

Conflicts of interest statements on biomedical papers

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Abstract This paper examines the varying prevalence of conflict of interest (COI), and “no conflict”, statements on biomedical research papers, which are increasingly being required by journal editors. They are important as they may detract from the perceived objectivity of the results if the authors are in the pay of commercial companies. However, the frequency of these statements in the web of science (WoS) is only a few percent of the total number of biomedical papers. A survey of journal editors revealed that many COI statements are excluded from the WoS because they are printed separately from the acknowledgement section of the paper. One consequence of the appearance of COI statements on papers is that the WoS mistakenly includes companies who have given money to some of the researchers for unrelated work among the sponsors listed among the funding organizations, and this will distort the analysis of the funding of the research being reported in some of the papers and appears nearly to double companies’ apparent tally of papers.

Keywords Conflict of interest · Funding · No conflict · Pharmaceutical companies · Web of science

Introduction

There is now quite an extensive literature on the problems that can arise when authors of research papers have a financial involvement with companies who may have a commercial interest in the results described. Since 1990, the numbers of papers in the web of science

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(WoS) with *conflict*-of-interest* (COI) in their title and that concern biomedical activity has increased dramatically, see Fig. 1. Much of this literature deplores the situation that has arisen, where links between pharmaceutical (and sometimes medical device) companies and supposedly objective researchers have become pervasive so that there is bias in the literature on clinical trials and the public trust in science is eroded (Kirkpatrick et al. 2012; Steinbrook and Lo 2012; Bariani et al. 2013; Gasparyan et al. 2013; Vasconcelos et al. 2013). [There is also a large literature on other aspects of conflict of interest, notably in the financial system, where advice on investments can be tainted by hidden assets]. However, conflicts of interest not only affect researchers and their papers, but journal editors (Smith et al. 2012; Qureshi et al. 2012; Bosch et al. 2013) and publishers who may depend on the lucrative sale of reprints, especially reports of clinical trials sponsored by companies (Lundh et al. 2010).

Many of the papers have examined the COI requirements stated by journals in their instructions to authors (Rowan-Legg et al. 2009; Alfonso et al. 2012; Khurana et al. 2012). The conclusion seems to be that most journals require such statements, both of the sponsorship of the research being described (funding sources) and any financial or non-financial ties between the authors and industry. However, examination of actual practice in particular journals or groups of them suggests that this requirement for COI statements is not being adhered to (*v.i.*). There are corresponding problems in the writing of clinical guidelines, and even Cochrane Reviews, where COIs could colour their recommendations for clinical diagnosis and treatment (Kesselheim et al. 2012; Khalil et al. 2012; Langer et al. 2012; Norris et al. 2012). Some papers have examined individual journals in order to determine the prevalence of COI statements on their papers, and to compare this with the journals' stated policy (Blum et al. 2009; Forbes 2011; Kesselheim et al. 2012; Das et al. 2013).

In the USA, the perception of possible bias in the advice and treatment provided by medical doctors and hospitals as a consequence of the payments they receive from pharmaceutical and device manufacturers led to a requirement in the Affordable Care Act to notify such payments to the Centers for Medicare and Medicaid Services, who have started to publish details. The first release of the Open Payments data took place in September 2014 (see <http://www.cms.gov/OpenPayments/Downloads/OpenPaymentsDataDictionary.pdf>),

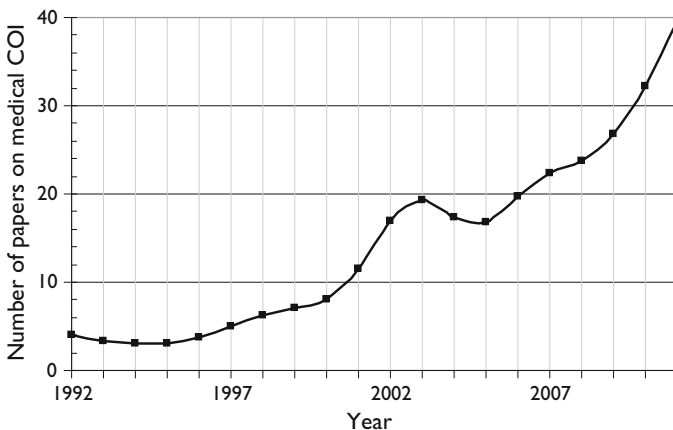


Fig. 1 Rise of the numbers of papers in the WoS on medical conflict of interest, 5-year running means

and it related to the 5 months from August to December 2013. Although some of the individual items have been disputed, and there are some admitted inaccuracies, it appears that payments for “speaking and consulting fees” amounted to \$380 million, equivalent to over \$900 million p.a., and those for “travel, food, lodging” provided an additional \$167 million, equivalent to \$400 million p.a. The overall total was nearly \$3.5 billion, or \$8.4 billion p.a., of which the largest component was for research (figures from the US Department of Health and Human Services, quoted by Thomas et al. 2014). So the sums involved are very substantial, and these figures only relate to the USA.

Declarations of potential conflicts of interest on biomedical papers can take several forms. The most common are when authors have undertaken consultancy work, or have spoken on behalf of a company and/or received honoraria or fees for some other activity such as serving on an advisory board. Some authors declare that they hold stock (or shares) in a company, hold patents or receive royalties. However negative statements of “no conflict” (NC) may occur, and sometimes these appear alongside COI statements for some of the authors of a paper.

Since late 2008, the WoS has routinely included details of financial acknowledgements (and personal ones) in two searchable fields, funding organisation (FO) and funding text (FT), where they occur on a paper. We have used information on funding organisations on several occasions to identify the sources of support for a research portfolio (Lewison and Markusova 2010; Lewison and Roe 2012); this has become a relatively routine aspect of research evaluation and may show a research group’s success by how often it obtains external support for its work and from which sources (Lewison 2003; Rigby 2013). Because of the aim of governments and charities to make the research they support lead to practical benefit, the involvement of commercial companies in the further development of this research is often seen as desirable. So there is an additional reason to determine how much industrial support has been provided to public-domain research. The data in the FO field (which when downloaded to file appears in a column headed FU) can be used for this purpose.

However, we happened to notice that the list of commercial funders sometimes included companies that had been mentioned in a COI statement that was reproduced in the FT field (which, when downloaded, is headed FX). It appeared that some of the companies credited in this way were not in fact supporters of the research being reported, but were merely listed as having had financial (or other) links with one or more of the paper authors. This could clearly distort the analysis of commercial funding for research, and also could artificially boost the number of research papers that a company could appear to have supported. We therefore began to investigate how often such COI statements appeared on published biomedical papers, primarily to correct the data in the FU column for our analysis of funding sources. It rapidly became apparent, however, that the frequency of COI statements (complemented by NC ones) was of interest in its own right and could shed light on current practice.

We therefore embarked on a large-scale study of the presence of COI (and NC) statements on journals and papers covered by the WoS (science citation index extended) during the 5 years, 2009–2013, when inclusion of acknowledgements would have been effectively complete. Since we wished to investigate the commercial influences on biomedical research and the practice of medicine, we limited the study to biomedical papers and examined the influence of various parameters—the nationality of the authors, the characteristics of the journals and the year of publication—on the prevalence of COI and NC statements. However, it turned out that most of the COI statements on biomedical papers were not included among the acknowledgements, and so our conclusions on their

prevalence were flawed. Our main concern was with the numbers of papers acknowledging support from the top 10 pharmaceutical companies (ranked by R&D spend), and by how much these numbers were inflated by the inclusion of papers where the company had had links with one or more authors but had not funded the research.

Methodology

We first identified and isolated the biomedical papers (articles and reviews only) in the WoS for the 5 years, 2009–2013 by means of a special filter based on address words or contractions (Lewison and Paraje 2004), such as *allerg**, *biochem*, *canc*, *dermatol*, *endocrin**, *family*, *Glaxo**, *hlth*. These numbered 2,879,698 in total, and an analysis was made (with the standard WoS software) of the journals in which they were published and the countries of their authors.

Next, we took a large sample of papers with pharmaceutical companies listed among the funding sources and parsed the acknowledgement full texts to see which words occurred most frequently that might be indicative of a possible COI statement. These were individually checked to ensure that they were not used to describe funding for the research being described in the paper. The words that remained, and that appeared to indicate that an author had been retained in some capacity by a company or received some form of payment, were as follows:

ADVISORY-BOARD or (CONSULT* not CONSULTATION*) or FEES or HONORARI* or LECTURE* or PATENT* or PAYMENT* or ROYALTIES or SERVED or SERVES or SERVING or SHAREHOLDER* or SHARES or (SPEAK* not SPEAKS) or STOCK or STOCKHOLDER

This was then used as the filter for COI statements. In parallel, a simple filter was developed for NC statements, as follows:

NO-CONFLICT* or NO-POTENTIAL-CONFLICT*

and these two filters were applied to the FT field for biomedical papers in the same years. This yielded 65,001 papers with a COI statement, 38,506 with an NC statement, and 91,760 with either one (or both). It was immediately apparent that COI or NC statements were very much the exception among biomedical papers—only 3.3 % of all biomedical papers had one.

This seemed very low, especially since most biomedical journals have strict instructions to authors to provide them. We therefore thought it desirable to check with some journal editors why there appeared to be so few COI statements on the papers in some clinical journals where more might have been expected in view of the clear requirement for authors to provide one. The responses we received (about half of the 14 who were polled) all said that they expected such statements to be provided and expressed surprise that our data showed such a low prevalence. There were a few cases where the lack of a COI had been picked up by a reviewer, and a handful of papers had been rejected or even withdrawn because of this, so evidently it was occasionally of importance—although it appeared that plagiarism was sometimes more of a problem. We examined some recent issues of one journal, the *British Journal of General Practice*, and found that the papers did indeed all have a clear COI or NC statement, but that this was not incorporated in the Funding Text of the WoS record. It thus appears that the statement percentage presence may be unduly low because COI and NC statements are appearing separately from the formal acknowledgement.

Table 1 List of the 10 top pharmaceutical companies (ranked by R&D expenditures) with their codes and subsidiaries

Company	ISO	Code	Subsidiaries
Roche	CH	HLR	Chugai Genentech Ventana
Novartis	CH	NVT	Alcon Chiron Ciba-Geigy Genoptix Sandoz
Merck (US)	US	MRK	Benyu Frosst Meriel MSD Organon Schering-Plough
Johnson and Johnson	US	J J J	Alza Centocor Cordis Crucell Depuy Ethicon Independence-Technology Janssen Lifescan Noramco Orapharma Ortho-Cilag Penaten Peninsula-Pharma Pricara Scios Tasmanian-Alkaloids Tibotec Transform-Pharma
Pfizer	US	PFZ	Alacer King-Pharma Pharmacia Searle Sugan Upjohn Warner-Lambert Wyeth
Sanofi-Aventis	FR	SLU	Aventis Genzyme Hoechst Marion-Roussel Medley Rhone-Poulenc Sanofi Synthelabo Uclaf Zentiva
GlaxoSmithKline	UK	GSW	
Eli Lilly	US	LLL	Icos
AstraZeneca	UK	ZAT	Ardea-Biosci Arrow-Therapeut Kudos-Pharma Medimmune Spirogen
Abbott Laboratories	US	ABB	Abbvie Advanced-Medical-Optics Facet-Biotech Knoll Solvay-Pharma

The 10 pharma companies were the ones listed in Table 1. This table gives their country, a code used in the table and figure that follow (based on our thesaurus of funding bodies), and the names of their subsidiaries whose research spending would be included with that of the parent in the EU Industrial R&D Scoreboard tables (EU 2013). The numbers of “their” papers were determined both from the presence of their names in the address field (AD, implicit acknowledgements) and in the funding organisations field (FO, explicit acknowledgements). However, their presence in the FT field together with one or more of the terms in the COI statement filter (*v.s.*) argued that these papers should be deducted from the total number of papers with explicit (FO) acknowledgements to give a reduced total. Inspection of a sample of individual papers showed that this almost always meant that the named company had been paying one or more of the authors and that consequently the inclusion of the company in the FO field was incorrect.

Results

Our analysis of the Statement Percentage Presence indicated, as expected, that clinical journals published these more frequently than did ones reporting basic research. The percentage frequency rose from 2009 to 2012, but then declined in 2013 and again in 2014. Authors from north America and western Europe included them more frequently than did authors from east Asian countries. This may have been because of their greater exposure to pharmaceutical companies, and because of a culture of transparency and openness. However since it appeared from our survey of journal editors that many COI statements were missing because they were not associated with the papers’ acknowledgements, these findings must be treated with reserve as they are based on a small sample of papers which may not be representative.

The results for the ten pharma companies are more robust and are given in Table 2. A graph of the number of papers for each of the ten (corrected for the presence of COI

statements involving the company) against their total R&D expenditure in the quinquennium 2 years earlier (i.e., from 2007–2011) is shown in Fig. 2.

The figures in Table 2 show that the reduction in the number of papers acknowledging one of the ten companies because of the presence of a COI statement is large, averaging 42 % with standard error of the mean 1.3 %. Overall, 49 % of the company papers have the name in the address field, and 62 % include it among the funding organizations, and 12 % show the company name in both fields. These results show that it is important to include implicit acknowledgements, and remove papers attributed to a company if a COI statement naming the company is present, when funding analyses are being performed.

Discussion

As a check on the importance of the list of funding bodies being redacted to account for companies not actually funding the research, we checked how many COI statements occurred on a large sample of European biomedical papers in the field of chronic respiratory diseases for 2009–2013 where we sought to determine their funding sources. The list of funders in the FU column might need to be redacted to account for them, and the statistics on the distribution of numbers of funders would change. Figure 3 shows the numbers of papers with a COI statement in the WoS with different numbers of explicit funders, before (F) and after (F*) redaction of the FU data. For these 689 papers, the mean number of funders before redaction was 10.3, but after redaction, only 4.4, a huge reduction.

The redaction process requires a delicate judgement based on a close reading of the full acknowledgement text in the FX column, and we needed to develop some rules for this. For a funding credit to be given, we looked for one or more of the following phrases or clauses:

- “this study was supported by...” or “sponsored by...”
- A. B. “was employed by...” or “was an employee of...” or “had a fellowship from”
- X company “provided (or donated) (a service, goods, or funded the manuscript preparation, or paid journal page charges)”

Table 2 R&D expenditure by 10 leading pharma companies, 2007–2011, € M, and their presence in the WoS

Company	Code	Spend	AD	FO	Total	FO × COI	Total × COI
Roche	HLR	31,259	6,136	12,976	17,707	5,644	10,762
Novartis	NVP	27,762	5,749	17,722	21,338	7,679	11,881
Merck (US)	MRK	23,365	6,385	18,963	23,452	7,609	12,667
Johnson and Johnson	J J J	26,508	3,941	12,396	15,008	4,427	7,443
Pfizer	PFZ	30,475	7,752	24,391	29,175	11,595	17,182
Sanofi-Aventis	SLU	22,925	2,530	12,624	14,180	5,234	7,071
GlaxoSmithKline	GSW	21,095	5,392	14,043	17,285	6,419	10,192
Eli Lilly	LLL	15,684	2,969	10,815	12,487	4,721	6,803
AstraZeneca	ZAT	17,034	4,462	10,385	13,133	4,609	7,762
Abbott Labs	ABB	11,528	2,544	8,335	10,126	3,002	5,046

AD = addresses; FO = funding credits, with and without COI statements, and corrected total number of papers in 2009–2013

- A. B. “receives/ed an unrestricted grant from...” or “receives/ed research support from...”

but we did not give funding credit when the wording was as follows:

- “data collection/analysis was performed by...” (a personal acknowledgement)
- A. B. “has received support/funding from...” or “currently has research grants from...”
- “the project was endorsed by...”
- A. B. “has carried out consultancy” or “has given lectures” or “is/was an advisory board member” or “receives royalties from...”
- A. B. “reports receiving” (unless it explicitly says that it applied to the present study)
- “departmental funding was received from...” (unless explicitly for the present study).

Ideally, this redaction process should take place before the funders are listed and coded in order to reduce unnecessary coding.

Although this redaction process is somewhat labour-intensive, it is necessary in order to remove false positive funding credits. But since many papers are published with detailed COI statements, showing that several of their authors are in the pay of commercial companies, and the results are still accepted and cited, do the COI declarations really have any value? There does appear to be a rather touching faith in the integrity of researchers and that they can put aside their significant commercial benefits when they are writing about their research findings. However this faith is not universal, as shown by the growing number of papers that are critical of these commercial conflicts, seen graphically in Fig. 1.

It appears therefore that there is a need for a register of COI statements for all intending biomedical authors that can be inspected easily, and kept up to date by them—at least annually. However it would be sensible to limit the declaration of financial links to companies to ones that had occurred during the last 5 years, or some other agreed period.

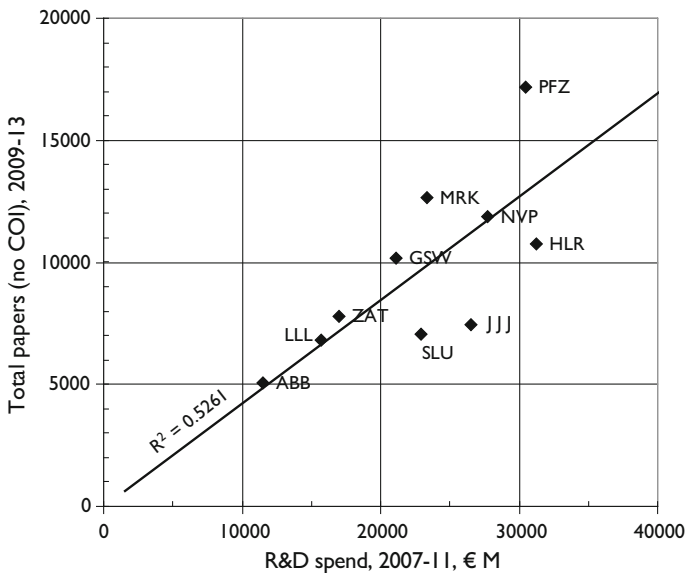


Fig. 2 Company research outputs, 2009–2013, excluding papers with a COI statement, compared with total R&D expenditure in 2007–2011

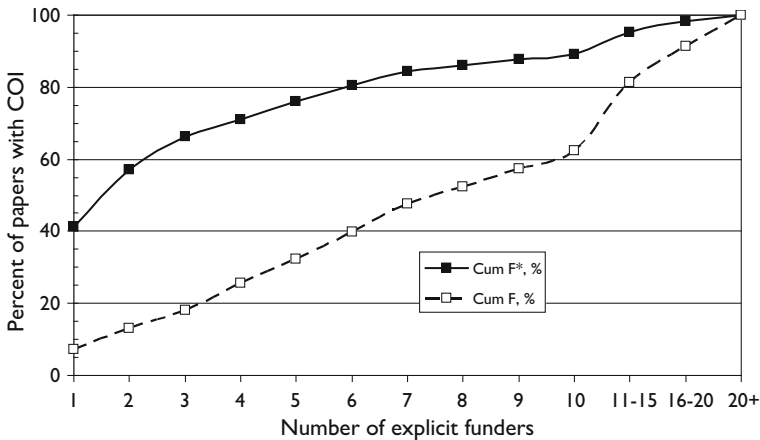


Fig. 3 Cumulative distribution of numbers of explicit funders on RESPI papers with COI statements ($n = 689$): F based on original FU data; F* based on redacted FU data

This register would be used both for journal papers and for conference presentations and proceedings. It would be web-based, and designed and managed by the International Committee of Medical Journal Editors to meet their standards. It would have the additional advantage that all prospective authors could be given a unique code that would allow all their publications to be identified without the problem of homonyms. (The present system of Researcher ID could be incorporated, but it would effectively become compulsory, and not voluntary). The register would not obviate the need for COI statements on papers but it would make it much easier for interested parties to investigate individual authors' commercial links. It would, of course, be international, unlike the Open Payments database which applies only to US doctors, and would also contain No Conflict declarations where appropriate.

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