Industry Collaboration and Randomized Clinical Trial Design and Outcomes

Industry-funded clinical trials are more likely to have favorable, proindustry results compared with nonindustry funded trials, but few studies have distinguished between industry funding in the context of industry collaboration in the design, analysis, or reporting of trials. For a sample of clinical trials published in high-impact journals, our objective was to examine whether industry funding with collaboration was associated with certain trial design features and outcomes.

Method | We identified randomized clinical trials of drugs and devices published between December 1, 2011, and November 31, 2012, in biomedical journals for which Journal Citation Reports 2012 reported an impact factor greater than 11 and that published details on the "Role of the Funding Source/Sponsor." We excluded phase 1 or 2 trials and secondary trial analyses.

We categorized trials as having industry funding with collaboration when any for-profit organization funded the trial and had any role in its design, analysis, or reporting; as having industry funding without collaboration when any for-profit organization funded the trial but had no role in its design, analysis, or reporting; and as having neither industry funding nor collaboration.

Two authors (N.R. and N.Z.), blinded to industry funding and collaboration, independently assessed the following trial design features and outcomes: blinding (double, single, or none), intention-to-treat analysis, discussion of limitations (defined as using the word stems “weak” or “limit” when describing trial design in the Discussion section), superiority or non-inferiority design, comparator drug (active vs placebo), primary outcome (positive [ie, statistically significant superiority or non-inferiority favoring the product of the sponsor or sponsors], negative, or mixed), primary end point (clinical, surrogate [any radiology, pathology, or laboratory value], or mixed). Differences were resolved by consensus. Interrater agreement was high (κ = 0.9350). One investigator (N.R.) subsequently recorded allocation concealment, funding (industry and/or government/nonprofit), and industry collaboration.

We conducted 2 sets of analyses comparing trial variables between trial groups (neither industry funding nor collaboration vs industry funding with collaboration and neither industry funding nor collaboration vs industry funding without collaboration) using relative risks (RRs) and Fisher exact tests. Statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc). All P values were 2-tailed, with significance defined as P < .05.

Results | There were 219 articles from 10 high-impact journals describing the results of drug and device trials included in our analysis; 86 trials (39%) had industry funding with collaboration, 66 (30%) had industry funding without collaboration, and 67 (31%) had neither industry funding nor industry collaboration (Table). When compared with trials having neither industry funding nor collaboration, trials having industry funding with collaboration were significantly more likely to report a positive primary outcome (69.8% vs 52.2%; RR, 1.34; 95% CI, 1.03-1.75 [P = .03]) and use a surrogate primary end point (51.2% vs 16.4%; RR, 3.11; 95% CI, 1.75-5.56 [P < .001]) and less likely to discuss limitations (40.7% vs 58.2%; RR, 0.70; 95% CI, 0.50-0.97 [P = .04]). In contrast, there were no differences between trials having neither industry funding nor collaboration and trials having industry funding without collaboration.

Discussion | Among clinical trials published in high-impact journals, industry funding with collaboration in the design, analysis, or reporting was associated with increased likelihood of reporting a positive primary outcome and decreased likelihood of reporting of trial limitations. Collaborative trials’ more common use of a surrogate primary end point may, in part, explain why these trials were more likely to have a positive primary outcome. While publication bias may contribute to our findings, our study was also limited by our exclusion of

Table. Industry Funding and Collaboration Status and Trial Design and Outcome

<table>
<thead>
<tr>
<th>Trial Variable</th>
<th>Neither Industry Funding Nor Collaboration (n = 67)</th>
<th>Industry Funding With Collaboration (n = 86)</th>
<th>Industry Funding Without Collaboration (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial used allocation concealment</td>
<td>65 (97.0)</td>
<td>80 (93.0)</td>
<td>62 (93.9)</td>
</tr>
<tr>
<td>Trial used double blinding</td>
<td>39 (58.2)</td>
<td>61 (70.9)</td>
<td>44 (66.7)</td>
</tr>
<tr>
<td>Trial used intention-to-treat analysis</td>
<td>40 (59.7)</td>
<td>46 (53.5)</td>
<td>39 (59.1)</td>
</tr>
<tr>
<td>Discussion of trial limitations in publication</td>
<td>39 (58.2)</td>
<td>35 (40.7)</td>
<td>44 (66.7)</td>
</tr>
<tr>
<td>Noninferiority trial design</td>
<td>11 (16.4)</td>
<td>17 (19.8)</td>
<td>12 (18.2)</td>
</tr>
<tr>
<td>Trial used placebo comparator</td>
<td>28 (41.8)</td>
<td>36 (41.9)</td>
<td>26 (39.4)</td>
</tr>
<tr>
<td>Trial with positive primary outcome</td>
<td>35 (52.2)</td>
<td>60 (69.8)</td>
<td>31 (47.0)</td>
</tr>
<tr>
<td>Trial used surrogate primary end point</td>
<td>11 (16.4)</td>
<td>44 (51.2)</td>
<td>13 (19.7)</td>
</tr>
</tbody>
</table>

Abbreviations: Ref, reference; RR, relative risk.
high-impact journals that do not publish details on the “Role of the Funding Source/Sponsor,” which was needed to assess trial collaboration.

Our results suggest that, in addition to disclosure of industry funding source, greater transparency of industry funders’ role in trial design, analysis, and reporting might be valuable for assessing potential bias in trial findings.

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Editor’s Note

It’s Not Just About the Money, Money, Money...

Global funding for biomedical research now approaches $270 billion per year, nearly two-thirds of which comes from industry, including pharmaceutical, biotechnology, and medical device companies.1 While industry’s investment in research has spawned breakthroughs and innovations, these investments have also fueled concerns that industry-funded clinical trials are more likely to have proindustry conclusions,2 potentially distorting the evidence base to favor more expensive, brand name products on which manufacturers continue to spend research dollars.

Having examined a year’s worth of clinical trials published in high-impact biomedical journals, the findings of Roper et al suggest that the problem may go beyond funding and instead be a consequence of collaboration. When compared with trials not funded by industry, trials funded by industry were no different with respect to key design features suggestive of methodological rigor or likelihood of reporting proindustry conclusions. However, trials funded by industry that also involved collaboration in its design, analysis, or reporting used less rigorous methods and were more likely to report proindustry conclusions.

Appropriate research collaborations focused on patient benefits should be fostered, taking advantage of the skills and knowledge of those in industry and academia (and government). However, perhaps collaboration breeds sufficient familiarity and generosity that decisions are affected, even if only subtly, in a way that diminishes the rigor and robustness of the research. Ensuring that these collaborations are made fully transparent, including the process of study design and decisions relevant to study conduct and statistical analysis, may help, as might independent oversight or advisory committees. By human nature, I suspect we are all inclined to make small concessions to those with whom we work, regardless of whether they are employed by a pharmaceutical company funding our research or work at the front desk of our clinics. So we must be mindful and remember, it’s not just about the money.

Joseph S. Ross, MD, MHS


Low Yield of Outpatient Serum Folate Testing: Eleven Years of Experience

Since the United States began folic acid fortification in 1998, the prevalence of folate deficiency in the general population has decreased.3 Despite this, folate testing continues to be recommended for the evaluation of macrocytic anemia2-3 and is commonly performed to evaluate macrocytosis without anemia, normocytic anemia, dementia, delirium, and peripheral neuropathy.4-6 We aimed to determine the utility of serum folate testing in an outpatient population.

Methods | We conducted a retrospective review of all outpatient serum folate tests performed at a large academic medical center in Boston, Massachusetts, from January 1, 2003, through December 31, 2013. The study was reviewed by the Beth Israel Deaconess Medical Center Institutional Review Board and was determined to be exempt. No informed consent was required because this study was retrospective and observational (and thus did not affect patient care in any way). Serum folate values were determined using a chemiluminescent competitive binding protein assay on an E170 analyzer as prescribed by the manufacturer (Roche Diagnostics Corporation). Serum folate levels were defined as deficient (<3.0 ng/mL; to convert to nanomoles per liter, multiply by 2.266), low-normal (3.0-3.9 ng/mL), normal (4.0-19.9 ng/mL), or high (>19.9 ng/mL).4-6 To determine whether changes in the number of serum folate tests ordered were specific to