
Overview of the Evidence on Sponsor Influence
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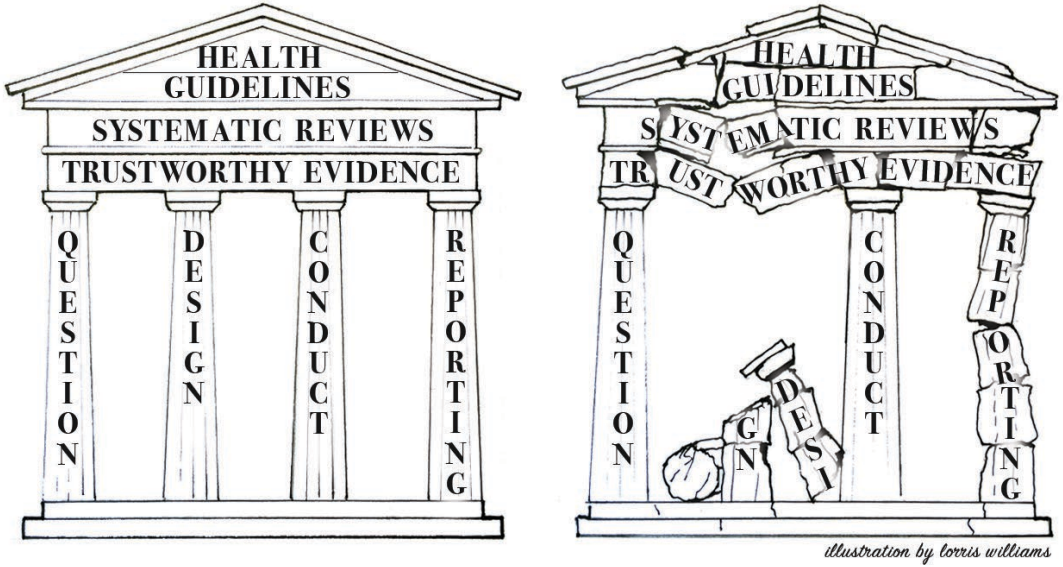
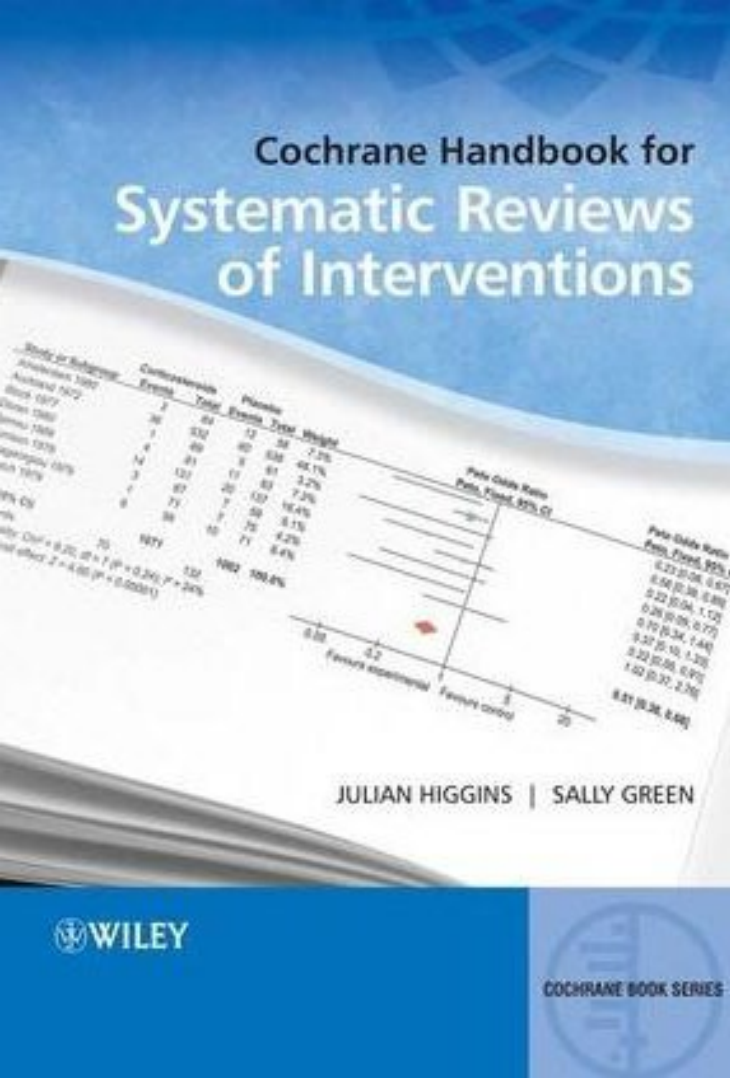
University of Colorado
Anschutz Medical Campus

Disclosure

- No funding for this presentation
- Remuneration paid to Univ of CO for service as Senior Research Integrity Editor, Cochrane
- Consulting fees - Canadian Health Products and Food Branch External Conflict of Interest (COI) Advisor
- Grant funding: NHMRC #1139997, State of CO, Greenwall Foundation, NIHR
- Prior grant funding: ORI, NIH, Ca Tobacco-related Disease Research Program, FAMRI, RWJ

Influence


HEALTH
GUIDELINES
SYSTEMATIC REVIEWS
TRUSTWORTHY EVIDENCE
QUESTION
DESIGN
CONDUCT
REPORTING
illustration by torris williams



What is bias and how can we study it?

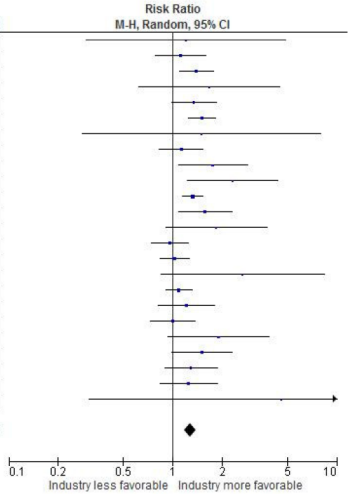
- "A **bias** is a systematic error, or deviation from the truth, in results."
    - Over or underestimate of true intervention effect

1.1 Number of studies with favorable efficacy results

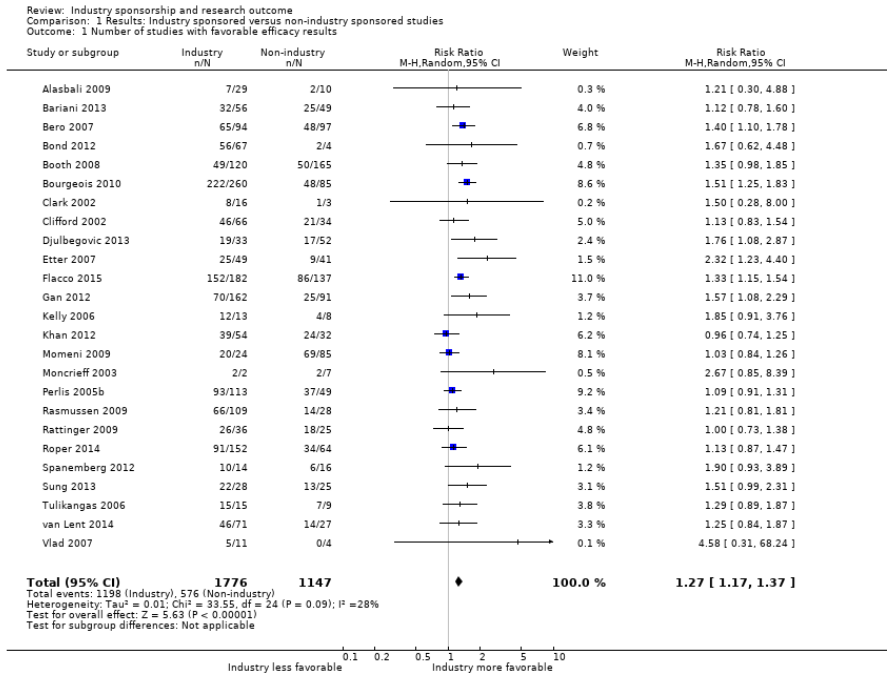
Study or Subgroup	Industry Events	Industry Total	Non-industry Events	Non-industry Total	Weight	Risk Ratio M-H, Random, 95% CI
Alasbali 2009	7	29	2	10	0.4%	1.21 [0.30, 4.88]
Bariani 2013	32	56	25	49	4.4%	1.12 [0.78, 1.60]
Bero 2007	65	94	48	97	7.2%	1.40 [1.10, 1.78]
Bond 2012	56	67	2	4	0.7%	1.67 [0.62, 4.48]
Booth 2008	49	120	50	165	5.2%	1.35 [0.98, 1.85]
Bourgeois 2010	222	260	48	85	9.0%	1.51 [1.25, 1.83]
Clark 2002	8	16	1	3	0.3%	1.50 [0.28, 8.00]
Clifford 2002	46	66	21	34	5.3%	1.13 [0.83, 1.54]
Djulbegovic 2013	19	33	17	52	2.7%	1.76 [1.08, 2.87]
Etter 2007	25	49	9	41	1.7%	2.32 [1.23, 4.40]
Flacco 2015	152	182	86	137	11.3%	1.33 [1.15, 1.54]
Gan 2012	70	162	25	91	4.0%	1.57 [1.08, 2.29]
Kelly 2006	12	13	4	8	1.4%	1.85 [0.91, 3.76]
Khan 2012	39	54	24	32	6.6%	0.96 [0.74, 1.25]
Momeni 2009	20	24	69	85	8.5%	1.03 [0.84, 1.26]
Moncrieff 2003	2	2	2	7	0.6%	2.67 [0.85, 8.39]
Perlis 2005b	93	113	37	49	9.6%	1.09 [0.91, 1.31]
Rasmussen 2009	66	109	14	28	3.7%	1.21 [0.81, 1.81]
Rattinger 2009	26	36	18	25	5.1%	1.00 [0.73, 1.38]
Spanemberg 2012	10	14	6	16	1.4%	1.90 [0.93, 3.89]
Sung 2013	22	28	13	25	3.3%	1.51 [0.99, 2.31]
Tulikangas 2006	15	15	7	9	4.1%	1.29 [0.89, 1.87]
van Lent 2014	46	71	14	27	3.6%	1.25 [0.84, 1.87]
Vlad 2007	5	11	0	4	0.1%	4.58 [0.31, 68.24]
Total (95% CI)		**1624**		**1083**	**100.0%**	**1.28 [1.17, 1.39]**
Total events	1107		542			

Heterogeneity: Tau² = 0.01; Chi² = 33.24, df = 23 (P = 0.08); I² = 31%

Test for overall effect: Z = 5.52 (P < 0.00001)



Do the results of drug studies differ by sponsor?



Comparison 1 Results: Industry sponsored versus non-industry sponsored studies, Outcome 1 Number of studies with favorable efficacy results.

Lundh, et al. Cochrane Library, 2017

25 included papers with 2923 included studies

Drug-industry sponsors compared to others (govt, nonprofits)

Studies with statistically significant efficacy results about 30% higher among industry sponsored studies compared to non-industry sponsored studies

No difference in risk of bias

Do effect sizes of nutrition study results differ by sponsor?

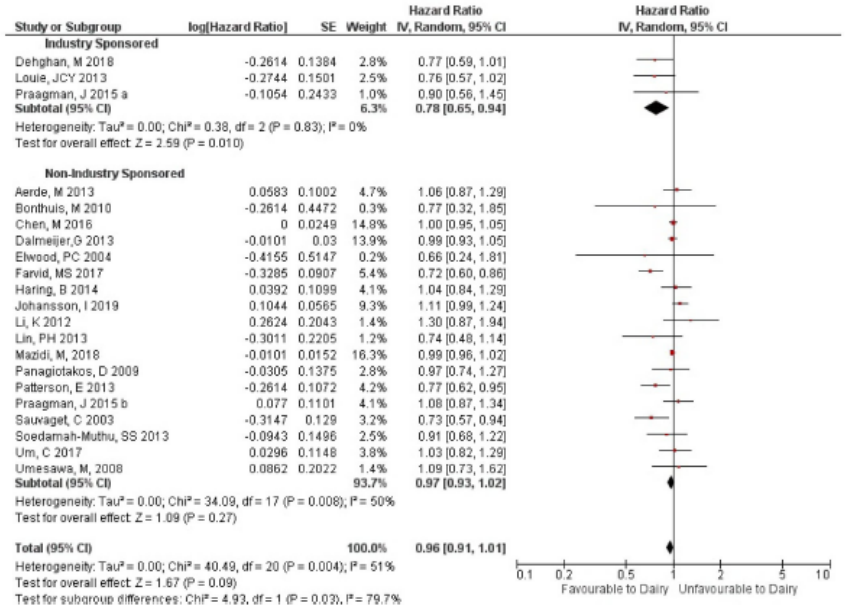


Figure 3 Effect size, cardiovascular disease: industry sponsorship versus no industry sponsorship, HR.

Chartres, BMJ Open, 2020

Do the conclusions of reviews on secondhand smoke differ by sponsor?

Factor	Odds Ratio (95% CI)
Quality	1.5 (<0.1-67.5)
Not PR vs PR	1.3 (0.3-5.4)
TI vs non-TI	88.4 (16.4-476.5)
Topic	
Lung cancer vs. multiple	1.6 (0.2-10.3)
Heart disease vs. multiple	1.6 (0.2-14.7)
Year of publication	1.1 (0.9-1.3)

Barnes and Bero 1998, JAMA

In nutrition research, is industry funding and / or author conflicts of interest associated with results or conclusions that favor the sponsor?

Yes! Conclusions *and* Results

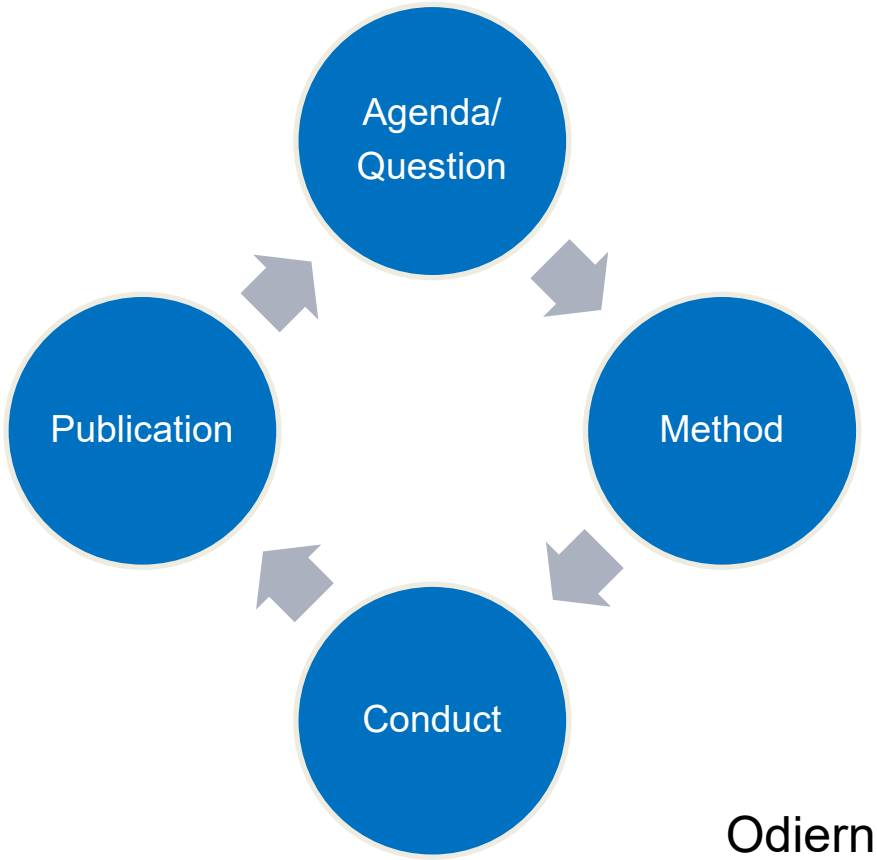
Funding bias

Conclusions

Results: statistical significance

Results: Effect sizes

The Cycle of Bias



Odierna, et al 2013

Methods


FDA
U.S. Department of
Health and Human Services
od and Drug Administration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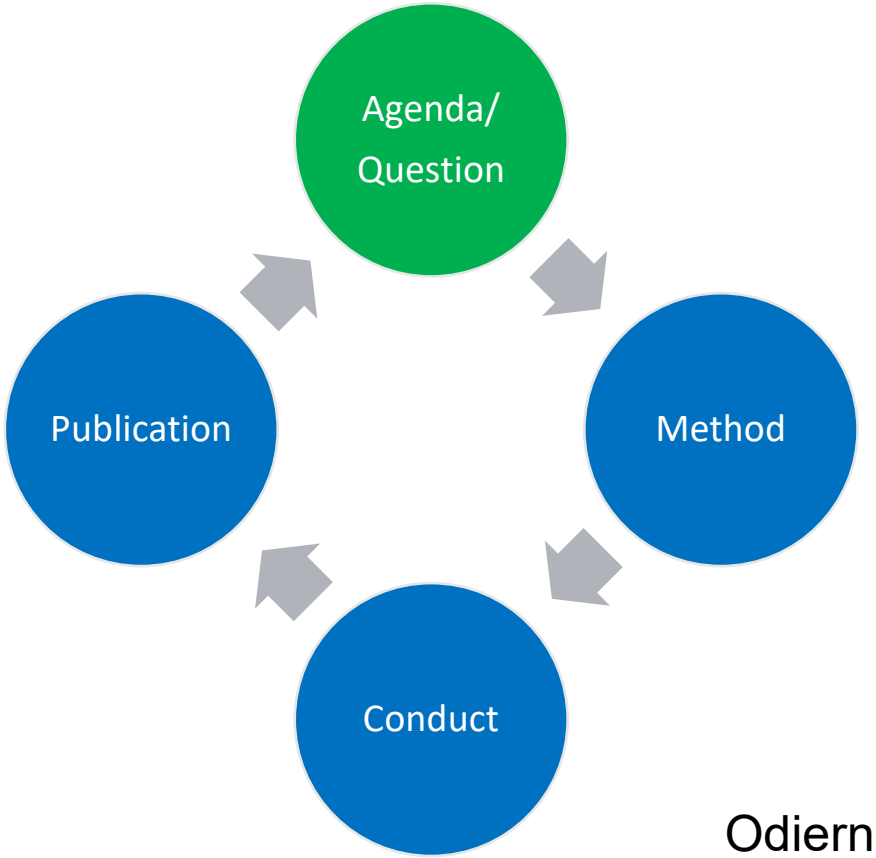
The Cycle of Bias



Odierna, et al 2013

SYSTEMATIC REVIEW

The Influence of Industry Sponsorship on the Research Agenda: A Scoping Review

Alice Fabbri, MD, PhD, Alexandra Lai, BPharm, Quinn Grundy, RN, PhD, and Lisa Anne Bero, PhD

Industry agendas not aligned with public health questions / prevention.

TABLE 1—Characteristics of Studies That Explored the Influence of Industry Sponsorship on Research Agendas: 1986–2017

Characteristic	No. (%)
Total	36
Type of study	
Cross-sectional	19 (52.8)
Content analysis	7 (19.4)
Survey	6 (16.7)
Qualitative	3 (8.3)
Systematic review	1 (2.8)
Level of evidence*	
1	4 (11.1)
2	1 (2.8)
3	2 (5.6)
4	29 (80.5)
5	0 (0.0)
Industry type	
Medically related	19 (52.8)
Tobacco	4 (11.1)
Food	3 (8.3)
Plant or animal biotechnology	3 (8.3)
Chemical	1 (2.8)
Alcohol	1 (2.8)
Mining	1 (2.8)
Not specified	4 (11.1)
Funding source of the study	
Not for profit	21 (58.3)
Mixed	1 (2.8)
None	4 (11.1)
No statement	10 (27.8)

*1 indicates the highest level of evidence and 5 the lowest; assessed using "The Oxford 2011 Levels of Evidence" from the Oxford Centre for Evidence-Based Medicine.[12]

Influencing the research agenda - nutrition

46%

V
S

12%

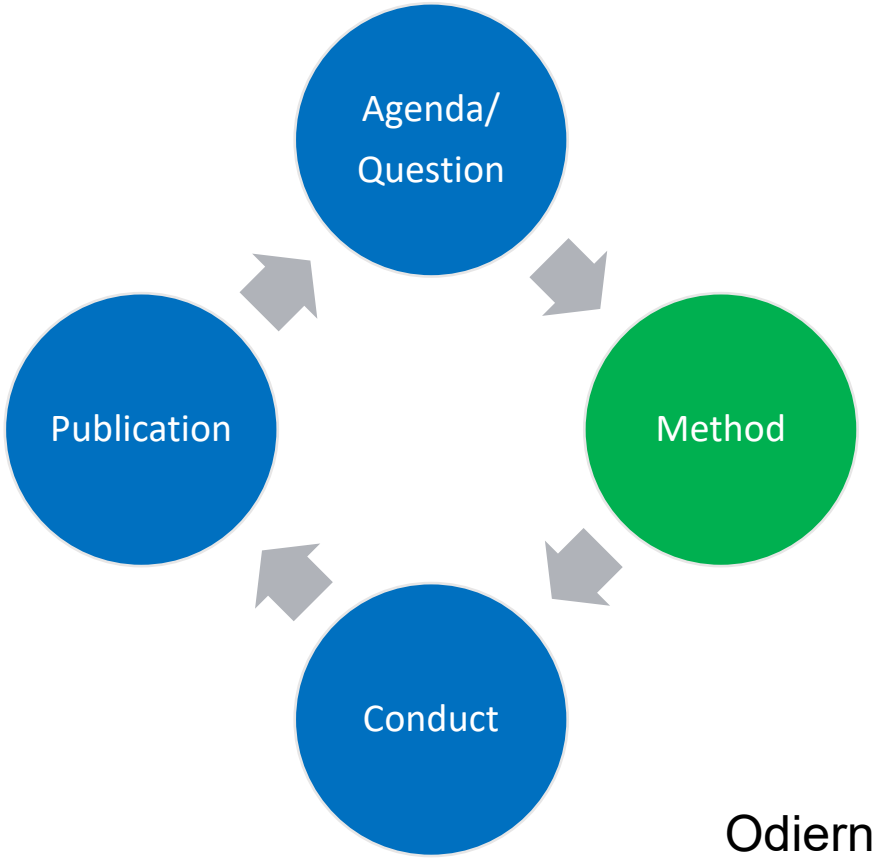
Fabbri, et al. 2018

Influencing the research agenda - tobacco

VS

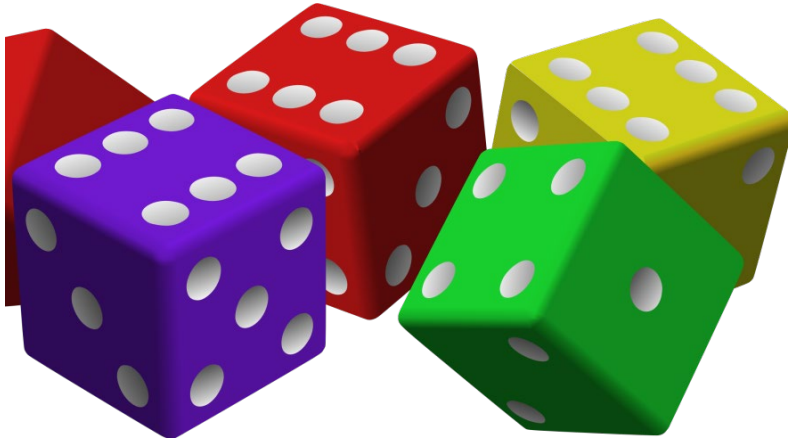
Barnes D & Bero L (1996) Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. J Health Polit Policy Law 21, 515–542.

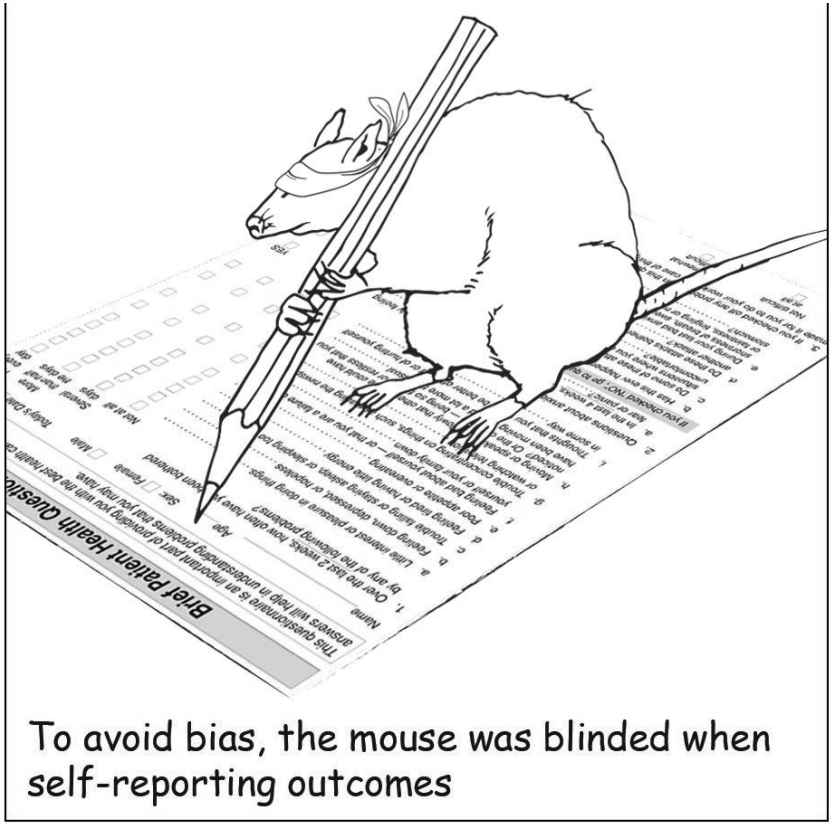
The Cycle of Bias



Odierna, et al 2013


iPod
iPod
iPod
I Got You




Brief Patient Health Questio
To avoid bias, the mouse was blinded when self-reporting outcomes

Methods

Table 3 | Conflict of interest in formula trials published between 2015 and 2020

	Independent funding (n=19)*	Formula donated by formula industry but no other industry support reported (n=7)	Formula industry funding reported (n=91)	Total
At least one author reported a conflict of interest related to formula industry	2/16 (13)	4/7 (57)	81/89 (91)	87/112 (78)
At least one author affiliated to formula industry	0/19	2/7 (29)	73/91 (80)	75/117 (64)
Formula industry sponsor involved in statistical analysis or trial reporting	—	1/6 (17)	59/75 (79)	60/81 (74)

Values are No of trials/total No of trials (%).
*Independent funding means a funding source not related to the formula industry (n=17) or authors reported that the study did not have any formal funding (n=2). Denominators vary because of lack of reporting for some variables. Source of funding was not reported for eight studies, author conflict of interest was not reported for nine studies, and role of formula sponsor in statistical analysis or trial reporting was not reported for 17 studies.

Low risk of bias related to low COI:
RR 11.36 (1.74 to 73.93)

Cite this as: *BMJ* 2021;375:n2202
http://dx.doi.org/10.1136/bmj.n2202

Who is setting the standards?

Legislating "Sound Science": The Role of the Tobacco Industry

Annamaria Baba, MPH, Daniel M. Cook, PhD, Thomas O. McGarity, JD, and Lisa A. Bero, PhD

In the late 1990s, in an effort to dispute the link between "research integrity," and draft language for the new acts. to revise its Circular A-110, which provides guidance to fe

American Journal of Public Health | Supplement 1, 2005, Vol 95, No. S1

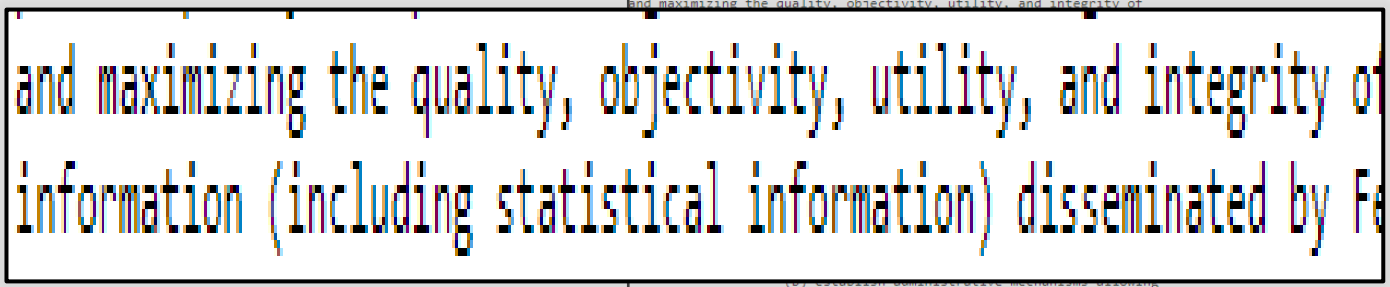
Promoting "Data Access and Quality"

- "to gain passage of federal law on criteria / standards for epidemiological studies"
    - "our plans must always include *developing the right criteria* that will favorably evaluate and be applicable to ETS [environmental tobacco smoke]"

- "to legislate public access to epidemiological data used in support of federal laws and regulations"

Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554)

Sec. 515. (a) In General.--The Director of the Office of Management and Budget shall, by not later than September 30,2001, and with public and Federal agency involvement, issue guidelines under sections 3504(d)(1) and 3516 of title 44, United States Code, that provide policy and procedural guidance to Federal agencies for ensuring and maximizing the quality, objectivity, utility, and integrity of



affected persons to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines issued under subsection (a); and

Who were the sponsors?

Tobacco Industry
Fisheries and Forestry trade organizations
Utilities and water companies
Mercury and methylene chloride producers
National Rifle Association
Food manufacturers

- *"… in order for this strategy to succeed, the tobacco industry needs to take the necessary precautions to remain in the background of the public debate and ultimately develop epidemiological criteria to evaluate the quality of research data."*

THE ACTION PLAN – Data Access and Data Quality

Demonstrate the public cares (a poll on issues of data access and rules of epidemiological studies)

Leverage / mobilize allied industries

Use scientists and technical conferences to focus on the issue (American Association for the Advancement of Science "*will offer considerable credibility to our overall effort*")

Organize coalitions for other epidemiology issues (mercury, methylene chloride)

Educate / mobilize the business community

Conduct policy briefings

Brief the media

Leverage lobbyists

And about 20 years on…….

- Promotes open access to data, rigorous methodological standards, disclosure of conflicts of interest, and acknowledgement of bias

- “Science can help provide the evidence base for public policy”

- “The integrity of science needs to be clear and the integrity of scientists…unimpeachable.”

- “Industry ..has every right to have its voice heard”

The Brussels declaration on ethics & principles for science & society policy-making

A EuroScientist Exclusive – 17th February 2017

How does The Brussels Declaration fit with the “Action Plan”?

Launched at the American Association for the Advancement of Science

Editorial in *Nature*

Originated with *‘Sci-Com’*

26 of 165 names on the Declaration were affiliated with tobacco or alcohol industries

Richard Horton, editor of Lancet, attended first meeting and was quoted as if offering an endorsement…. But had not seen later version or was aware of the Brussels Declaration

The Brussels declaration on ethics & principles for science & society policy-making

A EuroScientist Exclusive – 17th February 2017

Tips for spotting industry influence

Initiated by communications / PR firm

“bottoms up effort”

Lack of sponsorship disclosure

Nonfinancial interests are more influential than financial

“Vested interests can be beneficial”

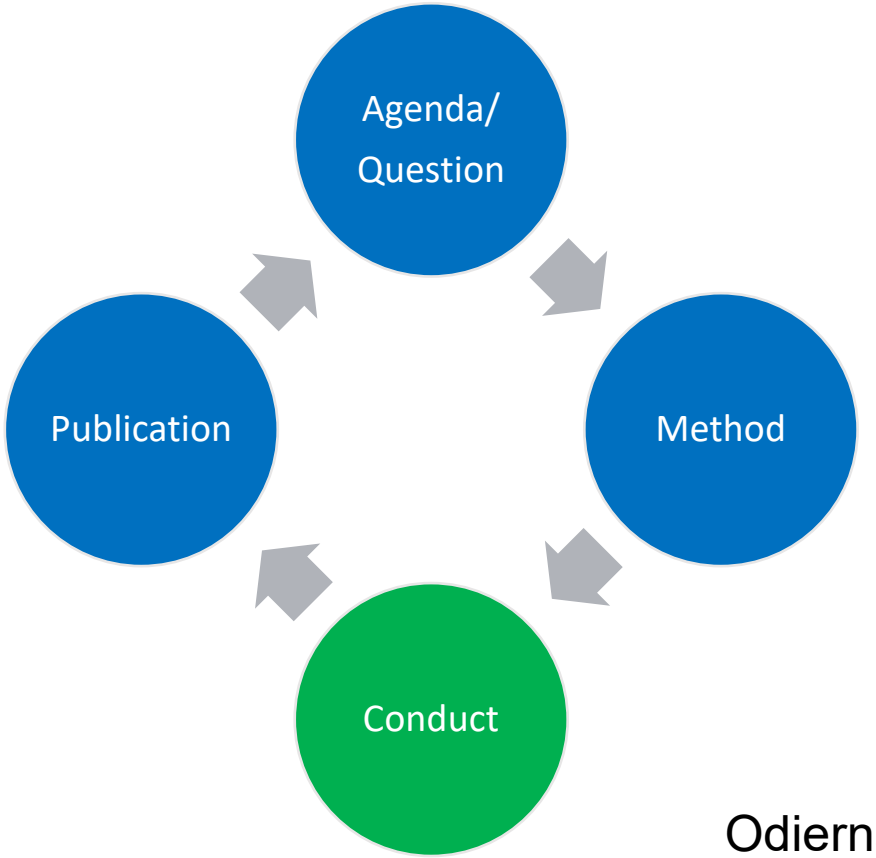
“thought leaders,” “carefully selected influencers”

“More than XX scientists from YY countries….”

Scientists are “aloof” and “arrogant”

Bero, Tobacco Control 2018

The Cycle of Bias



Odierna, et al 2013

Steinman, et al. The Promotion of Gabapentin: An Analysis of Internal Industry Documents. Ann Int Med 2006

“*Research and scientific publication*” are part of the pharmaceutical industry’s marketing strategy

“Publication Strategy” goal: to use research "to disseminate the information as widely as possible through the world’s medical literature”

Statements re sponsor involvement

Funding: This work was funded by Imperial Health Charity, grant FA1920_05. Imperial Health Charity had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report or decision to submit the article for publication. BH and RJB had

Role of the Funder/Sponsor: The Canadian Institutes of Health Research had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Are sponsors involved or not?

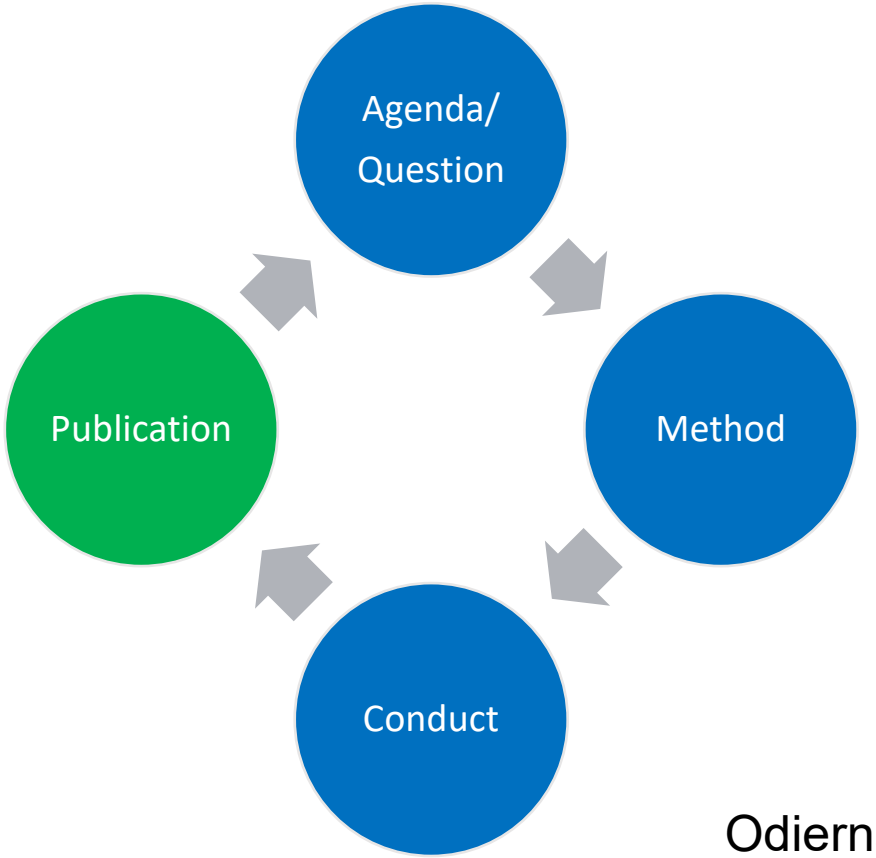
200 industry funded trials of drugs

Type of industry involvement	N	%
Design of study	183	92
Data analysis	146	73
Reporting	173	87

29 (33%) of 80 authors of these trials said that the academic author had the “final say.”

Rasmussen et al. BMJ 2018;363:k3654

The Cycle of Bias



Odierna, et al 2013

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July 31, 1995

O. Brandicourt, M.D. (PD, Product Planning, Morris Plains, NJ USA)

Neurontin® Marketing Assessments

Enclosed is the final version of the Marketing Assessment for Neurontin® in neuropathic pain and spasticity.

The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published, but there is no intention to fully develop this indication at this point. No investment is recommended for spasticity.

The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published, but there is no

WL 07520

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No overt difference in the trial methodology or the patients, which could explain the difference in the results between 945-77 and 945-177, has been detected. The question was raised whether it would be possible to investigate the patient history (primary care physician records) to determine if patient alcoholism could have been involved or patient screening was adequately performed.

ACTION:

- The results of 945-177 will not be published, nor will the combined results of 945-77 plus 945-177 be published.
- The effort required to investigate the potential cause for the difference in results between 945-77 and 945-177 was deemed not feasible relative to the potential need for such explanation. It was decided not to pursue any further investigation to explain the difference.

- 945-78, the open-label extension of 945-77, which permits Neurontin doses to be increased as high as deemed necessary, will be completed by year end 1997.

II. Monotherapy F

- Based on the cl… The results of 945-177 will not be published …t) and 945-77 (efficacy … should be sufficient to s…

- 945-82 (inconclusive results — doses not statistically different) must be included in the dossier for safety data, but is not considered a pivotal trial.
- 945-177 will be included in the dossier for safety data separate from and combined with 945-77.
- After review and discussion of the registration alternatives, national vs. mutual recognition vs. centralized, it was determined that national filings would permit individual countries to obtain faster registration (in some cases) while maintaining the current national labeling (considered favorable in some countries).

ACTION:

- Based on these discussions it was decided to submit national application in Europe.
- The clinical expert report will be prepared by **Dr. David Chadwick.**

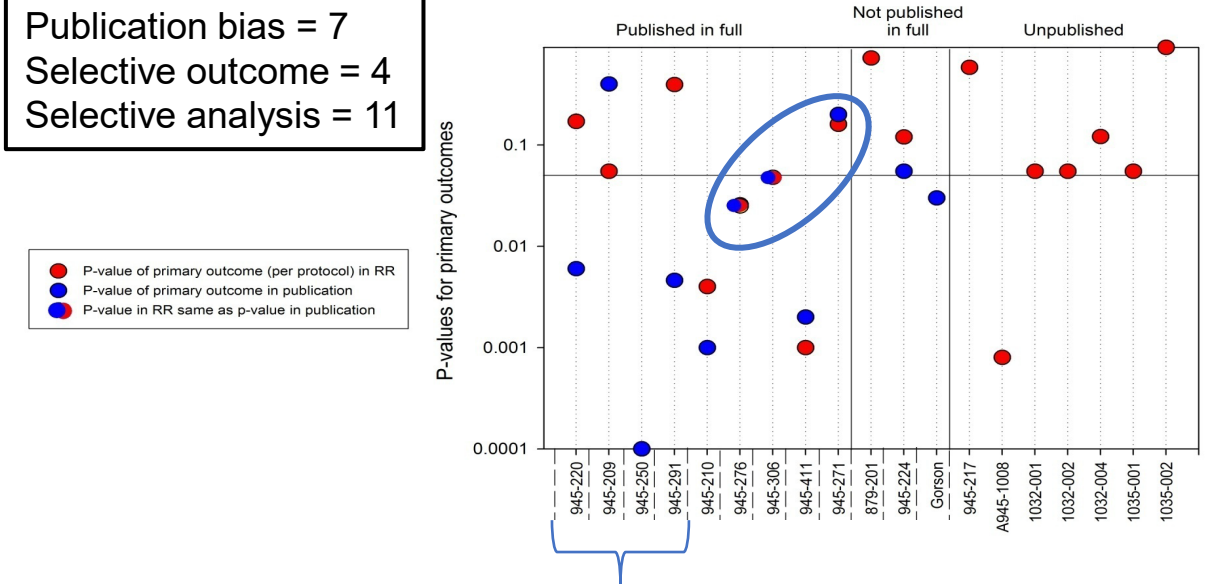
- It is anticipated that the Neurontin monotherapy claim will be fairly broad and similar to the following:

> "Neurontin is an anti-epileptic for monotherapy or add-on therapy in patients with partial seizures or partial seizures with secondary generalization, including patients with newly diagnosed seizures at doses of 900 mg to 3600 mg per day in divided doses (TID)."

- PD Italy and France will need to renegotiate pricing when monotherapy will be registered if the labeling is not indication and dose specific. Specific labeling, i.e., "900 mg per day is the usual maintenance dose for naive patients," could eliminate the need for price negotiations.

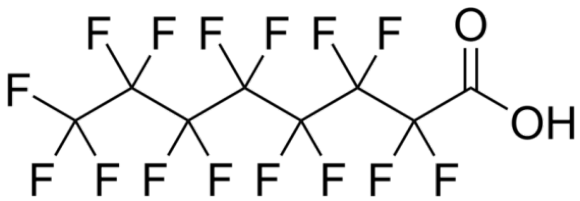
19 trials

Publication bias = 7
Selective outcome = 4
Selective analysis = 11



Did not report primary outcome

Vedula, et al. Outcome reporting in industry-sponsored trials of Gabapentin for off-label use. *New England Journal of Medicine* 2009.



“better late than never”

In collaboration with Tracey Woodruff and Nadia Gaber, UCSF

Breaking the cycle

Breaking the cycle: The Evidence

- Public prioritization of research agendas and funding
- Recognize industry funding and conflicts of interest as a source of bias and account for it
- Open data for all- Published protocols / registered reports
- Eliminate it – at a structural level
- Rethink funding and COI disclosures
- Independent publishers of research

Commercial influence in health: from transparency to independence

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Editorials

Commercial interests, transparency, and independence: a call for submissions

BMJ 2019 ; 365 doi: https://doi.org/10.1136/bmj.l1706 (Published 16 April 2019)
Cite this as: *BMJ* 2019;365:l1706

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COMMERCIAL INFLUENCE IN HEALTH: FROM TRANSPARENCY TO INDEPENDENCE

Achieving greater independence from commercial influence in research

As part of The BMJ's campaign for greater independence from commercial influence in the creation and use of evidence, **Joel Lexchin and colleagues** outline some approaches to minimise bias in clinical trials

Joel Lexchin, [1,2,3] Lisa A Bero, [4] Courtney Davis, [5] Marc-Andre Gagnon [6]