Is there evidence for biased reporting of published adverse effects data in pharmaceutical industry-funded studies?

Su Golder & Yoon K. Loke¹

CRD, University of York, York and ¹School of Medicine, University of East Anglia, Norwich, UK

Correspondence

Ms Su Golder, University of York, York
YO31 1AY, UK.

Tel: +44 1904 321055

Fax: +44 1904 321041

E-mail: spg3@york.ac.uk

Keywords

adverse effects, bias, industry funding,
systematic review

Received

23 May 2008

Accepted

22 Jul 2008

Published OnlineEarly

27 August 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Industry-funded studies tend to emphasize favourable beneficial effects of the sponsor's product, but we do not know if reports of adverse effects are downplayed.
- Pharmaceutical companies are required to collate and accurately report adverse effects data in order to fulfil regulatory requirements.

WHAT THIS STUDY ADDS

- The bias found in the studies looking at the association between industry funding and reporting of beneficial effects may not be as prominent when considering adverse effects data.
- Industry-funded studies do not appear to differ from non-industry-funded studies in reporting the raw adverse effects data, but the interpretation and conclusions may be slanted to favour the sponsor's product.
- Readers of industry-funded studies should critically examine the raw safety data themselves rather than be swayed by the authors' interpretation.

AIM

To investigate whether adverse effects data for the sponsor's product are presented more favourably in pharmaceutical industry-funded studies than in non-industry-funded studies.

METHODS

We conducted a systematic review of methodological evaluations that had assessed the relationship between industry funding and the reported risk of adverse effects. Searches were undertaken in 10 databases and supplemented with other sources of information such as handsearching, citation searching, checking conference proceedings and discussion with experts. Two reviewers independently screened the records and carried out data extraction for potentially relevant papers. We included studies that compared the results and interpretation of the adverse effects data according to funding source (e.g. adverse effects data in pharmaceutical industry research vs. data from nonprofit organizations, or from one manufacturer vs. another). Methodological evaluations were excluded if categories of funding source were not explicitly specified by the researchers, and if we were uncertain that industry-funded studies were present in the evaluation.

RESULTS

The search strategy yielded 4069 hits, of which six methodological evaluations met our inclusion criteria. One survey of 370 trials covering a wide range of topics found that trials with industry sponsors had more complete reporting of adverse effects compared with non-industry-funded trials, whereas another survey of 504 inhaled corticosteroid studies showed no apparent difference after confounding factors were adjusted for. In contrast, we found evidence from post hoc subgroup analyses involving two products where the likelihood of harm was of a lower magnitude in manufacturer-funded studies compared with nonmanufacturer-funded studies. There is also evidence from four methodological evaluations that authors with industry funding were more likely than authors without pharmaceutical funding to interpret and conclude that a drug was safe, even among studies that did find a statistically significant increase in adverse effects for the sponsored product.

CONCLUSIONS

Our review indicates that industry funding may not be a major threat to bias in the reporting of the raw adverse effects data. However, we are concerned about potential bias in the interpretation and conclusions of industry-funded authors and studies.

Introduction

Methodological evaluations have identified a potential association between source of funding and the publication of more favourable results for the sponsor's product [1, 2]. Existing evaluations have focused mainly on effectiveness outcomes, with the aim of determining the relationship between funding and more positive reporting of beneficial effects. However, favourable outcomes can consist of greater benefit, a reduction in harm, or a combination of both. It is not clear whether adverse effects profiles are affected by bias in industry-funded research, whereby potential harm is downplayed and positive aspects of safety are emphasized. Manufacturers are governed to some degree by the safety requirements of the regulatory authorities, and may therefore strive to provide unbiased data on adverse effects.

We aimed to review systematically any methodological evaluations that assessed the reporting of adverse effects and any potential association with source of funding. Information on the extent (if any) of this type of bias will help clinical pharmacologists and pharmacovigilance teams who are involved in the critical appraisal of drug safety data from different sources.

Methods

Our systematic review was conducted by two independent reviewers who retrieved potentially relevant articles and extracted data. The two reviewers then met, resolved discrepancies and reached a consensus on the final results.

Search strategy

Searches were undertaken in 10 electronic databases to retrieve methodology papers related to all aspects of the incorporation of adverse effects into systematic reviews. Due to the limitations of searching for methodological papers, it was envisaged that relevant papers may be missed by searching databases alone. We therefore undertook citation searches of all included papers using Web of Science, handsearching of selected key journals, conference proceedings and web sources, and contact with other researchers in the field (Appendix 1).

Selection criteria

A methodological evaluation was considered eligible for inclusion in this review if it looked at the results or interpretation of the reported adverse effects data according to funding source (e.g. adverse effects data in pharmaceutical industry research vs. data from nonprofit organization, or from one manufacturer vs. another). We accepted methodological evaluations of any design, including primary studies and systematic reviews. Methodological evaluations were excluded if categories of funding source were

not explicitly specified by the researchers and if we were uncertain that industry-funded studies were present in the evaluation.

Data extraction

Information was collected on the selection criteria, interventions and adverse effects, the number, design and funding sources of studies included in the methodological evaluation, and the outcomes used in assessing differences between studies.

Data analysis

We aimed to provide a narrative assessment of the available methodological evaluations, and did not plan on conducting a meta-analysis as the outcome measures were unlikely to be homogeneous. Where available, we recorded both the crude summary statistics and the adjusted estimates based on correction for confounding factors.

Assessment of methodological quality

The following criteria were used to assess the quality of the existing methodological evaluations;

1. Role of confounding factors: Did the researchers select comparison groups (i.e. data from different funding sources) that were equally matched? For example, did the industry-funded studies share similar aims, designs and sample sizes as the non-industry-funded ones? If not, were there adjustments for potentially confounding factors that could affect the association between funding and the nature of the adverse effects data? We looked to see if any of the following confounding factors had been considered: study design, methodological quality, type of intervention and control intervention, sample size, disease area, type of adverse effects.
2. Missing data or misclassification: How often were the researchers able to establish reliably the source of funding for the reported data?
3. Blinding: Were the researchers aware of the funding source when they were judging the nature of the adverse effects data?
4. Validity and representativeness: Did the researchers select an adequate sample of studies (in terms of size, diversity of topics and range of adverse effects) that were reasonably reflective of current literature?

Results

Included studies

The searches retrieved 4609 records, of which six methodological evaluations met the inclusion criteria (Table 1). The flow chart of study selection is given in Figure 1. All six reports were concerned with drug interventions, but five of six evaluations were limited to the adverse effects of a single agent or single class of drugs. We found only one

Table 1

Characteristics of included studies and outcome measures

Reference	Design	Main outcome measures	Quality assessment
Als-Nielsen et al. (2003) [7, 8]	370 trials from 25 randomly selected Cochrane Reviews across broad range of medical topics	Compared number of studies reporting adverse effects in experimental and control arms according to funding. Complete absence of any AE data was more common in nonprofit (35/67, 52.3%) vs. profit (18/146, 12.3%). Higher frequency of adverse effects in experimental group was noted in 33/146 (23%) studies funded by for-profit organizations compared with 3/67 (4%) of nonprofit-funded studies. Occurrence of AEs was not associated significantly with conclusions (logistic regression – no statistics given)	Confounding: Adverse effects data taken from Cochrane reviews; rigorous inclusion criteria used in systematic reviews suggest that trials would be reasonably homogeneous. Logistic regression was used to assess confounding factors – results not given though Misclassification: Funding source unclear for 106 studies, results given separately (data excluded from our review) Blinding: Mainly unblinded, but authors carried out blinded assessment in 60 trials, with good intraclass coefficient between blinded and unblinded assessment External validity: Good, covered wide range of topics in 2001
Juni et al. (2004) [9]	11 observational studies in meta-analysis of MI with Naproxen	Substantial heterogeneity found in meta-analysis of the cardiovascular adverse events with naproxen. Meta-regression showed that heterogeneity was largely due to three Merck-funded studies that showed substantial cardioprotective effects of naproxen. Any rise in cardiovascular risk with rofecoxib in trials against naproxen could then be attributed to the protective effect of naproxen rather than harm from rofecoxib (Merck's product)	Confounding: Authors used meta-regression to explore effects of variables on estimates of cardiovascular risk. However, only two of the 11 case-control studies were solely Merck funded, and it is hard to draw robust conclusions based on regression analysis of only two studies Misclassification: One study had mixed funding (Merck, Pharmacia, NIH), and was lumped into the industry-funded arm Blinding: Not reported External validity: Poor – considers only one drug within systematic review
Kemmeren et al. (2001) [6]	10 observational studies in meta-analysis of venous thrombosis with 2nd and 3rd generation oral contraceptives	Pooled odds ratio of venous thrombosis with 3rd generation oral contraceptives was 1.3 (95% CI 1.0, 1.7) in studies ($n = 4$) funded by pharmaceutical companies, whereas odds ratio in other studies ($n = 5$) was 2.3 (95% CI 1.7, 3.2) when compared with 2nd generation oral contraceptives	Confounding: Authors did not examine whether confounders such as study design, patient population may have contributed to lower risk estimates from industry-funded studies Misclassification: Not reported Blinding: Not reported External validity: Poor, only a few studies of a single class
Nieto et al. (2007) [10]	504 studies (trials and observational studies) of inhaled corticosteroids identified from MEDLINE	Statistically significant differences in adverse effects more commonly reported by nonpharmaceutical-funded studies (73.0% of 74) compared with those funded solely by drug manufacturer (26.5% of 226). Crude and multivariate association showed that pharmaceutical funded studies were (i) less likely to report significant differences in adverse effects – crude prevalence ratios 0.53 (95% CI 0.44, 0.64) but this was nonsignificant after adjustment for confounding (ii) more likely to conclude drug is safe despite statistically significant increase in adverse effects, prevalence ratio 3.68 (95% CI 2.14, 6.33)	Confounding: Major problem – industry studies were more likely to be efficacy trials, whereas non-industry-funded studies were aimed at adverse effects. Adjustment for confounding factors indicated that the observed difference in adverse effects data may be mediated by factors other than funding source Misclassification: Source of funding for 87 (17.3%) studies was unknown and these studies were classed as nonpharmaceutical funded Blinding: Not reported External validity: Poor, limited to inhaled corticosteroids
Rochon et al. (1994) [11]	56 randomized controlled trials of NSAIDs from MEDLINE, of which 54 had identifiable manufacturer support	Description of toxicity of manufacturer drug. 22/54 trials (40.7%) reported that one drug was less toxic than the competitor drug (10 provided evidence of statistical significance). In 19 of 22 trials (86.4%) report favoured manufacturer's drug rather than competitor's drug. In 3/22 trials (13.6%), manufacturer's drug was reported as more toxic than the comparison (placebo). 32/54 trials (59.2%) reported comparable toxicities.	Confounding: Not reported – for example, manufacturer may have deliberately chosen to use a comparator drug with poor safety profile, and the trial findings reflect a true difference Misclassification: Original aim of study was to evaluate non-industry-funded research, but authors changed their aims post hoc as they could not identify any non-industry studies Blinding: Not reported External validity: Poor, limited to NSAIDs only
Stelfox et al. (1998) [12]	69 authors of articles on calcium-channel blockers (original research, reviews and letters) were surveyed on their financial ties.	Blinded researchers classified tone of the articles as 'supportive, neutral or critical'. There was a financial relationship with manufacturer of calcium-channel antagonists for 23/24 (96%) authors of supportive articles compared with 11/30 (37%) of authors of critical articles. There was a financial relationship with manufacturer of competing drug for 21/24 (88%) authors of supportive articles compared with 11/30 (37%) of authors of critical articles. For the supportive articles, 24/24 (100%) authors had financial relationship with any manufacturer, whereas for the critical articles, 13/30 (43%) authors had financial relationship with any manufacturer.	Confounding: Temporal sequence of sponsorship is unclear; authors who are known to write positive articles may then be offered sponsorship, whereas established critics are seldom offered funding. Also, supportive authors were just as likely to receive funding from competing manufacturers Misclassification: There were 20/89 authors who did not respond to survey and had to be excluded. No way of establishing accuracy of declared sponsorship status Blinding: Yes, but there may have been information in the articles that could have led the researchers to become aware of potential pharmaceutical funding for a particular author External validity: Poor, limited to calcium-channel blockers only

Figure 1

Flowchart of study selection

report that assessed funding source and reporting of safety data across a wide range of diseases and drugs. The number of studies included in the methodological evaluations ranged between 10 and 504, with only two reports including more than 100 studies.

Half of the methodological evaluations focused on adverse effects data within randomized controlled trials, two included observational data, and one had a mixture of reports of original research, reviews and letters. Most methodological evaluations compared manufacturer funding with nonmanufacturer funding; however, one report looked for differences in adverse effects data in research funded by competing manufacturers.

Excluded studies

There were two methodological evaluations that potentially met the inclusion criteria but were subsequently excluded from this review [3–5]. One evaluation [3] contained duplicate data from an included article [6], whereas another evaluation (in two publications) was excluded after contacting the author, as the categories of funding source were unclear, but were unlikely to include industry-funded studies [4, 5].

Summary of methodological quality (Table 1)

Four of the methodological evaluations used some form of adjustment for potentially confounding factors, although

the comprehensiveness of the factors adjusted for varied [6–10]. A major constraint in assessing an association between source of funding and the reporting of adverse effects is the lack of information on funding source. Only two methodological evaluations described or used appropriate methodology to assess the number of studies not reporting any funding source; these evaluations both included trial data only and reported that 28.6% and 17.3% of studies did not disclose any funding source [7, 8, 10]. Blinding was reported by only two evaluations, one of which tested the effect of blinding on a subsample of included studies and found that blinding did not impact on the results [7, 8]. Overall, our assessment of quality and validity showed that Als-Nielsen's evaluation was probably the most robust [7, 8].

Definitions of manufacturer-associated funding varied, as did the methods and outcome measures used to assess the association between funding and adverse effects reporting, making it difficult to pool the results of the studies in a meta-analysis.

Impact of funding source and selective reporting of specific types of adverse effects

Als-Nielsen *et al.* looked at a diverse range of randomized trials funded by for-profit organizations and noted that these trials had more complete reporting of adverse events (128/146, 88%), particularly with a higher frequency of adverse events being found in the experimental arm [7, 8]. In contrast, trials funded by nonprofit organizations often failed to mention adverse effects (35/60, 52.3%) and were less likely to describe higher frequencies of adverse events for the experimental arm [7, 8].

Confounding factors

Nieto *et al.*'s evaluation of inhaled corticosteroids reported that statistically significant results for adverse effects were found less often in pharmaceutical industry-funded studies [crude prevalence ratio 0.53, 95% confidence interval (CI) 0.44, 0.64], whereas the non-industry-funded studies were more likely to report significant harm [10]. However, in many ways Nieto *et al.* may have been comparing apples with oranges. Studies funded by industry were more likely to be multicentre, parallel group, randomized controlled trials, with the stated primary objective of evaluating efficacy over a relatively short follow-up period. Conversely, non-industry-funded studies were more commonly observational in nature, with the primary objectives of evaluating adverse effects such as long-term problems with growth or bone metabolism. After adjustment for these confounders, Nieto *et al.* found a nonsignificant prevalence ratio 0.94 (95% CI 0.77, 1.15), thus indicating that the difference associated with funding may be mediated by other variables in the analysis [10].

Impact of funding source and magnitude of risk of harm

We looked for evidence that the risk of harm from the sponsor's product may have been downplayed in industry-funded studies. A subgroup evaluation from Kemmeren *et al.*'s meta-analysis showed that the pooled data from industry-funded studies yielded a weaker association between third-generation oral contraceptives and venous thrombosis [6]. Similarly, Juni *et al.*'s meta-analysis showed that studies funded by Merck were associated with greater cardioprotective effects of naproxen, thus implying a lesser risk of harm from Merck's product (rofecoxib) [9]. However, the weakness of this evidence is that they were post hoc subgroup analyses, involving only a small number of studies and subject to confounding.

Funding source and interpretation of adverse effects data

The included studies revealed some interesting potential associations between funding source and the subjective interpretation or conclusions regarding the adverse effects data. For example, Nieto *et al.* found that authors of pharmaceutical studies were more likely than authors of non-pharmaceutical studies to conclude that a drug was safe even among studies that did find a statistically significant increase in adverse effects [10]. Similarly, Rochon *et al.* also found that a manufacturer-associated drug was often judged to be less toxic, even though this interpretation was not always supported by test of statistical significance [11]. Finally, Als-Nielsen *et al.* noted an association between favourable recommendation for a product and the manufacturer's sponsorship, irrespective of the actual magnitude of treatment benefit or safety results seen in the trial [7, 8].

The study by Stelfox *et al.* focused on the association between financial relationship with manufacturers and the conclusions of studies, and identified that authors of articles supporting the safety of calcium-channel antagonists were more likely to have a financial relationship [12]. However, this study did not check the appropriateness of the conclusions of the authors against the actual adverse effects data of the studies. Moreover, authors of supportive articles were just as likely to have received funding from manufacturers of drugs that compete with calcium-channel blockers. This suggests that authors who are less critical of safety issues may be more likely to be receive funding from any manufacturer.

We should also bear in mind the considerable potential for error and bias when trying to judge whether the data interpretation and conclusions of a study are excessively favourable or not. Stelfox *et al.* [12] and Als-Nielsen *et al.* [7, 8] attempted to have some degree of blinding of the reviewers, but none of the remaining four studies used blinding.

Discussion

Our systematic review has identified somewhat mixed evidence surrounding the postulated link between industry funding and more favourable reporting of adverse effects data. Before drawing any conclusions, we need to look into the methodological problems that surround such research. First, we should bear in mind that all the existing methodological evaluations are 'observational' in nature. Whereas some of them had predefined objectives [7, 8, 12], others were post hoc or subgroup analyses. We consider confounding to be a major problem in most of the methodological evaluations, where the baseline features (e.g. study design, patient population, primary objectives) of the industry-funded studies may have differed from those of the non-industry-funded studies. This is particularly apparent in Nieto *et al.*'s evaluation, where the observed differences became nonsignificant after adjustment for confounding factors [10].

We are also concerned about the possibility of reporting or publication bias with respect to methodological evaluations [13]. Journal editors may look more favourably upon articles that show biased reporting of adverse effects in industry-funded studies. Researchers who did not find any industry-related bias may have decided to omit such results from their manuscripts or chosen not to submit their articles for publication. Equally, researchers who found evidence of industry-funded bias may have avoided publicizing the results so as not to jeopardize any industry ties that they might have.

The generalizability of the data is also contentious. It would be unfair for us to draw broad conclusions about bias in all industry-funded studies when the data are limited to a few studies or to only a specific class of drugs. Moreover, reporting recommendations have changed over time, with tightening of regulatory requirements, and the publication of the CONSORT statement on harms [14]. Existing methodological evaluations have not taken into account temporal changes, or the availability of complete adverse effects data from unpublished company trial reports such as that of the excellent GlaxoSmithKline Clinical Trials Registry (<http://ctr.gsk.co.uk/welcome.asp>). Unpublished trial data from many manufacturers are now unified under a single website (<http://www.clinicalstudyresults.org>), although it remains unclear whether the format of the data is of sufficient simplicity to allow easy interpretation by lay persons.

Failure to classify funding source accurately is the most prominent weakness in the methodological evaluations. In Nieto *et al.*'s work, 87 (17.3%) studies were lumped into the non-industry-funded group, despite there being no information on funding source [10]. Misclassification of such a large number of studies could have major influences on the direction and magnitude of any link between funding and adverse effects data. The largest methodological problem, however, lies with the difficulty in verifying

authorship and the reliability of financial declarations in published papers. Two recent papers have highlighted problems with ghost authorship and inaccurate financial disclosures (e.g. not disclosing a financial interest in one article, but found to have declared industry funding in another publication) [15, 16]. If studies categorized under non-industry funding have been misclassified (and were actually industry funded), this would dilute the strength of any argument that non-industry-funded studies provide less biased reports of adverse effects.

There is also a considerable amount of subjectivity involved in trying to determine whether the interpretation and conclusions of a study were biased towards the sponsor's product. Reviewers who are critical of the pharmaceutical industry may have taken a harsher view in finding fault with industry-funded studies, whereas those supportive of the industry may have been less likely to judge that bias was present. Unfortunately, blinding and inter-rater reliability are key parameters that were seldom specified by the methodological researchers.

As this is a systematic review, the main limitations stem from the weaknesses in the original data. We have attempted to address publication bias by using a comprehensive search strategy that included handsearching, checking conference proceedings and discussion with experts in the field for any information. Where possible, we have focused our review on results related to clearly defined funding sources, and looked for data where the researchers have made adjustments for confounding factors. We appreciate, however, that future methodological evaluations could be substantially improved if a wider range of drugs were studied, with more rigorous ascertainment of funding source, and closer matching of trial designs and quality in the comparator groups.

Bearing in mind these limitations, what conclusions might be drawn? First, there is no definite evidence that funding source leads to selective reporting of adverse effects outcomes that favoured the sponsor's product. Indeed, Als-Nielsen *et al.*, whose study probably has the strongest quality criterion, found that the opposite was true, with industry-funded studies providing more complete reporting and higher rate of adverse effects for the experimental arm [7, 8]. Unlike nonprofit organization-funded studies, pharmaceutical companies hoping to submit a licensing application may be more focused on providing an accurate depiction of adverse events as the data might be subjected to rigorous regulatory scrutiny. Indeed, the information submitted to the regulatory authorities may be less positive than that seen in the published articles [17].

We also do not have definite evidence that industry-funded studies present a lower magnitude of risk of harm from the sponsor's product. However, pharmaceutical trials have been accused elsewhere in the literature of using design modifications to ascertain lower adverse effects. Such methods may potentially include using lower doses

of the intervention and higher doses for the controls, monitoring for adverse effects using open-ended or nonspecific questions, and the choice of inappropriate comparators [10, 18–21].

Our systematic review does indicate, though, that funding source may impact on the nature of the authors' interpretation and conclusions regarding the safety profile. However, the interpretation of adverse effects data relies not only on statistical significance, but also on subjective judgements of clinical relevance, preventability and absolute risk. It would be prudent for readers to check the adverse effects data themselves using the approach recommended in the Cochrane Handbook [22], rather than rely on the authors' subjective interpretations.

Conclusion

Our systematic review indicates that industry funding may not be a major threat to bias in the reporting of the raw adverse effects data. However, we are concerned that industry funding may sway the interpretation and conclusions of the study.

Competing interests

S.G. is funded via a Health Sciences Research Fellowship from the Medical Research Council (MRC). Y.K.L. is European Editor of the *British Journal of Clinical Pharmacology*, but has no involvement in the review process for this manuscript.

We thank Jane Burch of CRD, York for her kind assistance in screening the titles and abstracts in the Endnote library.

REFERENCES

- 1 Bero L, Oostvogel F, Bacchetti P, Lee K. Factors associated with findings of published trials of drug–drug comparisons: why some statins appear more efficacious than others. *PLoS Med* 2007; 4: e184.
- 2 Sismondo S. Pharmaceutical company funding and its consequences: a qualitative systematic review. *Contemp Clin Trials* 2008; 29: 109–13.
- 3 Vandenbroucke JP, Helmerhorst FM, Rosendaal FR. Competing interests and controversy about third generation oral contraceptives. *BMJ* 2000; 320: 381.
- 4 Chou R, Fu R, Carson S, Saha S, Helfand M. Empirical Evaluation of the Association between Methodological Shortcomings and Estimates of Adverse Events. Rockville, MD: Agency for Healthcare Research and Quality (AHRQ), 2006. Report No.: Technical Review 13.
- 5 Chou R, Fu R, Carson S, Saha S, Helfand M. Methodological shortcomings predicted lower harm estimates in one of two sets of studies of clinical interventions. *J Clin Epidemiol* 2007; 60: 18–28.

- 6 Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001; 323: 119–20.
- 7 Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and authors' conclusions in randomized drug trials: a reflection of treatment benefit or adverse events? [abstract] In: XI Cochrane Colloquium: Evidence, Health Care and Culture. 2003 October 26–31; Barcelona, Spain; 2003; 2003; 36.
- 8 Als-Nielsen B, Chen W, Gluud C, Kjaergard LL. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA* 2003; 290: 921–8.
- 9 Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. *Lancet* 2004; 364: 2021–9.
- 10 Nieto A, Mazon A, Pamies R, Linana JJ, Amparo Lanuza A, Jiménez FO, Medina-Hernandez A, Nieto FJ. Adverse effects of inhaled corticosteroids in funded and nonfunded studies. *Arch Intern Med* 2007; 167: 2047–53.
- 11 Rochon PA, Gurwitz JH, Simms RW, Fortin PR, Felson DT, Minaker KL, Chalmers TC. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med* 1994; 154: 157–63.
- 12 Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med* 1998; 338: 101–6.
- 13 Dubben HH, Beck-Bornholdt HP. Systematic review of publication bias in studies on publication bias. *BMJ* 2005; 331: 433–4.
- 14 Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D, CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141: 781–8.
- 15 Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA* 2008; 299: 1800–12.
- 16 Weinfurt K, Seils D, Tzeng J, Lin L, Schulman K, Califf R. Consistency of financial interest disclosures in the biomedical literature: the case of coronary stents. *PLoS ONE* 2008; 3: e2128. doi:10.1371/journal.pone.0002128.
- 17 Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358: 252–60.
- 18 Djulbegovic B, Lacevic M, Cantor A, Fields KK, Bennett CL, Adams JR, Kuderer NM, Lyman GH. The uncertainty principle and industry sponsored research. *Lancet* 2000; 356: 635–8.
- 19 Safer DJ. Design and reporting modifications in industry-sponsored comparative psychopharmacology trials [Review]. *J Nerv Ment Dis* 2002; 190: 583–92.
- 20 Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003; 326: 1167–70.
- 21 Chan AW, Hrobjartsson A, Haahr MT, Gotzsche PC, Altman DG. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004; 291: 2457–65.
- 22 Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions 5.0.0* [updated February 2008]. The Cochrane Collaboration, 2008.

Supporting information

The following supporting information is available for this article online:

Appendix 1

Sources searched

This material is available as part of the online article

Please note: Blackwell Publishing is not responsible for the content or functionality of any supplementary materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.