concealment of allocation, blinding and follow-up) and concordance between study results and conclusions
Notes	

Bero 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two or more assessors included studies.
Comprehensive search?	Yes	MEDLINE and references.
Control for bias?	Yes	Multivariate logistic regression analysis. Final model controlled for journal Impact Factor, sample size and blinding

Bhandari 2004

Methods	To study the association between industry funding and the statistical significance of results in recently published medical and surgical trials. RCTs from January 1999 to June 2001 in 8 leading surgical journals (*Journal of Bone and Joint Surgery* [American and British volumes], *Clinical Orthopaedics and Related Research*, *Acta Orthopaedica Scandinavica*, *Annals of Surgery*, *American Journal of Surgery*, *Plastic and Reconstructive Surgery and Journal of Neurosurgery*) and 5 medical journals (*Lancet, BMJ, JAMA, Annals of Internal Medicine and New England Journal of Medicine*) .
Data	332 RCTs of drug, surgery, and other types of interventions (no description of comparisons)
Comparisons	Industry-for-profit, not-for-profit and undeclared funding.
Outcomes	Study results and methodological quality (Detsky quality index, 0-21 point scale)
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch and MEDLINE used.
Control for bias?	Yes	Multivariate logistic regression with adjustment for sample size, study quality and type of intervention

Booth 2008

Methods	To describe trends in methodology and reporting of RCTs, in addition to sponsorship, outcomes, and authors' interpretation of results. All RCTs of systemic therapy in breast, colorectal cancer, and non-small-cell lung cancer published during three decades (1975 through 2004) in: *Journal of Clinical Oncology*, *Journal of the National Cancer Institute*, *Cancer Treatment/Chemotherapy Reports*, *New England Journal of Medicine*, *Lancet*, and *JAMA*.
Data	321 drug RCTs (active comparators and placebo controlled).
Comparisons	For-profit/mixed, non-profit and not known funding.
Outcomes	Study results, study conclusions and effect size.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Database and handsearch.
Control for bias?	Yes	Multivariate logistic regression, final model controlled for time to event, effect size and P value

Bourgeois 2010

Methods	To describe characteristics of drug trials listed in ClinicalTrials.gov and examine whether the funding source of these trials is associated with favorable published outcomes. Clinical trials registered from 2000 to 2006 and published up to 2010
Data	546 clinical trials of cholesterol-lowering drugs, antidepressants, antipsychotics, proton-pump inhibitors and vasodilators (active or placebo controlled)
Comparisons	Industry, government and non-profit/non-federal (with or without industry contributions) funding
Outcomes	Study results.
Notes	

Risk of bias

Item	Authors' judgement	Description

Bourgeois 2010 (*Continued*)

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors independently carried out the literature search and disagreements were resolved by consensus
Comprehensive search?	Yes	Four databases, trial registries and contact to investigators and companies
Control for bias?	Yes	Post hoc multivariate logistic regression analysis to assess the association between funding source and trial outcome, while controlling for other trial characteristics (drug class, approval status of indication, study phase, multicenter status, anticipated sample size, age of study population, comparator type, and length of study)

Brown 2006

Methods	To evaluate the trends in the source of funding for gastrointestinal clinical research during the period from 1992 to 2002-2003; to determine whether the source of study funding predicted the likelihood that a study would publish results that favor the drug or device being tested; and to determine whether differences exist in the methodologic quality of the investigational study methods used in studies funded by private industry versus other sources. Clinical trials published in 4 gastrointestinal journals (*Gastroenterology*, *The American Journal of Gastroenterology*, *Hepatology*, and *Gastrointestinal Endoscopy*).
Data	450 clinical trials of drugs and devices in gastroenterology (active or placebo controlled)
Comparisons	Private industry sponsored, federal/state government sponsored, national society/non-profit agency sponsored and not specified
Outcomes	Study conclusions and methodological quality (Brown score, 0 to 5 point scale multiplied by 100)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearching of journals.

Brown 2006 (*Continued*)

Control for bias?	No	No control for bias.

Buchkowsky 2004

Methods	To characterize clinical trial funding, reporting, and sources; investigate author-industry affiliation; and describe clinical outcome trends over time. Random papers from January 1981 to December 2000 from *Annals of Internal Medicine*, *BMJ*, *JAMA*, *Lancet* and *New England Journal of Medicine*.
Data	500 clinical drug trials (drug versus placebo, active comparator or non-drug comparator)
Comparisons	Industry, mixed, non-industry and not stated funding.
Outcomes	Study conclusions
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	Unclear	Investigates choice of comparators over time, might have assessed other sources of bias

Chard 2000

Methods	To assess the published research base for interventions for osteoarthritis of the knee, and to identify areas in need of further research. Studies from 1950 to 1998
Data	930 studies of different interventions (various study designs with various comparators)
Comparisons	Commercial, government and not stated funding.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Chard 2000 (*Continued*)

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	One assessor on all studies and one on 10% sample, but only 87% agreement indicating two needed for all studies
Comprehensive search?	Yes	MEDLINE, EMBASE, BIDS, The Cochrane Library, previous reviews and experts contacted
Control for bias?	No	No control for bias.

Cho 1996

Methods	To compare the quality, relevance, and structure of drug studies published in symposium proceedings that are sponsored by drug companies with 1) articles from symposia with other sponsors and 2) articles in the peer reviewed parent journals of symposium proceedings; and to study the relation between drug company sponsorship and study outcome. Random selection of symposia from 625 symposia that had been identified for a previous study
Data	127 drug studies (various study designs with various comparators)
Comparisons	Drug company support and no support.
Outcomes	Study conclusions and methodological quality (Cho scale 0-1 point)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Unclear	Not clear enough to replicate how symposia were chosen and how matching papers were chosen
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Comprehensive search within their own database.
Control for bias?	Yes	Subgroup analysis of study design.

Clifford 2002

Methods	To examine the relationship between funding source, trial outcome and reporting quality;100 RCTs from *Annals of Internal Medicine*, *BMJ, JAMA*, *Lancet, New England Journal of Medicine*. From January 1999 to October 2000 with 20 RCTs/journal.
Data	100 drug RCTs (various comparators).
Comparisons	Entirely industry, entirely not-for-profit, mixed and not reported funding
Outcomes	Study results, methodological quality (Jadad score, 0-5 point scale and concealment of allocation)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearching of journals.
Control for bias?	No	No evidence of risk of bias assessment.

Crocetti 2010

Methods	To assess the risk of bias among pediatric RCTs reported in 8 high-impact journals (5 pediatric and 3 general medical) from July 2007 to June 2008
Data	146 pediatric drug, behavioral/educational and nutritional RCTs (various comparators)
Comparisons	Government, industry, internal hospital grant, multiple sources, none and private foundation funding
Outcomes	Methodological quality (sequence generation; allocation concealment; masking of participants, personnel, and outcome assessors; incomplete outcome data reporting; selective outcome reporting; and other sources of bias)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.

Crocetti 2010 (*Continued*)

Comprehensive search?	Yes	MEDLINE search of selected journals.
Control for bias?	Yes	Multivariate logistic regression to test for an association between the presence of a high risk of bias according to domain and the independent variables of funding source, intervention type, author number, and trial registration status

Davidson 1986

Methods	An analysis of the results of clinical trials according to funding source. Clinical trials from 1984 in *New England Journal of Medicine*, *Annals of Internal Medicine*, *the American Journal of Medicine*, *Archives of Internal Medicine*, and the *Lancet.*
Data	107 drug and non-drug clinical trials (various comparators).
Comparisons	Pharmaceutical support and general support.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Single assessor.
Comprehensive search?	Yes	Journals handsearched.
Control for bias?	No	Control for bias seems unlikely to have been done.

Davis 2008

Methods	The influence of several potentially biasing factors (e.g. industry support, extrapyramidal side effects) on efficacy of studies comparing second-generation antipsychotic with first-generation drugs. Dataset from previously published meta-analysis (search from 1953 to 2002)
Data	124 RCTs of second-generation antipsychotics versus first-generation antipsychotics
Comparisons	Industry and non-industry funding.
Outcomes	Effect size.

Davis 2008 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Comprehensive database search including search for unpublished data
Control for bias?	Unclear	Carried out various sensitivity analysis, but not clear whether they assessed bias in relation to funding and effect size

Djulbegovic 2000

Methods	To evaluate whether the uncertainty principle was upheld, comparison of the number of studies favoring experimental treatments over standard ones according to the source of funding. All RCTs for multiple myeloma from 1996 to 1998	
Data	136 multiple myeloma drug RCTs (various comparators).	
Comparisons	Commercial and public funding.	
Outcomes	Study conclusions and methodological quality (Jadad score, 0-5 point scale)	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Seems only one author involved in study inclusion.
Comprehensive search?	Yes	Using the Cochrane search strategy to identify trials.
Control for bias?	Yes	Controlled for types of comparator (active versus placebo/no treatment)

Etter 2007

Methods	To assess whether source of funding affected the results of trials of nicotine replacement therapy for smoking cessation. RCTs from 1979 to 2003 identified from Cochrane review
Data	105 RCTs of nicotine replacement therapy (gum or patch versus placebo or no treatment)
Comparisons	Industry/mixed and non-industry/not acknowledged funding.
Outcomes	Study results and effect size.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	From Cochrane review, seems more than one assessors was used
Comprehensive search?	Yes	Identification via Cochrane review.
Control for bias?	Yes	Multivariate logistic regression with adjustment for sample size

Finucane 2004

Methods	To evaluate the association between funding and findings of pharmaceutical research presented at an annual meeting of a clinically oriented US medical professional society
Data	48 presentations of drug studies (observational studies, RCTs and other study designs)
Comparisons	Industry supported and not industry supported.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Unclear	Unclear what "any abstract that reported results about effectiveness or safety of drugs" means. Not clear which study designs and whether reviews were included
Adequate study inclusion process?	Yes	Seems likely that two assessors were used.

Finucane 2004 (*Continued*)

Comprehensive search?	Yes	Comprehensive search within conference.
Control for bias?	Yes	Subgroup analysis of study design.

Freemantle 2000

Methods	To assess whether specific pharmacological characteristics of alternative antidepressants resulted in altered efficacy compared to that of selective serotonin reuptake inhibitors (SSRI) in the treatment of major depression. All RCTs of SSRI versus alternative antidepressants (search from 1966 to 1997)
Data	105 SSRI versus alternative antidepressant RCTs.
Comparisons	Sponsor and not sponsor.
Outcomes	Effect size.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, EMBASE, references and reviews.
Control for bias?	No	No assessment of bias in relation to funding and effect size

Gartlehner 2010

Methods	The objective of this study was to determine the effect of industry bias in a systematically reviewed sample of head-to-head trials. Trials of SSRI head-to-head comparisons from 1993 to 2005
Data	29 SSRI RCTs of head-to-head comparisons.
Comparisons	Sponsor and not sponsor.
Outcomes	Study results and effect size.
Notes	

Risk of bias

Gartlehner 2010 (*Continued*)

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE, EMBASE, The Cochrane Library, the International Pharmaceutical Abstracts database, references and reviews and letters to the editor. In addition, the Center for Drug Evaluation and Research database to identify unpublished research submitted to the US Food and Drug Administration (FDA)
Control for bias?	Yes	Sensitivity analysis based on definition of funding.

Halpern 2005

Methods	To determine whether there is a difference in average statistical power between pharmacoepidemiologic studies of anti-retroviral adverse drug effects (ADEs) sponsored by for-profit versus non-profit organizations (drugs approved from 1987 to 1999 and published until 2002)
Data	48 pharmacoepidemiological studies of adverse effects of ani-retroviral drugs
Comparisons	Non-profit, for-profit, charity/institution, none or unable to determine funding
Outcomes	Study results (harms).
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	One assessor only.
Comprehensive search?	Yes	MEDLINE, EMBASE and reference lists.
Control for bias?	No	No control for bias.

Heres 2006

Methods	To review the results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship exists between the sponsor of the trial and the drug favored in the study's overall outcome. All head-to-head trials of second-generation antipsychotics from 1997 to 2005
Data	42 head-to-head RCTs of second-generation antipsychotics.
Comparisons	Industry only (sponsor of test drug or comparator).
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	No	MEDLINE and screen of selected conference proceedings. Sample of conference proceedings limited to 1999-2004, which may introduce bias due to differences in approval dates for the different drugs
Control for bias?	Yes	Sensitivity analysis of peer-reviewed trials only.

Jefferson 2009

Methods	To explore the relation between study concordance, take home message, funding, and dissemination of comparative studies assessing the effects of influenza vaccines. Studies of various designs from 1961 to 2006
Data	274 studies of influenza vaccine versus placebo/no treatment
Comparisons	Government/private/unfunded, industry/mixed and not stated funding
Outcomes	Study conclusions, methodological quality (Cochrane risk of bias) and concordance between study results and conclusions
Notes	

Risk of bias

Item	Authors' judgement	Description

Jefferson 2009 (*Continued*)

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE, EMBASE, The Cochrane Library, web, and likely references and previous reviews since it is based on Cochrane reviews
Control for bias?	Yes	Sensitivity analysis based on definition of funding and regression analysis of various factors

Jones 2010

Methods	To compare the quality of publicly or privately funded randomized controlled trials. Trials included in Cochrane reviews on hypertension and preterm labour
Data	105 drug trials (mixed comparisons).
Comparisons	Commercial, mixed and non-commercial.
Outcomes	Methodological quality (selection bias, performance bias, detection bias and attrition)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Based on searches from Cochrane reviews.
Control for bias?	No	No control for bias.

Kelly 2006

Methods	To investigate the relationship between industry support and study outcome in the general psychiatric literature. Clinical studies from 1992 and 2002 in *American Journal of Psychiatry, Archives of General Psychiatry,* and *Journal of Clinical Psychopharmacology.*
Data	301 psychiatric drug studies (mixed comparisons).
Comparisons	Non-industry and industry (sponsor of test drug or comparator) funding

Kelly 2006 (*Continued*)

Outcomes	Study results, study conclusions and concordance between study results and conclusions	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals.
Control for bias?	Yes	Explanatory analysis of various mediating variables.

Kemmeren 2001

Methods	To evaluate quantitatively articles that compared effects of second- and third-generation oral contraceptives on risk of venous thrombosis. Cohort and case control studies from 1995 to 2000	
Data	12 cohort and case control studies of second- versus third-generation oral contraceptives	
Comparisons	Industry and non-industry funding.	
Outcomes	Study results and effect size.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, reviews, relevant papers and experts.
Control for bias?	No	Multiple regression used, but not for the association between funding and results or effect size

Kjaergard 2002

Methods	To assess the association between competing interests and authors' conclusions. RCTs published in *BMJ* 1997 to 2001.
Data	159 RCTs of mixed interventions (various comparators).
Comparisons	Profit, non-profit, non-profit and profit, non-profit and free drug, free drug only and no funding/ not stated
Outcomes	Study conclusions and methodological quality (sequence generation, concealment of allocation and blinding)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	MEDLINE journal search.
Control for bias?	Yes	Regression analysis for potential confounders.

Liss 2006

Methods	To determine whether drug studies in the pulmonary/allergy literature also demonstrate a publication bias towards more favorable results when a pharmaceutical company funds the study. Primary research studies of drug interventions published in *Allergy, American Journal of Respiratory and Critical Care Medicine, Annals of Allergy Asthma and Immunology, Chest, European Respiratory Journal, Journal of Allergy and Clinical Immunology, Respiratory Medicine,* and *Thorax* in 2002 to 2003.
Data	Studies of nasal or oral inhaled corticosteroids, long- or short-acting bronchodilators, and leukotriene receptor antagonists (various designs and comparisons)
Comparisons	Pharmaceutically and not pharmaceutically funded.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Liss 2006 (*Continued*)

Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	Handsearch of journals indirectly described.
Control for bias?	No	No control for bias.

Lubowitz 2007

Methods	To compare outcomes (and levels of evidence) between published Autologous Chondrocyte Implantation outcome studies that were commercially funded and studies that were not commercially funded. Clinical studies from 1994 to 2005
Data	23 studies of chondrocyte implantation (various designs and comparisons)
Comparisons	Commercially funded and not commercially funded.
Outcomes	Effect size.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	No	MEDLINE only, time period not stated and few search terms used
Control for bias?	No	No control for bias.

Lynch 2007

Methods	To test the following hypotheses regarding orthopedic manuscripts submitted for review: (1) non-scientific variables, including receipt of commercial funding, affect the likelihood that a peer-reviewed submission will conclude with a report of a positive study outcome, and (2) positive outcomes and other, non-scientific variables are associated with acceptance for publication. Cohort of manuscripts submitted involving original research on the subject of adult hip or knee reconstruction to *The Journal of Bone and Joint Surgery* (American Volume) between January 2004 and June 2005.
Data	209 studies of knee or hip surgery (various designs, interventions and comparisons)
Comparisons	Commercial, non-funded and noncommercial/philanthropic funding

Lynch 2007 (*Continued*)

Outcomes	Study conclusions and methodological quality (Sackett scale, 0 to 100%)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of papers via journal submission system.
Control for bias?	No	No control for bias.

Momeni 2009

Methods	To investigate if plastic surgical trials with industry-funding are more likely to be associated with statistically significant pro-industry findings. Trials in 4 plastic surgery journals (*Plastic and Reconstructive Surgery, British Journal of Plastic Surgery*, *Annals of Plastic Surgery,* and *Aesthetic Plastic Surgery*) from 1990 to 2005.
Data	346 RCTs and controlled clinical trials (various designs, interventions and comparisons)
Comparisons	Industry, public, university and not specified funding.
Outcomes	Study results.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	No	No control for bias.

Moncrieff 2003

Methods	To re-evaluate the evidence comparing clozapine with conventional antipsychotics and to investigate sources of heterogeneity. Trials from 1988 to 2001
Data	9 RCTs of clozapine versus conventional antipsychotics.
Comparisons	Industry, other and not declared funding.
Outcomes	Study results and effect size.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	No	Only one assessor included studies.
Comprehensive search?	Yes	MEDLINE, EMBASE and Cochrane review.
Control for bias?	No	Univariate controlled for various predictors in relation to effect size only

Montgomery 2004

Methods	To analyze RCTs of second-generation antipsychotics in schizophrenia with respect to funding source (industry versus non-industry funding). RCTs from 1974 to 2002
Data	86 RCTs of 2nd generation antipsychotics versus other types (various comparisons)
Comparisons	Industry and non-industry.
Outcomes	Study conclusions and methodological quality (Jadad score, 0-5 point scale)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, PsychInfo and references.

Control for bias?	No	No control for bias.

Nieto 2007

Methods	To evaluate differences between studies funded by the pharmaceutical manufacturer of the drug and those with no pharmaceutical funding regarding the findings and interpretation of adverse effects of inhaled corticosteroids. Studies from 1993 to 2002
Data	504 studies of inhaled corticosteroids (various study designs with various comparators)
Comparisons	Pharmaceutical funded and not pharmaceutical funded.
Outcomes	Study results (harms), study conclusions (harms) and concordance between study results and conclusions (harms)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals were identified by MEDLINE.
Control for bias?	Yes	Controlled for confounders using multivariate model.

Pengel 2009

Methods	To examine the quality of reporting of RCTs in solid organ transplantation that were published 2004 to 2006
Data	332 trials in solid organ transplantation (mixed interventions and comparisons)
Comparisons	Commercial, nonprofit, mixed, no funding and not described.
Outcomes	Methodological quality (concealment of allocation and Jadad score, 0-5 point scale)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Pengel 2009 (*Continued*)

Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, EMBASE and The Cochrane Library.
Control for bias?	No	No control for bias.

Peppercorn 2007

Methods	To evaluate the correlations between pharmaceutical company involvement, study design, and study outcome and to explore changes in these areas over time. Breast cancer trials of medical therapies that were published in the years 1993, 1998, and 2003 in 10 select English-language medical journals
Data	140 breast cancer drug trials (single arm studies and RCTs).
Comparisons	Pharmaceutical studies versus non-pharmaceutical studies.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch and MEDLINE used.
Control for bias?	No	Only assessment of differences in study design in relation to funding

Perlis 2005a

Methods	The purpose was to determine the extent and impact of industry sponsorship conflicts of interest in dermatology research. Drug trials from *Journal of Investigative Dermatology, Archives of Dermatology, British Journal of Dermatology,* and *Journal of the American Academy of Dermatology* from 2000 to 2003.
Data	179 RCTs of dermatological drugs (various comparators).

Perlis 2005a (*Continued*)

Comparisons	Industry and non-industry funding.	
Outcomes	Study conclusions and methodological quality (blinding and Jadad score, 0-5 point scale)	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals.
Control for bias?	Yes	Multivariate regression analysis adjusted for conflict of interest, Jadad score, and sample size

Perlis 2005b

Methods	To study the extent and implications of industry sponsorship and financial conflicts of interest in psychiatric trials. Drug trials from the *American Journal of Psychiatry, Archives of General Psychiatry, Journal of Clinical Psychiatry, andJournal of Clinical Psychopharmacology* from 2001 to 2003.	
Data	397 psychiatric clinical drug trials (various comparators).	
Comparisons	Industry and non-industry funding.	
Outcomes	Study results.	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Not sure if 3 assessors extracting data were involved in including studies
Comprehensive search?	Yes	MEDLINE and handsearch of journals.
Control for bias?	Yes	Logistic regression adjusted for confounders.

Popelut 2010

Methods	To examine financial sponsorship of dental implant trials, and to evaluate whether research funding sources affects the annual failure rate. Clinical trials from 1988 to 2005
Data	41 clinical trials of dental implants (single arm and active control)
Comparisons	Industry, non-industry and unknown funding.
Outcomes	Effect size.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	No	Inclusion criteria reported, but not possible to decipher and seems subjective
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	MEDLINE and handsearch.
Control for bias?	Yes	Controlled for confounders using multivariate analysis.

Rasmussen 2009

Methods	To compare the prevalence of favorable results and conclusions among published reports of registered and unregistered RCTs of new oncology drugs. Cohort of trials from 25 drugs granted first-time Food and Drug Administration (FDA) approval for oncology indications in 2000 to 2005 and published in 1996 to 2008
Data	137 RCTs of oncology drugs (placebo or active control).
Comparisons	Industry sponsor and other funding.
Outcomes	Study results, study conclusions, methodological quality (blinding) and concordance between study results and conclusions
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.

Rasmussen 2009 (*Continued*)

Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE and The Cochrane Library.
Control for bias?	Yes	Logistic regression adjusted for confounders.

Rattinger 2009

Methods	To examine the association between research funding source, study design characteristics aimed at reducing bias, and other factors with the results and conclusions of RCTs of thiazolidinediones compared to other oral hypoglycemic agents (search 1996 to 2006)
Data	61 RCTs of thiazolidinediones (active or placebo control).
Comparisons	Test drug company, other drug company, all others and not declared funding
Outcomes	Study results, study conclusions, methodological quality (sequence generation and allocation concealment, blinding and follow-up) and concordance between study results and conclusions
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, The Cochrane Library, references and reviews.
Control for bias?	Yes	Intended multivariate analysis, but due to few associations only univariate performed

Ridker 2006

Methods	To determine in contemporary randomized cardiovascular trials the association between funding source and the likelihood of reporting positive findings. Cardiovascular RCTs published in *JAMA*, *Lancet*, and the *New England Journal of Medicine* in 2000 to 2005.
Data	349 RCTs (mixed interventions and comparators).
Comparisons	For profit, mixed and not for profit funding.
Outcomes	Study conclusions.

Ridker 2006 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Sample of journals identified via MEDLINE.
Control for bias?	No	No control for bias.

Rios 2008

Methods	To assess the reporting quality of RCTs in general endocrinology and to identify predictors for better reporting quality. RCTs published in the *Journal of Clinical Endocrinology* and *Metabolism, Clinical Endocrinology,* and the *European Journal of Endocrinology* in 2005 or 2006.
Data	89 endocrinology drug RCTs (various comparators).
Comparisons	Industry, mixed, non-industry and not stated funding.
Outcomes	Methodological quality (allocation concealment and blinding)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Yes	Two assessors included studies.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	Yes	Controlled for confounders using multivariate analysis.

Rochon 1994

Methods	To study the relation between reported drug performance in published trials and support of the trials by the manufacturer of the drug under evaluation. All non-steroidal anti-inflammatory (NSAID) RCTs from September 1987 to May 1990
Data	56 NSAID RCTs (placebo and head-to-head comparisons).
Comparisons	Manufacturer associated only.
Outcomes	Study results (efficacy and harms), study conclusions (efficacy and harms) and methodological quality (Chalmers' scale, 0-100 points)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE searched.
Control for bias?	No	Control for bias seems unlikely to have been done.

Tulikangas 2006

Methods	To determine if there is a significant difference in outcomes of clinical trials funded by industry or not of antimuscarinic medications used to treat overactive bladder symptoms and detrusor overactivity. RCTs from 1980 to 2002
Data	24 RCTs of antimuscarinic drugs (various comparators).
Comparisons	Industry funded and public funded.
Outcomes	Study results.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.

Comprehensive search?	Yes	MEDLINE and references.
Control for bias?	No	No control for bias.

Tungaraza 2007

Methods	To compare drug trials reported in three major psychiatric journals to investigate whether treatments are more likely to report favorable outcomes when they are funded by the pharmaceutical industry. Studies published in the *British Journal of Psychiatry*, *American Journal of Psychiatry* and *Archives of General Psychiatry* from 2000 to 2004.
Data	198 psychiatric drug trials (various designs and comparators)
Comparisons	Industry sponsored, industry authored and independent.
Outcomes	Study conclusions.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	Handsearch of journals.
Control for bias?	No	No control for bias.

Vlad 2007

Methods	To identify factors that explain heterogeneity in trials of glucosamine. RCTs of glucosamine from 1980 to 2006
Data	15 RCTs of glucosamine versus placebo for osteoarthritis.
Comparisons	Industry funding, industry participation, industry author and independent
Outcomes	Study results, effect size and methodological quality (allocation concealment and Jadad score, 0-5 point scale)
Notes	

Risk of bias

Vlad 2007 (*Continued*)

Item	Authors' judgement	Description
Adequate selection criteria?	Yes	Objective criteria used.
Adequate study inclusion process?	Unclear	Does not describe number of assessors.
Comprehensive search?	Yes	MEDLINE, The Cochrane Library, conference abstracts, references and reviews
Control for bias?	Yes	Exploration of heterogeneity.

RCT: Randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Chowers 2009	No relevant outcomes
Conen 2008	No relevant outcomes
Cunningham 2007	No separate drug or device data
Friedman 2004	Conflicts of interest, not funding
Glick 2006	No relevant outcomes
Hall 2007	No relevant outcomes
Hill 2007	No relevant outcomes (not methodological quality, but reporting quality)
Jagsi 2009	No separate drug or device data
Khan 2008	No separate drug or device data
Kjaergard 1999	No separate drug or device data
Krzyzanowska 2003	No relevant outcomes
Kulier 2004	No quantitative data
Kulkarni 2007	No relevant outcomes
Lai 2006	No separate drug or device data

(*Continued*)

Leopold 2003	No separate drug or device data
Leucht 2009a	No relevant outcomes
Leucht 2009b	No relevant outcomes
McLennan 2008	No relevant outcomes
Montori 2005	No relevant outcomes
Nkansah 2009	Calcium supplementation, not a drug
Okike 2007	Conflicts of interest, not funding
Okike 2008	No relevant outcomes
Procyshyn 2004	No relevant data for non-industry studies
Roach 2008	No separate drug or device data
Sanossian 2006	No relevant outcomes
Shah 2005	No separate drug or device data
Thomas 2008	No relevant outcomes (not methodological quality, but reporting quality)
Watanabe 2010	No relevant outcomes
Yao 2007	No separate drug or device data
Yaphe 2001	No separate drug or device data

DATA AND ANALYSES

Comparison 1. Results: Industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results	14	1588	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.14, 1.35]
2 Number of studies with favorable harms results	3	561	Risk Ratio (M-H, Fixed, 95% CI)	1.87 [1.54, 2.27]

Comparison 2. Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment efficacy results	2	131	Risk Ratio (M-H, Fixed, 95% CI)	4.64 [2.08, 10.32]

Comparison 3. Conclusions: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable conclusions	21	3941	Risk Ratio (IV, Random, 95% CI)	1.31 [1.20, 1.44]

Comparison 4. Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable test treatment conclusions	3	154	Risk Ratio (M-H, Fixed, 95% CI)	5.90 [2.79, 12.49]

Comparison 5. Risk of bias: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with low risk of bias from sequence generation	3	487	Risk Ratio (IV, Random, 95% CI)	0.85 [0.52, 1.41]
2 Number of studies with low risk of bias from concealment of allocation	10	1311	Risk Ratio (IV, Random, 95% CI)	1.09 [0.86, 1.38]
3 Number of studies with low risk of bias from blinding	9	1216	Risk Ratio (IV, Random, 95% CI)	1.32 [1.05, 1.65]
4 Number of studies with low risk of bias from loss to follow-up	2	118	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.16]

Comparison 6. Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with concordant study results and conclusions	5	667	Risk Ratio (IV, Random, 95% CI)	0.84 [0.70, 1.01]

Comparison 7. Subgroup analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results	14	1588	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.14, 1.35]
1.1 High risk of bias	11	962	Risk Ratio (IV, Fixed, 95% CI)	1.14 [1.03, 1.25]
1.2 Low risk of bias	3	626	Risk Ratio (IV, Fixed, 95% CI)	1.50 [1.30, 1.74]
2 Number of studies with favorable conclusions	21	3941	Risk Ratio (IV, Random, 95% CI)	1.31 [1.20, 1.44]
2.1 High risk of bias	17	3062	Risk Ratio (IV, Random, 95% CI)	1.26 [1.14, 1.39]
2.2 Low risk of bias	4	879	Risk Ratio (IV, Random, 95% CI)	1.54 [1.24, 1.91]
3 Number of studies with favorable conclusions	21	3941	Risk Ratio (IV, Random, 95% CI)	1.30 [1.18, 1.42]
3.1 Drug studies	21	3821	Risk Ratio (IV, Random, 95% CI)	1.31 [1.19, 1.44]
3.2 Device studies	2	120	Risk Ratio (IV, Random, 95% CI)	1.09 [0.82, 1.45]
4 Number of studies with favorable efficacy results	14	1588	Risk Ratio (IV, Fixed, 95% CI)	1.24 [1.14, 1.35]

4.1 Specific treatments or diseases	12	1143	Risk Ratio (IV, Fixed, 95% CI)	1.19 [1.08, 1.31]
4.2 Mixed domain	2	445	Risk Ratio (IV, Fixed, 95% CI)	1.39 [1.18, 1.64]
5 Number of studies with favorable conclusions	21	3941	Risk Ratio (IV, Random, 95% CI)	1.31 [1.20, 1.44]
5.1 Specific treatments or diseases	16	2774	Risk Ratio (IV, Random, 95% CI)	1.34 [1.19, 1.51]
5.2 Mixed study domain	5	1167	Risk Ratio (IV, Random, 95% CI)	1.26 [1.08, 1.47]

Comparison 8. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of studies with favorable efficacy results, sponsorship recoded	5	517	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.27, 1.76]
2 Number of studies with favorable conclusions, sponsorship recoded	7	951	Risk Ratio (IV, Random, 95% CI)	1.26 [1.06, 1.50]
3 Number of studies with low risk of bias from sequence generation, sponsorship recoded	2	249	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.77, 1.44]
4 Number of studies with low risk of bias from concealment of allocation, sponsorship recoded	7	663	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.90, 1.52]
5 Number of studies with low risk of bias from blinding, sponsorship recoded	5	425	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.23, 1.94]
6 Results:Number of studies with favorable efficacy results, analysis adjusted for confounders	2		Odds Ratio (Fixed, 95% CI)	3.86 [1.93, 7.70]
7 Conclusions:Number of studies with favorable conclusions, analysis adjusted for confounders	3		Odds Ratio (Fixed, 95% CI)	4.15 [2.40, 7.19]
8 Number of studies with favorable efficacy results, random-effects model	14	1588	Risk Ratio (IV, Random, 95% CI)	1.26 [1.12, 1.41]
9 Number of studies with favorable harms results, random-effects model	3	561	Risk Ratio (M-H, Random, 95% CI)	1.87 [1.54, 2.27]
10 Number of studies with favorable test treatment efficacy results, random effects-model	2	131	Risk Ratio (M-H, Random, 95% CI)	3.88 [1.26, 11.94]

11 Number of studies with favorable test treatment conclusions, random-effects model	3	154	Risk Ratio (M-H, Random, 95% CI)	5.92 [2.80, 12.54]
12 Number of studies with low risk of bias from loss to follow-up, random-effects model	2	118	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.84, 1.15]

Analysis 1.1. Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with favorable efficacy results.

Review: Industry sponsorship and research outcome

Comparison: 1 Results: Industry sponsored versus non-industry sponsored studies

Outcome: 1 Number of studies with favorable efficacy results

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Alasbali 2009	7/29	2/10		0.3 %	1.21 [0.30, 4.88]
Bero 2007	65/94	48/97		11.5 %	1.40 [1.10, 1.78]
Booth 2008	49/120	50/165		6.8 %	1.35 [0.98, 1.85]
Bourgeois 2010	222/260	48/85		18.1 %	1.51 [1.25, 1.83]
Clifford 2002	46/66	21/34		7.1 %	1.13 [0.83, 1.54]
Etter 2007	25/49	9/41		1.7 %	2.32 [1.23, 4.40]
Kelly 2006	12/13	4/8		1.3 %	1.85 [0.91, 3.76]
Momeni 2009	20/24	69/85		15.9 %	1.03 [0.84, 1.26]
Moncrieff 2003	2/2	2/7		0.5 %	2.67 [0.85, 8.39]
Perlis 2005b	93/113	37/49		20.7 %	1.09 [0.91, 1.31]
Rasmussen 2009	66/109	14/28		4.2 %	1.21 [0.81, 1.81]
Rattinger 2009	26/36	18/25		6.7 %	1.00 [0.73, 1.38]
Tulikangas 2006	15/15	7/9		5.0 %	1.29 [0.89, 1.87]
Vlad 2007	5/11	0/4		0.1 %	4.58 [0.31, 68.24]
Total (95% CI)	**941**	**647**		**100.0 %**	**1.24 [1.14, 1.35]**

Total events: 653 (Industry), 329 (Non-industry)

Heterogeneity: Chi^2 = 20.09, df = 13 (P = 0.09); I^2 =35%

Test for overall effect: Z = 5.11 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 2 Number of studies with favorable harms results.

Review: Industry sponsorship and research outcome

Comparison: 1 Results: Industry sponsored versus non-industry sponsored studies

Outcome: 2 Number of studies with favorable harms results

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Halpern 2005	1/3	10/45		1.4 %	1.50 [0.28, 8.14]
Kemmeren 2001	3/4	2/5		2.0 %	1.88 [0.56, 6.31]
Nieto 2007	180/275	80/229		96.6 %	1.87 [1.54, 2.28]
Total (95% CI)	**282**	**279**		**100.0 %**	**1.87 [1.54, 2.27]**

Total events: 184 (Industry), 92 (Non-industry)

Heterogeneity: $Chi^2 = 0.07$, df = 2 (P = 0.97); $I^2 = 0.0\%$

Test for overall effect: Z = 6.35 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company, Outcome 1 Number of studies with favorable test treatment efficacy results.

Review: Industry sponsorship and research outcome

Comparison: 2 Results: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome: 1 Number of studies with favorable test treatment efficacy results

Study or subgroup	Test treatment sponsor n/N	Comparator treatm sponsor n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bero 2007	43/65	3/30		55.2 %	6.62 [2.23, 19.63]
Rattinger 2009	22/30	2/6		44.8 %	2.20 [0.70, 6.96]
Total (95% CI)	**95**	**36**		**100.0 %**	**4.64 [2.08, 10.32]**

Total events: 65 (Test treatment sponsor), 5 (Comparator treatm sponsor)

Heterogeneity: $Chi^2 = 2.02$, df = 1 (P = 0.16); $I^2 = 50\%$

Test for overall effect: Z = 3.76 (P = 0.00017)

Test for subgroup differences: Not applicable

Analysis 3.1. Comparison 3 Conclusions: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with favorable conclusions.

Review: Industry sponsorship and research outcome

Comparison: 3 Conclusions: industry sponsored versus non-industry sponsored studies

Outcome: 1 Number of studies with favorable conclusions

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Ahmer 2005	125/138	39/50		6.1 %	1.16 [0.99, 1.36]
Alasbali 2009	26/29	2/10		0.5 %	4.48 [1.29, 15.58]
Als-Nielsen 2003	92/197	43/173		4.2 %	1.88 [1.39, 2.53]
Bero 2007	66/94	39/97		4.5 %	1.75 [1.32, 2.30]
Booth 2008	66/118	55/153		4.6 %	1.56 [1.19, 2.03]
Buchkowsky 2004	138/181	224/319		6.7 %	1.09 [0.97, 1.21]
Chard 2000	106/108	373/383		7.3 %	1.01 [0.98, 1.04]
Cho 1996	39/40	89/112		6.7 %	1.23 [1.10, 1.36]
Davidson 1986	32/36	31/49		4.9 %	1.41 [1.10, 1.79]
Djulbegovic 2000	26/35	50/95		4.5 %	1.41 [1.07, 1.85]
Finucane 2004	30/30	12/18		3.9 %	1.50 [1.08, 2.07]
Jefferson 2009	64/76	131/194		6.3 %	1.25 [1.09, 1.43]
Kjaergard 2002	28/38	16/22		4.0 %	1.01 [0.74, 1.39]
Liss 2006	62/63	12/37		2.6 %	3.03 [1.90, 4.84]
Lynch 2007	26/34	49/65		5.0 %	1.01 [0.80, 1.28]
Peppercorn 2007	52/67	48/73		5.4 %	1.18 [0.96, 1.46]
Perlis 2005a	87/102	47/77		5.5 %	1.40 [1.15, 1.70]
Rasmussen 2009	83/109	15/28		3.5 %	1.42 [0.99, 2.04]
Rattinger 2009	31/36	21/25		5.3 %	1.03 [0.83, 1.27]
Ridker 2006	121/189	21/51		3.7 %	1.55 [1.10, 2.20]
Tungaraza 2007	124/146	28/44		5.0 %	1.33 [1.06, 1.69]
Total (95% CI)	**1866**	**2075**		**100.0 %**	**1.31 [1.20, 1.44]**

Total events: 1424 (Industry), 1345 (Non-industry)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 115.75$, df = 20 ($P<0.00001$); $I^2 = 83\%$

Test for overall effect: $Z = 5.70$ ($P < 0.00001$)

Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company, Outcome 1 Number of studies with favorable test treatment conclusions.

Review: Industry sponsorship and research outcome

Comparison: 4 Conclusions: Industry sponsorship by test treatment company versus sponsorship by comparator treatment company

Outcome: 1 Number of studies with favorable test treatment conclusions

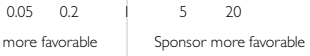
Study or subgroup	Test treatment sponsor n/N	Comparator treatm sponsor n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bero 2007	51/65	4/30		65.9 %	5.88 [2.34, 14.78]
Heres 2006	10/12	1/9		13.8 %	7.50 [1.16, 48.43]
Rattinger 2009	26/32	1/6		20.3 %	4.88 [0.81, 29.40]
Total (95% CI)	**109**	**45**		**100.0 %**	**5.90 [2.79, 12.49]**

Total events: 87 (Test treatment sponsor), 6 (Comparator treatm sponsor)

Heterogeneity: $Chi^2 = 0.11$, df = 2 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 4.64 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 5.1. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with low risk of bias from sequence generation.

Review: Industry sponsorship and research outcome

Comparison: 5 Risk of bias: industry sponsored versus non-industry sponsored studies

Outcome: 1 Number of studies with low risk of bias from sequence generation

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Als-Nielsen 2003	62/197	43/173		34.0 %	1.27 [0.91, 1.76]
Crocetti 2010	11/32	21/25		28.3 %	0.41 [0.25, 0.68]
Kjaergard 2002	34/38	19/22		37.6 %	1.04 [0.85, 1.26]
Total (95% CI)	**267**	**220**		**100.0 %**	**0.85 [0.52, 1.41]**

Total events: 107 (Industry), 83 (Non-industry)

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 13.92$, df = 2 (P = 0.00095); $I^2 = 86\%$

Test for overall effect: Z = 0.62 (P = 0.53)

Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 2 Number of studies with low risk of bias from concealment of allocation.

Review: Industry sponsorship and research outcome

Comparison: 5 Risk of bias: industry sponsored versus non-industry sponsored studies

Outcome: 2 Number of studies with low risk of bias from concealment of allocation

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Als-Nielsen 2003	55/197	27/173		12.9 %	1.79 [1.18, 2.70]
Bero 2007	19/95	21/97		9.8 %	0.92 [0.53, 1.60]
Clifford 2002	22/66	14/34		10.3 %	0.81 [0.48, 1.37]
Crocetti 2010	14/32	16/25		11.1 %	0.68 [0.42, 1.12]
Jones 2010	23/31	35/56		16.1 %	1.19 [0.89, 1.59]
Kjaergard 2002	26/38	15/22		14.3 %	1.00 [0.70, 1.44]
Pengel 2009	63/154	34/126		14.7 %	1.52 [1.07, 2.14]
Rattinger 2009	10/36	5/25		4.8 %	1.39 [0.54, 3.57]
Rios 2008	6/42	4/47		3.3 %	1.68 [0.51, 5.54]
Vlad 2007	2/11	3/4		2.6 %	0.24 [0.06, 0.96]
Total (95% CI)	**702**	**609**		**100.0 %**	**1.09 [0.86, 1.38]**

Total events: 240 (Industry), 174 (Non-industry)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 19.56$, df = 9 (P = 0.02); $I^2 = 54\%$

Test for overall effect: Z = 0.73 (P = 0.46)

Test for subgroup differences: Not applicable

Analysis 5.3. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 3 Number of studies with low risk of bias from blinding.

Review: Industry sponsorship and research outcome

Comparison: 5 Risk of bias: industry sponsored versus non-industry sponsored studies

Outcome: 3 Number of studies with low risk of bias from blinding

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Als-Nielsen 2003	150/197	84/157		16.7 %	1.42 [1.21, 1.68]
Bero 2007	53/95	36/97		13.6 %	1.50 [1.10, 2.06]
Crocetti 2010	28/32	23/25		16.5 %	0.95 [0.80, 1.13]
Jones 2010	16/31	14/56		8.6 %	2.06 [1.17, 3.64]
Kjaergard 2002	26/38	13/22		11.5 %	1.16 [0.77, 1.74]
Perlis 2005a	71/102	27/77		13.2 %	1.99 [1.43, 2.76]
Rasmussen 2009	33/109	3/28		3.4 %	2.83 [0.93, 8.54]
Rattinger 2009	20/36	15/25		11.0 %	0.93 [0.60, 1.43]
Rios 2008	7/42	13/47		5.4 %	0.60 [0.27, 1.37]
Total (95% CI)	**682**	**534**		**100.0 %**	**1.32 [1.05, 1.65]**

Total events: 404 (Industry), 228 (Non-industry)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 30.72$, df = 8 (P = 0.00016); $I^2 = 74\%$

Test for overall effect: Z = 2.37 (P = 0.018)

Test for subgroup differences: Not applicable

Analysis 5.4. Comparison 5 Risk of bias: industry sponsored versus non-industry sponsored studies, Outcome 4 Number of studies with low risk of bias from loss to follow-up.

Review: Industry sponsorship and research outcome

Comparison: 5 Risk of bias: industry sponsored versus non-industry sponsored studies

Outcome: 4 Number of studies with low risk of bias from loss to follow-up

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Crocetti 2010	28/32	22/25		51.1 %	0.99 [0.82, 1.21]
Rattinger 2009	28/36	20/25		48.9 %	0.97 [0.75, 1.26]
Total (95% CI)	**68**	**50**		**100.0 %**	**0.98 [0.84, 1.16]**

Total events: 56 (Industry), 42 (Non-industry)

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with concordant study results and conclusions.

Review: Industry sponsorship and research outcome

Comparison: 6 Concordance between study results and conclusions: industry sponsored versus non-industry sponsored studies

Outcome: 1 Number of studies with concordant study results and conclusions

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Alasbali 2009	11/29	10/10		10.1 %	0.40 [0.25, 0.64]
Bero 2007	72/95	80/97		26.6 %	0.92 [0.79, 1.06]
Jefferson 2009	39/66	120/172		21.6 %	0.85 [0.68, 1.06]
Rasmussen 2009	86/109	23/28		23.2 %	0.96 [0.79, 1.17]
Rattinger 2009	27/36	20/25		18.6 %	0.94 [0.71, 1.23]
Total (95% CI)	**335**	**332**		**100.0 %**	**0.84 [0.70, 1.01]**

Total events: 235 (Industry), 253 (Non-industry)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 12.00$, df = 4 (P = 0.02); $I^2 = 67\%$

Test for overall effect: Z = 1.86 (P = 0.063)

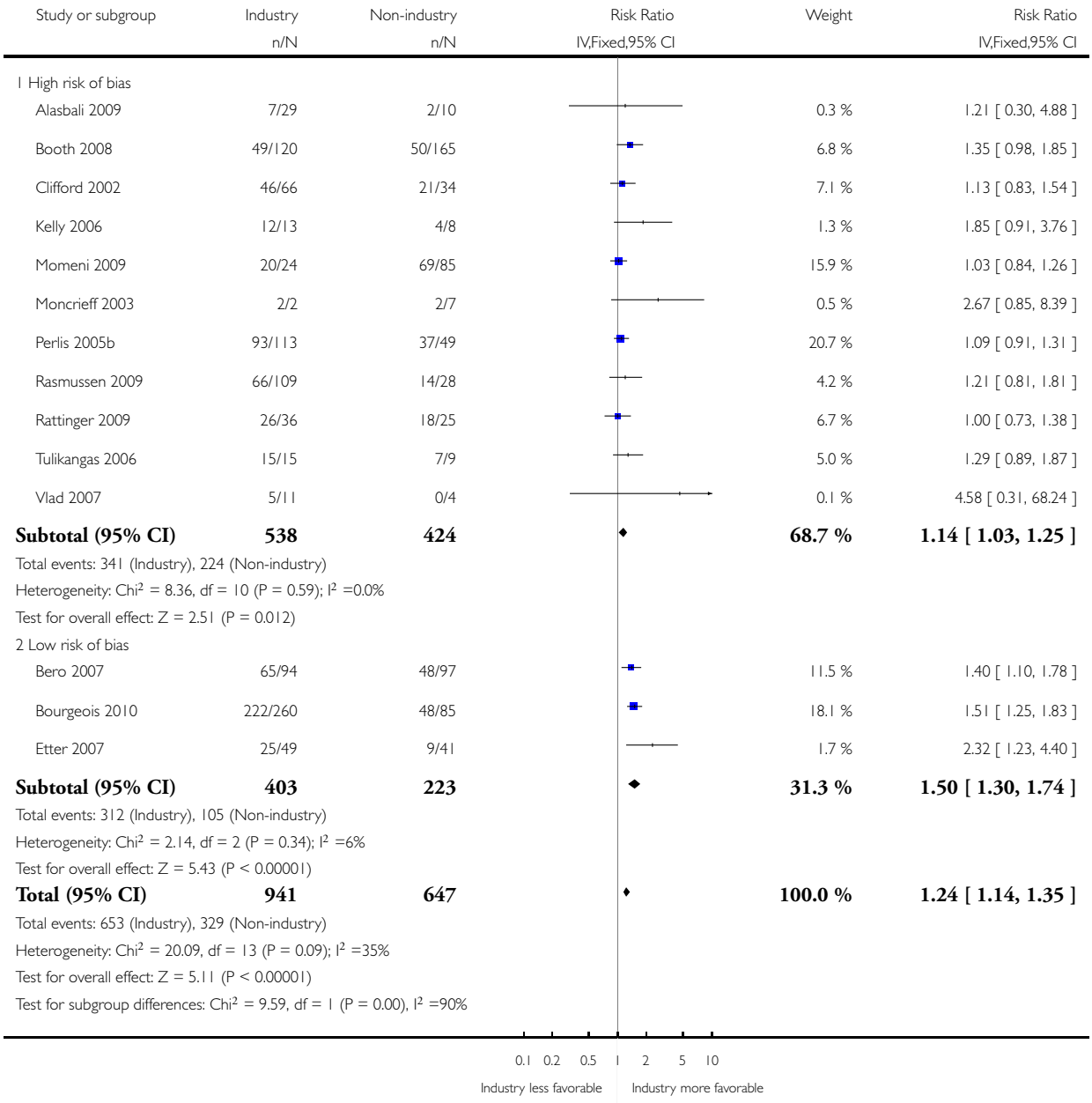
Test for subgroup differences: Not applicable

Analysis 7.1. Comparison 7 Subgroup analysis, Outcome 1 Number of studies with favorable efficacy results.

Review: Industry sponsorship and research outcome

Comparison: 7 Subgroup analysis

Outcome: 1 Number of studies with favorable efficacy results



Analysis 7.2. Comparison 7 Subgroup analysis, Outcome 2 Number of studies with favorable conclusions.

Review: Industry sponsorship and research outcome

Comparison: 7 Subgroup analysis

Outcome: 2 Number of studies with favorable conclusions

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 High risk of bias					
Ahmer 2005	125/138	39/50		6.1 %	1.16 [0.99, 1.36]
Alasbali 2009	26/29	2/10		0.5 %	4.48 [1.29, 15.58]
Booth 2008	66/118	55/153		4.6 %	1.56 [1.19, 2.03]
Buchkowsky 2004	138/181	224/319		6.7 %	1.09 [0.97, 1.21]
Chard 2000	106/108	373/383		7.3 %	1.01 [0.98, 1.04]
Cho 1996	39/40	89/112		6.7 %	1.23 [1.10, 1.36]
Davidson 1986	32/36	31/49		4.9 %	1.41 [1.10, 1.79]
Djulbegovic 2000	26/35	50/95		4.5 %	1.41 [1.07, 1.85]
Kjaergard 2002	28/38	16/22		4.0 %	1.01 [0.74, 1.39]
Liss 2006	62/63	12/37		2.6 %	3.03 [1.90, 4.84]
Lynch 2007	26/34	49/65		5.0 %	1.01 [0.80, 1.28]
Peppercorn 2007	52/67	48/73		5.4 %	1.18 [0.96, 1.46]
Perlis 2005a	87/102	47/77		5.5 %	1.40 [1.15, 1.70]
Rasmussen 2009	83/109	15/28		3.5 %	1.42 [0.99, 2.04]
Rattinger 2009	31/36	21/25		5.3 %	1.03 [0.83, 1.27]
Ridker 2006	121/189	21/51		3.7 %	1.55 [1.10, 2.20]
Tungaraza 2007	124/146	28/44		5.0 %	1.33 [1.06, 1.69]
Subtotal (95% CI)	**1469**	**1593**		**81.2 %**	**1.26 [1.14, 1.39]**
Total events: 1172 (Industry), 1120 (Non-industry)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 81.31$, df = 16 (P<0.00001); $I^2 = 80\%$					
Test for overall effect: Z = 4.67 (P < 0.00001)					
2 Low risk of bias					
Als-Nielsen 2003	92/197	43/173		4.2 %	1.88 [1.39, 2.53]
Bero 2007	66/94	39/97		4.5 %	1.75 [1.32, 2.30]

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Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Finucane 2004	30/30	12/18		3.9 %	1.50 [1.08, 2.07]
Jefferson 2009	64/76	131/194		6.3 %	1.25 [1.09, 1.43]
Subtotal (95% CI)	**397**	**482**		**18.8 %**	**1.54 [1.24, 1.91]**
Total events: 252 (Industry), 225 (Non-industry)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 9.02, df = 3 (P = 0.03); I^2 =67%					
Test for overall effect: Z = 3.89 (P = 0.00010)					
Total (95% CI)	**1866**	**2075**		**100.0 %**	**1.31 [1.20, 1.44]**
Total events: 1424 (Industry), 1345 (Non-industry)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 115.75, df = 20 (P<0.00001); I^2 =83%					
Test for overall effect: Z = 5.70 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.73, df = 1 (P = 0.10), I^2 =63%					

Analysis 7.3. Comparison 7 Subgroup analysis, Outcome 3 Number of studies with favorable conclusions.

Review: Industry sponsorship and research outcome

Comparison: 7 Subgroup analysis

Outcome: 3 Number of studies with favorable conclusions

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Drug studies					
Ahmer 2005	125/138	39/50		5.8 %	1.16 [0.99, 1.36]
Alasbali 2009	26/29	2/10		0.5 %	4.48 [1.29, 15.58]
Als-Nielsen 2003	92/197	43/173		4.0 %	1.88 [1.39, 2.53]
Bero 2007	66/94	39/97		4.3 %	1.75 [1.32, 2.30]
Booth 2008	66/118	55/153		4.4 %	1.56 [1.19, 2.03]
Buchkowsky 2004	138/181	224/319		6.4 %	1.09 [0.97, 1.21]
Chard 2000	106/108	373/383		7.0 %	1.01 [0.98, 1.04]
Cho 1996	39/40	89/112		6.4 %	1.23 [1.10, 1.36]
Davidson 1986	32/36	31/49		4.7 %	1.41 [1.10, 1.79]

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Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Djulbegovic 2000	26/35	50/95		4.3 %	1.41 [1.07, 1.85]
Finucane 2004	30/30	12/18		3.7 %	1.50 [1.08, 2.07]
Jefferson 2009	64/76	131/194		6.1 %	1.25 [1.09, 1.43]
Kjaergard 2002	28/38	16/22		3.8 %	1.01 [0.74, 1.39]
Liss 2006	62/63	12/37		2.5 %	3.03 [1.90, 4.84]
Lynch 2007	7/8	9/9		3.7 %	0.88 [0.63, 1.21]
Peppercorn 2007	52/67	48/73		5.1 %	1.18 [0.96, 1.46]
Perlis 2005a	87/102	47/77		5.3 %	1.40 [1.15, 1.70]
Rasmussen 2009	83/109	15/28		3.4 %	1.42 [0.99, 2.04]
Rattinger 2009	31/36	21/25		5.1 %	1.03 [0.83, 1.27]
Ridker 2006	98/159	17/43		3.1 %	1.56 [1.06, 2.30]
Tungaraza 2007	124/146	28/44		4.8 %	1.33 [1.06, 1.69]
Subtotal (95% CI)	**1810**	**2011**		**94.5 %**	**1.31 [1.19, 1.44]**
Total events: 1382 (Industry), 1301 (Non-industry)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 116.15, df = 20 (P<0.00001); I^2 =83%					
Test for overall effect: Z = 5.55 (P < 0.00001)					
2 Device studies					
Lynch 2007	19/26	40/56		4.2 %	1.02 [0.77, 1.36]
Ridker 2006	23/30	4/8		1.3 %	1.53 [0.75, 3.15]
Subtotal (95% CI)	**56**	**64**		**5.5 %**	**1.09 [0.82, 1.45]**
Total events: 42 (Industry), 44 (Non-industry)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 0.58 (P = 0.56)					
Total (95% CI)	**1866**	**2075**		**100.0 %**	**1.30 [1.18, 1.42]**
Total events: 1424 (Industry), 1345 (Non-industry)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 117.20, df = 22 (P<0.00001); I^2 =81%					
Test for overall effect: Z = 5.58 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.45, df = 1 (P = 0.23), I^2 =31%					

Analysis 7.4. Comparison 7 Subgroup analysis, Outcome 4 Number of studies with favorable efficacy results.

Review: Industry sponsorship and research outcome

Comparison: 7 Subgroup analysis

Outcome: 4 Number of studies with favorable efficacy results

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Specific treatments or diseases					
Alasbali 2009	7/29	2/10		0.3 %	1.21 [0.30, 4.88]
Bero 2007	65/94	48/97		11.5 %	1.40 [1.10, 1.78]
Booth 2008	49/120	50/165		6.8 %	1.35 [0.98, 1.85]
Etter 2007	25/49	9/41		1.7 %	2.32 [1.23, 4.40]
Kelly 2006	12/13	4/8		1.3 %	1.85 [0.91, 3.76]
Momeni 2009	20/24	69/85		15.9 %	1.03 [0.84, 1.26]
Moncrieff 2003	2/2	2/7		0.5 %	2.67 [0.85, 8.39]
Perlis 2005b	93/113	37/49		20.7 %	1.09 [0.91, 1.31]
Rasmussen 2009	66/109	14/28		4.2 %	1.21 [0.81, 1.81]
Rattinger 2009	26/36	18/25		6.7 %	1.00 [0.73, 1.38]
Tulikangas 2006	15/15	7/9		5.0 %	1.29 [0.89, 1.87]
Vlad 2007	5/11	0/4		0.1 %	4.58 [0.31, 68.24]
Subtotal (95% CI)	**615**	**528**		**74.8 %**	**1.19 [1.08, 1.31]**
Total events: 385 (Industry), 260 (Non-industry)					
Heterogeneity: Chi^2 = 15.02, df = 11 (P = 0.18); I^2 =27%					
Test for overall effect: Z = 3.61 (P = 0.00030)					
2 Mixed domain					
Bourgeois 2010	222/260	48/85		18.1 %	1.51 [1.25, 1.83]
Clifford 2002	46/66	21/34		7.1 %	1.13 [0.83, 1.54]
Subtotal (95% CI)	**326**	**119**		**25.2 %**	**1.39 [1.18, 1.64]**
Total events: 268 (Industry), 69 (Non-industry)					
Heterogeneity: Chi^2 = 2.48, df = 1 (P = 0.12); I^2 =60%					
Test for overall effect: Z = 3.96 (P = 0.000075)					
Total (95% CI)	**941**	**647**		**100.0 %**	**1.24 [1.14, 1.35]**
Total events: 653 (Industry), 329 (Non-industry)					
Heterogeneity: Chi^2 = 20.09, df = 13 (P = 0.09); I^2 =35%					
Test for overall effect: Z = 5.11 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.59, df = 1 (P = 0.11), I^2 =61%					

Analysis 7.5. Comparison 7 Subgroup analysis, Outcome 5 Number of studies with favorable conclusions.

Review: Industry sponsorship and research outcome

Comparison: 7 Subgroup analysis

Outcome: 5 Number of studies with favorable conclusions

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Specific treatments or diseases					
Ahmer 2005	125/138	39/50		6.1 %	1.16 [0.99, 1.36]
Alasbali 2009	26/29	2/10		0.5 %	4.48 [1.29, 15.58]
Bero 2007	66/94	39/97		4.5 %	1.75 [1.32, 2.30]
Booth 2008	66/118	55/153		4.6 %	1.56 [1.19, 2.03]
Chard 2000	106/108	373/383		7.3 %	1.01 [0.98, 1.04]
Djulbegovic 2000	26/35	50/95		4.5 %	1.41 [1.07, 1.85]
Finucane 2004	30/30	12/18		3.9 %	1.50 [1.08, 2.07]
Jefferson 2009	64/76	131/194		6.3 %	1.25 [1.09, 1.43]
Liss 2006	62/63	12/37		2.6 %	3.03 [1.90, 4.84]
Lynch 2007	26/34	49/65		5.0 %	1.01 [0.80, 1.28]
Peppercorn 2007	52/67	48/73		5.4 %	1.18 [0.96, 1.46]
Perlis 2005a	87/102	47/77		5.5 %	1.40 [1.15, 1.70]
Rasmussen 2009	83/109	15/28		3.5 %	1.42 [0.99, 2.04]
Rattinger 2009	31/36	21/25		5.3 %	1.03 [0.83, 1.27]
Ridker 2006	121/189	21/51		3.7 %	1.55 [1.10, 2.20]
Tungaraza 2007	124/146	28/44		5.0 %	1.33 [1.06, 1.69]
Subtotal (95% CI)	**1374**	**1400**		**73.6 %**	**1.34 [1.19, 1.51]**
Total events: 1095 (Industry), 942 (Non-industry)					
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 90.76$, df = 15 (P<0.00001); $I^2 = 83\%$					
Test for overall effect: Z = 4.77 (P < 0.00001)					
2 Mixed study domain					
Als-Nielsen 2003	92/197	43/173		4.2 %	1.88 [1.39, 2.53]
Buchkowsky 2004	138/181	224/319		6.7 %	1.09 [0.97, 1.21]
Cho 1996	39/40	89/112		6.7 %	1.23 [1.10, 1.36]
Davidson 1986	32/36	31/49		4.9 %	1.41 [1.10, 1.79]
Kjaergard 2002	28/38	16/22		4.0 %	1.01 [0.74, 1.39]

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Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Subtotal (95% CI)	**492**	**675**		**26.4 %**	**1.26 [1.08, 1.47]**
Total events: 329 (Industry), 403 (Non-industry)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 14.79, df = 4 (P = 0.01); I^2 =73%					
Test for overall effect: Z = 2.91 (P = 0.0036)					
Total (95% CI)	**1866**	**2075**		**100.0 %**	**1.31 [1.20, 1.44]**
Total events: 1424 (Industry), 1345 (Non-industry)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 115.75, df = 20 (P<0.00001); I^2 =83%					
Test for overall effect: Z = 5.70 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.37, df = 1 (P = 0.54), I^2 =0.0%					

Analysis 8.1. Comparison 8 Sensitivity analysis, Outcome 1 Number of studies with favorable efficacy results, sponsorship recoded.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 1 Number of studies with favorable efficacy results, sponsorship recoded

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bero 2007	54/76	10/23		14.4 %	1.63 [1.00, 2.66]
Bourgeois 2010	188/220	48/85		64.9 %	1.51 [1.25, 1.84]
Clifford 2002	30/44	15/28		17.2 %	1.27 [0.85, 1.90]
Moncrieff 2003	2/2	1/6		0.8 %	3.89 [0.86, 17.54]
Rattinger 2009	25/32	1/1		2.7 %	1.03 [0.45, 2.34]
Total (95% CI)	**374**	**143**		**100.0 %**	**1.50 [1.27, 1.76]**
Total events: 299 (Industry), 75 (Non-industry)					
Heterogeneity: Chi^2 = 3.11, df = 4 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 4.88 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 8.2. Comparison 8 Sensitivity analysis, Outcome 2 Number of studies with favorable conclusions, sponsorship recoded.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 2 Number of studies with favorable conclusions, sponsorship recoded

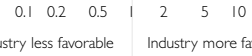
Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Ahmer 2005	75/84	34/43		22.5 %	1.13 [0.95, 1.34]
Als-Nielsen 2003	74/146	11/67		7.1 %	3.09 [1.76, 5.42]
Bero 2007	57/76	10/23		8.9 %	1.73 [1.06, 2.80]
Buchkowsky 2004	76/104	121/180		23.4 %	1.09 [0.93, 1.27]
Jefferson 2009	23/29	89/130		19.7 %	1.16 [0.93, 1.44]
Kjaergard 2002	21/23	10/13		14.4 %	1.19 [0.86, 1.64]
Rattinger 2009	28/32	1/1		3.9 %	1.15 [0.51, 2.59]
Total (95% CI)	**494**	**457**		**100.0 %**	**1.26 [1.06, 1.50]**

Total events: 354 (Industry), 276 (Non-industry)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 14.91$, df = 6 (P = 0.02); $I^2 = 60\%$

Test for overall effect: Z = 2.65 (P = 0.0079)

Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8 Sensitivity analysis, Outcome 3 Number of studies with low risk of bias from sequence generation, sponsorship recoded.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 3 Number of studies with low risk of bias from sequence generation, sponsorship recoded

Study or subgroup	Industry n/N	Nonindustry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Als-Nielsen 2003	43/146	20/67		68.2 %	0.99 [0.63, 1.54]
Kjaergard 2002	21/23	10/13		31.8 %	1.19 [0.86, 1.64]
Total (95% CI)	**169**	**80**		**100.0 %**	**1.05 [0.77, 1.44]**
Total events: 64 (Industry), 30 (Nonindustry)					
Heterogeneity: Chi^2 = 0.63, df = 1 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.31 (P = 0.76)					
Test for subgroup differences: Not applicable					

Analysis 8.4. Comparison 8 Sensitivity analysis, Outcome 4 Number of studies with low risk of bias from concealment of allocation, sponsorship recoded.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 4 Number of studies with low risk of bias from concealment of allocation, sponsorship recoded

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Als-Nielsen 2003	38/146	13/67		24.6 %	1.34 [0.77, 2.35]
Bero 2007	17/76	6/24		12.6 %	0.89 [0.40, 2.01]
Clifford 2002	16/44	13/28		21.9 %	0.78 [0.45, 1.37]
Kjaergard 2002	16/23	8/13		14.1 %	1.13 [0.68, 1.88]
Pengel 2009	52/128	11/38		23.4 %	1.40 [0.82, 2.41]
Rattinger 2009	9/32	0/1		1.3 %	1.15 [0.10, 13.47]
Rios 2008	3/16	2/27		2.1 %	2.53 [0.47, 13.57]
Total (95% CI)	**465**	**198**		**100.0 %**	**1.17 [0.90, 1.52]**

Total events: 151 (Industry), 53 (Non-industry)

Heterogeneity: Chi^2 = 3.90, df = 6 (P = 0.69); I^2 =0.0%

Test for overall effect: Z = 1.18 (P = 0.24)

Test for subgroup differences: Not applicable

Analysis 8.5. Comparison 8 Sensitivity analysis, Outcome 5 Number of studies with low risk of bias from blinding, sponsorship recoded.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 5 Number of studies with low risk of bias from blinding, sponsorship recoded

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Als-Nielsen 2003	108/146	32/67		63.5 %	1.55 [1.18, 2.03]
Bero 2007	45/76	5/24		11.0 %	2.84 [1.27, 6.34]
Kjaergard 2002	17/23	9/13		16.6 %	1.07 [0.69, 1.65]
Rattinger 2009	20/32	0/1		1.4 %	2.48 [0.22, 27.81]
Rios 2008	2/16	7/27		7.5 %	0.48 [0.11, 2.04]
Total (95% CI)	**293**	**132**		**100.0 %**	**1.54 [1.23, 1.94]**

Total events: 192 (Industry), 53 (Non-industry)

Heterogeneity: $Chi^2 = 7.61$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 3.71 (P = 0.00021)

Test for subgroup differences: Not applicable

Analysis 8.6. Comparison 8 Sensitivity analysis, Outcome 6 Results:Number of studies with favorable efficacy results, analysis adjusted for confounders.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 6 Results:Number of studies with favorable efficacy results, analysis adjusted for confounders

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
Bourgeois 2010	1.5686 (0.5142)		47.0 %	4.80 [1.75, 13.15]
Etter 2007	1.1569 (0.4846)		53.0 %	3.18 [1.23, 8.22]
Total (95% CI)			**100.0 %**	**3.86 [1.93, 7.70]**

Heterogeneity: $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 3.83 (P = 0.00013)

Test for subgroup differences: Not applicable

Analysis 8.7. Comparison 8 Sensitivity analysis, Outcome 7 Conclusions:Number of studies with favorable conclusions, analysis adjusted for confounders.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

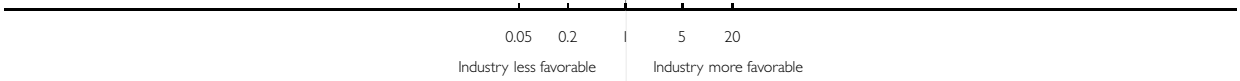
Outcome: 7 Conclusions:Number of studies with favorable conclusions, analysis adjusted for confounders

Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Fixed,95% CI	Weight	Odds Ratio IV,Fixed,95% CI
Als-Nielsen 2003	1.6677 (0.5082)		30.4 %	5.30 [1.96, 14.35]
Booth 2008	1.2528 (0.3868)		52.5 %	3.50 [1.64, 7.47]
Perlis 2005a	1.5129 (0.6776)		17.1 %	4.54 [1.20, 17.13]
Total (95% CI)			**100.0 %**	**4.15 [2.40, 7.19]**

Heterogeneity: $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 5.08 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 8.8. Comparison 8 Sensitivity analysis, Outcome 8 Number of studies with favorable efficacy results, random-effects model.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 8 Number of studies with favorable efficacy results, random-effects model

Study or subgroup	Industry n/N	Non-industry n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Alasbali 2009	7/29	2/10		0.7 %	1.21 [0.30, 4.88]
Bero 2007	65/94	48/97		11.6 %	1.40 [1.10, 1.78]
Booth 2008	49/120	50/165		8.5 %	1.35 [0.98, 1.85]
Bourgeois 2010	222/260	48/85		14.2 %	1.51 [1.25, 1.83]
Clifford 2002	46/66	21/34		8.8 %	1.13 [0.83, 1.54]
Etter 2007	25/49	9/41		2.8 %	2.32 [1.23, 4.40]
Kelly 2006	12/13	4/8		2.4 %	1.85 [0.91, 3.76]
Momeni 2009	20/24	69/85		13.5 %	1.03 [0.84, 1.26]
Moncrieff 2003	2/2	2/7		1.0 %	2.67 [0.85, 8.39]
Perlis 2005b	93/113	37/49		15.0 %	1.09 [0.91, 1.31]
Rasmussen 2009	66/109	14/28		6.1 %	1.21 [0.81, 1.81]
Rattinger 2009	26/36	18/25		8.4 %	1.00 [0.73, 1.38]
Tulikangas 2006	15/15	7/9		6.9 %	1.29 [0.89, 1.87]
Vlad 2007	5/11	0/4		0.2 %	4.58 [0.31, 68.24]
Total (95% CI)	**941**	**647**		**100.0 %**	**1.26 [1.12, 1.41]**

Total events: 653 (Industry), 329 (Non-industry)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 20.09$, df = 13 (P = 0.09); $I^2 = 35\%$

Test for overall effect: Z = 3.95 (P = 0.000079)

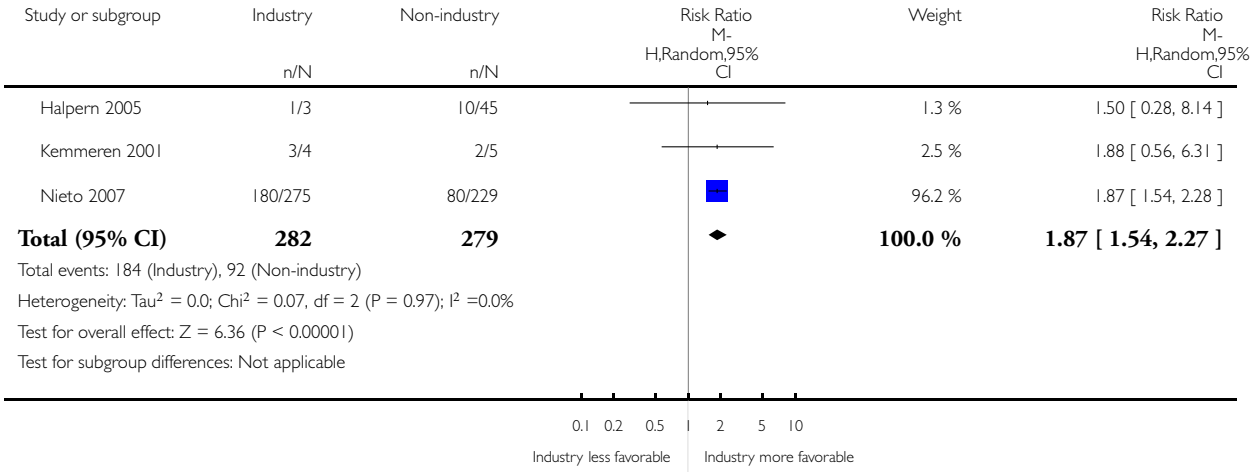
Test for subgroup differences: Not applicable

Analysis 8.9. Comparison 8 Sensitivity analysis, Outcome 9 Number of studies with favorable harms results, random-effects model.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 9 Number of studies with favorable harms results, random-effects model

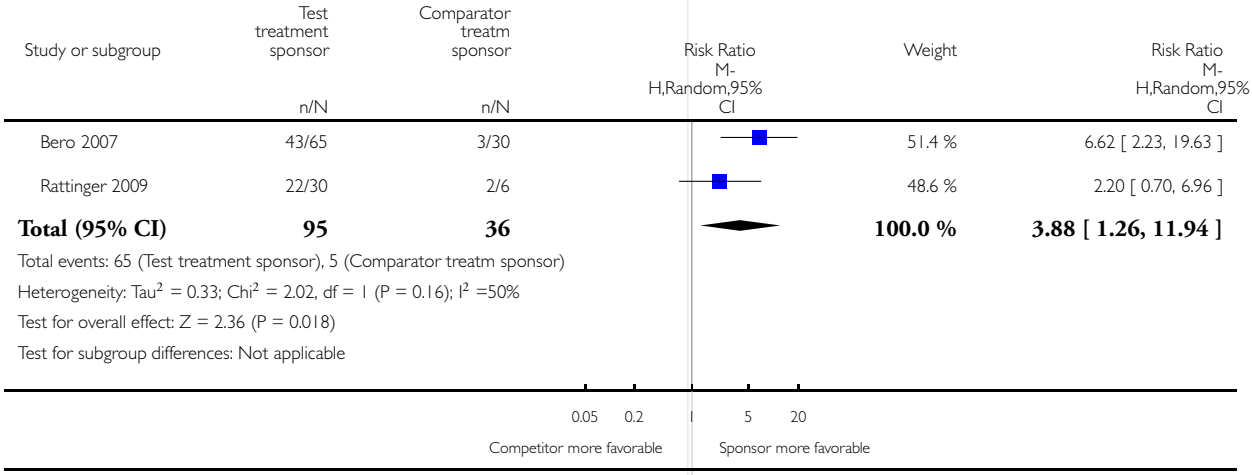


Analysis 8.10. Comparison 8 Sensitivity analysis, Outcome 10 Number of studies with favorable test treatment efficacy results, random effects-model.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 10 Number of studies with favorable test treatment efficacy results, random effects-model

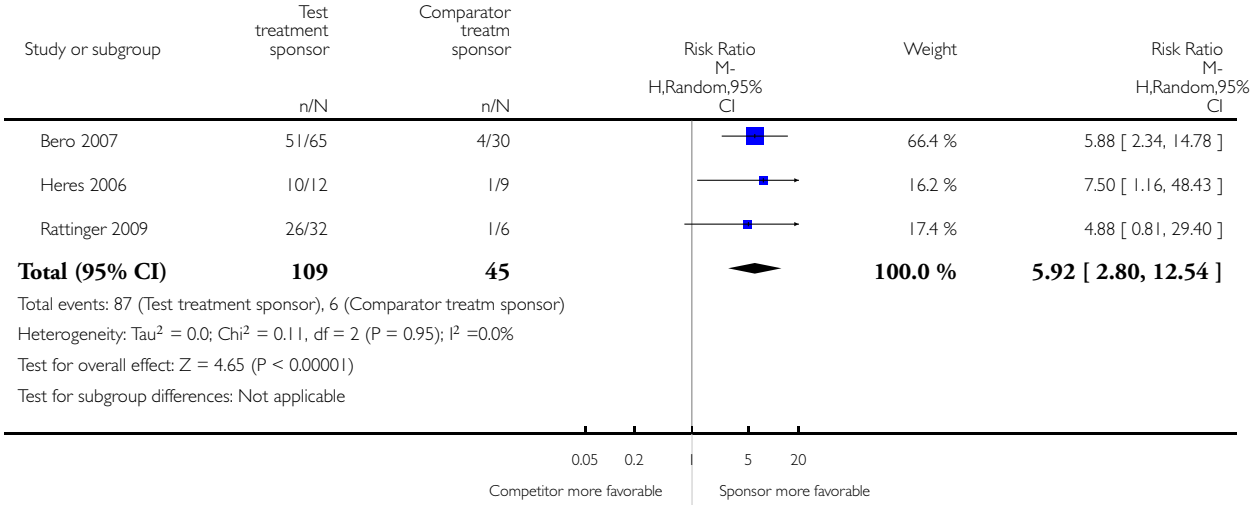


Analysis 8.11. Comparison 8 Sensitivity analysis, Outcome 11 Number of studies with favorable test treatment conclusions, random-effects model.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 11 Number of studies with favorable test treatment conclusions, random-effects model

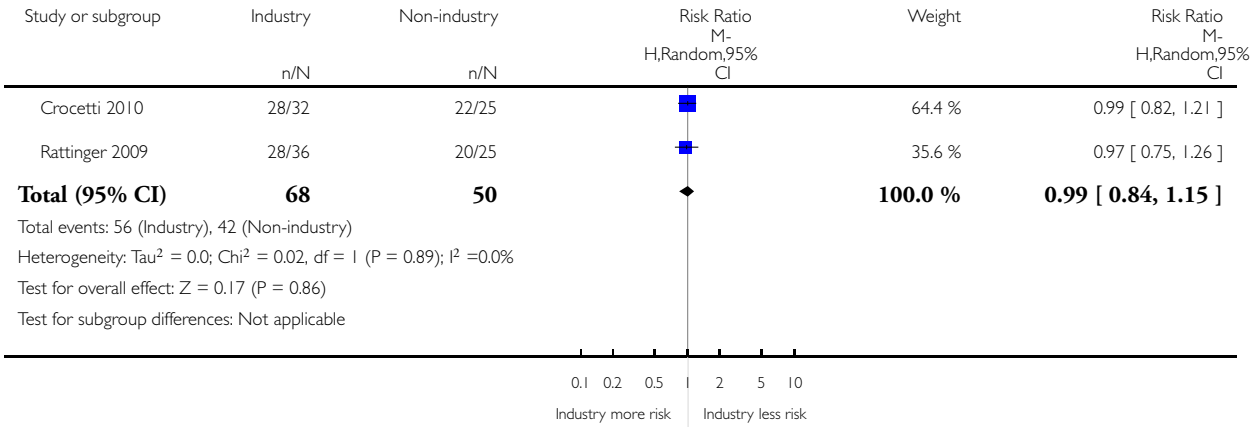


Analysis 8.12. Comparison 8 Sensitivity analysis, Outcome 12 Number of studies with low risk of bias from loss to follow-up, random-effects model.

Review: Industry sponsorship and research outcome

Comparison: 8 Sensitivity analysis

Outcome: 12 Number of studies with low risk of bias from loss to follow-up, random-effects model



APPENDICES

Appendix 1. Search strategy

1. Drug Industry/
2. ((drug$ or pharmaceutical$ or device$ or for-profit) adj (industr$ or company or companies or manufacturer$ or organisation$ or organization$ or agency or agencies)).ti,ab.
3. private industr$.ti,ab.
4. (industr$ or nonindustr$ or non-industr$).ti,ab.
5. 1 or 2 or 3 or 4
6. Conflict of interest/
7. Financial support/
8. Research support as topic/
9. (funded or funding or sponsor$ or support$ or financ$ or involvement).ti,ab.
10. "competing interest$".ti,ab.
11. or/6-10
12. 5 and 11
13. Publication bias/
14. "Bias (Epidemiology)"/
15. bias$.ti,ab.
16. or/13-15
17. 12 and 16
18. Treatment outcome/
19. "Outcome Assessment (Health Care)"/

20. (outcome$ or findings).ti,ab.
21. or/18-20
22. (favor$ or favour$ or positive or significan$ or beneficial or benefit$ or effective or effectual or efficacious).ti,ab.
23. (insignificant$ or nonsignificant$ or negative or adverse or ineffectiv$ or ineffectual or unfavorabl$ or unfavourabl$).ti,ab.
24. 22 or 23
25. 21 and 24
26. 12 and 25
27. ((favor$ or favour$ or positive or significan$ or insignificant$ or nonsignificant$ or negative or unfavorabl$ or unfavourabl$) adj result$).ti,ab.
28. 12 and 27
29. 17 or 26 or 28

HISTORY

Protocol first published: Issue 9, 2011

Review first published: Issue 12, 2012

CONTRIBUTIONS OF AUTHORS

Development of protocol (AL, JL, LB and SS); design of the search strategy (AL); initial screening of articles (AL and OAB); final selection of studies (all authors); data extraction (AL and SS); data analysis and interpretation of results (all authors); writing of manuscript (all authors).

DECLARATIONS OF INTEREST

Joel Lexchin, Lisa Bero and Sergio Sismondo are authors of the some of the previous reviews and included studies.

In 2007, Joel Lexchin was retained by a law firm representing Apotex to provide expert testimony about the effects of promotion on the sales of medications. From 2007 to 2008 he was retained as an expert witness by the Canadian federal government in its defense of a lawsuit challenging the ban on direct-to-consumer advertising of prescription drugs in Canada. In 2010 he was a consultant to a law firm acting for the family of a patient who died from an alleged side effect of a drug made by Allergan. He is also on the management group of Healthy Skepticism Inc. and is the chair of the Health Action International - Europe Association Board.

The authors have no other relevant interests.

SOURCES OF SUPPORT

Internal sources

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The author was personally salaried by his institution during the period of the review.

- York University, Toronto, Canada.

The author was personally salaried by his institutions during the period of the review.

- Queen's University, Kingston, Canada.

The second author was personally salaried by his institution during the period of the review.

- University of California, San Francisco, USA.

The author was personally salaried by her institution during the period of the review.

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Paper 2

Sponsors' participation in conduct and reporting of industry trials: a descriptive study

Trials. 2012;13:146.

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TRIALS

RESEARCH Open Access

Sponsors' participation in conduct and reporting of industry trials: a descriptive study

Andreas Lundh[1,2*], Lasse T Krogsbøll[1,2] and Peter C Gøtzsche[1,2]

Abstract

Background: Bias in industry-sponsored trials is common and the interpretation of the results can be particularly distorted in favour of the sponsor's product. We investigated sponsors' involvement in the conduct and reporting of industry-sponsored trials.

Methods: We included all industry-sponsored trials published in *The Lancet* in 2008 and 2009 and corresponding trial protocols provided by *The Lancet*. For each protocol and publication, we extracted information on trial conduct and reporting.

Results: We identified 169 publications of randomised trials and included 69 (41%) that were industry-sponsored, and 12 (7%) industry-funded but seemingly independently conducted as a subsample. Entry of data into the study database was done independently by academic authors without the involvement of the sponsor or a contract research organisation in one of the 69 trials. Two trials had independent data analysis and one independent reporting of results. In 11 of the trials, there was a discrepancy between the information in the protocols and papers concerning who analysed the data. In four of the 12 seemingly independent trials, the protocol described sponsors' involvement in writing the report while the published paper explicitly stated that the sponsor was not involved.

Conclusions: The sponsors are usually involved in the analysis and reporting of results in industry-sponsored trials, but their exact role is not always clear from the published papers. Journals should require more transparent reporting of the sponsors' role in crucial elements such as data processing, statistical analysis and writing of the manuscript and should consider requiring access to trial protocols, independent data analysis and submission of the raw data.

Keywords: Randomised trials, Industry sponsorship, Academic authors, Trial protocols

Background

The drug and device industries have a major impact on the research agenda. They funded 58% of US biomedical research in 2007 [1], and 56% of trials published in high-impact medical journals in 2005 and 2006 had industry funding; for *New England Journal of Medicine* it was 78% [2]. The involvement of the company in industry-sponsored trials varies from no involvement, besides the free provision of drugs, to running the whole trial and publishing the results without the involvement of academic authors.

Industry-sponsored trials usually favour the company's product [3,4]. This may happen through biases in study design, choice of comparators or selective reporting of favourable outcomes [5,6]. Some journals therefore require that the involvement of the sponsor is stated in the published article. *JAMA* goes further and requires independent data analysis by academic authors [7].

Many industry-sponsored trials are coordinated by seemingly independent steering committees. However, this may not prevent sponsor influence, as academic authors often have constraints on publication rights [8,9], the sponsor often owns the data [9,10], ghost authorship is common [11], and academic authors may have industry ties [12].

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We have previously reported the results from a cohort of trials published in *The Lancet* in 2008 and 2009 [10]. We found that academic authors involved in industry-sponsored trials may have limited access to the raw data, although they all declared in *The Lancet* that they had full access to the data. We report here on the sponsors' influence on trial conduct and reporting of the results.

Methods

Sample

We identified all randomised clinical trials published in *The Lancet* in 2008 and 2009 using the index term 'randomized controlled trial' in PubMed. We excluded papers that were not full trial reports (for example, letters and commentaries) or were not part of the planned trials (for example, secondary analyses). We selected all industry-sponsored trials, defined as trials fully funded by a drug or device company and where the sponsor participated in data management or analysis. Trials where part of trial conduct was outsourced to a contract research organization (CRO) were also included. Trials where all elements of trial conduct were managed by independent academic authors (for example, by 'unrestricted' grants) were analysed separately.

Since July 2002, *The Lancet* has required authors to submit protocols together with the trial report and we retrieved copies of these protocols.

Information on trial conduct and reporting in protocols and papers

One of us (AL) copied all information from protocols and papers on data management, storage, analysis, and writing of the protocol and manuscript into a pilot-tested data sheet. Two observers (AL, LTK) independently categorized these data into prespecified domains for protocols and papers, and disagreements were resolved by discussion and arbitration when needed by the third observer (PG). We made a final categorization based on data from both protocols and published papers and described discrepancies.

Results

We identified 209 papers in PubMed and excluded 40 that were not primary reports of trials published in 2008 and 2009 (Figure 1). We excluded another 85 trials that were not fully funded by the industry, two that had protocols similar to other included trials, and one that had no independent academic authors. Of the remaining 81 trials, we included 69 industry-sponsored trials. The other 12 trials were also fully industry-funded but appeared to have been independently conducted and we therefore analysed them separately.

For seven trials, the full protocols were missing: two were not in *The Lancet's* database, three were protocol synopses, one was a copy of the information from www.clinicaltrials.gov and one only consisted of amendments to the protocol.

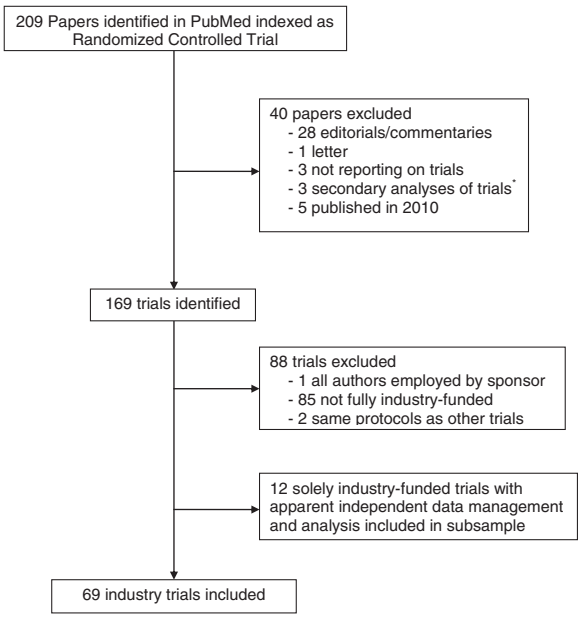

Figure 1 Flow chart showing inclusion of trials.
*Secondary analysis refers to when the trial data were used in an exploratory fashion. For example, the placebo group was analysed as a separate cohort study to investigate heart rate as a predictor for cardiovascular mortality in a trial of an anti-arrhythmic drug.

We received copies of five protocols from the academic authors and the other two from the sponsors.

Data management

In 49 of the 69 trials (71%), review and verification of information in case report forms (CRFs) were handled by the sponsor or a CRO without involvement of academic authors and only in two trials (3%) by academic authors independently (Table 1).

In 52 trials (75%), entry of data into the study database was done by the sponsor or a CRO without involvement of academic authors. In only two of these trials, it was described how data were processed, that is, interpreted for categorisation purposes, and in those two trials, all safety data were processed by sponsor staff. In only one trial (1%) was data entry performed independently by academic authors. However, based only on information in the published paper, it was not possible to tell who entered study data in 50 (72%) of the trials. In 44 trials (64%), the data were stored by the sponsor or a CRO and only in one trial (1%) by academic authors. In one trial (1%), the protocol suggested that academic authors stored the data whereas the paper suggested that the sponsor stored it.

According to 38 trial protocols (55%), the sponsor had access to accumulating data before study termination and according to two (3%) the sponsor had access via membership of the Data and Safety Monitoring Board. In 24 of these 40 trials, the sponsor could stop the trial prematurely

Table 1 Data management and analysis in industry-sponsored trials based on information in protocols and publications

(n = 69)	CRF review and verification	Data entry	Data storage	Data analysis
Sponsor	23 (33%)	32 (46%)	35 (51%)	29 (42%)
Sponsor and CRO	18 (26%)	8 (12%)	3 (4%)	6 (9%)
CRO	8 (12%)	12 (17%)	6 (9%)	5 (7%)
Sponsor/CRO and academic authors	10 (14%)	0 (0%)	0 (0%)	11 (16%)
Academic authors	2 (3%)	1 (1%)	1 (1%)	2 (3%)
Not described	8 (12%)	16 (23%)	23 (33%)	5 (7%)
Discrepancy between protocol and paper	0 (0%)	0 (0%)	1 (1%)	11 (16%)

Percentages do not always add up to 100 due to rounding.

for a broad range of reasons or without any constraints at all, in five additional trials it could also be stopped but no criteria were specified, and in the remaining 11 trials it was not described whether the sponsor could stop the trial prematurely.

Data analysis

In 40 trials (58%), the data were analysed by the sponsor or a CRO without involvement of academic authors and only in two trials (3%) independently by academic authors. In 11 trials (16%) the sponsor or a CRO, and academic authors analysed the data. However, in six of these trials, the sponsor or CRO biostatistician had the primary role and in five, the role was not clear as many authors were listed. In one of these five trials, the protocol named a sponsor-employed study biostatistician who was not mentioned in the paper.

In an additional 11 trials (16%), there were discrepancies between information in protocols and papers. In four, the protocol described analysis by sponsor or CRO alone whereas the published paper described analysis either by academic authors alone or in collaboration with the sponsor. In five trials, there were discrepancies between information in protocols and papers as to whether the sponsor or a CRO did the analysis, and in two the protocol described an independent analysis by academic authors whereas the papers also described involvement of a CRO or the sponsor. Based only on information in the published paper, it was not possible to tell who analysed the data in another 10 (14%) of the trials.

Publication of the results

In 24 of the 69 trials (35%), the sponsor or a hired CRO was involved in coordinating writing of the manuscript, in 10 (14%) the sponsor was not involved and in 35 (51%) it was not described. In 64 trials (93%), the sponsor had influence over publication of the results through co-authorship or an explicitly stated right to approve, review or comment on the paper (Table 2). In three trials (4%), there were discrepancies between information in protocols and papers: one protocol described sponsor-employed co-authors without this being stated in the paper; in one protocol the sponsor needed to approve the manuscript, but the paper stated that the sponsor was not involved in writing of the report; and in one protocol the sponsor needed to approve the manuscript, but the paper stated that the report was written in consultation with the sponsor.

Ten of the protocols (14%) referred to separate agreements (for example, clinical trial agreements or publication agreements) concerning reporting of results or data ownership and five other protocols (7%) stated that such agreements might be issued, overriding statements concerning reporting of results or data ownership in the protocol. None of these agreements had been provided to *The Lancet*. Finally, five protocols explicitly described that the sponsor could publish the results without author approval, but this did not seem to have happened (there were academic authors on all 69 papers).

Medical writing assistance from the sponsor or persons hired by the sponsor was described in 37 of the 69 papers (54%), in seven papers (10%) it seemed no assistance was provided and in 25 (36%) it was not described. Sixty-eight of the 69 protocols (99%) seemed to have been written by the sponsor, for example, by including the company logo, and one protocol contained no information indicating who had written it. In 19 protocols, specific authors were named and 10 of these protocols specified them as authors of the protocol. However, for

Table 2 Sponsors' influence on publication of results of industry-sponsored trials based on information in protocols and publications

(n = 69)	Publication of results
Sponsor has co-authorship	56 (81%)
Sponsor needs to approve manuscript	3 (4%)
Sponsor needs to review or comment	5 (7%)
No influence	1 (1%)
Not described	1 (1%)
Discrepancy between protocol and paper	3 (4%)

Percentages do not add up to 100 due to rounding.

14 of these 19 protocols these authors were not mentioned in the publications.

Independently conducted trials

In eight of the additional 12 trials that appeared to have been conducted independently of the sponsor, the sponsor nevertheless appeared to have written the protocol, could stop the trial early, had issued confidentiality clauses or had influence on writing of the manuscript (Table 3).

Discussion

Approximately half the trials published in *The Lancet* were fully funded by the industry and most of these had industry involvement in the conduct, analysis and reporting of the results. The sponsor often entered, stored and owned the data, which were rarely analysed independently by the academic authors. Even for the additional 12 trials that appeared to have been conducted independently of the sponsor, the sponsor could stop the trial prematurely in some cases, issued confidentiality clauses, was involved in the reporting of results or appeared to have written the protocol.

Our study describes sponsor involvement in the conduct and reporting of industry-sponsored trials published in a high-impact medical journal. Our access to trial protocols gave us additional information on sponsor involvement not possible to decipher from the published papers alone. A study of cancer trials found that only 18% of the industry-sponsored trials described the sponsors' role and usually in vague terms [13]. There are some limitations that should be taken into account though. First, we restricted our sample to trials published in a single journal, *The Lancet*, which may limit generalisability. However, *The Lancet's* access to protocols and editorial resources might indicate that the sponsors' role is greater for trials published in other journals. Second, despite access to trial protocols, in many cases we could not tell who entered, processed or stored data, and we did not have copies of trial agreements and publication agreements. We find it likely that tasks not described were handled by the sponsor because the protocols in all except one case were most likely written by the sponsor. It might therefore be regarded as implicit that what had been left out would be managed by the sponsor. The role of the sponsor may therefore be even more extensive than our results indicate.

Bias in industry-sponsored trials can be introduced at various levels of data processing, from the information being recorded on CRFs to the data appearing in the published paper. In most cases, the sponsor or a hired CRO was in charge of data entry and while it was rarely described, they probably also processed the data for categorisation purposes.

Processing data is bias-prone. Important data are often omitted from publications or are described in a way favourable for the sponsor. For example, suicidality was coded as 'emotional lability', 'hospital admission' or 'lack of effect' in trials of selective serotonin reuptake inhibitors (SSRIs) [14,15], myocardial infarctions on rofecoxib were omitted in the VIGOR trial [16,17] and on rosiglitazone in the RECORD trial [18,19]. As academic authors were rarely involved in data entry, and as data analysis by academics often did not involve anything more than checking the tabulated data in the clinical study report [10], such practices will most likely not be discovered.

Academic authors were rarely involved in data analysis and only two trials had a completely independent analysis. When data analysis was performed jointly, the sponsor seemed to take the leading role and, for some trials, the role of academic authors in the actual statistical analysis was

Table 3 Eight seemingly independent trials with evidence of influence by sponsor

Trial number	Writing of protocol	Stopping trial early	Author confidentiality clause	Writing of manuscript	
				According to protocol	According to publication
1	-	-	In protocol	-	Sponsor not involved in writing
2	-	-	-	Sponsor needs to review manuscript	Sponsor not involved in writing
3	Appears written by sponsor	-	-	Sponsor involved in writing	Sponsor not involved in writing
4	-	-	-	Sponsor needs to review manuscript	Sponsor not involved in writing
5	-	Sponsor must be consulted before stopping	In protocol	Sponsor needs to approve manuscript	Sponsor not involved in writing
6	-	-	-	Sponsor needs to review manuscript	Nothing stated about writing
7	-	-	In protocol	-	Sponsor not involved in writing
8	-	Sponsor can stop trial	-	Sponsor allowed comments	Sponsor allowed comments

- Indicates no evidence of influence by sponsor.

probably limited, as many authors were named as contributors to data analysis. We find it highly unlikely that many academic authors with a clinical background actually participated in the statistical analysis, as such analyses are time-consuming and require statistical expertise. Based on our previous study [10], such involvement might actually, again, be limited to merely reading the clinical study report.

Data analysis done solely by the sponsor is problematic, as independent analysis may yield different results [20]. In some cases, the data were analysed by CROs, but they are not independent. They are hired by the sponsor, they sometimes have financial interests in the sponsoring companies [21,22], and - like for medical writers - if they do not do a job that satisfies the sponsors' marketing department, they might go out of business. Furthermore, analysis by academic authors does not ensure independence, as such authors often have financial ties to the industry [12]. Based on their declarations in the paper, in the two trials with independent analysis, the academic authors were paid by the companies for their contribution.

The sponsors' dominating role in data analysis is not only problematic in relation to selective reporting of positive outcomes and spin of the results [23,24], but also in relation to stopping trials early. If the sponsor has access to accumulating data, as was the case for at least 40 trials, and is allowed to terminate the trials prematurely, this could lead to overestimation of treatment effects [25] and underestimation of harms [26].

Journal editors should consider whether independent statistical analysis by academic authors should be a requirement, as is the case for *JAMA* [7]. This policy has had repercussions, as fewer industry-sponsored trials have been published [27]. Such policies might therefore be difficult to implement, as they will likely result in loss of revenue from reprint sales of industry trials [2]. However, this only reinforces the need for independent analyses. Lastly, journals should require copies of protocols and any additional agreements to ensure that access to the data was planned before the trial started. Journals should allocate editorial resources to ensure that what appears in publications corresponds to statements written in protocols, which was not always the case in our study. Such protocols should be written in accordance with evidence-based standards such as the upcoming SPIRIT guidelines [28] and should contain detailed information on authors' access to data. To ensure that such declarations are more than window dressing [10], journal editors might also consider asking for the raw data as a condition for publication, like *Science* and the *Nature* journals require [23] and preferably make such data available at public websites.

Conclusions

The sponsors are usually involved in the analysis and reporting of the results in industry-sponsored trials, but their exact role is not always clear from the published papers. Even for fully industry-funded trials that appear to have been conducted independently, the sponsors are also sometimes explicitly involved in the reporting of results. Journals should require more transparent reporting of the sponsors' role in crucial elements such as data processing, statistical analysis and writing of the manuscript and should consider requiring access to trial protocols, independent data analysis and submission of the raw data.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

PCG conceived the idea for the study. The protocol was primarily developed by AL, and LTK and PCG contributed. AL identified trials and protocols; AL and LTK extracted data. All authors participated in data analysis and writing of the paper. AL, LTK and PCG are guarantors. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

Ethics

The study was based on protocol data and published data and did not need ethical approval according to the Danish Act on a Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects.

Funding source

The study was partly funded by The Health Insurance Foundation and The Danish Council for Independent Research - Medical Sciences, partly by The Nordic Cochrane Centre.

Role of sponsors

The study was conducted independently of study sponsors. There was no sponsor involvement in the design; collection, analysis, and interpretation of the data; in writing of the report; or in the decision to submit for publication.

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Paper 3

Access to data in industry-sponsored trials

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medical journals to open the shutters on the scientific process. *The Lancet* should take the lead.

I declare that I have no conflicts of interest.

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1 Boulton G, Rawlins M, Vallance P, Walport M. Science as a public enterprise: the case for open data. *Lancet* 2011; **377:** 1633–35.
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Geoffrey Boulton and colleagues[1] make a strong case for sharing of research data. If we want to maximise the value of data sharing, the issues raised certainly need to be solved. These issues include how to win over researchers to this cause. It would be disappointing if the promising development of open sharing of data led to no more than scientists piling their data in fairly unsearchable data repositories because they are forced to by journal editors or funders.

Dutch experiences with the National Care for the Elderly Programme,[2] the String of Pearls Initiative,[3] and the Mondriaan Project[4] show that researchers can be convinced. In all three initiatives, researchers are leading the development. In the first programme on health care for frail older people, the joint researchers have agreed on a minimum set of baseline characteristics and outcome measures that each project (more than 60 in total) will collect.[5] In the String of Pearls Initiative, all eight university hospitals in the Netherlands collect and share clinical data and biomaterial on nine different diseases. The Mondriaan Project aims to optimise the use of routine health-care data for pharmacoepidemiological research.

However, the development takes time, money, effort, and expertise. Therefore, the aim of data sharing would benefit from the establishment of an international research network to support the exchange of best practices and experiences and to produce international consensus guidelines on the subject.

We declare that we have no conflicts of interest.

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Access to data in industry-sponsored trials

The importance of transparency and data sharing in clinical research is increasingly emphasised, and public funders increasingly require that all data from publicly sponsored research are made available.[1] The same cannot be said for industry-sponsored trials, for which the sponsors often own the data and the academic authors have limited publication rights.[2]

The International Committee of Medical Journal Editors recommends that authors declare that they had full access to all of the data.[2] However, the definition of "data" is open to interpretation. It should mean all raw data, including those written on case report forms (CRFs), to enable independent coding of events and data analysis. But it could also mean tabulated, processed data in clinical study reports, for which the sponsor has already interpreted the events and done imputations for missing data. We investigated what types of data academic authors had access to in industry-sponsored trials published in *The Lancet* and how they used them.

Using PubMed, we identified 169 randomised clinical trials published in *The Lancet* in 2008–09 and included the 69 (41%) that were industry-sponsored. The editors provided us with the protocols, except in seven cases where the full protocols were missing and were obtained from the authors or sponsors. We categorised data ownership and access on the basis of information in protocols and papers.

We contacted the corresponding author of each trial, apart from six trials where this author was sponsor-employed and where we contacted the academic author who seemed to have been most involved with data analysis. Using a pilot-tested questionnaire, we asked about the type of data access: CRFs; data file with raw data identical to information in CRFs; data file with processed data (eg, nausea and constipation coded as gastrointestinal complaints); or clinical study report. We also asked whether they used this access, and if so, how. To improve response rates, we contacted authors by repeated emails, letter, and telephone.

Finally, using repeated emails we asked the *Lancet* editors handling clinical trials which type of data they regarded as mandatory when corresponding authors declared "full access to all the data".

27 of the 69 protocols described that the sponsor owned the data. In 67 protocols, there was no information on academic authors' access to data, in striking contrast to the papers, which indicated that one or more academic authors had access to the data in 64 trials. These data


Helen King/Corbis

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meant "full access" in 62 cases, "study results" in one case, and "study report" in one case. In three of the remaining five trials, only the sponsor-employed authors had declared full access, and, in two, access was unclear (the authors had access to summary data only according to the protocol but full access according to the paper).

Survey responses were obtained from 39 academic authors (57% response rate). In 31 cases, the academic authors reported that they had full or partial access to CRFs, in 31 to raw data, in 33 to processed data, and in 38 to clinical study reports (table). In 27 trials, academic authors had access to both CRFs and to raw data. These replies might have been somewhat optimistic, since it was clear from the survey that some authors interpreted access as having been met if the sponsor would provide data on request.

11 of the 39 academic authors reported that they checked individual CRFs and compared them with the data in the study database. 13 reported that they used raw data, 13 processed data, and 32 clinical study reports, to redo statistical analyses done by the company or to compare data with what was reported in the manuscript. Ten academic authors used only clinical study reports and six did not use any data, although five were corresponding authors and one principal investigator. 18 used some of the data to do additional statistical analyses, which were not part of the protocol.

	Case report forms	Raw data	Processed data	Clinical study report
Access to data				
Yes	23	26	31	36
Partly	8	5	2	2
No	6	6	6	1*
Don't know	2	2	0	0
Use of data				
Yes	6	10	9	27
Partly	5	3	4	5
No	28	26	24	7
Don't know	0	0	2	0

*One author did not have access to clinical study report, but had access to case report forms, raw data, and processed data.

Table: **Access and use of data by 39 academic authors**

11 of 18 editors replied to our survey (61% response rate). Nine editors considered that full access to any CRF on request and access to raw data were mandatory when corresponding authors declared "full access to all the data".

Our most important finding was the huge discrepancy between the protocols and the papers on access to data. Considering also that the academic authors were somewhat reluctant to respond to our survey, and their liberal interpretation of what it means to have access, our survey results about data access could be far too positive. In support of this possibility, a survey of US academic institutions found that trial agreements rarely ensured that authors had independent access to all trial data.[3] Furthermore, the Pharmaceutical Research and Manufacturers of America have stated that academic authors should be provided with summary data only.[4]

Steinbrook and Kassirer[5] have highlighted that journals should define what is meant by "full access" to avoid confusion. We suggest that journals require submission of protocols, and any amendments and additional agreements, and the full dataset to ensure that "full access" is more than window dressing. We also believe that raw data should be available to peer reviewers and the public, as some journals require—eg, *Science*. As an intermediate solution, journals could consider requiring an independent data analysis, as is the case for *JAMA*.

Most importantly, we should work towards a situation in which anonymised raw data are made freely available to the public.[1] Our patients deserve nothing less than this, which would be highly beneficial for health care.

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Paper 4

Conflicts of interest at medical journals: the influence of industry-supported randomised trials on journal impact factors and economy – cohort study

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(Additional information is included in the Appendix on p165-70)

Conflicts of Interest at Medical Journals: The Influence of Industry-Supported Randomised Trials on Journal Impact Factors and Revenue – Cohort Study

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Abstract

Background: Transparency in reporting of conflict of interest is an increasingly important aspect of publication in medical journals. Publication of large industry-supported trials may generate many citations and journal income through reprint sales and thereby be a source of conflicts of interest for journals. We investigated industry-supported trials' influence on journal impact factors and revenue.

Methods and Findings: We sampled six major medical journals (*Annals of Internal Medicine*, *Archives of Internal Medicine*, *BMJ*, *JAMA*, The *Lancet*, and *New England Journal of Medicine* [*NEJM*]). For each journal, we identified randomised trials published in 1996–1997 and 2005–2006 using PubMed, and categorized the type of financial support. Using Web of Science, we investigated citations of industry-supported trials and the influence on journal impact factors over a ten-year period. We contacted journal editors and retrieved tax information on income from industry sources. The proportion of trials with sole industry support varied between journals, from 7% in *BMJ* to 32% in *NEJM* in 2005–2006. Industry-supported trials were more frequently cited than trials with other types of support, and omitting them from the impact factor calculation decreased journal impact factors. The decrease varied considerably between journals, with 1% for *BMJ* to 15% for *NEJM* in 2007. For the two journals disclosing data, income from the sales of reprints contributed to 3% and 41% of the total income for *BMJ* and The *Lancet* in 2005–2006.

Conclusions: Publication of industry-supported trials was associated with an increase in journal impact factors. Sales of reprints may provide a substantial income. We suggest that journals disclose financial information in the same way that they require them from their authors, so that readers can assess the potential effect of different types of papers on journals' revenue and impact.

Please see later in the article for the Editors' Summary.

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Abbreviations: ACP, American College of Physicians; AMA, American Medical Association; MMS, Massachusetts Medical Society; RCT, randomised controlled trial.

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Introduction

Many medical journals require that authors and peer reviewers declare whether they have any conflicts of interest. Such knowledge can be important for readers when assessing the paper and for editors when assessing the peer review comments.

Editors can also have conflicts of interest, and the International Committee of Medical Journal Editors states that: "Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues they might judge" [1]. Furthermore, editors are advised to "publish regular disclosure statements about potential conflicts of interest related to the commitments of journal staff" [1].

Journals may have other conflicts of interest than those of their editors, and the most important of these is likely related to the publication of industry-supported clinical trials. It is important for the industry to publish reports of large trials in prestigious journals, as such reports are essential for clinical decision making and for the sales of drugs and devices [2,3]. However, journals not only stand to gain financially through the sales of reprints, but also publication of such trials may increase their impact factors, as a large number of reprints distributed to key clinicians by drug companies will likely increase citation rates. For example, *The New England Journal of Medicine* (*NEJM*) sold about one million reprints to Merck of its paper on the VIGOR trial of rofecoxib [4].

One survey found that the policies on conflicts of interest for individual editors vary between journals [5], but we have not been able to identify any empirical studies on conflicts of interest at medical journals.

We investigated the influence of industry-supported randomised trials on impact factors for major general medical journals and describe the relative income from the sales of advertisements, reprints, and industry-supported supplements.

Methods

The impact factor for a given year is calculated as the number of citations in that year to papers published in the two previous years, divided by the number of citable papers published in the two previous years [6]. We focused on two time periods, citations in 1998 for randomised clinical trials (RCTs) published in 1996–1997 and citations in 2007 for RCTs published in 2005–2006, and retrieved citation data using Web of Science on the ISI Web of Knowledge [7].

On the basis of a pilot (see Text S1) that included journals categorised as "Medicine, General & Internal" in Journal Citation Reports on the ISI Web of Knowledge [8] with an impact factor of five or higher in 2007, which identified ten journals, we decided to include six major general medical journals: *Annals of Internal Medicine* (*Annals*), *Archives of Internal Medicine* (*Archives*), *BMJ*, *JAMA*, The *Lancet* (*Lancet*), and *NEJM*. Trials published in these journals in the two time periods were identified using PubMed's limits function for journal name, publication date, and the publication type Randomized Controlled Trial. Papers that were not full reports of trials (e.g., letters, commentaries, and editorials) were excluded. We extracted information on journal name, title, publication year, and type of support into a standardised data sheet. Data extraction and retrieval of citation data were done independently by two authors (AL, MB), and discrepancies were resolved by discussion.

Type of Support

We categorised the support as industry support, mixed support, nonindustry support, or no statement about support. We defined industry support as any financial support, whether direct or indirect (e.g., grants, industry-employed authors, assistance with data analysis or writing of the manuscript, or provision of study medication or devices by a company that produces drugs or medical devices). We did not regard a study as industry-supported if the only interaction with industry was author conflicts of interest (e.g., honorariums, consultancies, and membership of advisory boards). We defined nonindustry support as any other type of financial support. Mixed support was any support provided by both industry and nonindustry sources, and no statement about support if nothing was stated in the paper.

Citations of Individual Trials and of All Papers

We identified the number of citations for each identified RCT using the function "refine by publication year" in Web of Science. This was done in July and August 2009, blinded to the study support of the individual trials. We also identified the total number of citations (the numerator of the impact factor) using the function "create citation report" in Web of Science.

In our pilot study we compared the number of citations using Web of Science with the numbers used for the "official" impact factor calculation published in Journal Citation Reports and we discovered that the numbers of citations in Web of Science were lower (see Text S1). Correspondence with the publisher, Thomson Reuters, revealed that the citations from Web of Science and Journal Citation Reports are not similar, as they are not based on the same data. For example, studies that are referenced incorrectly are only included in Journal Citation Reports. But determinants leading to a citation not being identified in Web of Science can be assumed to be random and unrelated to study type and support. As our aim was to look at the relative contribution of industry-supported trials to the impact factor, we proceeded with our planned analyses, calculating an approximate impact factor.

Denominator of Impact Factor

We identified the number of citable papers (denominator of impact factor) published in 1996–1997 and 2005–2006 for each journal using the most recent Journal Citation Report with available data.

Financial Income and Reprint Sales

In November 2009, we contacted the Editor-in-Chief of each of the six journals by e-mail and requested data on income from sales of advertisements, reprints, and industry-supported supplements (if any), as percentage of total income for the journal, and the total number of reprints sold, in both cases in 2005 and 2006.

BMJ and *Lancet* provided the data, but the editors of Archives, *JAMA*, and *NEJM* did not provide the data, as it was their policy not to disclose financial information. *Annals* forwarded our request to the publisher who declined for similar reasons.

For these four American journals, we therefore needed to use proxy data. We obtained the publicly available tax information stated in the Internal Revenue Service Form 990 (tax form required for nonprofit organizations) for 2005 and 2006 for the journal owners: American College of Physicians (ACP) for *Annals*, American Medical Association (AMA) for *Archives* and *JAMA*, and Massachusetts Medical Society (MMS) for *NEJM*. These data report on the total income from all types of publishing by the societies, and as all societies publish more than one journal, we could not obtain data for individual journals. ACP publishes three other journals in the ACP series and books; AMA publishes eight other journals in the Archives series, an additional journal, and Web-based material; and MMS publishes various article summaries in their Journal Watch series. We contacted the journal

owners for confirmation of our calculations for the relative income from industry sources based on tax information. ACP confirmed our calculations, but AMA and MMS did not reply, despite numerous e-mails.

Statistical Analyses

For each journal, we compared the distribution of support of trials published in the two time periods with the Mann-Whitney U-test (two-sided). In an a priori stated sensitivity analysis, we recategorised trials with no statement about support as nonindustry supported.

On the basis of our own citation data derived from the individual trials, we compared the number of citations of trials with industry support with those with mixed support and those with nonindustry support using the Jonckheere-Terpstra test for trend (two-sided). As the category "not stated" is a mix of the three other categories we did not include this in our test. To test the robustness of our findings, we did various a priori stated sensitivity analyses (e.g., change in criteria used for industry support) (see Text S1).

We calculated what an approximate impact factor would have been, for each of the six journals for each time period, if no trials with industry support had been published; this calculation was done by excluding trials with industry support from the numerator and the denominator. We did the same calculations using a broader category of industry-supported trials that also included those with mixed support. We estimated the percentage reduction in impact factor that resulted from exclusion of these trials.

We had intended to study the association between mean number of citations to trials and percent income from reprints, but this was not possible as only the two European journals provided the data we requested.

Results

We identified 1,429 papers indexed as Randomized Controlled Trials in PubMed (see Text S1) and excluded 61 letters, three editorials, five commentaries, and seven papers that were e-published ahead of print, which yielded a total sample size of 1,353 included RCTs (651 from 1996–1997 and 702 from 2005–2006).

For *Annals* and *Lancet*, the number of trials decreased over time, whereas it increased for the other journals (see Table 1). The total number of citable papers decreased for all journals, except *Archives*. Hence, there was an increase in the proportion of trials out of all citable papers for all journals over time, with *BMJ* and *JAMA* having around a 3-fold increase and *NEJM* having the highest proportion of trials in both periods.

Type of Support

The type of support varied markedly across journals (see Table 1). In 2005–2006, *NEJM* had the highest proportion of trials with industry support (32%) and *BMJ* the lowest (7%). The proportion of trials that were industry-supported declined from 1996 to 2005 for all journals except *NEJM*, where it was constant. The decline was statistically significant for *Annals* and *Archives*; for *BMJ*, the proportion declined by nearly half (from 13% to 7%), but this was not statistically significant.

Citations of Individual Trials

For trials published in 1996–1997, there was a significant relation between the number of citations and the degree of industry support (three categories on a ranking scale) for *Lancet* ($p = 0.003$) and *NEJM* ($p = 0.003$), whereas for trials published in 2005–2006, the relation was statistically significant for all journals (see Table 2). Industry-supported trials published in *Annals*, *Archives*, and *Lancet* in 2005–2006 were cited more than twice as often as nonindustry trials, and one and a half times more in *BMJ*, *JAMA*, and *NEJM*.

Our a priori defined sensitivity analyses found minor discrepancies, but overall the results were robust (see Text S1).

Approximate Impact Factor

The approximate impact factor we calculated decreased for all journals when industry-supported trials were excluded from the calculation, and the decrease was larger when trials with mixed support were also excluded (see Table 2). The decrease was highest for *NEJM*, followed by *Lancet*, whereas the impact factor of *BMJ* was barely affected. The decrease in approximate impact factor varied minimally between the two time periods for all journals, except for *Lancet*, where the decrease was 11% in 1996–1997 and 6% in 2005–2006 when trials with industry and mixed support were excluded.

Financial Income and Reprint Sales

In 2005–2006, 16% of the income for *BMJ* was from display advertisements, 3% from reprints, and 0% from supplements, and 967,930 reprints were sold (see Table 3). For *Lancet*, the percentages were 1% from display advertisements, 41% from

Table 1. Description of support of randomised controlled trials published in major general medical journals.

Support	*Annals*		*Archives*		*BMJ*		*JAMA*		*Lancet*		*NEJM*	
	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006
n trials (%)	71 (16)	58 (17)	67 (13)	80 (13)	91 (6)	116 (16)	76 (7)	113 (19)	186 (12)	129 (20)	160 (20)	206 (34)
Total *n* citable papers	458	339	519	593	1624	745	1120	590	1515	661	785	611
Support of trials												
Industry support (%)	19 (27)	11 (19)	22 (33)	12 (15)	12 (13)	8 (7)	23 (30)	29 (26)	47 (25)	28 (22)	51 (32)	66 (32)
Mixed support (%)	27 (38)	20 (34)	14 (21)	23 (29)	19 (21)	23 (20)	21 (28)	33 (29)	46 (25)	46 (36)	54 (34)	95 (46)
Nonindustry support (%)	19 (27)	27 (47)	24 (36)	37 (46)	52 (57)	82 (71)	26 (34)	50 (44)	61 (33)	55 (43)	42 (26)	41 (20)
Not stated (%)	6 (8)	0 (0)	7 (10)	8 (10)	8 (9)	3 (3)	6 (8)	1 (1)	32 (17)	0 (0)	13 (8)	4 (2)
Change in support (*p*-value)*	—	0.047	—	0.041	—	0.101	—	0.255	—	0.251	—	0.498

*Comparison of number of trials with industry, mixed, and nonindustry support in 1996–1997 versus 2005–2006 using Mann-Whitney U-test (two-sided).

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Table 2. Citations for randomised trials published in major general medical journals and change in impact factors when industry-supported trials are excluded.

Citation and Impact Factor	*Annals*		*Archives*		*BMJ*		*JAMA*		*Lancet*		*NEJM*	
	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006	1996–1997	2005–2006
Mean *n* citations[a]												
Industry support	13.3	27.7	6.5	14.4	7.6	9.9	21.3	35.7	30.4	53.5	58.1	82.2
Mixed support	18.7	17.1	9.4	11.8	7.3	11.3	20.1	31.6	31.5	31.3	46.9	66.7
Nonindustry support	9.3	12.0	5.5	6.5	7.3	5.7	13.8	21.1	14.0	25.7	34.5	47.3
Not stated	10.8	—	10.9	8.3	8.0	5.0	5.7	32.0	10.0	—	33.4	30.3
Difference in citations (*p*-value)[b]	0.186	$\ll$0.001	0.237	$\ll$0.001	0.949	0.033	0.115	0.011	0.003	0.016	0.003	$\ll$0.001
Change in impact factor												
Without trials with industry support (%)	−1	0	−1	−2	0	0	−3	−3	−5	−4	−7	−7
Without trials with industry and mixed support (%)	−6	−4	−3	−4	−1	−1	−5	−5	−11	−6	−13	−15

[a]For each journal citations are reported for their impact factor year (i.e., citations in 1998 to trials published in 1996–1997 and in 2007 to trials published in 2005–2006).
[b]Difference in citations depending on type of support using Jonckheere-Terpstra test for trend (two-sided, support not stated excluded from the analysis).
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reprints, and 0% from supplements, and 11,514,137 reprints were sold. For ACP, the Internal Revenue Service data did not specify the income, for AMA 53% of the income was from advertisements and 12% from reprints (no data on supplements), and for MMS 23% of the income was from advertisements, whereas there were no data on reprints and supplements.

Discussion

We found that the proportion of industry-supported trials varied widely across journals but changed very little for each journal within the studied time period. Industry-supported trials boosted the approximate impact factor we calculated for all six journals—the most for *NEJM* and the least for *BMJ*. Only the two European journals disclosed their main sources of income, and the income from selling reprints was hugely different, as it comprised 41% of the total income for *Lancet* and only 3% for *BMJ*.

We believe this is the first study that investigates potential conflicts of interest at medical journals in relation to citations and financial income from publication of industry-supported trials. Our data collection was systematic and thorough, but there are also limitations. First, we selected major general medical journals that publish many trials, and our findings may therefore not be generalisable to other journals. Second, our assumption that trials with no statement of support, or with nonindustry support, were not industry supported may have led to an underestimation, as undeclared industry involvement is common, e.g., in relation to ghost authorship by medical writers' agencies [9]. However, the proportion of trials with no statement of support was very small in the second period. Third, owing to the nature of the Web of Science database, our identified citations were not the same as those used when calculating journal impact factors in the Journal Citation Reports. But as our aim was to study the relative influence of industry-supported trials on the impact factor, this discrepancy is likely not so important, as errors in citing studies would be expected to be unrelated to the type of support they received.

A problem related to the impact factor is that so-called noncitable papers such as editorials, news pieces, and letters to the editor contribute to the numerator, but not to the denominator [10,11]. Because of this serious deficiency in the calculation, we believe we have underestimated considerably the true influence of industry-supported trials on the approximate impact factor. For example, if we only include citations to citable papers (i.e., original research and reviews) in an analysis of trials with industry and mixed support, we find that the 2007 impact factor of *NEJM* decreases by 24% instead of 15%.

There are several reasons why industry-supported trials are generally more cited than other trials and other types of research. They are often large and the most used interventions are drugs, which are known to increase citations [12,13]. One explanation might be that industry-supported trials are of higher quality than

Table 3. Relative income of journals and medical societies from sales of advertisements, reprints, and supplements and number of reprints sold in 2005–2006.

Income and *n* Reprints Sold	*BMJ*	*Lancet*	*ACP* (*Annals*)	*AMA* (*Archives* and *JAMA*)	MMS (*NEJM*)
Advertising (%)	16	1	Not stated	53	23
Reprints (%)	3	41	Not stated	12	Not stated
Supplements (%)	0	0	Not stated	Not stated	Not stated
n reprints sold	967,930	11,514,137	Not stated	Not stated	Not stated

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nonindustry supported trials, though there is little evidence to support this [14]. Interestingly, industry trials more often have positive results than nonindustry trials [14], the conclusions in negative trials are often presented in such a way that they appear to be more positive than they actually are [15], and positive industry trials are more cited than negative ones [12,13]. Furthermore, sponsoring companies may employ various strategies to increase the awareness of their studies, including ghost authored reviews that cite them [16–19], purchase and dissemination of reprints [20], and creation of media attention [12,21,22]. Such strategies are likely to be predominantly used for trials favourable to the sponsors' products, and this may put editors under pressure, as they know which papers are especially attractive for the companies [3].

Editors have an interest in increasing the impact factor for their journal [23], whereas journal finances are generally regarded to be in the hands of the publisher. However, editors also have an interest in this, as they might be forced to fire staff if the journal does not remain profitable, or at least viable. The former editor of the *BMJ*, Richard Smith, reported that a single trial may lead to an income of US$1 million for a journal from reprint sales [21], and with a large profit margin of around 70% [3]. Journal publishers therefore have an incentive to advertise the benefits of reprints. As examples, the BMJ Group states that "Medical specialists determine the success of your product or service. They influence teaching, practice and purchase decisions within their workplace and the whole specialty. Reach them through the BMJ Group reprints service" [24], and *NEJM* states that "Article reprints from the New England influence treatment decisions" [25]. The editor of The *Lancet*, Richard Horton, has described how companies sometimes offer journals to purchase a large number of reprints and may threaten to pull a paper if the peer review is too critical [26]. For *Lancet*, a little less than half of the journal income came from reprints, and though this applied to only 12% of *AMA*'s income, it could be more for its most prestigious journal, *JAMA*. Large incomes from reprint sales would also be expected for *NEJM*, as it publishes more industry-supported trials than the other journals.

This area warrants further research. Speciality journals could also be investigated, particularly as conflicts of interest there could be more pronounced as editors are often investigators themselves and the degree of industry support may vary across specialities. Influence from other types of industry-sponsored papers could also be investigated. It would also be interesting to examine whether income from advertisements can affect editorial decisions; for example, one could compare the number of advertisements from specific companies with the number of publications from the same companies in a sample of journals. Such income can be substantial for some journals [27]. When *Annals* published a study that was critical of industry advertisements [28], it resulted in the loss of an estimated US$1–1.5 million in advertising revenue [29]. Another source of income that should be investigated is sponsored subscriptions whereby companies pay for subscriptions for clinicians, sometimes with a cover wrap displaying a company product [30].

Although publication of industry-supported trials is favourable for medical journals we cannot tell from our results whether industry-supported trials have affected editorial decisions. The high number of industry-supported trials in *NEJM* could merely result from the fact that it has the highest impact factor and therefore also receives more trial reports than other journals. Nevertheless, disclosure of conflicts of interest is not about whether relationships have actually influenced decisions, but whether they potentially could have [1]. The International Committee of Medical Journal Editors requires authors to "disclose interactions with ANY entity that could be considered broadly relevant to the work" [31]. We suggest that journals abide by the same standards related to conflicts of interest, which they rightly require from their authors, and that the sources and the amount of income are disclosed to improve transparency.

Supporting Information

Text S1 Appendix. Additional information on the methods used and results of study inclusion and sensitivity analyses.
Found at: doi:10.1371/journal.pmed.1000354.s001 (0.06 MB DOC)

Author Contributions

ICMJE criteria for authorship read and met: AL MB AH PCG. Agree with the manuscript's results and conclusions: AL MB AH PCG. Designed the experiments/the study: AL AH PCG. Analyzed the data: AL. Collected data/did experiments for the study: AL MB. Wrote the first draft of the paper: AL. Contributed to the writing of the paper: AL MB AH PCG. Conceived the study: AH PCG.

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Editors' Summary

Background. Medical journals publish many different types of papers that inform doctors about the latest research advances and the latest treatments for their patients. They publish articles that describe laboratory-based research into the causes of diseases and the identification of potential new drugs. They publish the results of early clinical trials in which a few patients are given a potential new drug to check its safety. Finally and most importantly, they publish the results of randomized controlled trials (RCTs). RCTs are studies in which large numbers of patients are randomly allocated to different treatments without the patient or the clinician knowing the allocation and the efficacy of the various treatments compared. RCTs are best way of determining whether a new drug is effective and have to be completed before a drug can be marketed. Because RCTs are very expensive, they are often supported by drug companies. That is, drug companies provide grants or drugs for the trial or assist with data analysis and/or article preparation.

Why Was This Study Done? Whenever a medical journal publishes an article, the article's authors have to declare any conflicts of interest such as financial gain from the paper's publication. Conflict of interest statements help readers assess papers—an author who owns the patent for a drug, for example, might put an unduly positive spin on his/her results. The experts who review papers for journals before publication provide similar conflict of interest statements. But what about the journal editors who ultimately decide which papers get published? The International Committee of Medical Journal Editors (ICMJE), which produces medical publishing guidelines, states that: ''Editors who make final decisions about manuscripts must have no personal, professional, or financial involvement in any of the issues that they might judge.'' However, the publication of industry-supported RCTs might create ''indirect'' conflicts of interest for journals by boosting the journal's impact factor (a measure of a journal's importance based on how often its articles are cited) and its income through the sale of reprints to drug companies. In this study, the researchers investigate whether the publication of industry-supported RCTs influences the impact factors and finances of six major medical journals.

What Did the Researchers Do and Find? The researchers determined which RCTs published in the *New England Journal of Medicine* (*NEJM*), the *British Medical Journal* (*BMJ*), The *Lancet*, and three other major medical journals in 1996–1997 and 2005–2006 were supported wholly, partly, or not at all by industry. They then used the online academic citation index Web of Science to calculate an approximate impact factor for each journal for 1998 and 2007 and calculated the effect of the published RCTs on the impact factor. The proportion of RCTs with sole industry support varied between journals. Thus, 32% of the RCTs published in the *NEJM* during both two-year periods had industry support whereas only 7% of the RCTs published in the *BMJ* in 2005–2006 had industry support. Industry-supported trials were more frequently cited than RCTs with other types of support and omitting industry-supported RCTs from impact factor calculations decreased all the approximate journal impact factors. For example, omitting all RCTs with industry or mixed support decreased the 2007 *BMJ* and *NEJM* impact factors by 1% and 15%, respectively. Finally, the researchers asked each journal's editor about their journal's income from industry sources. For the *BMJ* and The *Lancet*, the only journals that provided this information, income from reprint sales was 3% and 41%, respectively, of total income in 2005–2006.

What Do These Findings Mean? These findings show that the publication of industry-supported RCTs was associated with an increase in the approximate impact factors of these six major medical journals. Because these journals publish numerous RCTs, this result may not be generalizable to other journals. These findings also indicate that income from reprint sales can be a substantial proportion of a journal's total income. Importantly, these findings do not imply that the decisions of editors are affected by the possibility that the publication of an industry-supported trial might improve their journal's impact factor or income. Nevertheless, the researchers suggest, journals should live up to the same principles related to conflicts of interest as those that they require from their authors and should routinely disclose information on the source and amount of income that they receive.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000354.

- This study is further discussed in a *PLoS Medicine* Perspective by Harvey Marcovitch
- The International Committee of Medical Journal Editors provides information about the publication of medical research, including conflicts of interest
- The World Association of Medical Editors also provides information on conflicts of interest in medical journals
- Information about impact factors is provided by Thomson Reuters, a provider of intelligent information for businesses and professionals; Thomson Reuters also runs Web of Science

Paper 5

Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses

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RESEARCH

Effect of reporting bias on meta-analyses of drug trials: reanalysis of meta-analyses

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Abstract

Objective To investigate the effect of including unpublished trial outcome data obtained from the Food and Drug Administration (FDA) on the results of meta-analyses of drug trials.

Design Reanalysis of meta-analyses.

Data sources Drug trials with unpublished outcome data for new molecular entities that were approved by the FDA between 2001 and 2002 were identified. For each drug, eligible systematic reviews containing at least one meta-analysis were identified by searches of Medline, Embase, and the Cochrane Library in November 2010.

Selection criteria Eligible systematic reviews were done after FDA approval of the drug, were published in English, and had outcomes and comparators that were the same as those of the trials with unpublished FDA trial outcomes, and the characteristics of participants in the systematic reviews were consistent with the FDA approved indication for the drug. Clinical guidelines, conference proceedings, duplicate systematic reviews, and systematic reviews in which included trials were not referenced or that combined trials across multiple drug classes were excluded. Systematic reviews using non-standard meta-analytic techniques (such as Bayesian or network meta-analyses) and those that used inappropriate or invalid methods for calculation of summary statistics (such as unweighted pooled analyses) were also excluded.

Data extraction Two authors independently extracted data from both the published systematic reviews and the FDA's medical and statistical reviews of the trials submitted to FDA.

Main outcome measure Summary statistics (risk ratios, odds ratios, or weighted mean differences) for relevant outcomes with and without unpublished FDA trial data.

Results 42 meta-analyses (41 efficacy outcomes, one harm outcome) for nine drugs across six drug classes were reanalysed. Overall, addition of unpublished FDA trial data caused 46% (19/41) of the summary estimates from the meta-analyses to show lower efficacy of the drug, 7% (3/41) to show identical efficacy, and 46% (19/41) to show greater efficacy. The summary estimate of the single harm outcome showed more harm from the drug after inclusion of unpublished FDA trial data.

Conclusion The effect of including unpublished FDA trial outcome data varies by drug and outcome. Unpublished FDA trial outcome data should be available and included in meta-analysis. Making these data easily accessible is particularly important because the effects of including unpublished data vary.

Introduction

Systematic reviews or meta-analyses of clinical trials are one of the foundations of healthcare and clinical practice guidelines informed by evidence.[1 2] Bias in the design, conduct, or reporting of clinical trials can result in inaccuracies in meta-analyses or guidelines, and subsequent errors in clinical practice. Reporting bias can take multiple forms, including publication bias, which is the tendency for published trials to be more likely to report statistically significant results than non-significant results.[3 4] Outcome reporting bias, or the selective publication of some but not all outcome data from a trial, is another form of reporting bias.[5]

Much of the evidence of reporting bias has been found in trials testing the efficacy of new drugs. Reporting bias has been detected by comparing publications of drug trials in the scientific literature with trial results submitted to drug regulatory authorities, trial protocols, and internal trial reports obtained through litigation.[6-9] Comparison of the published papers with the unpublished data found that entire trials were not reported and that when trials were reported, outcomes in the published report were deleted, added, or changed compared with the unpublished data. Outcome data that favour the efficacy of the drug are more likely to be published.[8-10]

When unfavourable results of drug trials are not published, meta-analyses and systematic reviews that are based only on published data may overestimate the efficacy of the drugs. Little is known about the effect of reporting bias on systematic reviews in general. The Outcome Reporting Bias in Trials (ORBIT) study examined the prevalence of outcome reporting bias in trials included in Cochrane reviews and found that

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approximately half of the reviews did not seem to include all data from the relevant trials.[11] Furthermore, in about a quarter of the reviews, treatment effects from meta-analyses were reduced by 20% or more by adjustment for outcome reporting bias.[11]

The effect of unpublished data on the results of meta-analyses has been studied extensively for antidepressants. Inclusion of unpublished outcome data from trials of antidepressants in meta-analyses decreased the efficacy and increased the harms of the drugs.[12 13] Whether these findings about the effect of reporting bias on meta-analyses of antidepressants are generalisable to other classes of drugs is not known.

We have previously shown that reporting bias exists across a variety of drug classes.[8] This study expands on our previous work by investigating whether the selective publication of drug efficacy trials submitted to the Food and Drug Administration (FDA) affects a key "downstream" aspect of the medical literature, meta-analyses. Given that very little published information exists on newly approved drugs, the failure to include unpublished trial data in meta-analyses could make them particularly vulnerable to overestimated or imprecise treatment effects. On the other hand, obtaining and extracting unpublished trial data from drug regulatory authorities with current procedures is time consuming and difficult and may not be feasible owing to the poor reporting of the data. Therefore, assessing the effect of such data on meta-analyses across a variety of drug classes is important.

We investigated the effect of including unpublished data obtained from the FDA on the results of meta-analyses of trials of drugs. We hypothesised that inclusion of unpublished data in meta-analyses would decrease drugs' efficacy and increase their harms compared with meta-analyses that did not include the unpublished data.

Methods

Sample of drugs with unpublished outcome data

We identified drug trials with unpublished outcome data in our previous study of new molecular entities that were approved by the FDA between 2001 and 2002.[8] We chose this time period to allow sufficient time for publication of the trials. New molecular entities contain novel active ingredients never before marketed in the United States. In contrast, "me-too" drugs, which are very similar to existing drugs, or combinations of previously approved drugs are not considered new molecular entities. Because of the novelty of new molecular entities, prescribers need complete and valid information on their efficacy and safety. The trial data supporting the efficacy and safety of new molecular entities is submitted in new drug applications. The reviews of these data are summarised in the FDA's medical and statistical reviews, which are publicly available, along with approval letters, at www.accessdata.fda.gov/scripts/cder/drugsatfda.

By comparing the FDA's medical and statistical reviews of the submitted data from drug trials with published trial reports, we identified 299 unpublished outcomes for 24 drugs. The unpublished outcomes resulted from lack of publication of entire trials (n=34 unpublished trials with 258 outcomes), as well as unpublished outcomes from published trial reports (n=41 unpublished outcomes). We will refer to these outcomes as unpublished FDA trial outcomes.

Identification of systematic reviews containing at least one meta-analysis

For each drug, we identified systematic reviews containing at least one meta-analysis (which we will call "systematic reviews") by searching Medline, Embase, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects (DARE) in November 2010. We tailored the search strategy for each drug by combining terms for the drug's name (proprietary, generic, and international non-proprietary name), the FDA approved indication for the drug, and a previously validated search filter for the identification of systematic reviews and meta-analyses.[14 15]

Two authors independently screened titles and abstracts to assess eligibility. We retrieved full papers for relevant studies. Discrepancies were resolved by discussion among all authors.

Selection of systematic reviews for assessing effect of unpublished FDA trial outcomes

We included systematic reviews that contained at least one meta-analysis, were done after FDA approval of the drug (so any unpublished FDA trial outcome data would have been available), were published in English, had one or more outcomes that were the same as unpublished FDA trial outcomes, in which the comparator (active or placebo) was the same as the comparator in trials with unpublished FDA outcomes, and in which the characteristics of participants included were consistent with the FDA approved indication. We also required that the FDA trials with unpublished outcomes met all the inclusion and exclusion criteria of the systematic review.

We excluded clinical guidelines, conference proceedings, duplicate systematic reviews (in the event of duplicates, we included the first published review), and systematic reviews in which included trials could not be identified or that combined trials across multiple drug classes. We also excluded systematic reviews that used non-standard meta-analytic techniques that we would not be able to reproduce (such as Bayesian, network, or individual patient data meta-analyses) and those that used inappropriate or invalid methods for calculating summary statistics (such as unweighted pooled analyses).

For some drugs, multiple systematic reviews met our eligibility criteria. However, we did not consider systematic reviews of a particular drug to be independent of one another, as the trials they included often overlapped. For this reason, we used the following decision tree to select a single systematic review for each drug: firstly, we selected the systematic review with the greatest number of included trials; if tied, secondly, we selected the systematic review with the greatest availability of data for extraction (that is, whether the effect size and variance were reported for each trial included in the relevant meta-analyses); if still tied, thirdly, we selected the systematic review with the greatest number of relevant meta-analyses; if still tied, finally, we selected the systematic review containing meta-analyses with the largest sample sizes. We designed our decision tree in a way that emphasised both practical considerations and the selection of more robust meta-analyses with regard to the amount of evidence synthesised.

Data extraction from systematic reviews and FDA reviews

From each included systematic review, we selected all the meta-analyses that could potentially include the unpublished FDA trial data. Two authors independently extracted data from both the published meta-analyses and the FDA's reviews of the

submitted trials, which are publicly available on its website (www.accessdata.fda.gov/scripts/cder/drugsatfda).

From the published meta-analyses, we extracted data that we needed to recalculate the relevant meta-analyses (events, number of patients in each group, means, standard deviations, and so on). From the FDA reviews, we extracted data by using the same methods as described in the published meta-analysis to obtain the same data the authors of the meta-analysis would have extracted had the unpublished FDA trial outcome data been included in the meta-analysis. For example, we based use of intention to treat versus a per protocol analysis, definition of the intention to treat population, drug dosages, and time points extracted on methods described by the authors of the meta-analysis. If individual meta-analyses were done for different time points, dosages, or analytical techniques (such as intention to treat versus per protocol) for the same outcomes (for example, pain relief at one hour and two hours), we regarded each as a separate outcome for reanalysis.

We also extracted the following data: type of outcome (primary, secondary, not specified) stated in the meta-analysis and FDA review, the type of journal where the systematic review was published (dichotomised as medical journal or Cochrane Library), and the year of publication. We contacted authors of the published systematic reviews to request missing information. We had to contact two authors, and they provided all the requested information.

Analysis

For the systematic reviews selected for recalculation (one per drug), we calculated summary statistics (risk ratios, odds ratios, or weighted mean differences) and the I^2 statistic (a measure of heterogeneity) for each meta-analysis with relevant outcomes both with and without unpublished FDA trial data. If the published meta-analysis already included unpublished data, we removed them and recalculated the summary statistic. We coded the resulting recalculated meta-analysis for each outcome, both with and without unpublished data, as favourable to the drug if it was statistically significant in favour of the FDA reviewed drug in the direction of greater efficacy or less harm ($P<0.05$, 95% confidence interval for difference excluding 0, or 95% confidence interval for ratio excluding 1); not favourable to the drug if it was statistically significant in favour of the comparator; null if it was not statistically significant; or unknown. We also coded a meta-analysis as favourable if it was a superiority outcome that was statistically significant in favour of the FDA reviewed drug or a non-inferiority or equivalence outcome for which the FDA reviewed drug and comparator had similar effects. We considered superiority outcomes that were not statistically significant or non-inferiority or equivalence outcomes that favoured the comparator to be not favourable. We reported the magnitude of the change in the result of the meta-analysis as a percentage change in the summary statistic after inclusion of all unpublished FDA trial data. For risk ratios and odds ratios, we calculated the percentage change of the log transformation as $(\log(E)-\log(I))\times100/\log(E)$, where E=effect estimate excluding unpublished data and I=effect estimate including unpublished data. We calculated the log transformation for relative risks and odds ratios so that the point of "no effect" was equal to zero instead of 1, thus allowing for a calculation of percentage change. For weighted mean differences, we calculated the percentage change by using the formula $(E-I)\times100/E$.

We reported the direction of the change in the results of the meta-analyses as showing an increase in efficacy when the point estimate of the summary statistic showed the drug to be more efficacious when the unpublished FDA trial data were included, a decrease in efficacy when the point estimate of the summary statistic showed the drug to be less efficacious when the unpublished FDA trial data were included, or no change (to two decimal places). For the single safety outcome, we noted if addition of the unpublished FDA trial data changed the point estimate to show more or less harm. We also noted any changes in statistical significance.

We calculated the proportion of unpublished FDA data in each recalculated meta-analysis by dividing the number of patients included from unpublished FDA trials by the total number of patients included in the meta-analysis.

We used RevMan 5.1 software to reanalyse each meta-analysis. We replicated the published meta-analysis with regard to the statistical method (Peto, Mantel-Haenszel, inverse variance), strategies for assessing heterogeneity, analysis model (fixed *v* random effects), and measure of effect (risk ratio, odds ratio, weighted mean difference). With regard to strategies for assessing heterogeneity, if the authors of the meta-analysis applied the results of a test of heterogeneity to determine their analysis model (for example, $\chi^2<0.1$ will result in the application of a random effects analysis model), we would apply that same rule.

Imputation of data

When standard deviations for continuous outcomes were unavailable in the FDA trial data, we explored the possibility of imputing standard deviations from other statistical information in the FDA reviews. For one trial of aripiprazole, we imputed standard deviations as the pooled standard deviations that would produce the reported P values in a *t* test given the reported means and numbers of participants from the FDA trial data. For olmesartan, we imputed standard deviations for two trials by using the same methods for imputing data that were described in the published systematic review.

Sensitivity analysis

When the FDA trial data contained multiple analyses for a particular outcome and the methods of the meta-analysis did not use the most conservative method, we did a sensitivity analysis. For example, if the authors of the meta-analysis included per protocol data for their primary analysis, we would also extract per protocol data for our primary analysis. We would then extract intention to treat data for our sensitivity analysis to determine if the summary statistic was sensitive to the more conservative estimate of the effect of treatment.

Results

Selection of systematic reviews and drugs

Our search identified 1825 unique citations (figure⇓). After screening the titles and abstracts, we retrieved and screened 296 articles in full text. Of the full text articles screened, we excluded 259 because they did not meet our eligibility criteria, leaving a total sample of 37 systematic reviews (figure⇓). These 37 systematic reviews included nine drugs from our original sample of 24 drugs with unpublished FDA trial outcome data. For 15 drugs, we did not identify any systematic reviews that met our eligibility criteria. Our final sample, therefore, contained nine drugs: three for migraine, two antipsychotics, and one each for dementia/Alzheimer's disease, antihypertensive, antibiotic, and topical anti-inflammatory indications.

For eight of the nine drugs, more than one systematic review met our eligibility criteria. For six of these drugs, we selected the systematic review with the greatest number of included trials for reanalysis. For two of the drugs, systematic reviews were tied as to the greatest number of included trials and we selected the one with the most complete available data (that is, the effect size and variance was listed for each trial included in the relevant meta-analyses). We thus selected one systematic review for each of the nine drugs.

Characteristics of systematic reviews

As shown in table 1⇓, four of the nine systematic reviews included in the study were Cochrane reviews. The publication years ranged from 2003 to 2010. Seven of the nine systematic reviews were comparisons with placebo.

We recalculated the summary statistics for all meta-analyses in the systematic reviews for which unpublished FDA trial outcome data were available. A single systematic review can contain multiple meta-analyses, one for each outcome. The nine included systematic reviews for which unpublished FDA outcome data were available had a total of 41 efficacy outcomes and one safety outcome, creating a final sample of 42 meta-analyses reanalysed.

Thirty-eight per cent (16/42) of the outcomes that we reanalysed were designated as primary outcomes in the selected systematic reviews; 26% (11/42) were designated as primary outcomes in the FDA review. Nine of the 16 primary outcomes in the systematic reviews were not considered to be primary in the FDA reviews. Many outcomes were not designated as primary, secondary, or tertiary in both the systematic reviews (48%; 20/42) and FDA reviews (60%; 25/42).

Effect of unpublished FDA trial outcome data on meta-analyses

Table 2⇓ shows the summary statistics for relevant outcomes both with and without unpublished FDA trial data for each meta-analysis. All published summary statistics were replicated, with the exception of one (eletriptan pain relief at two hours—published effect estimate without unpublished data: relative risk 2.48 (95% confidence interval 1.99 to 3.11); our calculated effect estimate without unpublished data: relative risk 2.42 (1.97 to 2.98)). We used our calculation for the percentage change in the summary statistic calculation.

Overall, addition of the unpublished FDA trial outcome data caused 46% (19/41) of the meta-analyses of each efficacy outcome to estimate decreased efficacy of the drug, 7% (3/41) to estimate the same drug efficacy, and 46% (19/41) to estimate increased drug efficacy. The one meta-analysis with a harm outcome estimated increased harm from the drug when unpublished data were added. The changes in estimates of effect varied widely by outcome, even for the same drug. For example, aripiprazole showed a 53% decrease in improvement of brief psychiatric rating scale score and a 166% increase in improvement of positive and negative syndrome scale score. For those outcomes showing an increase in drug efficacy when unpublished FDA trial outcome data were added, the median magnitude of change in summary statistic was 13% (range 2-166%). For those outcomes showing a decrease in drug efficacy with the unpublished data included, the median magnitude of change in summary statistic was 11% (range 1-53%).

For each drug with multiple unpublished outcomes, the direction of the effect of including the unpublished FDA trial outcome data varied; some meta-analyses changed to show more efficacy and some changed to show less efficacy of the drug. Only for one drug (galantamine) did all outcomes show decreased efficacy after inclusion of unpublished data.

In the meta-analyses calculated without unpublished FDA data, 34 of 41 efficacy outcomes were statistically significant in favour of the drug and seven showed the drug was not significantly different from its comparator. When the unpublished FDA data were added to the meta-analyses, four of the seven outcomes that were not statistically significant became statistically significant in favour of the drug (frovatriptan, headache recurrence after response at four hours; olmesartan medoxomil 10 mg, change in trough systolic blood pressure; pimecrolimus, clear or almost clear eczema at two and four weeks). The other 34 outcomes remained statistically significant in favour of the drug.

Unpublished FDA trial outcome data comprised more than half of the data contained in the meta-analyses for 14/41 (34%) meta-analyses of efficacy outcomes. These meta-analyses had a median magnitude of change in estimated effect of 19% (range 2-109%). Unpublished FDA trial outcome data comprised less than half of the data contained in the meta-analyses for 27/41 (66%) meta-analyses. These meta-analyses had a median magnitude of change in estimated effect of 7% (range 0-166%).

Overall, heterogeneity, as measured by the I^2 statistic, decreased when unpublished data were added for seven of 42 meta-analyses. The I^2 statistic was unchanged for 23 of 42 meta-analyses and increased for 12 of 42 meta-analyses. Of the 12 meta-analyses for which I^2 increased, no increases led to changes in analysis model; five remained "fixed effects" and seven remained "random effects."

For 24% (10/42) of the recalculated meta-analyses, the unpublished FDA trial outcome data had already been added by the authors of the systematic review. To assess the effect of including the unpublished data under these circumstances, we removed the unpublished data and then added it back into the analysis. We recorded the summary statistics both with and without unpublished data. Of the meta-analyses that already had unpublished FDA data added in the publication, seven out of nine efficacy outcomes showed less benefit of the drug with the unpublished data added and one harm outcome showed more harm with the unpublished data added.

Sensitivity analyses

When the FDA trial data contained multiple analyses for a particular outcome and the methods of the meta-analysis did not use the most conservative method, we did a sensitivity analysis as shown in table 3⇓. None of these sensitivity analyses showed that the summary statistic was sensitive to the decisions about more or less conservative data extraction.

Discussion

We have documented that the addition of unpublished trial outcome data obtained from the Food and Drug Administration to published meta-analyses changes their results. We recalculated 42 meta-analyses (41 efficacy outcomes, one harm outcome) for nine drugs across six drug classes. The even distribution of increases and decreases in estimates of efficacy caused by the addition of unpublished FDA trial outcome data argues against our hypothesis that inclusion of unpublished data obtained from the FDA would decrease the efficacy of the drugs compared with meta-analyses that did not include the unpublished data. Overall, inclusion of the unpublished FDA trial outcome data changed 46% of the meta-analyses to show a decrease in efficacy of the drug and 46% to show an increase

in drug efficacy. The one meta-analysis with an unpublished harm outcome changed to show an increase in harm from the drug. The direction of the effect of including unpublished FDA trial outcome data varied by drug and outcome.

Meaning of study

Although inclusion of the unpublished FDA trial data changed the magnitude of the effect sizes, it changed the statistical significance of few of the individual meta-analyses. Changes in effect sizes may be more meaningful to clinicians and patients than changes in statistical significance. Furthermore, when the unpublished data comprise only a part of the meta-analysis, effect sizes can change substantially without affecting statistical significance. For example, for the migraine treatment eletriptan, the relative risk of being pain-free at one hour decreased by 25%, from a relative risk of 7.94 (2.88 to 21.87) to 4.70 (2.01 to 10.98), even though the confidence intervals overlap and uncertainty remains similar.

Meta-analyses in which more than half of the included data were unpublished showed larger changes in estimates of effect than did those containing smaller proportions of unpublished data. Therefore, when the occurrence of selective outcome reporting is high, meta-analyses of published drug trial data will overestimate or underestimate the efficacy of treatment more than will those in which the occurrence of selective outcome reporting is low. For meta-analyses that have a large proportion of unpublished FDA trial outcome data, an advantage of including the data, and thereby minimising bias, is that the larger number of events will increase the precision of the effect estimates.

Comparison with other studies

The psychiatric drugs (aripiprazole, ziprasidone, galantamine) showed the most consistent changes; four of the five outcomes changed to show decreased efficacy when unpublished FDA trial data were included. Our findings for the psychiatric drugs are similar to those of previous studies of antidepressant trials showing that inclusion of unpublished outcome data in meta-analyses decreased efficacy and increased harms.[12 13] Our study focused on unpublished data from efficacy trials submitted to the FDA. Turner has shown that for 12 antidepressants, the effect sizes of meta-analyses of the published efficacy data were 11-69% larger than the effect sizes of meta-analyses including the unpublished FDA data.[13] In our study, inclusion of the unpublished FDA trial outcome data decreased the efficacy measures by 22-53%.

Strengths and weaknesses of study

We were able to identify systematic reviews for only nine drugs for which unpublished FDA trial outcome data were available. Our previous study identified 24 drugs with unpublished FDA trial outcome data.[8] One reason for the lack of relevant systematic reviews for 15 of the drugs may be that reviewers are unaware of unpublished outcomes and do not include these outcomes in their protocols. Thus, selective reporting of FDA trial outcomes could affect systematic reviews by influencing the research questions that are asked, as well as the data included in the analyses.

A limitation of our study is that we identified selectively reported outcomes from efficacy trials submitted to the FDA.[8] Although the safety outcome of "any adverse event" was unreported from an efficacy trial of one drug (pimecrolimus), the unreported data for the other drugs consisted of efficacy outcomes only. We did not do a review of all safety data that was submitted to the FDA to identify unpublished data on harms. Although our findings suggest that inclusion of unpublished FDA trial outcome data changes the results of meta-analyses of efficacy outcomes, we cannot determine the overall effect of unpublished data on the safety of drugs or on the risk-benefit ratio of each included drug.

Conclusions and policy implications

Controversy about including unpublished data from studies of drugs may stem from the belief that unpublished studies are not as methodologically rigorous as their published counterparts or from the stigma associated with the lack of peer review.[4] One survey showed that 78% of meta-analysts and methodologists thought that unpublished material should be included in meta-analyses, whereas only 47% of journal editors believed the same.[16] We had previously assessed risk of bias for all the unpublished FDA trials we identified and found them to have a low risk of bias.[8] In addition, all the unpublished data we included in the recalculated meta-analyses met the inclusion criteria of the original meta-analysis. Therefore, poor quality of unpublished FDA trial data is not a sufficient reason for excluding them from meta-analyses.

Unpublished FDA trial outcome data should be available and included in meta-analyses. Making these data easily accessible is particularly important because the effects of including unpublished data vary by drug. Variability across drugs may be due to the extent of selective outcome reporting or the proportion of unpublished data versus published data in the meta-analysis. As our findings suggest that the direction and magnitude of the effect of including unpublished drug trial data in meta-analyses cannot be predicted, the effect of including unpublished data must be measured for each drug and each outcome as the important differences may be found for some outcomes but not others.

Systematically identifying unpublished data from drug trials is difficult. In addition to data identified from FDA reviews, some data are available in data repositories,[17 18] and the European Medicines Agency has recently granted access to clinical study reports.[19] In addition to these sources, mechanisms are being developed to promote the full reporting of trial data. For example, some journals, such as *Science*, require that raw data should be available to readers,[20] and public funders are moving towards requiring that data from sponsored research be made publicly available.[21] However, how such data are reported is important.[22] Journals could also consider demanding a list of all trial outcomes, the full protocol, and raw data as a requirement for publication. Groups that do systematic reviews and meta-analyses, such as the Cochrane Collaboration, should consider developing policies about whether regulatory databases (such as the FDA database) should be systematically searched for data to include in the meta-analyses.

Our findings show that data from FDA's medical and statistical reviews are a valuable source of unpublished data for meta-analyses of drugs. The advantage of the FDA reviews is that they are readily available on the internet, but the data obtained from them have several problems. We excluded some meta-analyses from recalculation because we could not find usable data for the unpublished outcomes in the FDA reviews. For example, means were often not reported with their standard deviations, changes from baseline were reported without baseline data or final endpoint data, or continuous data from the FDA review were dichotomised for the meta-analysis in a way that we were unable to replicate. The FDA reviews contain redacted data, and the text can be difficult to read. The reviews do not

adhere to a standard format, so the ease of finding data varies by drug. Whether the FDA reviews contain all data from the clinical study reports submitted to the FDA or a biased selection of the data is also unclear.

To ensure the accuracy and completeness of meta-analyses of the efficacy and safety of drugs, we urge the FDA and other drug regulatory authorities to make the full clinical study reports available to researchers, as the European Medicines Agency has recently agreed to do.[19] Even data from drug trials submitted to regulatory authorities are based on the sponsor's analysis and may, therefore, be biased. Therefore, access to study protocols and the raw data is necessary to minimise bias in the results of meta-analyses.[9]

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Ethical approval: This study involves secondary data analysis of publicly available information. Therefore, the University of California, San Francisco Committee on Human Research classifies this research as exempt from review.

Data sharing: All data from this study—including literature searches, additional explanatory material, and data extraction forms—are available on request.

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What is already known on this topic

Reporting bias exists across a variety of drug classes

When unfavourable results of drug trials are not published, meta-analyses and systematic reviews that are based on only published data may overestimate the efficacy of drugs

What this study adds

Addition of unpublished trial outcome data to published meta-analyses changed their results

The direction of effect of including unpublished trial outcome data varied by drug and outcome

Unpublished trial outcome data should be available and included in meta-analyses; this is particularly important as the effects of including unpublished data are not predictable

Tables

Table 1| **Characteristics of systematic reviews**

Drug class and name (brand name)	Comparator	Journal type	Publication year
Migraine			
Almotriptan (Axert)	Placebo	Medical	2007
Eletriptan (Relpax)	Placebo	Medical	2007
Frovatriptan (Frova)	Placebo	Medical	2005
Antipsychotic			
Aripiprazole (Abilify)	Haloperidol	Cochrane	2010
Ziprasidone (Geodon)	Placebo	Medical	2003
Dementia/Alzheimer's disease			
Galantamine (Reminyl)	Placebo	Cochrane	2009
Antihypertensive			
Olmesartan medoxomil (Benicar)	Placebo	Cochrane	2009
Antibiotic			
Cefditoren pivoxil (Spectracef)	Penicillin VK	Medical	2004
Topical anti-inflammatory			
Pimecrolimus (Elidel)	Placebo	Cochrane	2007

Table 2| **Effect of unpublished Food and Drug Administration (FDA) trial outcomes on meta-analyses**

Drug class and name (brand name) and outcome	Proportion of unpublished FDA data in meta-analysis (%)*	Summary statistic		Change in summary statistic (%)†	Direction of change in efficacy
		Without unpublished FDA data	With unpublished FDA data		
Migraine					
Almotriptan (Axert):					
Headache relief at 2 hours	11	RR 1.63 (1.07 to 2.48)	RR 1.69 (1.26 to 2.27)	7	Increase
Pain-free response at 2 hours	11	RR 2.93 (1.68 to 5.12)	RR 2.80 (1.97 to 3.99)	4	Decrease
Eletriptan (Relpax):					
Pain relief at 30 minutes	51	RR 1.17 (0.29 to 4.80)	RR 1.24 (0.61 to 2.53)	37	Increase
Pain relief at 1 hour	22	RR 2.54 (1.95 to 3.31)	RR 2.23 (1.65 to 3.00)	14	Decrease
Pain relief at 2 hours	18	RR 2.42 (1.97 to 2.98)	RR 2.27 (1.89 to 2.73)	7	Decrease
Pain-free at 1 hour	26	RR 7.94 (2.88 to 21.87)	RR 4.70 (2.01 to 10.98)	25	Decrease
Pain-free at 2 hours	17	RR 4.83 (3.05 to 7.66)	RR 4.49 (3.00 to 6.71)	5	Decrease
Recurrence at 24 hours	22	RR 0.72 (0.59 to 0.87)	RR 0.68 (0.58 to 0.78)	17	Increase
Frovatriptan (Frova):					
Pain-free at 2 hours	8	RR 3.63 (2.45 to 5.38)	RR 3.80 (2.59 to 5.59)	4	Increase
Pain-free at 4 hours	8	RR 2.69 (2.19 to 3.30)	RR 2.69 (2.21 to 3.28)	0	No change
Headache response at 2 hours	8	RR 1.66 (1.45 to 1.90)	RR 1.68 (1.47 to 1.90)	2	Increase
Headache response at 4 hours	8	RR 1.81 (1.64 to 2.00)	RR 1.80 (1.64 to 1.99)	1	Decrease
Headache recurrence‡	6	RR 0.79 (0.62 to 1.02)	RR 0.74 (0.58 to 0.94)	28	Increase
Nausea at 2 hours	8	RR 0.88 (0.80 to 0.96)	RR 0.86 (0.79 to 0.94)	18	Increase
Photophobia at 2 hours	8	RR 0.83 (0.78 to 0.89)	RR 0.82 (0.77 t o 0.88)	7	Increase
Phonophobia at 2 hours	8	RR 0.87 (0.80 to 0.94)	RR 0.86 (0.80 to 0.93)	8	Increase
Nausea at 4 hours	8	RR 0.64 (0.57 to 0.71)	RR 0.64 (0.57 to 0.71)	0	No change
Photophobia at 4 hours	8	RR 0.65 (0.59 to 0.70)	RR 0.66 (0.60 to 0.71)	4	Decrease
Phonophobia at 4 hours	8	RR 0.68 (0.62 to 0.76)	RR 0.69 (0.62 to 0.76)	4	Decrease
Antipsychotic					
Aripiprazole (Abilify):					
Improvement in BPRS total score	14	WMD 1.07 (–2.09 to 4.22)	WMD 0.50 (–1.05 to 2.04)	53	Decrease
Improvement in PANSS total score	18	WMD 0.70 (–4.13 to 5.53)	WMD 1.86 (–2.21 to 5.93)	166	Increase
Ziprasidone (Geodon):					
Leaving study early—lack of efficacy	47	RR 0.59 (0.40 to 0.87)	RR 0.67 (0.52 to 0.87)	24	Decrease
Dementia/Alzheimer's disease					
Galantamine (Reminyl)					
Global rating (no change or improvement 32-36 mg/day)—OC	37	OR 2.04 (1.50 to 2.79)	OR 1.72 (1.35 to 2.20)	24	Decrease
Global rating (no change or improvement 32-36 mg/day)—ITT	37	OR 1.87 (1.42 to 2.45)	OR 1.63 (1.31 to 2.02)	22	Decrease
Antihypertensive					
Olmesartan medoxomil (Benicar):					
Change in trough SBP—10 mg	75	WMD –7.00 (–14.70 to 0.70)	WMD –9.59 (–12.95 to –6.23)	37	Increase
Change in trough SBP—20 mg	35	WMD –9.91 (–13.15 to –6.68)	WMD –9.91 (–12.41 to –7.41)	0	No change
Change in trough SBP—40 mg	73	WMD –13.00 (–20.55 to–5.45)	WMD –11.98 (–15.50 to –8.47)	8	Decrease
Change in trough DBP—5 mg	94	WMD –6.20 (–11.24 to –1.16)	WMD –4.70 (–5.77 to –3.62)	24	Decrease
Change in trough DBP—10 mg	92	WMD –5.40 (–10.07 to –0.73)	WMD –6.12 (–7.41 to –4.83)	13	Increase
Change in trough DBP—20 mg	54	WMD –7.11 (–8.94 to –5.28)	WMD –6.99 (–8.16 to –5.82)	2	Decrease
Change in trough DBP—40 mg	74	WMD –6.80 (–11.39 to –2.21)	WMD –7.35 (–9.46 to –5.24)	8	Increase
Antibiotic					
Cefditoren pivoxil (Spectracef):					

Table 2 (continued)

Drug class and name (brand name) and outcome	Proportion of unpublished FDA data in meta-analysis (%)*	Summary statistic		Change in summary statistic (%)†	Direction of change in efficacy
		Without unpublished FDA data	With unpublished FDA data		
Clinical cure rate	27	OR 2.29 (1.61 to 3.28)	OR 2.09 (1.55 to 2.82)	11	Decrease
Bacterial cure rate	26	OR 1.83 (1.37 to 2.44)	OR 1.87 (1.47 to 2.38)	4	Increase
Topical anti-inflammatory					
Pimecrolimus (Elidel) efficacy outcomes:					
Clear or almost clear eczema (IGA 0 or 1) at 1 week	55	RR 2.00 (1.06 to 3.76)	RR 2.78 (1.26 to 6.11)	48	Increase
Clear or almost clear eczema (IGA 0 or 1) at 2 weeks	55	RR 1.58 (1.00 to 2.52)	RR 2.20 (1.22 to 3.98)	72	Increase
Clear or almost clear eczema (IGA 0 or 1) at 3 weeks	52	RR 2.52 (1.65 to 3.84)	RR 2.72 (1.84 to 4.03)	8	Increase
Clear or almost clear eczema (IGA 0 or 1) at 4 weeks	55	RR 1.42 (1.00 to 2.03)	RR 2.08 (1.04 to 4.17)	109	Increase
Clear or almost clear eczema (IGA 0 - 1) at 6 weeks	68	RR 2.29 (1.43 to 3.66)	RR 2.03 (1.50 to 2.74)	15	Decrease
Mild or absent pruritus (pruritus score 0 or 1) at 1 week	15	RR 1.89 (1.51 to 2.35)	RR 1.92 (1.57 to 2.35)	3	Increase
Mild or absent pruritus (pruritus score 0 to 1) at 3 weeks	52	RR 2.10 (1.66 to 2.65)	RR 2.02 (1.69 to 2.42)	5	Decrease
Mild or absent pruritus (pruritus score 0 to 1) at 6 weeks	68	RR 2.17 (1.51 to 3.13)	RR 1.82 (1.48 to 2.25)	23	Decrease
Pimecrolimus (Elidel) safety outcome:					
Any adverse events	49	RR 0.85 (0.71 to 1.03)	RR 0.92 (0.82 to 1.02)	49	More harm

BPRS=brief psychiatric rating scale; DBP=diastolic blood pressure; IGA=investigator global assessment; ITT=intention to treat; OC=observed cases; PANSS=positive and negative syndrome scale; SBP=systolic blood pressure; RR=relative risk; OR=odds ratio; WMD=weighted mean difference.

*Calculated as number of participants from unpublished outcome(s) divided by total number of participants.

†RR, OR: (log(E)−log(I))×100/log(E), where E=effect estimate excluding unpublished data and I=effect estimate including unpublished data; WMD: (E− I)×100/E; absolute values are reported.

‡After response at 4 hours.

Table 3| **Sensitivity analyses**

Drug class and name (brand name) and outcome	Summary statistic with unpublished data	Sensitivity analysis
Antipsychotic		
Ziprasidone (Geodon)*:		
Leaving study early—lack of efficacy	RR 0.67 (0.52 to 0.87)	RR 0.64 (0.52 to 0.80)
Dementia/Alzheimer's disease		
Galantamine (Reminyl)†:		
Global rating (no change or improvement 32-36 mg/day)—OC	OR 1.72 (1.35 to 2.20)	OR 1.73 (1.36 to 2.21)
Global rating (no change or improvement 32-36 mg/day)—ITT	OR 1.63 (1.31 to 2.02)	OR 1.63 (1.31 to 2.02)
Antihypertensive		
Olmesartan medoxomil (Benicar) (dose)‡:		
Change in trough SBP mm Hg (10 mg)	WMD −9.59 (−12.95 to −6.23)	WMD −8.60 (−12.06 to −5.13)
Change in trough SBP mm Hg (20 mg)	WMD −9.91 (−12.41 to −7.41)	WMD −9.25 (−11.73 to −6.77)
Change in trough SBP mm Hg (40 mg)	WMD −11.98 (−15.50 to −8.47)	WMD −12.21 (−15.65 to −8.76)
Change in trough DBP mm Hg (5 mg)	WMD −4.70 (−5.77 to −3.62)	WMD −4.46 (−5.56 to −3.37)
Change in trough DBP mm Hg (10 mg)	WMD −6.12 (−7.41 to −4.83)	WMD −6.05 (−7.35 to −4.74)
Change in trough DBP mm Hg (20 mg)	WMD −6.99 (−8.16 to −5.82)	WMD −6.78 (−7.97 to −5.59)
Change in trough DBP mm Hg (40 mg)	WMD −7.35 (−9.46 to −5.24)	WMD −6.80 (−8.98 to −4.62)
Antibiotic		
Cefditoren Pivoxil (Spectracef)§:		
Clinical cure rate	OR 2.09 (1.55 to 2.82)	OR 1.62 (1.27 to 2.08)
Bacterial cure rate	OR 1.87 (1.47 to 2.38)	OR 1.64 (1.33 to 2.04)

DBP=diastolic blood pressure; ITT=intention to treat; OC=observed cases; OR=odds ratio; RR=relative risk; SBP=systolic blood pressure; WMD=weighted mean difference.

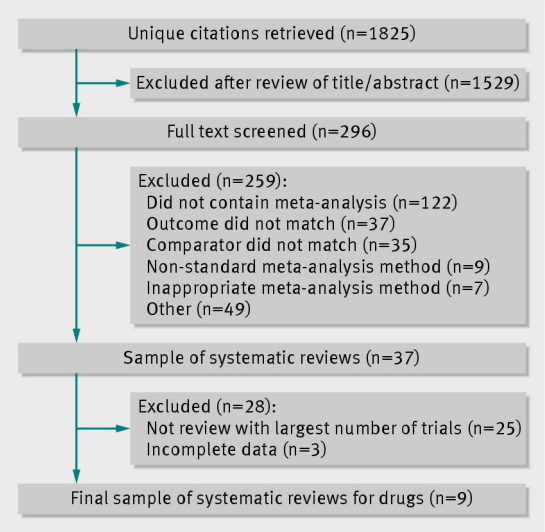
*Authors of meta-analysis received unpublished data directly from trial's sponsor and included events for one dosage in their meta-analysis of outcome "leaving study early—lack of efficacy;" events were summed across multiple dosages for other trial outcomes included in meta-analysis; therefore, primary analysis here replicated authors' findings by including unpublished data for one dosage; sensitivity analysis summed events across multiple dosages.

†Authors of meta-analysis received unpublished data directly from trial's sponsor for both outcomes assessed in this study; Food and Drug Administration (FDA) data differed from what authors of meta-analysis included in their meta-analysis; therefore, primary analysis here replicated authors' findings by adding sponsor's unpublished data to data originally used in meta-analysis; sensitivity analysis instead used data extracted directly from FDA reviews.

‡Authors of meta-analysis used per protocol analysis at post-treatment time point, which was used as primary analysis here; sensitivity analysis was done with unpublished data from intention to treat analysis at follow-up time point.

§Data from FDA medical review included in primary analysis and data from FDA statistical review in sensitivity analysis; statistical review was considered to be more conservative.

Figure



Flow chart for selection of systematic reviews containing at least one meta-analysis

Paper 6

Sponsorship of medical textbooks by drug or device companies

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Major Contribution/Research Article

Sponsorship of Medical Textbooks by Drug or Device Companies

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Abstract

Background: To study whether medical textbooks are sponsored by drug or device companies, and if so, whether they have tried to influence their contents.

Methods: Cross-sectional study of the medical textbooks written in Danish for graduate clinical courses at the University of Copenhagen and anonymous web-based survey of editors. For sponsored books, we also contacted the authors.

Results: Eleven of 71 medical textbooks (15%) were sponsored. We contacted 11 editors, and for 8 books that had authors that were not editors, we also contacted one author. Ten editors and 5 authors replied. One editor was contacted 5 times by the various sponsors concerning the content of specific chapters and in another case the sponsor had the content of a chapter changed regarding its own drug. Two of the authors noted that they did not know that the book was sponsored.

Conclusions: Sponsorship of medical textbooks was not uncommon and may lead to lack of academic freedom. Medical students may be particularly vulnerable to commercial influences, as they have had little or no training in commercial biases and generally believe what they read in textbooks.

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Introduction

The contact with the pharmaceutical industry starts early in the medical career. A survey showed that more than half of third-year medical students had been exposed to industry influences such as free food, small non-educational gifts, journal reprints, books and grand rounds.[1] The students generally had a positive attitude towards these activities. To regulate this relationship, medical associations, industry and governmental authorities have made policies and guidelines[2], and campaigns have been initiated to draw attention to the problem.[3-5]

A survey of doctors showed that medical textbooks were their preferred information resource.[6] Medical textbooks are opinion-based and recommendations can conflict with the current evidence.[7] As textbooks do not give the readers the possibility of inspecting the data and drawing their own conclusions, biased recommendations based on conflicts of interest could lead to suboptimal clinical decision making.

Sponsorship of scientific books has been described in relation to the tobacco[8,9] and alcohol[10] industries. A court case concerning off-label promotion of the epilepsy drug gabapentin (Neurontin) revealed that Warner-Lambert paid over $300,000 to support the production, printing and distribution of 75,000 copies of an epilepsy textbook.[11,12] Half of the budget was allocated to soliciting interest among and delivering books to high prescribers of anticonvulsant agents. Apart from this case, sponsorship of medical textbooks has to our knowledge not been described previously and has not been investigated empirically. In this study, we describe sponsorship of Danish medical textbooks by the pharmaceutical and medical device industry and report a survey of the editors and authors.

Methods

Identification of sponsored textbooks

In December 2007, one author (AL) examined all medical textbooks written in Danish and potentially used for the graduate clinical courses in medicine at the Medical Faculty, University of Copenhagen available at either the University Medical Library or the University Medical Bookstore. We defined clinical courses as those which address treatment of patients (therefore, for example, including pharmacology and microbiology, but excluding radiology and occupational medicine). Textbooks translated into Danish, or published before 1997, or written for other medical professions, or previous editions were excluded.

Data were extracted into a standardized datasheet on title, editors, authors, publisher, year of publication, edition, categorization according to clinical discipline, any statements of conflict of interest, and sponsorship. If a sponsorship was stated, information was extracted on sponsor's name and of sponsor's involvement.

We included all textbooks that were sponsored or that contained advertisements for drugs or medical devices.

Survey

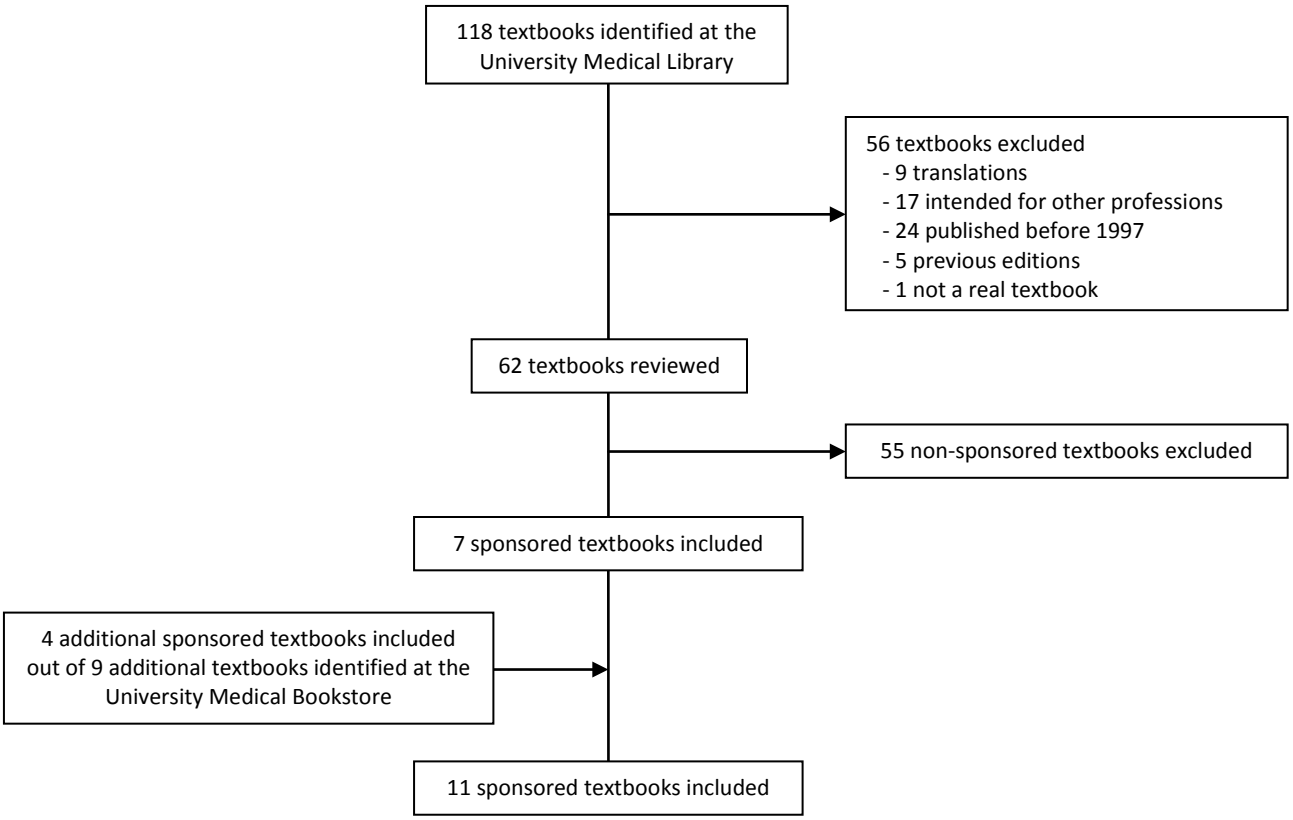
For each sponsored textbook, we contacted the first-mentioned editor and the first-mentioned author who was not also an editor. One author was a physiotherapist and as physiotherapists are not allowed to prescribe drugs, we chose the second author in this case. If a book had no description of editors (e.g. a book by a single author) or if it only described a technical editor (e.g. a non-physician without content knowledge) we regarded the authors as editors. We contacted these people in May 2008 via e-mail and asked them to fill in an anonymous web-based survey (SelectSurvey.NET 1.5.4) with 10 questions and a unique ID code in case we needed to contact them for clarifications. We sent a reminder by e-mail after one week and by letter after three weeks. We excluded duplicate replies, guided by the respondents IP address.

To investigate whether some textbooks without description of sponsorship were in fact sponsored, we did a second survey. In February 2009, we contacted the first-mentioned editors of the textbooks without sponsorship via e-mail and asked them to fill in an anonymous web-based survey (SelectSurvey.NET 1.5.4) regarding undisclosed sponsorship with 6 questions and a unique ID code in case we needed to contact them for clarifications. We sent a reminder by e-mail after 3 weeks.

Results

We identified 118 textbooks for clinical courses in Danish at the University Medical Library (Figure 1). Fifty-six were excluded: 9 were translations, 17 were

Figure 1. Flow chart of inclusion of textbooks



intended for other professionals than physicians (e.g., nurses, physiotherapists and psychologists), 24 were published before 1997, 5 were previous editions, and 1 was not a textbook, but a drug information guide. Of the 62 remaining textbooks, 7 were sponsored and included. We found an additional 9 books at the University Medical Bookstore of which 4 were sponsored, giving a total of 11 included sponsored medical textbooks (15% of 71 books).[13-23]

Nine textbooks only included the name of the sponsors whereas one textbook also included whole-page drug advertisements from the sponsoring companies. This textbook is also available for free if the doctor agrees to receive a visit from a drug representative from one of the sponsoring companies. One textbook for general practitioners did not indicate sponsorship in the version we identified for our study, but the sponsorship was known to us because of earlier correspondence with the editor. Furthermore, we discovered that an alternative version exists with a sponsorship statement and the company logo. Previously, this version could be obtained for free by contacting the sponsoring company, but it is now only available for free if the doctor agrees to receive a visit from the company's drug representative.

One textbook stated that the sponsors had no influence on the contents and recommendations, one that sponsorship included practical help and typing of manuscript, and four that the sponsorship covered printing cost and illustrations. The remaining 5 books had no such text. None of the books had any statements about editors' and authors' conflicts of interest.

We sent the e-mail invitation to 11 editors, 10 of whom were also authors, and to 8 authors who were not also editors. We received 15 unique surveys (79% response rate), of which 14 were complete. Ten respondents were editors and 5 were authors, one of whom had filled in the incomplete survey.

Initiation of sponsorship

Table 1 describes the responses to the first survey concerning sponsored textbooks. In 8 out of 10 cases, the editors participated in initiating the contact with the sponsoring companies. Four of them additionally explained that they sought help with production costs, in part to allow for higher quality of illustrations, as medical textbooks in Danish are expensive due to the limited number of potential purchasers. In two cases, it was the publisher who wanted the book to be sponsored, and the editor had no influence on this decision.

One out of 4 authors stated that he had had influence on whether the book should be sponsored, but not on who the sponsor should be. Two other authors stated that they did not know that the textbook they authored was sponsored before receiving our survey.

Agreements with sponsoring companies

Four out of the 10 editors and 1 out of 5 authors stated that they were presented with written information from the publisher that described the sponsor's influence, or lack thereof, on the editorial process and publication. Nine out of 10 editors stated there were no explicit terms in the agreement on sponsorship regarding

Table 1. Answers to survey about sponsorship of medical textbooks

Respondents		Editors	Authors*
No. of invitations sent		11	8
No. of responses received		10	5
Who took initiative to seek sponsorship? (more than one answer possible)	Editors	8	1
	Co-authors	0	0
	Publisher	5	0
	Companies	1	0
	Other	0	0
	Don't know	0	3
Had you as an author or editor any influence on the decision to seek sponsorship?	Yes	8	1
	No	2	3
If yes, did you have any influence on who the sponsor should be?	Yes	8	0
	No	0	1
Were you as author or editor presented with written information from the publisher that described sponsors influence, or lack of, on the editorial process and publication?	Yes	4	1
	No	6	4
Agreement on sponsorship:	No explicit terms	9	4
	Wanted to see chapter/book before agreement	1	0
	Other	0	0
Which influence did the sponsor have on the editorial process?	None	8	1
	Notify company with no explicit terms	0	0
	Notify company with right to comments	1	0
	Notify company with right to approval	0	0
	Other	1	0
	Don't know	0	3
Did you at any time have direct contact with the sponsor?	Yes	8	0
	No	2	4
Did you as author or editor receive fee from:	Sponsors	1	0
	Publisher	9	4
	Other	0	0

*One author did not respond to all questions in the survey

editorial independence, but in the last case some of the sponsoring firms wanted to see a draft of a chapter or the whole book before decision on sponsorship.

Contacts with sponsoring companies after the agreement

Two editors described that the sponsoring companies had contacted them after the agreement concerning the content of the textbook. In the first case, the editor had no influence on sponsorship, but was contacted by sponsoring companies approximately five times concerning questions in relation to the indication and choice of drug recommendations in specific chapters. The editor sent the questions to the authors of the specific chapters and stated that in no cases were the contents of the chapters changed.

In the second case, the editor - who was also the sole author - had no direct contact with the sponsoring company, but was contacted indirectly through the publisher. The publisher wanted the author to rewrite a chapter concerning recommendations on a drug produced by the sponsoring company. The publisher stated that the indications for the drug were not updated with the current evidence, as the indications were broader than what the author had written. The publisher then supplied the author with recommendations that the author was sure originated from the sponsoring company. When the author asked the publisher if these recommendations came from the sponsoring company, the publisher denied it. The author then refused to change the contents and the publisher rewrote the chapter and threatened the author with legal action if he intervened. Due to the specific details of this answer the anonymity was broken and it was later verified through contact to the editor that this was the book where the sponsorship was concealed.

Undisclosed sponsorship

We sent an e-mail invitation to the first-mentioned editor of the 60 textbooks without any description of sponsorship and received 43 unique surveys (72% response rate), which were all complete. Forty replied that the textbook was not sponsored while 3 replied that they did not know. One of the editors who replied that the textbook was not sponsored stated that a previous edition from 1985 received industry support for production costs.

Discussion

We identified eleven sponsored medical textbooks in Danish for graduate clinical courses. We found that in most cases the editors initiated the sponsorship agreement to improve the graphical quality of the textbooks and lower sales prices, and that in most cases the sponsoring firms did not have any influence on the editorial process and the contents of the books. However, in one case the sponsoring companies contacted the authors regarding questions to the contents of the book, and in another case where sponsorship was concealed, the sponsoring company indirectly changed the contents of a chapter through contact with the publisher without the author's approval.

Our study is limited by its small sample, by being restricted to Danish medical textbooks and by our choice of surveying only some of the editors and authors. It can be debated whether our findings of sponsorship are related to the fact that Danish is only spoken by a small number of people. One editor replied that more than 1000 copies sold per year is considered a huge success, and another remarked that his estimated income from producing the book amounted to 12 US cents per hour. Editors and authors can therefore be tempted to seek sponsorship in order to compete with cheaper books written in English. Even so, we have identified serious problems of general interest that we discuss below.

Unknown sponsorship

In three cases, the editors of textbooks without statements about sponsorship did not know whether the textbook was sponsored. In two other cases the authors of sponsored textbooks firstly became aware of this fact when they received our survey. This lack of transparency is a serious oversight, as potential editors and authors have been deprived of the possibility to decline the invitation, due to the sponsorship, in order to protect their reputation and scientific integrity. Furthermore, authors obviously cannot state their conflicts of interest in future publications when they don't know about them, and they might therefore undeservedly become suspected of misconduct, or of having broken the rules they are expected to live up to. For example, the authors of an article that was published in the online version of the BMJ[24] expressed concern subsequently[25] that they had not been

informed that their paper was sponsored by a drug company. Underneath the series name ("Medical Milestones"), and almost as if it were part of the title of their paper, this text appeared: "Publication of this online supplement is made possible by an educational grant from Astra Zeneca", and a drug ad was the banner along the top of the page. Two of the authors are Cochrane Centre Directors and questions had been raised with them about whether they had followed Cochrane policy regarding receiving support from industry. It is also problematic that concealed sponsorship makes it more difficult for authors to judge whether comments or requests for changes from the editors are sound or are commercially motivated. In one of our cases, the wish to change the contents of a chapter was only discovered as originating from the sponsor because of the author's knowledge about concealed sponsorship of the textbook.

A non-clinical textbook not included in our sample was "Rational Diagnosis and Treatment"[26] that is an obligatory textbook for the course on theory in medicine. A previous edition[27] was translated into Polish[28], but it was not made clear at the outset that it would be sponsored. This was revealed to the second author when much of the translation had already taken place and when it was difficult to back out. The second author was one of us, and he would not have accepted the sponsorship if it had been discussed openly from the outset. The book is sponsored by Pfizer and Glaxo-Smith Kline, and this industry sponsorship is particularly unfortunate for this book, as it was written to promote the principles of evidence-based medicine. In contrast, the aim of the drug industry is to sell as many drugs to as many people as possible, and flawed research and marketing often leads to irrational prescribing and overprescribing.[29]

Editorial independence and authorship

In two cases the sponsor tried to influence the contents of the textbook. In one case, it was part of the agreement between the sponsors and the participating editor and authors that the sponsors were allowed to read the whole book or selected chapters and to comment on the contents before they decided whether they would sponsor the book. The authors were contacted approximately five times by the sponsoring companies with questions. While the editor stated that no changes were made, it is nevertheless problematic, as self-censorship might have occurred. Editors and authors may be tempted to spin the contents to attract sponsors and to avoid withdrawal of sponsorship. The latter seemed to be the problem in the second case where the sponsoring company by contacting the publisher accomplished changes to the contents of a chapter with recommendations on a drug produced by the company. We suggest that, at the very least, agreements regarding editorial processes, authorship and sponsorship should be drawn up to support academic integrity, similar to authorship of scientific articles.[30] Furthermore, medical textbooks should describe what the sponsorship covered, what the conditions were, and whether the sponsor had any influence on the text.

Transparency of sponsorship

Only one textbook had any statements about the sponsors' influence on the editorial process, and five stated which production costs were covered by the sponsorship (e.g. secretarial assistance or graphical layout). None of the textbooks had any statements about the editors' and authors' ties to any of the sponsoring companies or companies that manufacture similar drugs or devices. This is problematic as medical textbooks may be more direct in their endorsement of specific treatments than research articles and seldom provide any data to back up recommendations. The readers must therefore rely on their trust in the editors and authors. Ties to industry can affect recommendations[31] and conflicts of interests can therefore also be a problem in non-sponsored books. This suggests that textbooks should contain conflict of interest statements for editors and authors.

Conclusion

Sponsorship of medical textbooks was not uncommon and while few editors and authors described any problems in relation to the sponsors' possible influence on the contents, we discovered some major problems. We suggest that industry sponsorship of medical textbooks should be avoided, as it may lead to lack of academic freedom, for example through self-censorship. Medical students may be particularly vulnerable to commercial influences, as they have had little or no training in commercial biases and generally believe what they read in textbooks. If textbooks are sponsored they should at least live up to the same principles regarding

transparency and editorial independence as journal articles. Furthermore we recommend that all textbooks state any conflicts of interest for participating editors and authors.

Conflict of interest

We declare that we have no competing interests.

Contributors

AL conceived the study and wrote the draft protocol and draft manuscript. AL identified sponsored books, extracted data, developed the survey, contacted editors and authors and analysed the data. Both authors contributed to study design, acquisition and interpretation of data and writing the paper. Both authors are guarantor and gave final approval of the manuscript.

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Ethics

This study did not require ethical approval according to the Danish Act on a Biomedical Research Ethics Committee System and the Processing of Biomedical Research Projects.

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Paper 7

Underreporting of conflicts of interest in clinical practice guidelines: cross-sectional study

Submitted.

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Abstract

Objective
To determine the prevalence of conflicts of interest among authors of clinical practice guidelines on drug treatments by Danish specialty societies.

Design
Cross sectional study.

Setting
Guidelines published from July 2010 to March 2012 from Danish specialty societies.

Participants
Authors of clinical guidelines.

Main outcome measures
Prevalence and degree of underreporting of conflicts of interest among authors of clinical practice guidelines using the publicly available disclosure list of the Danish Health and Medicines Authority, and methodological characteristics of guideline development.

Results
Forty-five guidelines from 14 specialty societies were included. Of 254 authors, 135 (53%) had conflicts of interest, corresponding to 43 of the 45 guidelines (96%) having one or more authors with a conflict of interest. Only one of the 45 guidelines (2%) disclosed any conflict of interest for any of the authors. The most common type of conflict of interest (83 of the 135) was being a consultant, an advisory board member or a company employee. Only 10 guidelines (22%) described the methods used for guideline development, 27 (60%) used references in the text and 11 (24%) graded the types of evidence.

Conclusions
Conflicts of interest among Danish specialty guideline authors are very common, but disclosures are very rare. Most guidelines do not describe how they were developed and many do not describe the evidence behind specific recommendations. Publicly available disclosure lists may assist guideline issuing bodies in ensuring that all conflicts are disclosed.

Introduction

The amount of medical information is overwhelming and it increases rapidly.[1] Clinical practice guidelines are therefore an important tool for assisting clinicians and patients in clinical decision-making.[2] Clinical practice guidelines should be based on valid scientific evidence, critical assessment of that evidence, and objective clinical judgement that relates the evidence to the needs of practitioners and patients.[3] However, treatment recommendations in guidelines are often based on expert opinion and low levels of evidence, which make them prone to biases and prejudices.[4] Conflicts of interest among guideline authors may therefore pose problems[4], as they may influence prescriptions[5] and treatment recommendations.[6,7]

The potential effects of conflicts of interest might have profound effects on health care because guidelines are written to influence the practice of physicians[8] and can be used for economic prioritisation.[9]. Studies of conflicts of interest have found that up to 87% of guideline authors had interactions with drug companies.[9,10] Many of these conflicts are not disclosed because guideline issuing bodies do not publish this information[11] or because the authors choose not to disclose them.[12] This makes it likely that previous studies, which have relied on disclosed information, have underestimated the actual prevalence of conflicts of interest.

In Denmark, a nation of approximately 5.6 million inhabitants, there are around 22,500 practising physicians, 8.5% of which have a registered affiliation with a drug company.[13] Any physician wishing to receive payment from a drug company is obliged to apply for permission through the Danish Health and Medicines Authority and all physicians with permissions are named on a publicly available list.[14] Similar to the US Physician Payments Sunshine Act[15], the list makes it possible to study the level of underreporting of conflicts of interest among guideline authors.[16]

Our aims were:

- to determine the prevalence and types of conflicts of interest among authors of clinical practice guidelines published by Danish specialty societies;
- to estimate the proportion of disclosed conflicts of interest;
- to describe the methodology used in the guidelines.

Methods

We sampled guidelines from each of the 38 Danish specialty societies as defined by the list of the Organization of Danish Medical Societies.[17] We excluded guidelines from non-clinical societies (e.g. radiology and pathology).

Selection of guidelines

In March 2012, using the website for each specialty society, one observer included up to five of the most recent drug guidelines published from July 2010. We limited the number to five in order to avoid clustering by specialties with many guidelines. As we focused on conflicts of interest in relation to drugs, we selected guidelines with a focus on drug treatment of medical conditions. For example, for anaesthesia we included a guideline on strategies for sedation,

but excluded one on tracheotomy. In case of multiple guidelines of similar publication date, we selected them randomly. Societies without guidelines on their website were contacted by e-mail to determine whether any guidelines had been published. Guidelines referenced on the societies' website that had been developed by other national or international organisations were not considered a guideline for the particular society. Guidelines made in collaboration between different specialties were included in a separate category. Some societies had not produced five guidelines meeting our selection criteria and in those cases we included those that were available. A second observer verified the selection of guidelines according to our criteria.

Guideline information

For each included guideline, two observers independently extracted information on title, date, number of authors, names of authors, funding of guideline and disclosures of conflicts of interest into a standardised datasheet. Disagreements were resolved through discussion. We contacted the specialty society for missing information on date of publication and funding.

Conflicts of interest

We used the publicly available Danish registry of authorization to practise medicine to ensure the identity of authors and that they were physicians.[18] For each author, information on conflicts of interest was identified using the disclosure list of the Danish Health and Medicines Authority.[14] The list is updated continuously and we used three different versions from the period June 2010 to March 2012. If we were uncertain about whether a guideline author matched a physician on the disclosure list (e.g. due to variation in spelling of the name), we contacted the guideline issuing specialist society and the Danish Health and Medicine Authority for clarification. Two observers extracted information on conflicts of interest and disagreements were resolved through discussion. We coded a conflict of interest to be present if an author had an affiliation with a drug company up to 3 years prior to the published guideline, similar to the ICMJE criteria for biomedical journals.[19] When we were in doubt, we obtained additional information by applying for this through the Danish Health and Medicines Authority.

The type of conflict of interest with drug companies was classified into the following categories, which we defined a priori based on our previous experience with the disclosure list:[13]

- Consultant/advisory board member/employee
- Speaker/educational activities
- Investigator/research collaboration
- Equity/stockholder

Authors who have received reimbursement for conference expenses or fees for single activities such as speaking at only one meeting are not listed on the disclosure list.

Pilot
Our datasheets were developed using a pilot version on one guideline on drug treatments from each of five randomly selected specialty societies.

Guideline methodology
We initially planned to use the AGREE II instrument to assess the reporting of guideline methodology[20], but due to the low standards of reporting we encountered in our pilot study, we decided to use a simplified version adapted for key domains. For each guideline, two observers independently extracted information on description of methods for guideline development, use of references, and grading of types of evidence. Use of references was categorized as: references in text (for example when a particular drug was recommended in the text and a trial of this drug was cited), references, but not in text (when the references were at the end of the guideline only), and no references. We coded grading of evidence to be present if authors described the levels of evidence behind specific recommendations or the strength of recommendations according to a system (for example Ia, Ib, IIa, IIb, III, IV or A, B, C, D).

Data analysis
We calculated the prevalence of disclosed and undisclosed conflicts of interest overall, at guideline level, and at specialty society level. For authors with conflicts of interest, we calculated the proportions of the individual types of conflicts of interest. Guidelines made in collaboration between different specialties were analysed separately.

Sensitivity analysis
The estimated overall prevalence of authors with conflicts of interest depends on the number of authors per society and the prevalence of conflicts of interest at society level. Wetherefore performed a simple sensitivity analysis to test the robustness of our results. We estimated the prevalence as an average of the mean prevalence of conflicts of interest among individual societies, assigning each society the same weight.

We also tried to quantify to which extent authors without conflicts of interest according to the disclosure list had such conflicts, in a random sample of 25% of the authors. We searched the authors' conflicts of interest statements in scientific publications published in the three years prior to the guideline data, searched Google by combining their names with names of companies that authors of the same guideline were affiliated with, and contacted the Danish Health and Medicines Authority for additional information.

Results

We included 45 clinical practice guidelines, 40 from 14 Danish specialty societies and 5 collaborative guidelines (Fig. 1), with a total of 257 guideline authors. We excluded two authors who were psychologists and one midwife resulting in 254 physician authors. The number of authors per guideline ranged from 1 to 16 (median 5). As 7 authors participated in 2 guidelines, there were 247 unique authors. Two guidelines (4%) contained information

about funding. Six drug companies supported the distribution of a guideline, but not its development. In the other guideline with information on funding, two medical societies and the Danish Institute for Rational Pharmacotherapy funded the guideline development. According to the specialist societies' replies to our emails, none of the other 43 guidelines had received funding from drug companies.

Conflicts of interest

Only one guideline (2%) included a conflicts of interest statement for three of its four authors; all three were conflicted. We identified conflicts of interest for 132 additional authors, giving a total of 135 out of 254 authors (53%) with conflicts of interest. The true prevalence of conflicts of interest of guideline authors ranged from 0% to 100% among individual guidelines (Fig. 2). Forty-three guidelines (96%) had one or more authors with a conflict of interest, and in only two guidelines were all authors without conflicts (4%). In 24 guidelines (53%), the majority of authors had conflicts of interest and in 8 guidelines (18%), all authors had conflicts of interest.

The most common type of conflict was consultant/advisory board member/employee followed by speaker/educational activities, investigator/research collaboration and equity/stockholder (Table 1).

The lowest prevalence of authors with conflicts was found for the Danish Society of Anaesthesiology and Intensive Care (14%), the Danish Paediatric Society (23%) and the Danish Society of Neurology (25%) (Table 2). The highest prevalence was found for the Danish Society of Dermatology (100%) and the Danish Society of Endocrinology (100%).

Sensitivity analysis

The overall prevalence of conflicts of interest among guideline authors changed from 53% to 57% in our sensitivity analysis (simple average of percentage for each specialty society). When we searched for additional information about conflicts of interest among the 30 authors without conflicts (25% of 119) we found that 3 (10%) had conflicts that were not disclosed on the Danish Health and Medicines Authority’s list, the reason being that the activities predated our earliest available version of the list. Assuming that the 10% of authors without conflicts, according to the list, actually had conflicts, the prevalence changed from 53% to 58%.

Guideline methodology

A description of the methods used for guideline development was found in 10 guidelines (22%). Nine of those were produced by only two societies, the Danish Society of Gastroenterology and Hepatology and the Danish Society of Obstetrics and Gynaecology, and the tenth guideline was a collaborative one. Twenty-seven guidelines (60%) included references in the text, 10 (22%) used references, but did not include them in the text, and 8 (18%) did not use references at all. Eleven guidelines (24%) graded the types of evidence; 10 of those were produced by the same two societies the Danish Society of Gastroenterology and Hepatology and the Danish Society of Obstetrics and Gynaecology and one by Danish Society of Gastroenterology and Hepatology in collaboration with five other societies.

Discussion

We found that 53% of guideline authors had conflicts of interest, corresponding to 43 out of 45 guidelines being written by one or more authors with conflicts, and that only 2% disclosed them, in just one guideline. Most guidelines did not state how they were developed or graded the evidence, and many did not include references in the text.

Our study was based on very comprehensive data from the Danish Health and Medicines Authority, and physicians and drug companies are required by law to report their collaboration to the authority.[21] Our findings demonstrate that reliance on voluntary disclosure underestimates the prevalence of conflicts of interest substantially. Using a publicly available disclosure list made it possible to identify undisclosed conflicts of interest, but one limitation of the list is that drug company affiliations are deleted as soon as the collaboration ends. As judged by our sensitivity analysis, this seemed to have had little impact on our results, but we suggest that such lists include affiliations up to 3 years prior to the current date, similar to the ICMJE criteria.[19]

It is therefore likely that previous studies of conflicts of interest among clinical guideline authors have underestimated the prevalence of conflicts of interest, as they have relied on voluntary disclosure. We note, however, that the underreporting of conflicts of interest in our study of Danish guidelines may have been atypical, e.g. US guidelines have more disclosures.[9] Albeit our study was based on Danish guidelines, our sample represents 14 different specialties and we have thereby obtained more generalisable information on the extent of conflicts of interest among guideline authors than in other studies, which have usually only included guidelines from a few specialties.[9]

In a recent systematic review by Norris and colleagues, the prevalence of conflicts of interest ranged widely among the different studies included, from 18% to 100%.[9] The large variation in prevalence may have several explanations.

Firstly, many studies identified conflicts of interest solely based on authors' disclosures in guidelines, which will generally underestimate the prevalence.[8,22] Other studies have identified conflicts of interest based on authors' disclosure in their additional journal publications[12,23,24] or by surveys.[25,26] However, such strategies are often inadequate,[9] e.g. many journals do not include disclosure statements in their articles or have only started recently, response rates in surveys were often low, and authors often do not to disclose conflicts in their scientific publications.[27,28] Only a few studies have used other sources such as the US patent databases.[23,29]

Secondly, we coded a conflict of interest to be present if authors had an affiliation with a company up to 3 years prior to the published guideline. This interval differs among studies[9] as do perceptions about what constitutes a conflict of interest. For example, some studies included paid travel fees[10,22], which we did not, as such conflicts are not listed on the disclosure list. We coded any financial tie as a conflict of interest, although some ties might be related to companies producing drugs not relevant to the guideline. However, this will likely be

less important, as guideline authors are usually affiliated with companies producing drugs in areas where they are experts and write guidelines in the same areas.

Thirdly, the overall extent of conflicts of interest varies between countries. In Denmark, the prevalence is approximately 8.5%[13], whereas it is 14.1% among US physicians[30], which is surprising, as small countries will have a smaller pool of authors without conflicts to choose from.

While disclosure improves transparency, it does not remove the potential bias related to conflicts of interest[6,7,31,] and a better strategy is to prohibit authors with conflicts from guideline production or minimise their influence on formulating recommendations.[32] It has been argued that authors without conflicts of interest lack the content area knowledge and skills necessary to interpret the scientific data. But this is a flawed argument. Industry relations, such as being on a company's speakers bureau or advisory board, does not serve any academic purpose and authors can choose to avoid these relationships. Furthermore, there is a substantial pool of authors without conflicts.[31] Lastly, content area experts often have preconceptions about treatment effects, which may bias their interpretation of the evidence.[33-35] A better strategy would be to include more methodologists as guideline authors as they are often free from preconceptions and rarely have conflicts of interest.

Conclusions

Conflicts of interest among guideline authors from Danish specialty societies were common but very rarely disclosed. Most guidelines also lacked transparency as to their development and the evidence in support of the recommendations. Thus, there is a need for better management and disclosure of conflicts of interest, and greater transparency of guideline methodology. Publicly available and law-enforced disclosure lists may assist guideline issuing bodies in ensuring that all conflicts are disclosed.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

AL conceived the idea for the study. The protocol was primarily developed by AL; JBBB, JS and PCG contributed. JBBB identified guidelines and AL verified the selection. AL and JBBB extracted guideline data and JBBB and JSS identified conflicts of interest. All authors participated in data analysis and writing of the paper. All authors had full access to all the data in the study. AL and JBBB are guarantors and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Ethical approval
This study did not require ethical approval as it was based on publicly available information.

Data sharing statement
Anonymised data available upon request.

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Table 1. Types of conflicts of interest among conflicted guideline authors.

	(n=135)
Consultant/advisory board member/employee	83 (61%)
Speaker/educational activities	77 (57%)
Investigator/research collaboration	65 (48%)
Equity/stock	10 (7%)

Table 2. Prevalence of authors' conflicts of interest according to specialty society.

Name of society	Number of included guidelines	Number of authors	Number of authors with conflicts
Danish Society of Anaesthesiology and Intensive Care	1	7	1 (14%)
Danish Society of Cardiology	5	22	16 (73%)
Danish Society of Child and Adolescent Psychiatry	5	19	9 (47%)
Danish Society of Dermatology	1	3	3 (100%)
Danish Society of Endocrinology	1	6	6 (100%)
Danish Society of Gastroenterology and Hepatology	5	29	9 (31%)
Danish Society of Haematology	2	17	11 (65%)
Danish Society of Infectious Diseases	1	5	4 (80%)
Danish Society of Obstetrics and Gynaecology	5	13	6 (46%)
Danish Society of Nephrology	1	8	5 (63%)
Danish Society of Neurology	1	8	2 (25%)
Danish Society of Paediatrics	5	26	6 (23%)
Danish Society of Respiratory Medicine	5	18	11 (61%)
Danish Society of Rheumatology	2	17	13 (76%)
Collaborative guidelines	5	56	33 (59%)

Figure 1. Inclusion of guidelines produced by specialty socities.

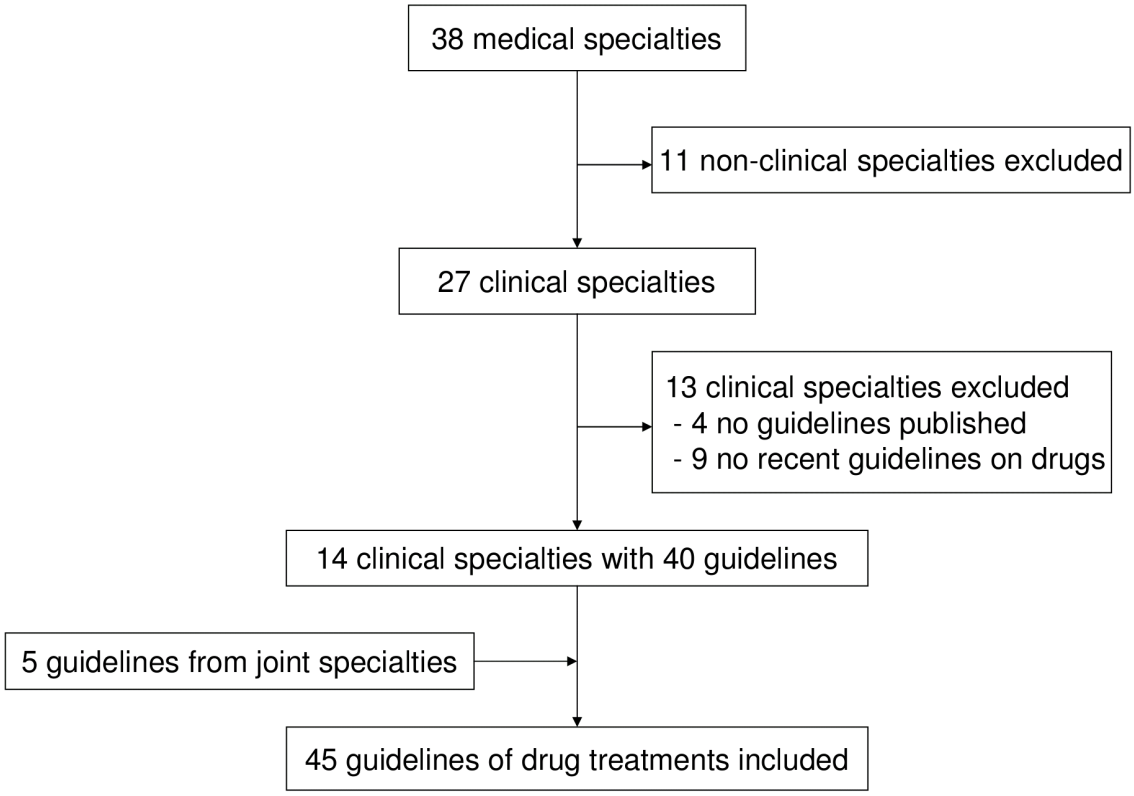
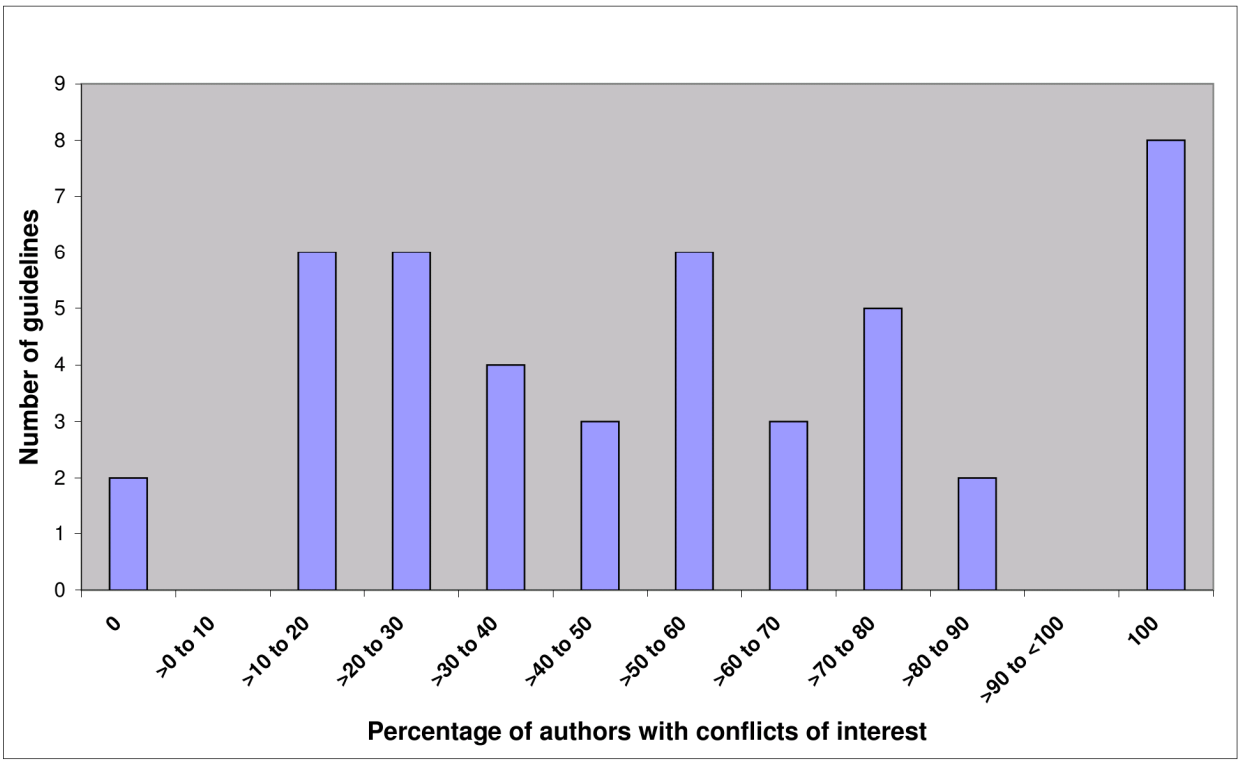


Figure 2. Prevalence of conflicts of interest among author groups in the 45 guidelines.



Discussion

We found that conflicts of interest in biomedical publishing are important. The high prevalence of conflicts of interest for both authors and editors may affect how research data are interpreted and disseminated through publication in high impact journals, medical textbooks and clinical guidelines.

Industry sponsored research

In our Cochrane review (paper 1), we found that sponsorship of drug and device studies by the manufacturing company leads to more favourable results and conclusions than studies sponsored by other sources. These results are in line with previous systematic reviews.[1-4]

The previous reviews, by Bekelman et al. and Lexchin et al.[1,2], were both published almost a decade ago and an update of these reviews has therefore been warranted. While the reviews by Sismondo and Schott et al.[3,4] are more recent, they did not assess bias of the included studies or use meta-analysis to provide quantitative estimates of the association between industry sponsorship and research outcomes. Additionally, the review by Lexchin et al. suggested that industry trials are of better methodology and therefore have a lower risk of bias than non-industry sponsored trials, but it has been argued that this could simply be due to regulatory requirements.[5] When we investigated the domains used in the Cochrane Risk of Bias Assessment tool, we did not find any difference in the risk of bias between industry and non-industry sponsored trials, except in relation to blinding, where industry trials had a lower risk of bias.

Our findings of more favourable outcomes in industry sponsored studies (industry bias) could also be due to differences in unmeasured covariates (confounding) between industry sponsored studies and non-industry sponsored studies. Furthermore, it has been argued that industry bias should not be regarded as a conventional type of bias, but as a proxy for bias producing mechanisms such as selective outcome reporting.[6] However, we found a strong association to industry sponsorship for favourable outcomes even when we restricted our analyses to papers controlling for confounders. In addition, there is considerable empirical evidence for industry's use of inferior comparators, biased coding of events and selective reporting of results, which adds weight to the assumption of the existence of an industry bias.[7-9] Since these bias producing mechanisms are introduced as part of the study design and conduct, they can be regarded as intermediates in the causal pathway. Therefore, industry sponsorship should be regarded as the real bias, not a proxy.

Clinical trials

The assumption that the industry may influence the results of their research in a favourable direction is strengthened by the findings from our second study (paper 2 and 3). We found that the sponsors have major influence on how data are processed, analysed and reported in clinical trials and that the role of academic authors is minor in these trials and that they often do not try to confirm sponsor's analyses using the raw data.

While selective reporting of outcomes is known to be present in industry trials[10], deliberate attempts from companies to manipulate and bury data have been more difficult to document.[8] High-profile cases are the omission of data on myocardial infarction in Merck's VIGOR trial of rofecoxib (Vioxx) for rheumatoid arthritis[11,12], the biased referral of patients for adjudication of myocardial infarction in GlaxoSmithKline's RECORD trial of rosiglitazone (Avandia) for diabetes[13], and the downplaying of cases of suicidality in GlaxoSmithKline's trials of paroxetine (Paxil) for childhood depression.[14]

To remedy this industry bias, editors may require that academic authors have full access to trial data.[15] However, a previous systematic review[2] and an investigation of industry trial protocols[16] have yielded results similar to ours, namely lack of academic freedom concerning data ownership, data access and reporting of results. These restrictions are in striking contrast to the authors' statements in the published papers where they declared that they had full access to the data. When we published our results, the editors' of *The Lancet* echoed our concerns.[17] Hopefully, the International Committee of Medical Journal Editors and medical journals will begin clarifying what constitutes full access to data as suggested by Steinbrook and Kassirer.[18] If this happens, academic authors cannot declare full access to the data if they only had access to the clinical study report.

In line with requiring that authors should have full access to the data, journal editors also now require that trials should be registered in publicly available databases prior to patient enrolment.[19] Despite this being the case for trials conducted from 1st of July 2005, selective outcome reporting bias is still a major problem[20], particularly for industry trials[21-23], which has been demonstrated by comparing the outcomes in registers with those published.

Providing reliable estimates of the benefits and harms of drugs requires an overview of whole trial programs and access to individual patient data.[24] Journal editors, peer reviewers and medicines agencies do not have the necessary resources to scrutinise the data. This was recently highlighted for oseltamivir (Tamiflu) against influenza. In this case, independent academics undertook a Cochrane review and due to considerable media attention accomplished to get copies of selected parts of the clinical study reports.[25] The Cochrane authors found considerable discrepancies between the data in published papers and the clinical study reports. Additionally, the available data did not support the notion that oseltamivir reduces influenza complications[26], a finding that contrasted a previous industry sponsored meta-analysis[27] and claims by the European Medicines Agency (EMA), the US Centers for Disease Control and Prevention and the WHO.[28]

In light of these problems, there have been international calls to make trial protocols, all results and the raw data publicly available.[8,29] The Food and Drug Administration Amendment Act of 2007 requires that all trials of Food and Drug Administration (FDA) approved drugs should report results (with some possibility of delay) within one year. However, a study by Prayle et al. found this only to have been done for 22% of trials subject to mandatory reporting.[30] Also, though many top journals now have data sharing policies and some require authors to make raw data available, depositing full raw datasets is rarely done[31], and when authors are asked for the data, they do not deliver them in most cases.[32]

Biomedical journals

One might think that the potential risk of bias in industry trials would dissuade editors from publishing these trials. However, in our third study (paper 4), we found that publication of industry trials may increase journal impact factors, and sales of reprints from these trials may contribute substantially to journal economy. Editors may therefore be faced with a dilemma since publication of industry trials is a highly profitable business for journals.

While editors have been highly committed to ensuring that studies are free from commercial biases and that authors report their conflicts of interest, they have not exerted similar diligence about conflicts of interest of editors and journals. In fact, a 2004 survey of 30 journals of general and internal medicine found that 7 out of 26 journal editors did not consider editorial conflicts of interest to be important, 11 out of 30 did not intend to declare their conflicts of interest and only 9 out of 30 journals had a policy on editorial conflicts of interest.[33]

Such policies often focus on the personal conflicts of interest of editors in relation to the industry, but the income from industry sources via reprint sales and advertising may also create editorial conflicts of interest. As Richard Smith, former editor of *BMJ,* has put it: "publish a trial that will bring US $100,000 of profit or meet the end-of-year budget by firing an editor".[34]

The most cited example of the huge income from reprint sales stems from the *New England Journal of Medicine's* publication of the VIGOR trial in 2000.[35] It has been estimated that the journal sold almost 1 million reprints, which provided the journal with an income between US $700,000 and US $836,000.[36] A recent study by Handel and colleagues of high reprint orders at seven top journals also found disturbing numbers.[37] The median income from reprint sales for *The Lancet* from 2002 to 2009 was around US $450,000 per paper and one paper yielded 835,100 reprints for around US $2.4 million.

We have few facts about whether these conflicts of interest actually affect the decision making of editors. A systematic review found that industry funded influenza vaccine studies were more often published in prestigious journals than non-industry funded influenza vaccine studies.[38] Richard Horton, editor of *The Lancet*, has described how companies sometimes offer journals to purchase a large number of reprints and may threaten to pull a paper if the peer review is too critical.[39] Editor Harvey Marcovitch, former editor of Archives of Disease in Childhood, has described how the sponsoring company of a trial, his journal had accepted to publish, offered to purchase reprints for tens of thousands of pounds if a critical commentary was not included along with the trial.[40] In both cases, the editors resisted the companies' tactics. In another case, the editor of *Transplantation and Dialysis* rejected to publish an editorial critical of the drug erythropoietin because he had been overruled by the journal's marketing department[41], though when the case was made public, the journal reversed its decision.[42]

Cases where editors' decision are influenced by industry will likely not be revealed and more importantly, conflicts of interest are not primarily about whether decisions are de facto being influenced, but whether there is a substantial risk of influence. Therefore, disclosure of such conflicts is important for readers.

When we published our paper, on conflicts of interest at medical journals, in *PLoS Medicine* in 2010, the journal editors disclosed the journal's income from reprints and advertising and stated that they would continue to do so each year[43] and BMJ recently disclosed their income from reprints.[44] In the study by Handel et al., both the *BMJ Group* and *The Lancet Group* provided the authors with reprint data for individual papers, but the editors and owners of the US journals (*Annals of Internal Medicine*, *JAMA* and *New England Journal of Medicine)* would not share their data with the authors. The reluctance of the editors of the US journals to disclose this information is similar to our experience and it is puzzling since the US is often ahead of Europe when it comes to transparency of conflicts of interest.

Systematic reviews and meta-analyses

While it is important for the industry to publish trials with favourable results in high impact journals, the opposite is the case for unfavourable results, leading to reporting bias.[10] In our fourth study (paper 5), we found that when we included unpublished outcome data it changed the results of meta-analyses of drug trials, but that the effect varied by drug and outcome.

The unpublished data in our study was based on data reported in the FDA's medical and statistical reviews. Our strategy was similar to the one used in the studies by Erick Turner's group of reporting bias in trials of antidepressants and antipsychotics.[45,46] In those studies, reporting bias led to 32% overestimation of treatment effects for antidepressants, but only 8% for antipsychotics, which is similar to the variations among the different drugs found in our study. The studies by Turner et al. and ours were limited to a small number of drugs. A more comprehensive study was based on a large cohort of Cochrane reviews and it found that reporting bias affected treatment effects substantially in almost one fourth of the reviews.[47] However, the authors did not have access to actual unpublished data and instead they imputed data. The findings should therefore be interpreted with caution.

While FDA reviews are a valuable resource for authors of systematic reviews, they have limitations. Sometimes data in the reviews have been redacted and sometimes important data, such as standard deviations or baseline values, are missing. Access to clinical trial reports or preferably the raw data would give authors a better chance of providing more reliable effect estimates.

Access to clinical study reports is now possible due to a precedent from a case that was initiated by the Nordic Cochrane Centre. In 2007, Anders Jørgensen and Peter Gøtzsche asked EMA for copies of protocols and clinical study reports of the anti-obesity drugs rimonabant (Acomplia) and sibutramine (Meridia). EMA initially refused, but after the European Union's Ombudsman had criticised the EMA of maladministration, EMA declared in 2010 that it would widen public access to documents, including protocols and clinical study reports.[48] However, such data are still not available from the FDA and neither agency provides copies of the actual raw data in statistical files.

Medical textbooks and clinical guidelines

Medical textbooks and clinical guidelines give an overview of treatments by summarising evidence from various sources, from expert opinion to high-quality systematic reviews. In

our fifth study (paper 6), we found that sponsorship of Danish medical textbooks was fairly common and may lead to lack of academic freedom. In our sixth study (paper 7), we found that conflicts of interest were common among authors of Danish clinical guidelines, although disclosure of these conflicts was rare. We also found that it was often unclear what evidence was behind specific treatment recommendations.

Recommendations in textbooks and guidelines rely greatly on interpretation of the available evidence. It may be expert opinion alone because no relevant studies have been undertaken, it may involve choosing between various systematic reviews with conflicting results, or it may be difficult because the balance between benefit and harms is very close. Recommendations are therefore prone to influence from preconceptions about individual treatments and conflicts of interest.[49-51] Interestingly, textbooks and guidelines, which run a particularly high risk of biased interpretation, are the information sources with the lowest degree of transparency concerning conflicts of interest.

Authors of textbooks and guidelines are specialists who are experts in their field, and such experts are more likely to have conflicts of interest.[52] Furthermore, while conflicts of interest may pose a considerable problem, a related problem may be the experts' preconceptions about treatment effects. For example, guidelines on mammography screening written by radiologists are more likely to recommend routine screening compared to guidelines written by general practitioners.[53] Other studies have found that specialists tend to overestimate treatment effects compared to methodologists[54,55], which questions the predominant role of experts as authors.

Implications for practice – authors

Academic authors should ensure that their academic freedom is not restricted when participating in industry trials and writing of sponsored textbooks. For example by making certain that trial protocols and publication agreements grant them copies of the raw data, that the sponsor does not have any influence on how they interpret and report the evidence and preferably that the raw data are deposited in public available data repositories.

Implications for practice – editors

Journal editors should acknowledge the conflicts of interest related to the journal income from industry and live up to the same principles as they require from authors by disclosing the journals' income from industry sources. This could be done by posting the overall income on their website and by listing the income and number of reprints sold for each individual paper, similar to the citation data that are often presented alongside individual papers.

Editors should ensure better reporting of the sponsor's involvement in industry trials, particularly for important aspects such as coding of adverse events and statistical analysis. They should also ensure that authors in reality had access to the raw data, for example by requiring submission of protocols and trial agreements. An even better way to ensure this would be by requiring that the actual statistical analysis was done by an independent academic[56] or by requiring submission of the raw data and making such information available to peer reviewers and others.

Another approach could be not to publish in a journal but to make the results and raw data available on public websites so that all the relevant results, and not only a selection of these, can be included in an updated systematic review.[34,57] The role of journals would then be to publish discussions of the trial results in the context of a systematic review. A less radical approach would be only to publish trials in open access journals, where readers can read and print articles for free; this would remove the journals' incentive of getting income from reprint sales.[58]

Implications for practice – policymakers

Patients are at the centre of drug development, both as participants in clinical trials and as payers of drug costs. It is therefore surprising that the commercial interests of companies have been prioritised over the safety of patients for so long.[8] Society should require that all results of all clinical trials are made publicly available, not only the selected results from the trials that the industry submits for publication, so they can be scrutinised by independent researchers. Publication of all industry trial data will not eliminate all commercial bias, as, for example, biased choice of comparator drug and dose, study population or coding of events will still be possible. Therefore, society should also require that more independent trials be conducted either by increasing public funding or by requiring that approval of drugs entail at least one trial conducted without any sponsor involvement.

To ensure transparency about authors' conflicts of interest, public authorities should legally require physicians to disclose their industry ties in publicly available databases, similar to the list from the Danish Health and Medicines Authority. Preferably with a level of detail as proposed in the US Physician Payments Sunshine Act.[59] This will also help journal editors and guideline issuing organisations in ensuring that all conflicts of interest are disclosed.

Future research

The evidence for industry bias in drug studies is strong and future research should particularly focus on medical device studies, as this area has received little attention. Devices are often approved by regulatory agencies based on studies with methodological problems[60] and recent cases suggests that the device industry also has problematic research conduct.[61,62] Furthermore, while much research has been done on the prevalence of conflicts of interest among authors, few studies have been done on the relationship between authors' conflicts of interest and recommendations and they have not focused specifically on clinical guidelines.

Additionally, clinical study reports are now available to researchers through request to the EMA, and GlaxoSmithKline recently stated that they would allow independent researchers access to patient level data[63], but only if the project is approved by a committee established by the company. Similarly, the YODA project, a collaboration between Yale University and Medtronic, aims at developing a platform for providing researchers with access to raw data.[64] Based on these sources, studies quantifying reporting biases for different drug classes are possible. However, while access to clinical study reports may ensure less biased estimates of treatment effects, these reports are still written by the industry, and the coding of events and the statistical analysis have been undertaken by the

sponsor. Consequently, future research should also reanalyse trials using case report forms and raw datasets and compare these results to the results in the clinical study reports and the subsequent publications.

Conclusion

In conclusion, the drug and device industry influences the results and conclusions of research studies, which impacts on the evaluation of drug and device treatment effects. Additionally, conflicts of interest exist for journal and textbook editors and authors of textbooks and clinical guidelines. This may in turn affect which studies are published in high impact journals and how the evidence is described and interpreted. Results from industry-sponsored research should be read with caution, and journals should disclose their income from industry sources and editors' personal conflicts of interest. They should also give readers access to protocols and raw data, not only from industry trials but from all trials, as publicly funded research performed by academic researchers is also often biased.[65] Finally, conflicts of interest in medical textbooks and clinical guidelines should be disclosed and better managed, preferably by avoiding having any.

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Appendix

Additional Information for paper four

Methods

Journal Selection

In order to obtain a sample of major general medical journals publishing randomised clinical trials (RCTs), we chose journals categorised as “Medicine, General & Internal” in Journal Citation Reports on the ISI Web of Knowledge (1) with an impact factor of five or higher in 2007 and identified 10 journals. To ensure similarities for comparison across journals, we excluded Annual Review of Medicine, as it is only published once a year and does not publish RCTs. PLoS Medicine, Canadian Medical Association Journal and Annals of Medicine were also excluded, as only 4/166, 5/94 and 0/54, respectively, of their papers in 2007 were indexed in PubMed as the publication type Randomized Controlled Trial, which we regarded as too low a proportion of RCTs for our study. Our final inclusion consisted of six journals: Annals of Internal Medicine (Annals), Archives of Internal Medicine (Archives), BMJ, JAMA, The Lancet (Lancet) and The New England Journal of Medicine (NEJM).

Pilot study

In a pilot study done in December 2008, one author (AL) extracted data on support for all randomised trials published in NEJM in 2000 and 2001. Using Web of Science on the ISI Web of Knowledge (2) (see method below) the mean number of citations in 2002 was 82.1 for RCTs with industry support, 50.9 for RCTs with mixed support, 36.3 for RCTs with non-industry support and 26.9 for RCTs with no statement about support ($p < 0.0001$ for difference; Jonckheere-Terpstra test for trend). The impact factor for 2002 was lowered by 11% when industry-supported RCTs were excluded from the calculation, and by 17% if RCTs with mixed support were also excluded (see method below).

Citation data

Based on the citation data from Web of Science we tried to recalculate the impact factor for 2002 for the New England Journal of Medicine in. This led to an impact factor that was 9% lower than the ‘official’ impact factor reported in the Journal Citation Report for 2002.

Further exploration and correspondence with Thomson Reuters (the publisher of Web of Science) led us to the conclusion that it was impossible to recalculate the exact impact factor for a given journal using data available in Web of Science. First, the data in the database are not static, but new data are added and old data are corrected. Therefore, the data used to calculate the impact factor vary over time. Second, some citations are erroneous (e.g. wrong page number or issue) and are therefore not linked to the correct study. These citations will be missed when searching Web of Science, as it only identifies the properly linked studies, but they are used for calculating the impact factor in the Journal Citation Reports. Third, the only option available for getting data for total citations for a given journal in a given year (numerator of impact factor) is the “create citation report” function in Web of Science. Unfortunately, this method uses the ‘date-of-entry’ of the citation into the database and not the ‘date of publication’. We requested data using ‘date of publication’ from Thomson Reuters, but were told that it would cost us 4,500 US $ to

obtain the data. Due to these costs and because editors have complained about the quality of these data (3,4) we did not pursue this matter further.

Due to the discrepancies between the data in Journal Citation Reports and Web of Science encountered in our pilot, we also extracted the total number of citations for the six different journals for each year from 1998 to 2007. Data from Web of Science gave between 80% and 97% of the citations in Journal Citation Reports depending on the specific journal and year.

Sensitivity analysis

To test the robustness of our support data we did an a priori stated sensitivity analysis where we re-categorised RCTs with no statement about support as non-industry supported.

To test the robustness of our citation data, we did three a priori stated sensitivity analyses. First, we re-categorised RCTs with no stated support as non-industry support. Second, we re-categorised RCTs where the only support was free study drugs or devices as mixed instead of industry support. Third, we calculated the mean number of citations based on the function “create citation report” in Web of Science. This strategy uses the ‘date-of-entry’ of the citation rather than the ‘date of publication’.

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Description of included randomised trials.

Journal name	Year published	Identified papers	Excluded papers	Included trials
Annals	1996-7	73	2 letters	71
	2005-6	59	1 paper*	58
Archives	1996-7	68	1 letter	67
	2005-6	81	1 editorial	80
BMJ	1996-7	103	9 letters 2 editorials 1 commetary	91
	2005-6	122	6 papers*	116
JAMA	1996-7	76	-	76
	2005-6	113	-	113
Lancet	1996-7	234	44 letters 4 commentaries	186
	2005-6	129	-	129
NEJM	1996-7	163	3 letters	160
	2005-6	208	2 letters	206

* Papers were excluded because they were only e-published in 2006, but published in the journal in 2007 and indexed in Web of science as a 2007 publication.

Sensitivity analysis for type of support of randomised controlled trials published in major general medical journals when no statement about support was categorised as non-industry.

	Annals		Archives		BMJ		JAMA		Lancet		NEJM	
	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6
Change in support (p value)*	-	0.164*	-	0.063*	-	0.191*	-	0.551*	-	0.544*	-	0.130*

* Comparison of number of RCTs with industry, mixed and non-industry support in 1996-7 vs. 2005-6 using Mann-Whitney U test (two sided).

Sensitivity analysis for citations for randomised controlled trials published in major general medical journals when no statement about support was categorised as non-industry supported, when RCTs with free drug provision as only type of support were categorised as mixed and when citation data was based on "create citation report".

	Annals		Archives		BMJ		JAMA		Lancet		NEJM	
	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6	1996-7	2005-6
Difference in citations - "not stated" (p-value)#	0.096	<< 0.001	0.316	< 0.001	0.892	0.030	0.023	0.013	<<0.001	0.016	0.001	<0.001
Difference in citations - "free drug" (p-value)*	0.115	<< 0.001	0.205	< 0.001	0.818	0.030	0.070	0.011	0.003	0.016	0.002	<0.001
Difference in citations - "create citation report" (p-value)$	0.212	<< 0.001	0.232	< 0.001	0.912	0.082	0.118	0.002	0.004	0.007	0.003	<0.001

Difference in citations depending on type of support using Jonckheere-Terpstra test for trend (two sided).
* Difference in citations depending on type of support using Jonckheere-Terpstra test for trend (two sided).
$ Difference in citations depending on type of support using Jonckheere-Terpstra test for trend (two sided).