Why the Cochrane Risk of Bias Tool should include Funding Source as a Standard Item

Lisa Bero

Cochrane Methods Symposium 2013
1. Funding source fits the definition of bias
A **statistic** is **biased** if it is calculated in such a way that is systematically different from the **population parameters** of interest. The following lists some types of, or aspects of, bias which should not be considered mutually exclusive:

**Funding bias** may lead to selection of outcomes, test samples, or test procedures that favor a study's financial sponsor.
“…the BMG, in addition to our original remit now considers the following forms of bias, and topics to be of focus….funding bias”
Cochrane Definition of Bias

• “A bias is a systematic error, or deviation from the truth, in results or inferences.”

• “over or underestimate of true intervention effect”

• “In clinical trials, biases can be broadly categorized as selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases that do not fit into these categories”
2. There is evidence of bias related to funding source
Industry sponsorship and research outcome (Review)

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L.
Drug studies and pharmaceutical industry funding

• Direction of effect: Industry studies more likely to have favorable efficacy results (1.32 [1.21, 1.44]) and harm results (1.87 [1.54, 2.27]) than non-industry sponsored studies

• Effect size: five papers found larger effect sizes in industry sponsored studies compared with non-industry sponsored studies and five papers did not find a difference in effect size.
1.1 Number of studies with favorable efficacy results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Industry Total</th>
<th>Non-industry Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alasbali 2009</td>
<td>29</td>
<td>10</td>
<td>0.9%</td>
<td>1.21 [0.30, 4.88]</td>
</tr>
<tr>
<td>Bero 2007</td>
<td>94</td>
<td>97</td>
<td>13.7%</td>
<td>1.40 [1.10, 1.78]</td>
</tr>
<tr>
<td>Booth 2008</td>
<td>120</td>
<td>165</td>
<td>12.2%</td>
<td>1.35 [0.98, 1.85]</td>
</tr>
<tr>
<td>Bourgeois 2010</td>
<td>260</td>
<td>85</td>
<td>21.0%</td>
<td>1.51 [1.25, 1.83]</td>
</tr>
<tr>
<td>Clifford 2002</td>
<td>66</td>
<td>34</td>
<td>8.1%</td>
<td>1.13 [0.83, 1.54]</td>
</tr>
<tr>
<td>Etter 2007</td>
<td>49</td>
<td>41</td>
<td>2.8%</td>
<td>2.32 [1.23, 4.40]</td>
</tr>
<tr>
<td>Kelly 2006</td>
<td>13</td>
<td>8</td>
<td>1.4%</td>
<td>1.85 [0.91, 3.76]</td>
</tr>
<tr>
<td>Momeni 2009</td>
<td>69</td>
<td>85</td>
<td>8.8%</td>
<td>1.03 [0.84, 1.28]</td>
</tr>
<tr>
<td>Moncrieff 2003</td>
<td>2</td>
<td>7</td>
<td>0.4%</td>
<td>2.67 [0.85, 8.39]</td>
</tr>
<tr>
<td>Perlis 2005b</td>
<td>113</td>
<td>49</td>
<td>15.0%</td>
<td>1.09 [0.91, 1.31]</td>
</tr>
<tr>
<td>Rasmussen 2009</td>
<td>109</td>
<td>28</td>
<td>6.5%</td>
<td>1.21 [0.81, 1.81]</td>
</tr>
<tr>
<td>Rattinger 2009</td>
<td>36</td>
<td>25</td>
<td>6.2%</td>
<td>1.00 [0.73, 1.38]</td>
</tr>
<tr>
<td>Tulikangas 2006</td>
<td>15</td>
<td>9</td>
<td>2.7%</td>
<td>1.29 [0.89, 1.87]</td>
</tr>
<tr>
<td>Vlad 2007</td>
<td>11</td>
<td>4</td>
<td>0.2%</td>
<td>4.58 [0.31, 68.24]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>941</strong></td>
<td><strong>647</strong></td>
<td>100.0%</td>
<td>1.32 [1.21, 1.44]</td>
</tr>
</tbody>
</table>

- Total events: 653
- Heterogeneity: Chi² = 22.26, df = 13 (P = 0.05); I² = 42%
- Test for overall effect: Z = 6.05 (P < 0.00001)

1.2 Number of studies with favorable harms results

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Industry Total</th>
<th>Non-industry Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halpern 2005</td>
<td>3</td>
<td>45</td>
<td>1.4%</td>
<td>1.50 [0.28, 8.14]</td>
</tr>
<tr>
<td>Kommeren 2001</td>
<td>4</td>
<td>5</td>
<td>2.0%</td>
<td>1.88 [0.56, 6.31]</td>
</tr>
<tr>
<td>Nieto 2007</td>
<td>275</td>
<td>229</td>
<td>96.6%</td>
<td>1.87 [1.54, 2.28]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>282</strong></td>
<td><strong>279</strong></td>
<td>100.0%</td>
<td>1.87 [1.54, 2.27]</td>
</tr>
</tbody>
</table>

- Total events: 184
- Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
- Test for overall effect: Z = 6.35 (P < 0.00001)
3. The observed bias related to funding source cannot be explained by risk of bias criteria currently assessed with the Cochrane RoB tool.
Mechanism of bias

• Cochrane RoB: sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting

• Cochrane review comparing industry funded vs non-industry funded drug studies (*Lundh et al*)
  – No difference in sequence generation, concealment of allocation, loss to followup.
  – Industry studies have lower RoB related to blinding 1.32 [1.05, 1.65]
Mechanisms of Funding Bias

Question → Population → Method → Conduct → Publication → Question

Bias related to dose selection

• RCTs of NSAIDS, 1987 – 1990
• 56 trials associated with a manufacturer
  – 16 manufacturer’s drug better
  – 40 both drugs about the same
  – 0 competitor’s drug better
• How did they get this result?

Unfair Dose Comparison

Dosage of Manufacturer's Drug vs. Comparison Drug

4. Risks of bias are not mutually exclusive ... and may be difficult to detect
5. Bias may be related to funding source even when ALL studies are industry funded
Head-to-head comparisons of statins

• Cross-sectional study of published RCTs (1999-May 2005) evaluating the efficacy of a statin drug compared to another statin or alternative drug.

• Search: electronic, ref lists, contact authors. Non-English included (N = 192; n = 95 industry sponsored)

Which statin is better?

... the one made by the company that funded the study
What study characteristics were associated with favorable outcomes?

• NOT
  – Concealment of allocation
  – All subjects enrolled included in analysis
  – Use of surrogate outcomes
  – Dose

• Also NOT
  – Journal peer review
  – Author characteristics
## Multivariate analysis: industry funded (n = 95)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Results Favor OR (95% CI)</th>
<th>Conclusions Favor OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impact factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.97 (0.35, 10.93)</td>
<td>2.37 (0.36, 15.54)</td>
</tr>
<tr>
<td>Adequate blinding</td>
<td>0.27 (0.08, 0.89)</td>
<td>0.29 (0.07, 1.21)</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 4</td>
<td>4.40 (0.84, 23.01)</td>
<td>63.29 (6.65, 602.4)</td>
</tr>
<tr>
<td>Funded by test drug company vs. comparator drug company</td>
<td><strong>20.16 (4.37, 92.98)</strong></td>
<td><strong>34.55 (7.09, 168.4)</strong></td>
</tr>
</tbody>
</table>
6. Cochrane reviews are not doing an adequate job of disclosing funding sources of included trials
Reporting of trial funding sources in Cochrane Reviews

<table>
<thead>
<tr>
<th>Type of conflict of interest</th>
<th>Fully (for all included trials)</th>
<th>Partially (for some included trials)</th>
<th>Fully or partially</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial funding sources</td>
<td>30</td>
<td>16</td>
<td>46</td>
</tr>
<tr>
<td>Trial author-industry financial ties</td>
<td>2</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Trial author-industry employment</td>
<td>0</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

*See supplementary appendix 5 for coding notes on reporting of included trial funding sources, trial author-industry financial ties, and trial author-industry employment.

Where were funding sources reported?

- 7 different locations
- Risk of bias assessment in 28 reviews (19%)
  - 8 (5%) only in the risk of bias text
  - 4 (3%) only in the risk of bias table
  - 14 (9%) in both of these locations
  - 2 (1%) in both of these locations plus the risk of bias figure.
- 24 (16%) in included studies table
MECIR (Methodological Expectations of Cochrane Intervention Reviews)

- Details of funding sources for each included study and declarations of interest of the primary researchers of the included studies to be mandatory for inclusion in the “Characteristics of Included Studies Table”

- Funding source is not mandatory for the risk of bias assessment table

- Cochrane Plain Language Summaries: ‘highly desirable’ that all funding sources of included studies be disclosed in the Plain Language Summary
In summary.....

1. Funding source fits the definition of bias
2. There is evidence of bias related to funding source
3. The observed bias related to funding source cannot be explained by risk of bias criteria currently assessed with the RoB tool
4. Risks of bias are not mutually exclusive.. May be difficult to detect
5. Bias may be related to funding source even when ALL studies are industry funded
6. Cochrane reviews are not doing an adequate job of disclosing funding sources of included trials