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

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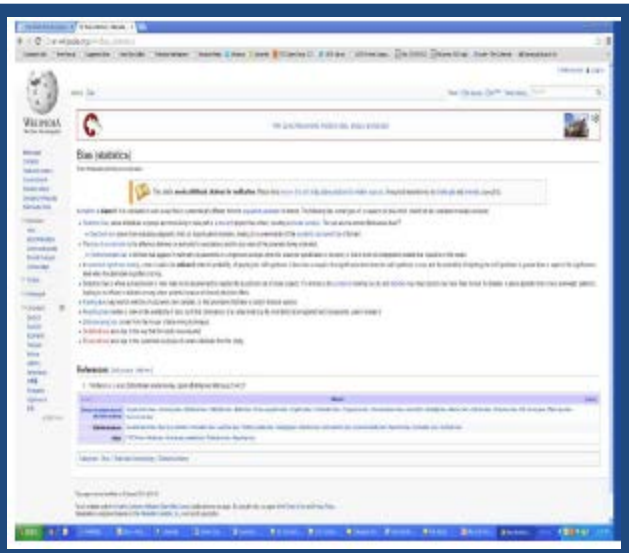
Cochrane Methods Symposium
2013

1. Funding source fits the definition of bias

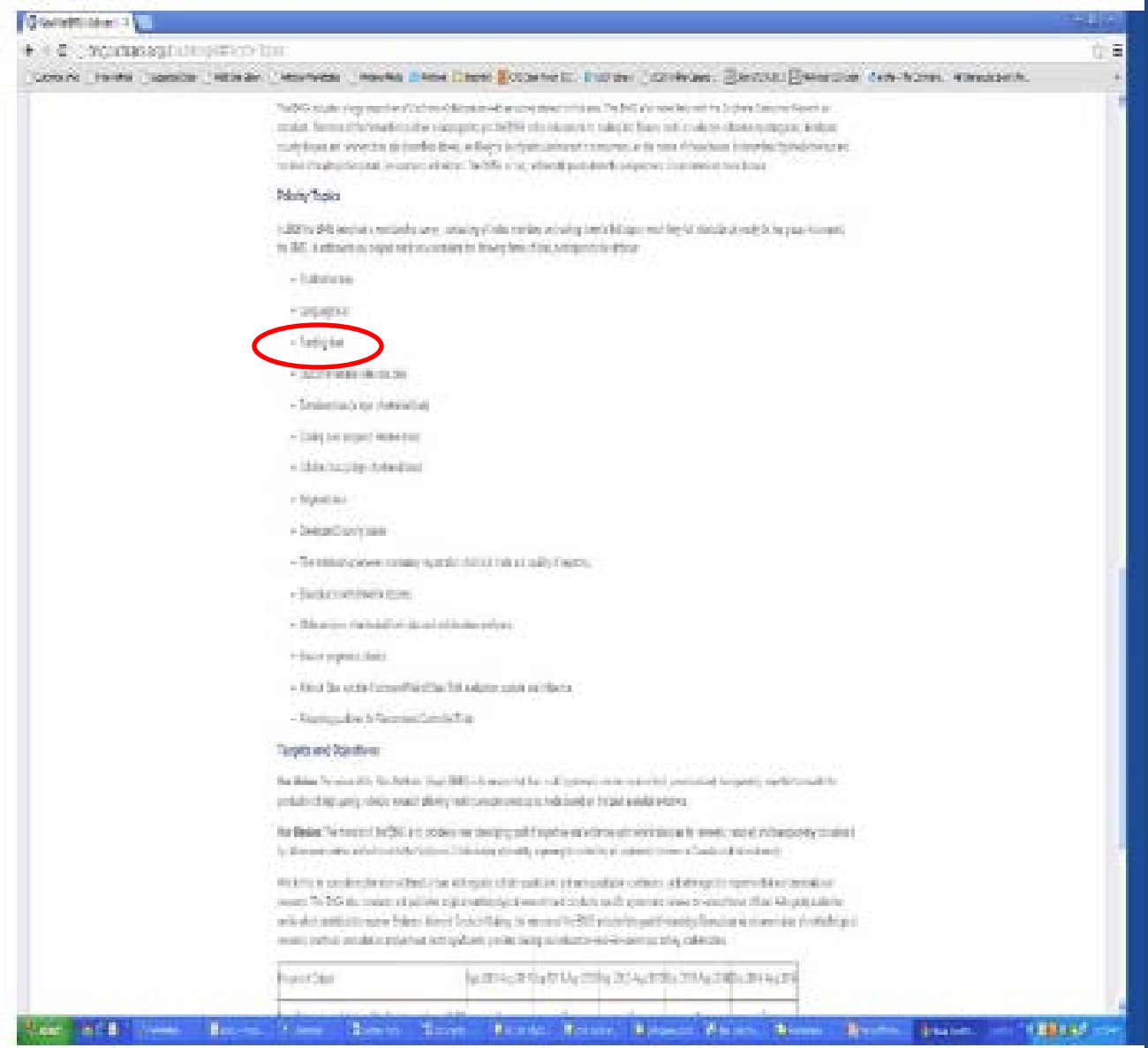
http://en.wikipedia.org/wiki/Bias_(statistics)

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.

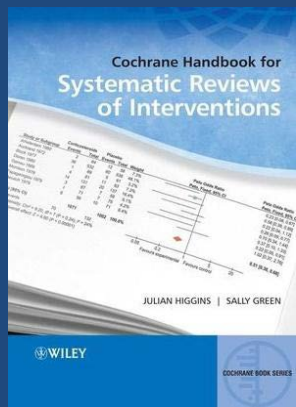


"…the BMG, in addition to our original remit now considers the following forms of bias, and topics to be of focus….funding bias"



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

THE COCHRANE COLLABORATION®

Drug studies and pharmaceutical industry funding

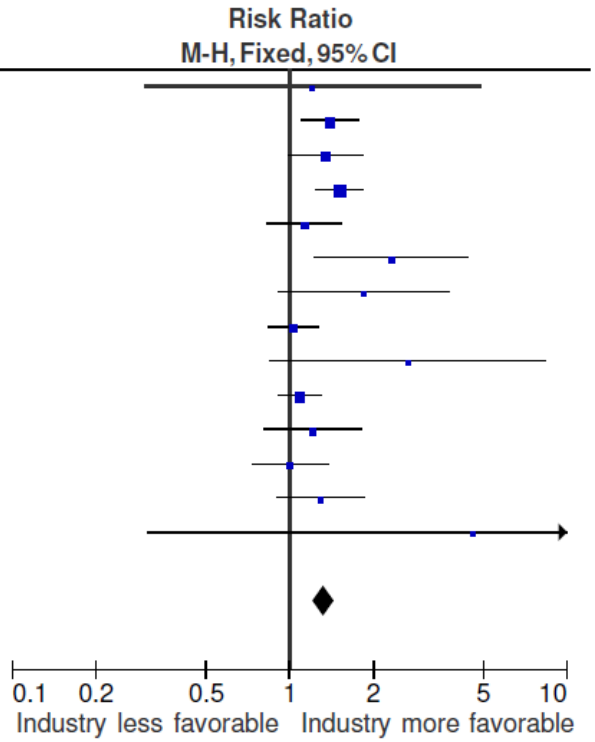
- Direction of effect: Industry studies more likely to have favorable efficacy results (1.32 [1.21, 1.44]) and harm results (1.87 [1.54, 2.27]) than non-industry sponsored studies
- Effect size: five papers found larger effect sizes in industry sponsored studies compared with non-industry sponsored studies and five papers did not find a difference in effect size.

1.1 Number of studies with favorable efficacy results

Study or Subgroup	Industry Events	Industry Total	Non-industry Events	Non-industry Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alasbali 2009	7	29	2	10	0.9%	1.21 [0.30, 4.88]
Bero 2007	65	94	48	97	13.7%	1.40 [1.10, 1.78]
Booth 2008	49	120	50	165	12.2%	1.35 [0.98, 1.85]
Bourgeois 2010	222	260	48	85	21.0%	1.51 [1.25, 1.83]
Clifford 2002	46	66	21	34	8.1%	1.13 [0.83, 1.54]
Etter 2007	25	49	9	41	2.8%	2.32 [1.23, 4.40]
Kelly 2006	12	13	4	8	1.4%	1.85 [0.91, 3.76]
Momeni 2009	20	24	69	85	8.8%	1.03 [0.84, 1.26]
Moncrieff 2003	2	2	2	7	0.4%	2.67 [0.85, 8.39]
Perlis 2005b	93	113	37	49	15.0%	1.09 [0.91, 1.31]
Rasmussen 2009	66	109	14	28	6.5%	1.21 [0.81, 1.81]
Rattinger 2009	26	36	18	25	6.2%	1.00 [0.73, 1.38]
Tulikangas 2006	15	15	7	9	2.7%	1.29 [0.89, 1.87]
Vlad 2007	5	11	0	4	0.2%	4.58 [0.31, 68.24]
Total (95% CI)		**941**		**647**	**100.0%**	**1.32 [1.21, 1.44]**
Total events	653		329			

Heterogeneity: $Chi^2 = 22.26$, df = 13 (P = 0.05); $I^2 = 42\%$

Test for overall effect: Z = 6.05 (P < 0.00001)

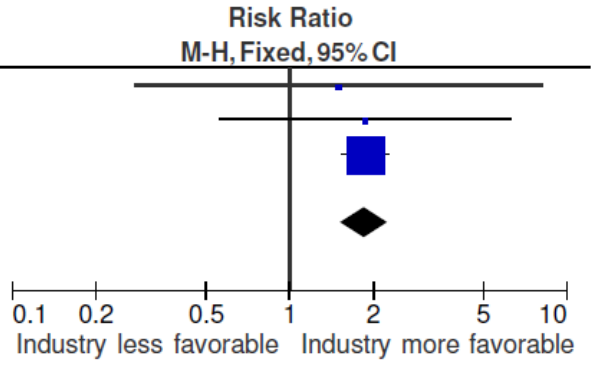


1.2 Number of studies with favorable harms results

Study or Subgroup	Industry Events	Industry Total	Non-industry Events	Non-industry Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Halpern 2005	1	3	10	45	1.4%	1.50 [0.28, 8.14]
Kemmeren 2001	3	4	2	5	2.0%	1.88 [0.56, 6.31]
Nieto 2007	180	275	80	229	96.6%	1.87 [1.54, 2.28]
Total (95% CI)		**282**		**279**	**100.0%**	**1.87 [1.54, 2.27]**
Total events	184		92			

Heterogeneity: $Chi^2 = 0.07$, df = 2 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 6.35 (P < 0.00001)



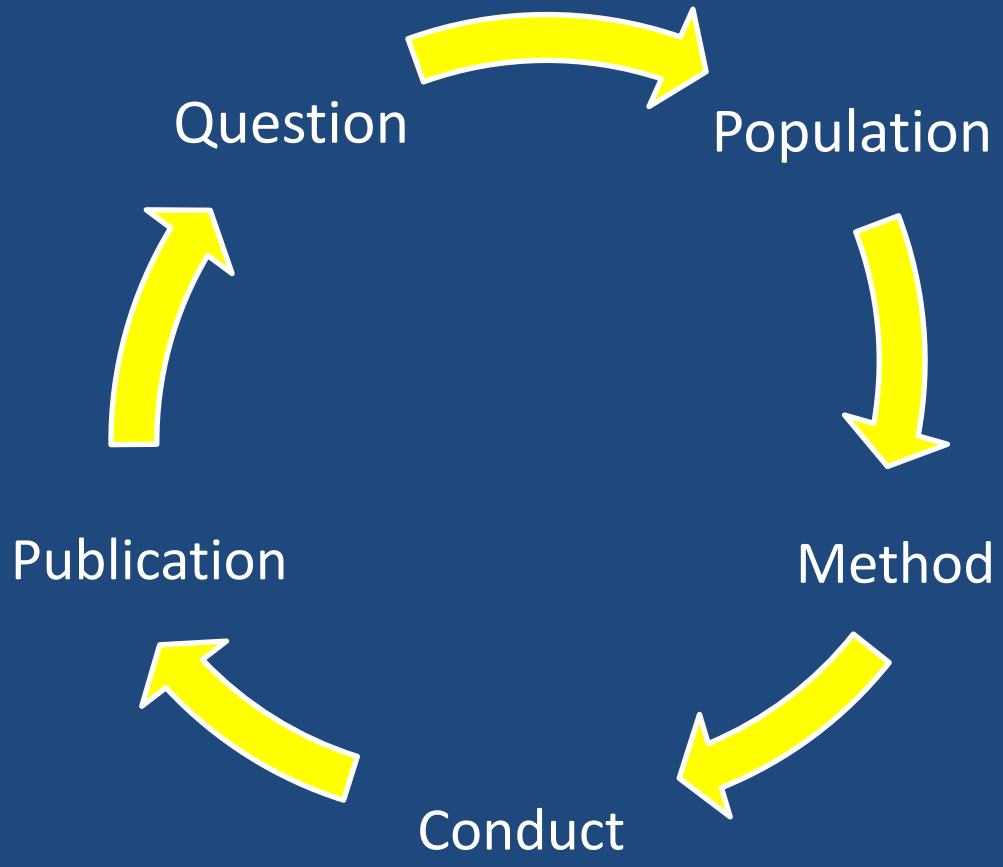
Industry sponsorship and research outcome. Lundh, et al. Cochrane Library, 2012

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



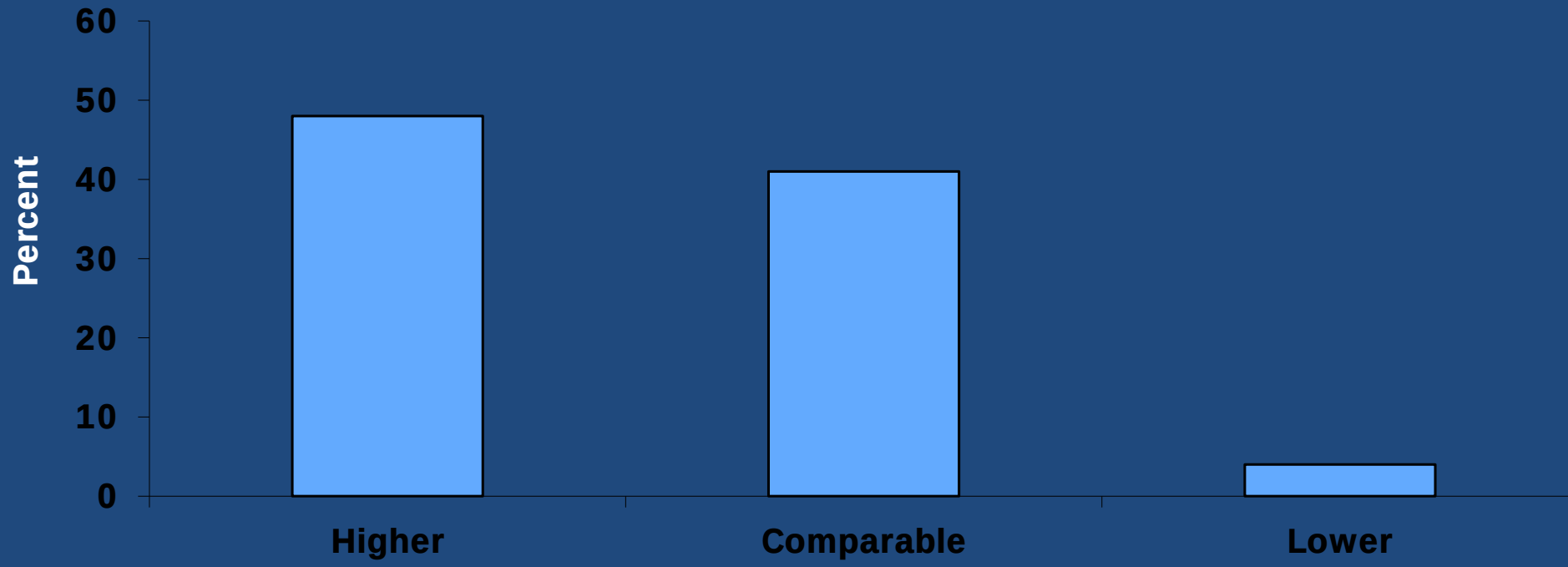
Donna H. Odierna Dr.P.H. M.S. , Susan R. Forsyth R.N. M.S. , Jenny White M.Sc. M.P.H. & Lisa A. Bero Ph.D. (2013): The Cycle of Bias in Health Research: A Framework and Toolbox for Critical Appraisal Training, Accountability in Research: Policies and Quality Assurance, 20:2, 127-141

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?

Rochon, Arch Intern Med 1994; 154: 157-63.

Unfair Dose Comparison



Dosage of Manufacturer's Drug vs. Comparison Drug

Rochon, Arch Intern Med 1994; 154: 157-63.

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)

Bero, L, Oostvogel, F, Bacchetti, P, and Lee, K. Factors associated with findings of published trials of drug-drug comparisons: Why some statins appear more efficacious than others, PLOS Medicine, 2007: 4: 6: e184 doi:10.137/journal.pmed.0040184.

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)

Characteristic	Results Favor OR (95% CI)	Conclusions Favor OR (95% CI)
Impact factor		
Quartile 4	1.97 (0.35, 10.93)	2.37 (0.36, 15.54)
Adequate blinding	**0.27 (0.08, 0.89)**	0.29 (0.07, 1.21)
Sample size		
Quartile 4	4.40 (0.84, 23.01)	**63.29 (6.65, 602.4)**
Funded by test drug company vs. comparator drug company	**20.16 (4.37, 92.98)**	**34.55 (7.09, 168.4)**

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 1| **Reporting of trial funding sources, trial author financial ties to the pharmaceutical industry, and trial author employment by the pharmaceutical industry among 151 Cochrane reviews of drug trials published in 2010***

	No of reviews reporting		
Type of conflict of interest	**Fully (for all included trials)**	**Partially (for some included trials)**	**Fully or partially**
Trial funding sources	30	16	46
Trial author-industry financial ties	2	9	11
Trial author-industry employment	0	10	10

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

Roseman, M, Turner, EH, Lexchin, J, Coyne, JC, **Bero, LA**, Thombs, BD. Reporting of conflicts of interest from drug trials in Cochrane reviews: cross sectional study. BMJ 2012;**345**:e5155.

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