Impact of Funding Source on Clinical Trial Results Including Cardiovascular Outcome Trials

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Previous authors have suggested a higher likelihood for industry-sponsored (IS) studies to have positive outcomes than non-IS studies, though the influence of publication bias was believed to be a likely confounder. We attempted to control for the latter using a prepublication database to compare the primary outcome of recent trials based on sponsorship. We used the “advanced search” feature in the clinicaltrials.gov website to identify recently completed phase III studies involving the implementation of a pharmaceutical agent or device for which primary data were available. Studies were categorized as either National Institutes of Health (NIH) sponsored or IS. Results were labeled “favorable” if the results favored the intervention under investigation or “unfavorable” if the intervention fared worse than standard medical treatment. We also performed an independent literature search to identify the cardiovascular trials as a case example and again categorized them into IS versus NIH sponsored. A total of 226 studies sponsored by NIH were found. When these were compared with the latest 226 IS studies, it was found that IS studies were almost 4 times more likely to report a positive outcome (odds ratio [OR] 3.90, 95% confidence interval [CI] 2.6087 to 5.9680, $p < 0.0001$). As a case example of a specialty, we also identified 25 NIH-sponsored and 215 IS cardiovascular trials, with most focusing on hypertension therapy (31.6%) and anticoagulation (17.9%). IS studies were 7 times more likely to report favorable outcomes (OR 7.54, 95% CI 2.19 to 25.94, $p = 0.0014$). They were also considerably less likely to report unfavorable outcomes (OR 0.11, 95% CI 0.04 to 0.26, $p < 0.0001$). In conclusion, the outcomes of large clinical studies especially cardiovascular differ considerably on the basis of their funding source, and publication bias appears to have limited influence on these findings. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;116:1944–1947)

There has been a rising concern about industry-sponsored (IS) studies influencing the design and result of clinical trials.^{1–5} This apprehension has been augmented by several observations of published IS studies yielding positive outcomes compared to less-impressive findings from independently funding investigations.^{1,3,4,6–8} Temporal trends reflect that more and more studies are being sponsored by the pharmaceutical companies compared with state-funded sponsors. Furthermore, funding of the National Institutes of Health (NIH) has gone down in the recent years, creating further need for the industry funding of studies.^{9,10} In 1994, Rochon et al¹¹ noted that all 56 clinical trials that evaluated the role of nonsteroidal anti-inflammatory drugs in arthritis reported results that favored the sponsors. A systematic review by Lexchin et al⁴ reported that pharmaceutical companies were significantly more likely to report positive

outcomes and that this was at least partially explained by publication bias. Because results frequently appear in the clinicaltrials.gov Web site before being published in the peer-reviewed journals, prepublication results may represent a less-biased sample. As such, we performed an analysis of recent clinical trials published on this Web site to compare the outcomes between IS and independently sponsored studies in terms of the primary outcome.

Methods

Clinical trials were reviewed from the clinicaltrials.gov Web site. The Web site maintains details of both federally and privately funded studies under the investigational new drug program. In 2007, Congress passed the Food and Drug Administration Amendment Acts requiring that certain results and adverse effects should also be made available on the website.

Using the options of “advanced search,” we applied the filters of “completed” in the “recruitment status,” “completed” in the “study results,” “interventional” in the study type, adult (aged 18 to 65 years) in the age, and “phase 3” as the phase. Studies sponsored by “other US federal agency” and “All others (individuals, universities, organizations)” were excluded. To study a case example of studies in a particular specialty, we also performed an independent literature search to identify the cardiovascular trials and again categorized them into IS versus federally

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See page 1946 for disclosure information.

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Table 1
Comparison of National Institute of Health and industry sponsored articles

All Trials	National Institute of Health Articles (n=226)	Industry Sponsored Articles (n=226)	Odds ratio (95% CI)
Favorable Outcomes	47 (20.8%)	115(50.9%)	3.90 (2.61-5.97, P <0.0001)
No Analysis	82(36.3%)	81(35.8%)	0.98 (0.67-1.44, P=0.92)
Non-Favorable Outcomes	97(42.9%)	30(13.3%)	0.20 (0.13 - 0.32, P < 0.0001)
Only Cardiovascular Trials	(n=25)	(n=215)	
Favorable Outcomes	3 (12%)	109(50.7%)	7.54(2.19-25.94, P= 0.0014)
No Analysis	9(36%)	84(39.1%)	1.14(0.48-2.69, P=0.77)
Non-Favorable Outcomes	13(52%)	22(10.2%)	0.10(0.04-0.26, P <0.0001)

Table 2
National Institute of Health and industry sponsored articles classified according to specialty

Specialty	Favorable Outcomes		Non-Favorable Outcomes		No Analysis		Total	
	NIH	IS	NIH	IS	NIH	IS	NIH	IS
Infectious diseases	4	6	12	3	11	5	27	14
Neurology	3	8	10	0	9	15	22	23
Renal	0	1	4	1	3	2	7	4
Respirology	2	12	5	0	15	6	22	18
Endocrinology / Immunology	4	41	6	7	6	16	16	64
Oncology	10	3	29	4	11	7	50	14
Cardiology	3	15	12	5	7	4	22	24
Psychiatry	12	9	8	6	11	5	31	20
Hematology	1	3	3	1	2	3	6	7
Eye	3	6	5	2	2	1	10	9
Hepatology	3	8	3	0	2	11	8	19
ENT	1	0	0	0	1	0	2	0
Gynecology	1	3	0	1	2	6	3	10

sponsored studies. We chose to study the cardiovascular studies as cardiovascular disease continues to be the leading cause of death in the industrialized nations.

Using the mentioned search criteria, we found a total of 226 studies sponsored by the NIH. Data from all these studies were extracted in the form of primary outcomes. Results were categorized as “favorable” if the results favored the drug or intervention under investigation; “unfavorable” when the standard treatment or placebo had significantly improved primary outcome measures compared with the drug or the intervention; or “no analysis provided” when the results were provided in the form of tabulation, but no tests of statistical significance were provided to provide inference on the outcomes. The similar search retrieved over 3,000 titles for the IS studies, but only the last 226 were included for 1:1 comparison. We intentionally restricted the analysis to studies sponsored by the NIH or industry as that constitute the bulk of studies enlisted on the clinicaltrials.gov. For instance, of the 3,783 studies that were retrieved through the search strategy described, 3,491 were either sponsored by the industry or NIH, leaving a small number of studies sponsored by non-NIH or private organizations.

For the purpose of analysis, the 2 groups were considered “NIH” versus “IS.” Data were analyzed through the

Statistical Package of Social Sciences (SPSS) version 17.0 (International Business Machines Corp.; Armonk, New York). We compared the percentages of positive results using simple statistical testing (chi-square) to see if statistically significant differences existed in the positive results reported by the 2 funding sources. Data were also expressed as range in the form of 95% confidence intervals (CIs).

Results

Based on the literature search described in the methods, 226 NIH-sponsored reports were identified from the Web site clinicaltrials.gov using the filters from the advanced search. Of these 226 reports, approximately only 1/5 (n = 47, 20.8%) reports reported favorable outcomes in comparison with approximately 1/2 (n = 115, 50.9%) of the IS studies that reported a favorable outcome. Thus, the IS studies were almost 4 times more likely to report a positive outcome (odds ratio [OR] 3.90, 95% CI 2.6087 to 5.9680, p <0.0001). The proportion of reports in the IS group (n = 81, 35.8%) with no reported statistical analysis was similar to the NIH group (n = 82, 36.3%; OR 0.98, 95% CI 0.6682 to 1.4402, p = 0.92; [Table 1](#)). Of the total 226 reports, the largest subset of reports (n = 50, 22.1%) was related to oncology, although cardiology, neurology and pulmonary medicine contributed 22 (9.7%) reports each ([Table 2](#)). According to specialty, the highest proportion of unfavorable reports (58%) was found in oncology followed by nephrology (57%) and cardiology (54.5%). The IS reports were almost 5 times less likely to report negative outcomes compared to NIH-sponsored reports (OR 0.20, 95% CI 0.1277 to 0.3243; p <0.0001). In pharmaceutical company-sponsored reports, >60% of the reports related to endocrinology (64%), cardiology (62.5%), and pulmonary medicine (67%) reported favorable outcomes. In contrast, NIH-sponsored reports related to cardiology (13.6%), endocrinology (25%), and pulmonary medicine (9%) showed a much smaller proportion of favorable outcomes. Moreover, only 28% of IS oncology reports reported unfavorable outcomes compared with 58% unfavorable outcomes of NIH-sponsored oncology-related reports (p <0.0001).

We further analyzed the cardiovascular outcome trials, identifying 25 NIH and 215 IS trials during the same period. Most focused on hypertension therapy (31.6%) and anti-coagulation (17.9%). The proportion of studies with no

analysis reported was similar in IS and NIH studies (OR 1.14, 95% CI 0.48 to 2.70, $p = 0.77$). IS studies were 7 times more likely to report favorable outcomes (OR 7.54, 95% CI 2.19 to 25.94, $p = 0.0014$). They were also considerably less likely to report unfavorable outcomes (OR 0.11, 95% CI 0.04 to 0.26, $p < 0.0001$). Only 8 IS trials of antihypertensives (10.5%) reported nonfavorable outcomes, whereas only 3 IS trials of anticoagulants (7%) reported nonfavorable outcomes.

Discussion

Our study suggests that IS studies are significantly more likely to report positive (or favorable) outcomes and less likely to report unfavorable results compared with federally sponsored studies. These findings have significant clinical and academic implications. Previous authors have suggested a higher likelihood for IS studies to have positive outcomes than non-IS studies, though the influence of publication bias (author and journal-related) was believed to be a strong confounder that was likely responsible for much of the difference. Because our findings are derived from an analysis of the clinicaltrials.gov Web site, this reflects that these differences between the results of studies from the funding sources are existent even before time of publication in the peer-reviewed journals.

In the current era of evidence-based medicine, we are heavily reliant on the outcomes of large clinical studies to ensure that we deliver the best possible and evidence-based therapy to our patients. The evidence in turn depends on high-quality, peer-reviewed publications providing transparent and unbiased findings. It is therefore critical that such studies provide reliable information to positively impact patient safety and clinical outcomes. Bekelman et al² showed that the research sponsored by industry was as rigorous as that of the state-sponsored agencies but always reported outcomes that were beneficial for the sponsor.

One of the arguments to explain the differences is that studies with positive outcomes are more likely to be reported (publication bias). Lexchin et al⁴ reported interesting differences in the publication pattern of the studies sponsored by industry, where pharmaceutical company-sponsored studies were less likely to be published, more likely to be published in conference proceedings than in peer-reviewed journals, and had longer lag times between presentation and publication.

If publication bias alone accounted for this pattern, these findings would probably be less bothersome. Unfortunately, evidence suggests that there are multiple ways that outcomes can be manipulated. This includes ghost authorship, where writers or statisticians are hired to complete the manuscript with their identities concealed.^{12–14} Another such phenomenon is guest authorship, where well-known physicians who had little to do with the study are included as authors to give credibility to the report.^{15,16} Industry may also influence which findings should be emphasized in the discussion.¹⁷

However, it is important to note that industry should not be vilified. In fact, pharmaceutical companies remain the driving force for the current bulk of clinical trials. It has been estimated that industry invests significantly more

finances into medical research than the NIH.¹⁸ Also, IS trials are generally larger and tend to have greater clinical impact.¹⁹ Moreover, IS trials are more likely to adopt a noninferiority study design. Although this may allow drugs with similar clinical efficacy to enter the market, it also greatly helps to increase competition, leading to cheaper and safer drugs becoming available.^{20,21} A recent study has also shown that IS studies have more satisfactory blinding compared with non-IS trials.²²

Our study has limitations that need to be taken into account. First, because there were more than 3,000 IS trials and only 226 NIH-sponsored studies, we simply considered the latest 226 IS articles for a one-to-one analysis. This might have resulted in lead-time bias as we compared trials from 1997 to 2015 to a much more recent group of trials, especially considering the latest technological advancements in many medical fields. However, we attempted to control for this limitation by conducting a separate analysis of all the cardiovascular trials that our search retrieved. Second, we only considered trials contained in clinicaltrials.gov. Although this limits our analysis mainly to larger studies, these tend to have more rigorous designs and are generally adequately powered for their outcome. Moreover, IS studies generally have larger sample sizes compared with NIH studies translating into lower type 2 statistical error which may affect results of these studies. Third, there were many trials which had not reported statistical analyses despite having the frequency of outcome measures. Thus, there remains a slight chance that we may not be accurately reporting the true number of favorable outcomes in either group. Fourth, usually phase 3 trials for IS studies are started when there is favorable outcomes in lower mammals such as rats, which have almost similar physiology to human body. Hence, one of the reasons of positive outcomes in IS articles may be previous animal investigation which may not be seen with NIH studies. Finally, we did not account for the study design in our analysis (noninferior vs superior), and it is possible that this approach may have impacted some of the results.

Disclosures

The authors have no conflicts of interest to disclose.

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