Sponsor's influence on conduct and reporting of industry trials: a comparison of protocols and published papers

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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 sponsor's involvement in the conduct and reporting of industry-sponsored trials.

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

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 in 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 1 of the 69 trials. One trial had independent data analysis and two reporting of results. In 11 of the trials there was a disagreement between the protocol and paper concerning who analysed the data and in another 10 trials it was not possible to tell who analysed the data based on the published paper alone. In 4 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 sponsor's role in crucial elements such as data processing, statistical analysis and writing of the manuscript and consider requiring access to trial protocols and independent data analysis.

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 2005-2006 had industry funding; for *New England Journal of Medicine* it was 78% [2]. The involvement of the company in industry-sponsored trials vary from no involvement besides 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].

We have previously reported the results from a cohort of trials published in *The Lancet* in 2008-2009 [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 2008–2009 using the index term “Randomized Controlled Trial” in PubMed. We excluded papers that were not full trial reports (e.g. letters and commentaries) or were not part of the planned trials (e.g. 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 (e.g. by ‘unrestricted’ grants) were analysed separately.

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

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 manuscript into a pilot-tested data sheet. Two observers (AL, LTK) independently categorized these data into pre-specified domains for protocols and papers, and discrepancies were resolved by discussion and arbitration when needed by the third observer (PG). We compared protocols with published papers and described disagreements.
Results

We identified 209 papers in PubMed and excluded 40 that were not primary reports of trials published in 2008–2009 (Figure 1). We excluded another 88 trials, 85 that were not fully funded by the industry, 2 that had protocols similar to other included trials, and 1 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 *Lancet’s* database, three were protocol synopses, one was a copy of the information from [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and one only consisted of amendments to the protocol. We received copies of five protocols from the academic authors and of 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) was handled by the sponsor or a CRO, by the sponsor or a CRO and academic authors jointly in 10 (14%), by academic authors independently in 2 (3%), and in 8 cases (12%) it was not described (Table 1).

In 35 trials (51%), it was not described how the clinical data were processed, i.e. interpreted for categorisation purposes. Thirty-one of the remaining 34 trials described processing of some efficacy and safety outcomes by adjudication committees and 2 that all safety data were processed by sponsor staff. In the remaining trial, the protocol
described processing of safety data by the sponsor whereas the paper only mentioned an independent safety committee.

In 52 trials (75%), the sponsor or a CRO entered the data into the study database without involvement of academic authors, in 1 (1%) the academic authors did this independently of the sponsor, and in 16 cases (23%) it was not described (Table 1). 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 either the sponsor or a CRO, in 1 (1%) by academic authors, in 1 (1%) the protocol suggested that academic authors stored the data whereas the paper suggested that the sponsor stored it, and in 23 (33%) it was not described.

In 38 trial protocols (55%), it was described that the sponsor had access to accumulating data before study termination and in 2 (3%) via membership of the Data and Safety Monitoring Board. This continuous access to accumulating data could potentially have led to premature stopping of the trial. In 24 of these 40 trials, the sponsor could stop the trial prematurely for a broad range of reasons or without any constraints at all, in 5 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, in 11 (16%) jointly by sponsor or CRO and academic authors, in 2 (3%) by academic authors independently and in 5 (7%) it was not described (Table 1). In the
remaining 11 trials (16%), there were disagreements between 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 disagreements on whether the sponsor or 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.

In the 11 trials with joint data analysis, 5 had primary statistical analysis by a sponsor or CRO biostatistician and confirmatory analysis by an independent biostatistician, 1 had statistical analysis by a sponsor biostatistician who was supervised by an academic author and 5 described various sponsor-employed and academic authors as participating in data analysis, but it was not clear who performed the actual statistical analysis. In one of these five trials, the protocol named a sponsor-employed study biostatistician who was not mentioned in the paper.

Publication of the results
In 24 out of the 69 trials (35%), the sponsor or a hired contract research organization 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 one of the five remaining trials, the sponsor had no influence, in one it was not described, and in three there were
disagreements between 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 (e.g. clinical trial agreements 
and publication agreements) concerning reporting of results and data ownership and five 
other protocols (7%) stated that such agreements might be issued, overriding statements 
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, as 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 7 papers (10%) it seemed no assistance was 
provided and in 25 (36%) it was not described. In 19 of the 69 protocols (28%), author 
names were mentioned and 10 protocols specified them as authors of the protocol. 
However, for 14 of these 19 protocols the authors were not mentioned in the publications.

**Independently conducted trials**

In the additional sample of 12 trials that appeared to have been conducted independently 
of the sponsor, one protocol described that the sponsor could stop the trial prematurely, 
one that the sponsor needed to be consulted concerning stopping of the trial and three
contained author confidentiality statements. In five trials, the protocol had information about that the sponsor was involved with writing the report, and in four of these the paper described that the sponsor was not involved and in one paper there was no information on the sponsor's involvement. In one additional trial both protocol and paper described that the sponsor had the right to comment on the manuscript.

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 or was involved with the reporting of results.

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 ones described the sponsor’s 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. 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 were written by the sponsor. It was therefore 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 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 else 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 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 requires 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 don't do a job that
satisfies the sponsor's 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 sponsor's 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, which, however,
only reinforces the need for independent analyses [27]. Lastly, journals should require
copies of protocols and any additional agreements to ensure that access to the data was planned before the trial started. 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], journals editors might also consider asking for the raw data as a condition for publication, like Science and the Nature journals require [23].

Conclusions
The sponsors are usually involved with 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 sponsor’s role in crucial elements such as data processing, statistical analysis and writing of the manuscript, 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.

Acknowledgements
We thank the editors of *The Lancet* for providing us with copies of trial protocols. We thank the authors and companies for providing us with copies of the missing protocols.

Funding/Support
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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.

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


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Figure 1. Flow chart showing inclusion of trials.
Table 1. Data management and analysis in industry-sponsored trials.

<table>
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<th></th>
<th>CRF review and verification</th>
<th>Data entry</th>
<th>Data storage</th>
<th>Data analysis</th>
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<td><strong>(n = 69)</strong></td>
<td></td>
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<tr>
<td>Sponsor</td>
<td>23 (33%)</td>
<td>32 (46%)</td>
<td>35 (51%)</td>
<td>29 (42%)</td>
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<tr>
<td>Sponsor and CRO</td>
<td>18 (26%)</td>
<td>8 (12%)</td>
<td>3 (4%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>CRO</td>
<td>8 (12%)</td>
<td>12 (17%)</td>
<td>6 (9%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Sponsor/CRO and academic authors</td>
<td>10 (14%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Academic authors</td>
<td>2 (3%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>2 (3%)</td>
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<tr>
<td>Not described</td>
<td>8 (12%)</td>
<td>16 (23%)</td>
<td>23 (33%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Disagreement between protocol and paper</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>11 (16%)</td>
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</tbody>
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Table 2. Sponsor’s influence on publication of results of industry-sponsored trials.

<table>
<thead>
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<th>(n = 69)</th>
<th>Publication of results</th>
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<tr>
<td>Sponsor has co-authorship</td>
<td>56 (81%)</td>
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<td>Sponsor needs to approve manuscript</td>
<td>3 (4%)</td>
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<tr>
<td>Sponsor needs to review or comment</td>
<td>5 (7%)</td>
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<tr>
<td>No influence</td>
<td>1 (1%)</td>
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<tr>
<td>Not described</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Disagreement between protocol and paper</td>
<td>3 (4%)</td>
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</tbody>
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209 Papers identified in PubMed indexed as Randomized Controlled Trial

40 papers excluded
- 28 editorials/commentaries
- 1 letter
- 3 not reporting on trial
- 3 secondary analysis of trial
- 5 published in 2010

169 trials identified

88 trials excluded
- 1 all authors employed by sponsor
- 85 not solely industry-funded
- 2 same protocol as other trial

12 solely industry-funded trials with apparent independent data management and analysis included in subsample

69 industry trials included