Taming the Beast: Managing Conflicts of Interest in Research

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Conflict of interest: What is it?

- Circumstances that create a risk that professional judgments or actions regarding a primary interest will be unduly influenced by a secondary interest
- A risk--not necessarily the existence of biased judgment or action
- It's real – not potential

What did you say!?

- Conflict of interest
- Competing interest
- Vested interest
- Financial ties
- Non-financial ties
- Anything to disclose?

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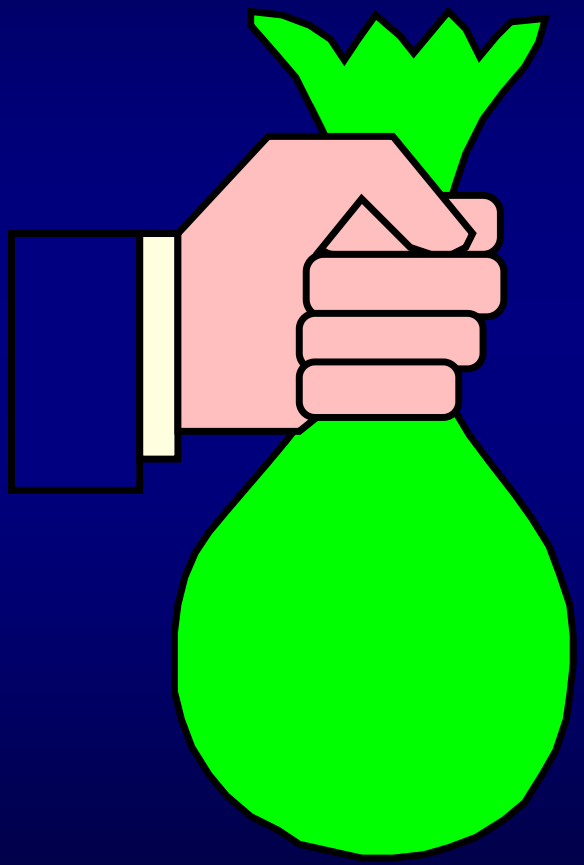
Duality of interest This study was partially funded by a grant from AstraZeneca.

Diabetologia (2008) 51:1731–1740
DOI 10.1007/s00125-008-1060-6

Why do we care about COI?



- Industry funding for research, education is substantial
- A growing number of clinicians also have personal financial ties to their sponsors
- Financial ties = conflicts of interest
- COI associated with bias

Company	Events Reported (*n*)	Details of Company-Sponsored Functions[a] (% of All Functions Sponsored by the Company)			
		Journal Club or Grand Rounds	Hospital or Professional Rooms	Restaurant, Hotel, or Function Centre	Average Cost/Head (AUD$) Spent on Hospitality
AstraZeneca	1,310	43.0	61.3	35.1	$40.37
Pfizer	1,266	38.9	52.5	41.4	$34.81
Sanofi Aventis	1,119	21.6	66.8	29.0	$48.12
Jannsen Cilag	1,080	28.6	64.2	32.4	$33.96
Eli Lilly	940	17.4	60.2	38.1	$47.38
Novartis	927	10.4	79.9	17.7	$56.22
Roche	776	18.3	78.0	18.9	$29.25
GlaxoSmithKline	738	18.6	57.6	37.0	$37.24
Merck Sharp Dohme	734	20.0	74.0	23.6	$26.81
Servier	608	8.6	57.7	39.8	$48.35
Wyeth	501	26.7	45.7	51.9	$56.33
Alphapharm	441	0.0	89.3	10.7	$18.24
Merck Serono	397	6.8	77.8	15.6	$18.78
Novo Nordisk	372	13.4	73.9	23.4	$22.65
Amgen	357	22.4	68.3	27.2	$43.55
Boehringer Ingelheim	340	0.0	0.3	99.1	$69.80
Organon	275	17.1	49.5	46.5	$42.58
Abbott	249	16.5	75.5	22.5	$31.18
Mundipharma	205	37.1	57.6	36.1	$32.76
Schering Plough	190	15.8	23.2	74.2	$65.24
Nycomed	165	14.5	15.2	77.6	$77.10
Bayer	158	3.8	34.8	59.5	$47.44
Allergan	155	0.0	29.0	58.7	$55.09
BristolMyersSquibb	151	0.0	15.2	76.8	$95.26

The educational event reports were downloaded as pdf files and converted into Excel spreadsheets; a coding scheme was devised by two authors (EW and JR). The codes were designed to differentiate the events based on: the duration; type of event; whether there were continuing professional development (CPD) or medical education (CME) points awarded; the venue; the professional status of attendees; the hospitality provided; and the cost of the hospitality. A number of companies specifically stated they were "not responsible" for the educational content of some events and we coded separately for these. The "not responsible" code included descriptors such as "topic set by hospital," "third party organisation," "external training company," or "sponsorship only." A series of primary analyses were conducted in Excel, providing descriptive statistics about the events sponsored by each company, and overall summary statistics. Ethics approval was not required to examine these publicly available data.

[a]An independent audit of the first posting of educational events was commissioned by Medicines Australia, with 951 events identified as requiring review. Further

Robertson J, Moynihan R, Walkom E, Bero L, Henry D (2009) Mandatory Disclosure of Pharmaceutical Industry-Funded Events for Health Professionals. PLoS Med 6(11): e1000128.

Why do we care about bias?

- Empirical evidence of bias
  - Research
  - Guidelines / recommendations
  - Prescribing / purchasing decisions
- Multiplicative effect in medical literature … and elsewhere
- Erodes evidence-base for health care decisions
- We may “do no good” or “more harm than good”

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Expanding Disease Definitions in Guidelines and Expert Panel Ties to Industry: A Cross-sectional Study of Common Conditions in the United States

Raymond N. Moynihan[1]*, Georga P. E. Cooke[1], Jenny A. Doust[1], Lisa Bero[2], Suzanne Hill[3], Paul P. Glasziou[1]

- US diagnostic guidelines published 2000-2013
- 16 publications on 14 conditions – 10 widened the definitions of disease
- Among 14 panels with financial disclosures – on average, 75% of panel members had industry ties; twelve were chaired by people with ties

2013 Adult Treatment Panel IIII

- New guidelines will “increase the number of healthy people for whom statins are recommended by nearly 70%”
    - J Abramson and R Redberg, NYT, Nov 13, 2013
- Under the new guidelines, 56 million Americans ages 40-75 are eligible to consider a statin; 43 million were under the old advice. Both numbers include 25 million taking statins now.

5 pages of financial disclosures: 7 conflicted, 8 not conflicted panel members

Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol in Adults to Reduce Atherosclerotic Cardiovascular Risk

Panel Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Expert Witness
Neil J. Stone *Chair*	Northwestern Memorial Hospital—Bonow Professor of Medicine, Feinberg School of Medicine, Northwestern University	2008-2012: None	2008-2012: None	2008-2012: None	2008-2012: None	2008-2012: None
		2013: None	2013: None	2013: None	2013: None	2013: None
Alice H. Lichtenstein *Co-Chair*	Tufts University, USDA Human Nutrition Research Center on Aging—Gershoff Professor of Nutrition Science and Policy; Professor of Public Health and Family Medicine	2008-2012: None	2008-2012: None	2008-2012: None	2008-2012: None	2008-2012: None
		2013: None	2013: None	2013: None	2013: None	2013: None
Jennifer Robinson *Co-Chair*	University of Iowa—Professor of Epidemiology and Medicine; Prevention Intervention Center—Director	2008-2012: None	2008-2012: None	2008-2012: None	2008-2012: • Aegerion • Amarin* • Amgen* • AstraZeneca* • Esperion • Genentech/Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/Regeneron *	2008-2012: None
		2013: None	2013: None	2013: None	2013: • Amarin* • Amgen* • AstraZeneca* • Genentech/Hoffman LaRoche* • GlaxoSmithKline* • Merck* • Sanofi-aventis/Regeneron*	2013: None

Case: Guideline Panel member…

- Has been paid by a relevant company to attend the meeting, meeting not industry sponsored
- Receives consulting fees from companies whose products will be considered for guideline (1 vs 15)
- Is co-author on almost every published trial of the products, funded by manufacturer
- Submitted a negative disclosure, but panel staff happens to notice disclosures of relevant financial ties in publically available databases

BMJ

RESEARCH

Financial ties and concordance between results and conclusions in meta-analyses: retrospective cohort study

Veronica Yank, clinical instructor,[1] Drummond Rennie, professor,[2] Lisa A Bero, professor[3]

124 meta-analyses evaluating antihypertensive medicines in non-pregnant adults

Variable	Favorable Results Odds ratio (CI)	Favorable Conclusion Odds ratio (CI)
Financial ties with one drug company	0.99 (0.44-2.23)	5.11 (1.54-16.92)
Methodology	1.16 (1.06-1.27)	1.07 (0.97-1.19)

Case: A systematic review

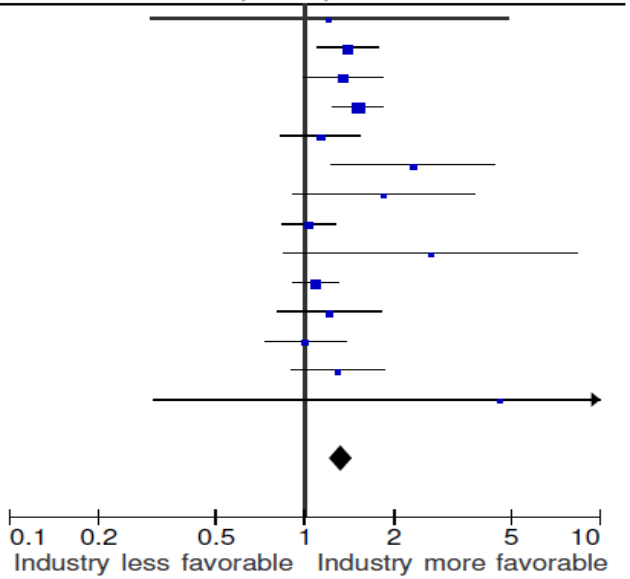
- A proposed systematic review is to be funded by a government agency. The review could recommend pharmacological treatments.
- One author of the systematic review has financial ties (honoraria, research funding) with a company that makes one of the considered pharmacological treatments.
- One author has only research funding (has been a PI on trials funded by the company)
- The review has 2 additional authors with no conflicts.

Empirical evidence: Funding bias

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			

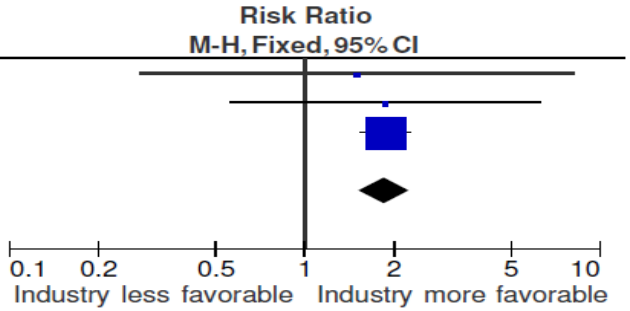
Heterogeneity: Chi² = 22.26, df = 13 (P = 0.05); I² = 42%
Test for overall effect: Z = 6.05 (P < 0.00001)



1.2 Number of studies with favorable harms results

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			

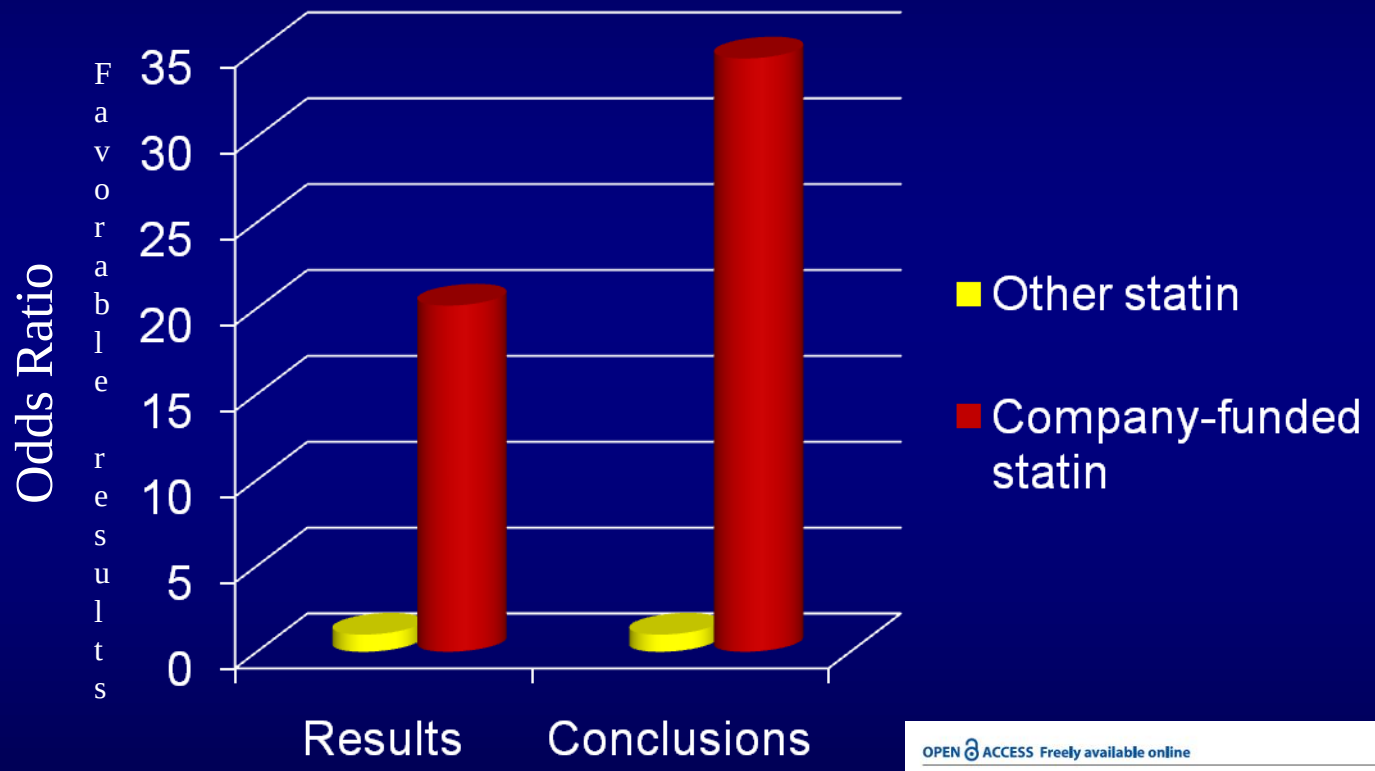
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 6.35 (P < 0.00001)



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

Which statin is better?

… the one made by the company that funded the study



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Factors Associated with Findings of Published Trials of Drug–Drug Comparisons: Why Some Statins Appear More Efficacious than Others

Lisa Bero[1*], Fieke Oostvogel[2], Peter Bacchetti[3], Kirby Lee[4]

Case: Trialist, Dr. Jane Dough

- Invented an insulin delivery system (drug)
- Founder of Gluco-gone which has an exclusive license for the drug
  - 55% of stock, 0$
  - $5000 honoraria annually
  - $40,000 consulting fee
- Gluco-gone partners with venture capital group and Diabetes Society
  - Dr. Dough on Education Committee of Diabetes Society, 0$
- Gluco-gone funds a multi-center RCT of drug, Dr. Dough is a Principal Investigator

So what is going on?

Odierna DH , Forsyth SR, White J, Bero LA (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

“Reporting Bias”

Selective reporting of an entire study (“*publication bias*”)

Selective reporting of outcomes (“*selective outcome reporting*”)

Selective reporting of analyses (“selective analysis bias”)

Are all the data submitted to the FDA published?

Examined all approved new drug applications (NDAs) for new molecular entities (NMEs) from 2001-2002 and all published clinical trials corresponding to the efficacy trials referred to within the NDAs.

33 NDAs with 164 trials

(1 – 13 efficacy trials per NDA)

Of 164 Trials submitted in NDAs…

PUBLISHED within 5 years: 78% (128)

OF 33 NDAs….

ALL trials published: 52 % (17)

NO trials published: 2 (with a total of 5 trials)

Rising, K, Bacchetti, P, and **Bero, L**. Reporting bias in drug trials submitted to the Food and Drug Administration . *PLoS Medicine*, 2008; 5 (11) e217 doi:10.1371/journal.pmed.0050217.

Papers include more outcomes favoring the test drug

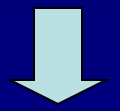
- Outcomes were omitted from papers
  - Of 179 primary outcomes reported in NDAs, 41 did not appear in any papers
- 5 outcomes changed statistical significance
- Outcomes appeared in papers
  - PLUS 15 additional outcomes that favored the test drug
  - PLUS 2 other neutral outcomes

‘Downstream’ effects of reporting bias

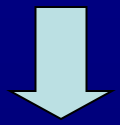
Over-estimation of treatment efficacy

&

Under-estimation of drug harms



Systematic reviews & meta-analyses



Policymakers’ decisions & clinical guidelines

Patient care

Effect of unpublished FDA data on meta-analytic estimates for drug efficacy in RCTs

Drug class	# of Meta-Analyses	# of Meta-Analyses with no change in meta-analytic estimate for drug efficacy	Meta-Analyses with an INCREASE in meta-analytic estimate for drug efficacy		Meta-Analyses with an DECREASE in meta-analytic estimate for drug efficacy	
			# of meta-analyses	Range of Increase	# of meta-analyses	Range of Decrease
Migraine	19	2	9	2% to 37%	8	1% to 25%
Antipsychotic	3	-	1	166%	2	24% to 53%
Dementia/ Alzheimer's	2	-	-	-	2	22% to 24%
Anti-hypertensive	7	1	3	8% to 37%	3	2% to 24%
Antibiotics	2	-	1	4%	1	11%
Topical Anti-inflammatory	8	-	5	3% to 109%	3	5% to 23%
TOTAL	**41**	**3**	**19**	**2% to 166%**	**19**	**1% to 53%**

Hart, B, Lundh, A and Bero, L. The effect of reporting bias on meta-analyses of drug trials: Re-analysis of meta-analyses. BMJ, 2011;343:d7202. doi: 10.1136/bmj.d7202

What have we learned from drug industry documents?

- **Drug Industry Document Archive (DIDA)**
- **http://dida.library.ucsf.edu**

Research and scientific publication are part of the pharmaceutical industry's marketing strategy

The Promotion of Gabapentin: An Analysis of Internal Industry Documents. Ann Int Med 2006
Michael A. Steinman, MD, Lisa A. Bero, PhD, Mary-Margaret Chren, MD, C. Seth Landefeld, MD

“Publication strategy”

- **Goal: to use research not as a means to gain FDA approval for new indications but “to disseminate the information as widely as possible through the world’s medical literature”**

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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

CONFIDENTIAL

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 t) and 945-77 (efficacy should be sufficient to s

The results of 945-177 will not be published

◆ 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.**

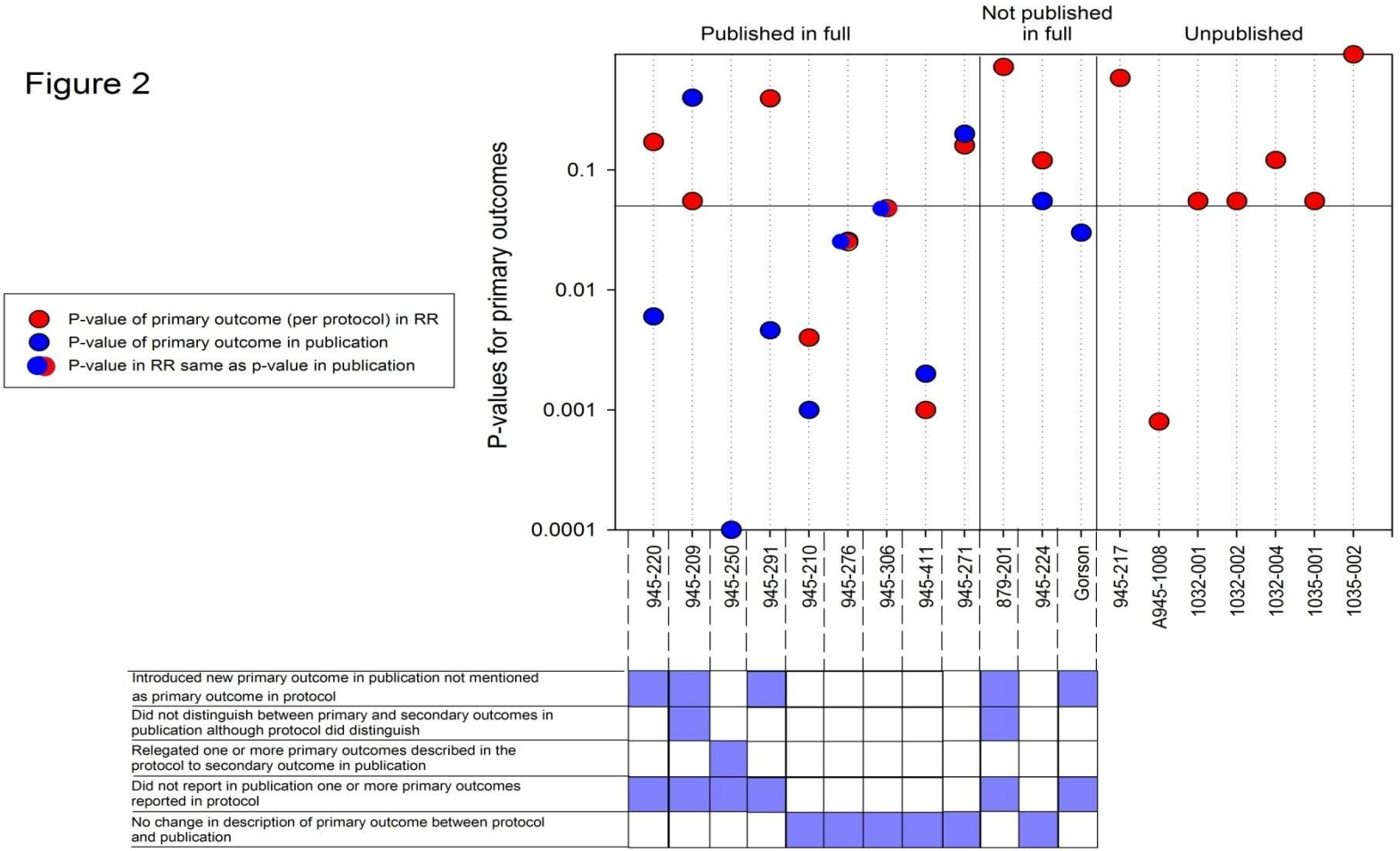
◆ It is anticipated that the Neurontin monotherapy claim will be fairly broad and similar to the following:

> "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.

V047122

Figure 2



Vedula, S, **Bero, L**, Scherer, R, Dickersin, K. Outcome reporting in industry-sponsored trials of Gabapentin for off-label use. *New England Journal of Medicine*, 2009; 361(20): 1963-1971.

Seeding Trials

Seizure 2000; **9**: 241–248
doi: 10.1053/seiz.2000.0407, available online at http://www.idealibrary.com on IDEAL

Efficacy of gabapentin as adjunctive therapy in a large, multicenter study

M. J. MORRELL[*], M. J. MCLEAN[†], L. J. WILLMORE[‡], M. D. PRIVITERA[§], R. E. FAUGHT[¶], G. L. HOLMES[‖], L. MAGNUS[¶], P. BERNSTEIN[¶] & A. ROSE-LEGATT AND THE STEPS STUDY GROUP[¶]

[*]*Columbia University, The Neurological Institute, New York, NY, USA;* [†]*Vanderbilt University Medical Center, Nashville, TN, USA;* [‡]*University of Texas Health Science Center Medical School, Houston, TX, USA;* [§]*University of Cincinnati Medical Center, Cincinnati, OH, USA;* [¶]*University of Alabama School of Medicine, Birmingham, AL, USA;* [‖]*Harvard Medical School, Boston, MA, USA;* [**]*Parke-Davis Pharmaceuticals, Morris Plains, NJ, USA*

- **Uncontrolled open-label study; gabapentin titrated up to 3600 mg/day (twice the maximum FDA-approved limit)**
- **700 physicians enrolled 2100 patients**
- **Published report: “examined the effectiveness of gabapentin” in this dose range**

STEPS

- Goal: Teach Physicians to Titrate Neurontin to Clinical Effect

- Study Highlights:
  - Expand Physician Experience with Neurontin
  - Establish Broad Patient Types Appropriate for Neurontin Therapy
  - Pre-empt Launch of Lamictal

Case: You don't know…

- You have been invited to give a presentation at a medical society meeting. The topic is quality use of medicines.
- When you arrive, you are informed that the session in which you are speaking (including your honorarium) and the following lunch are sponsored by a single drug company.

“Medical education drives this market!!”

Target audience

- "Thought leaders," "key influencers," and "movers and shakers"
- Residents
  - "in order to influence physicians from the bottom up" and "to solidify Parke-Davis' role in the resident's mind as he/she evolves into a practicing physician."

TOPICS

- Applying Evidence-Based Medicine to Clinical Practice
- Understanding Statistical vs Clinical Significance
- Understanding Absolute Risk, Relative Risk, and NNT in Research and Practice
- Association vs Causation

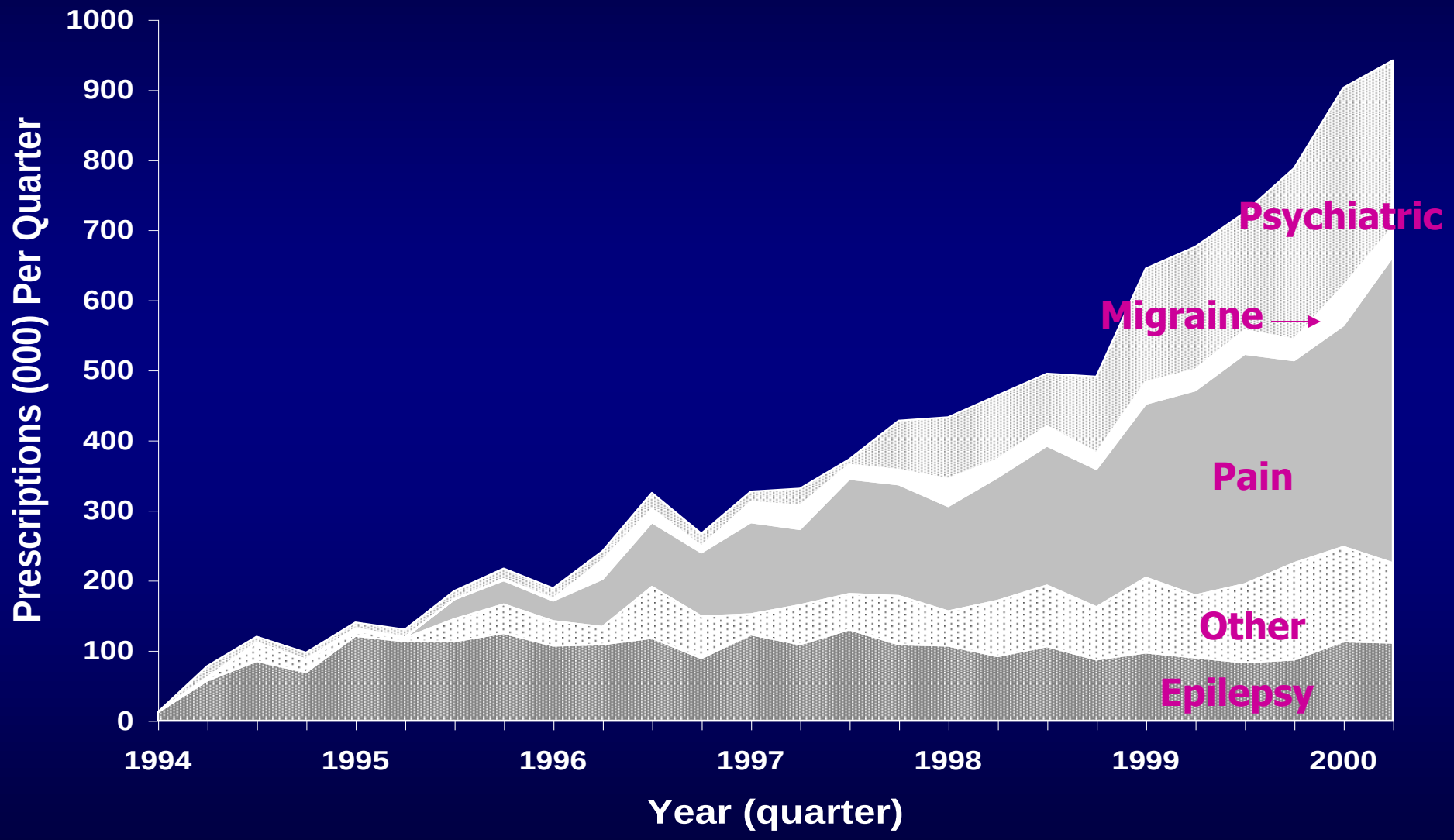
Case: The enterprising students

- 2 students working at different institutions develop a hand held diagnostic device for use in the field
- They copyright the software, file for a patent for the device, and form a company to market the device
- They each own 50% of the company = 0$
- Propose a multi-site study to collect data on the sensitivity and specificity of the device – they will be Co-Principal Investigators and collect the data

Clinical Practice

What we say is not the same as what we do!

Gabapentin: "indicators of success"



What do we do about conflicts of interest?

Ban → Manage → Disclose

Reviewing Conflicts

- Disclose to institution
  - Who, what, when, how much, how often?
- Review by institution
  - COI committee?
- Is there a conflict?
- Management strategy
- Monitoring / enforcement of management strategy

Why a committee?

- **"What are the problems of having financial relationships with sponsors? This should not be an issue to even discuss. If the investigators decide to take on a project with any sponsors or a sponsor is willing to fund a project, that is a FAVOR to the university."**
- **"I recognize that I am in conflict, but believe that I can handle it. If I couldn't handle the conflict, I wouldn't have gotten involved."**
- **"There is no conflict. I am the best one to determine if there is a conflict."**
- **"I can manage the conflict."**

Lipton, S, Boyd, E, and **Bero, LA**. Conflicts of interest in research: Policies, processes and attitudes, Accountability in Research 2004; 11: 83-102.

Committee Members

- Diverse backgrounds / continuity
- Decisions to be made are: 1) Is this a significant conflict that requires management? 2) If yes, what is the management strategy?
- Appeal process: Individuals are allowed to appeal and appear in person at a later meeting.

Factors considered to manage COI

- Length or nature of involvement with sponsor, number of relationships
- Type of sponsor
- Separation between sponsored project and investigator's paid activities
- Risks to human subjects
- Risk of bias
- Culture of the institution

Boyd, Lipton and Bero.
Health Affairs, 2004

Clinical Practice Guidelines

- Sources of bias:
  - Commercial sponsorship of guideline development
  - Conflicts of interest among guideline committee members
  - Conflicts of interest for underlying evidence review

Norris, SL, Burda, BU, Holmer, HK, Ogden, LA, Fu, R, **Bero, L**, Schunemann, H and Deyo, R. *J Clin Epidemiol*. 2012 Jul; 65(7):725-33.

Risk Model

1) Commercial Sponsorship + Financial Ties → High Risk → Management: Prohibited
2) Commercial Sponsorship + No Financial Ties → Moderate Risk → Management: Firewalls/General Fund
3) No Commercial Sponsorship + Financial Ties → Moderate Risk → Management: Balance of views/documentation of process
4) No Commercial Sponsorship + No Financial Ties → Low Risk → Management: None → IDEAL

Boyd, EA, and **Bero, LA**. *Health Research Policy and Systems*, 2006; 4: 16 doi: 10.1186/1478-4505-4-16.

Strategies to eliminate conflicts

- Resign from work with company
- Resign from primary activity (PI, committee membership)
- Eliminate all financial ties (clinical trials and systematic reviews)
- Identify committee members without COI
- Committee chair to have no COI

Strategies to mitigate conflicts

- Publicly disclose financial interests
- Reduce the COI (eg, equity holding to under 5%)
- Clearly separate research from paid consulting activities
- Oversight committee
- Recusal from decisions

What do we know about disclosure?

- Most frequently used strategy to "manage" financial conflicts of interest
- Difficult to enforce / is not done
- Does not prevent bias in research
- Makes those giving advice *more* biased
- Makes readers more critical
- Necessary *but not sufficient*

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group*

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Too much……

Too little….

From a guideline:

"Actual competing interests: None

Declarations of potential interests only available on request."

What can we do?

- Clinical Trial Registries / Data access
- Journal policies
- Guideline and review methods
- New models for funding
- Institutional COI policies
- Beware of bias!
  - Lenzer and Brownlee list - http://www.healthnewsreview.org/list-of-independent-experts.php
  - Training

Open access to drug trial data

POLICY

Drug-company data vaults to be opened

European agency will publish firms' clinical-trial results

420 | NATURE | VOL 495 | 28 MARCH 2013 | CORRE

"Europe is now ahead of the United States in this area," says Lisa Bero, a pharmacologist at the University of California, San Francisco, who studies bias in scientific publication. "We're all waiting", she adds, to see what will unfold. "This is all very new."

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"You're kind of held hostage to the paper that you are reading," she says.

ScienceNews
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Model COI Policy

- Comprehensive and explicit
- Publically accessible
- Must equally apply to all parties
- Include management strategies beyond disclosure
- Provide guidance for uncertainty
- Indicate a responsible party for enforcement
- Standard core components

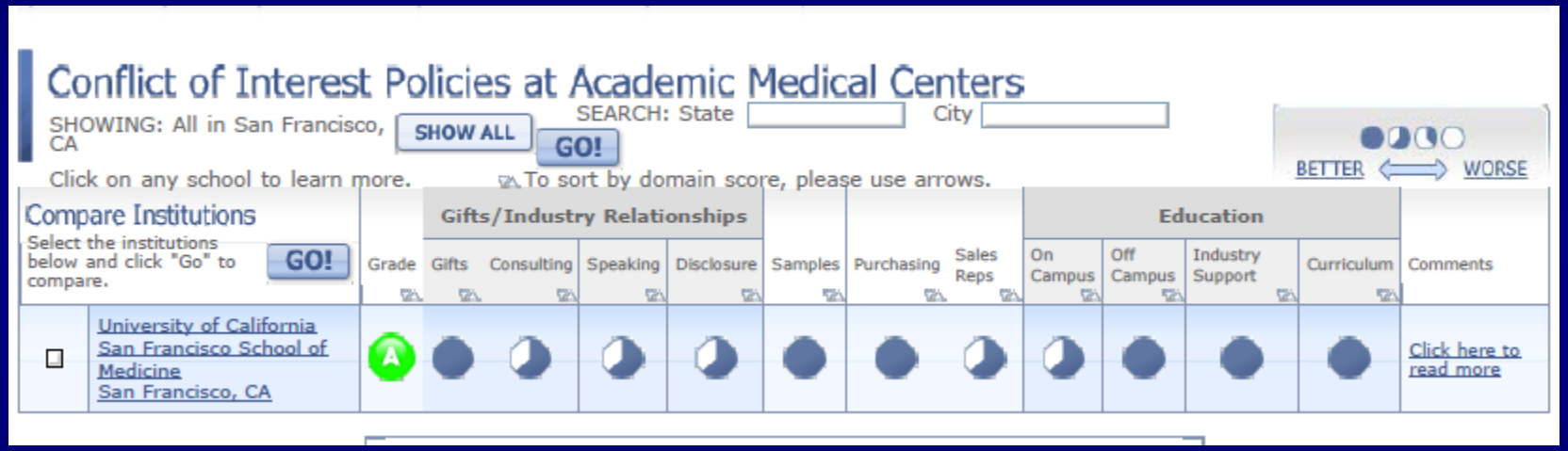
Conclusions

- Conflicts of interest exist
- Conflicts of interest are associated with bias in research and practice
- Strategies to protect against bias:
  - In some cases, conflict should be eliminated
  - Disclosure is not enough
  - Institutions need mechanisms to manage conflicts of interest

Mechanism of bias

- **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]**

AMSA score



Conflict of Interest Policies at Academic Medical Centers

SHOWING: All in San Francisco, CA SHOW ALL GO! SEARCH: State City

Click on any school to learn more. To sort by domain score, please use arrows.

BETTER ⟷ WORSE

Compare Institutions
Select the institutions below and click "Go" to compare. GO!

		Grade	Gifts/Industry Relationships							Education				Comments
			Gifts	Consulting	Speaking	Disclosure	Samples	Purchasing	Sales Reps	On Campus	Off Campus	Industry Support	Curriculum	
☐	University of California San Francisco School of Medicine San Francisco, CA	A	●	◑	◑	◑	●	●	◑	◑	●	●	●	Click here to read more

http://www.amsascorecard.org/

IOM Recommendations: Medical research

- **Research institutions should adopt policy that investigators generally *may not conduct research with human subjects* if they have a significant financial interest in the outcome of the research**

AMSA scorecard

- Gifts and meals
- Consulting relationships
- Industry-funded speaking relationships
- Disclosure
- Pharmaceutical samples
- Purchasing and Formularies
- Industry sales representatives
- On-campus education
- Attendance at off campus industry-sponsored events
- Industry support for trainees
- Medical school curriculum
- Oversight mechanism?
- Sanctions for non-compliance?

IOM Recommendations: Medical education

- Prohibit gifts, ghostwriting, speakers bureaus
  - Limit drug samples, consulting, sales reps
- Provide education on relationships with industry and conflicts of interest
- Develop new system of funding accredited continuing medical education that is free of industry influence and provides high-quality education

IOM Recommendations: Practice guidelines

- Groups that develop clinical practice guidelines should
  - Not accept direct funding from industry
  - Exclude panel members with conflicts
    - Document efforts to find experts without conflicts
    - Exception if critical need for expertise
    - Limit participation of conflicted members
    - Chair should have no conflicts of interest
  - Disclose funding and relationships of panelists

IOM Recommendations: Practice guidelines

- Guidelines should report (7.1)
  - Conflict of interest policies of developer
  - Sources and amounts of funding for guideline
  - Relevant financial relationships of panelists
- Public health insurance plans should (7.2)
  - Avoid using guidelines that do not follow the report recommendations

Evidence vs. Perception

- "The perception that a commercial entity, especially pharmaceutical or medical device companies, influenced the conclusions and recommendations of a practice guideline committee could undermine the credibility of both the guidelines and the group that produced it." Cochrane Collaboration 2004

Drug Industry Document Archive - Mozilla Firefox

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

DRUG INDUSTRY DOCUMENT ARCHIVE

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Search the Documents

Search

The Drug Industry Document Archive (DIDA) contains thousands of documents and resources about pharmaceutical industry clinical trials, publication of study results, pricing, marketing, relations with physicians and involvement in continuing medical education.

Most of these previously secret internal documents were made public as a result of lawsuits against a number of pharmaceutical companies including: Merck & Co., Parke-Davis, Warner-Lambert, Wyeth, and Pfizer. For further information on documents connected to these lawsuits, please consult The Documents.

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UCSF LIBRARY and Center for Knowledge Management

Done

Opinions about COI and research

- Researchers (17 studies)
- Mixed opinions
- Professionals with industry ties are more supportive of financial ties than those without
- Recognize general risks of COI, but not for themselves
- Support disclosure

Glaser, B, and Bero, L. Attitudes of academic and clinical researchers toward financial ties in research: A systematic review, Science and Engineering Ethics, 2005; 11: 553-573.

- Consumers (21 studies)
- More concerned about financial gain than academic bias
- Unconcerned about corporate funding of trials
- Most wary of trials where the investigator or university owns stock
- More supportive of investigators' disclosure of financial to professionals rather than themselves

“Best disclosure ever…..”

“The authors are interested in encouraging tobacco harm reduction (reducing the morbidity and mortality caused by tobacco use by encouraging smokers to switch to smokeless tobacco or other low-risk alternatives). As a result, they have an interest in doing research like this that explores factors that make tobacco harm reduction more or less likely to work. In addition to this actual substantial interest, the authors also have what some mistakenly consider to be the only real conflict of interest, funding from the private sector: Dr. Phillips and his research group (including Dr. Heavner and Mr. Rosenberg) are partially supported by an unrestricted (completely hands-off) grant to the University of Alberta from U.S. Smokeless Tobacco Company. The grantor is unaware of this study, and thus had no scientific input or other influence on it. ……

"…Dr. Phillips has consulted for U.S. Smokeless Tobacco Company in the context of product liability litigation and subsequent to the completion of this paper became a member of British American Tobacco's External Scientific Panel advising on issues of tobacco harm reduction. Though these do and might (respectively) represent interests, and credibly influence what research we consider important, our interest in accurately assessing the barriers to harm reduction means it is not clear to us how these interests might be seen as justifying the knee-jerk accusation of bias -- that we somehow altered the presentation of these results based on nonscientific interests -- that we often face from the political activists who work to influence the science in this area."

Survey of smokers' reasons for not switching to safer sources of nicotine and their willingness to do so in the future
Karyn K Heavner , Zale Rosenberg and Carl V Phillips
Harm Reduction Journal 2009, 6:14doi:10.1186/1477-7517-6-14

Case 7: Institutional COI

- Your department accepts a very large grant from a single commercial sponsor who makes products relevant to the research of the department.
- This becomes the main source of funding for the department.
- The funds are used to support staff salary, student stipends, equipment purchases, and travel, but NOT specific research projects.

Case 6: Family ties

- An individual is a staff person at a drug regulatory authority. The regulatory agency has committees that advise on drug approval.
- The individual's spouse works at a drug company that periodically submits new drug applications to the regulatory authority.

Ghost authors

- MECC offered substantial assistance in the development of manuscripts, reporting in a status report that ”at [the author’s] request, we did an extensive literature search and submitted selected articles to him for reference…. We have offered him help in identifying and collecting his appropriate cases, analyzing data, writing a manuscript, or whatever he needs.”
- 7 published articles: 4 favorable, 3 neutral
- Only 1 article disclosed author tie with Parke-Davis

Committee Process

- Staff screens all disclosures
- Staff gathers additional information.
- Each “case” (ie disclosure) is assigned to one committee member as lead reviewer. This is discussed by the committee, followed by a vote. Initial recommendation may be revised based on discussion.
- Decisions to be made are: 1) Is this a significant conflict that requires management? 2) If yes, what is the management strategy?
- Appeal process: Individuals are allowed to appeal and appear in person at a later meeting.

Reviewing COI

- **Step 1:** ***Identifying COI (disclosure)***

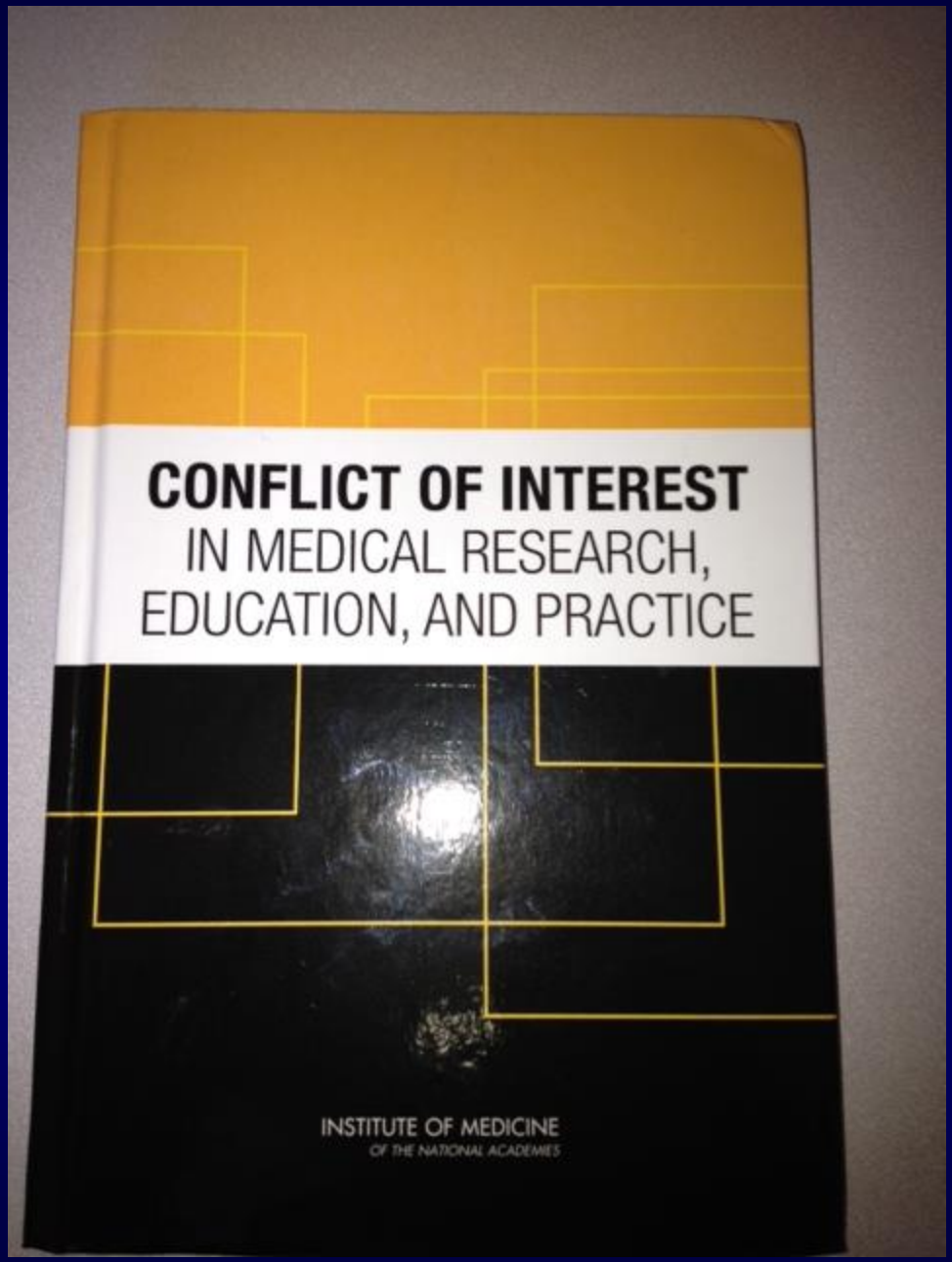
Disclose to institution

  - **Who, what, when?**

- **Step 2: Managing the COI**

IOM Recommendations: Disclosure

- Standardize disclosures to institutions
- Minority Report: Standardize disclosures to the public
- Require pharmaceutical, medical device, and biotechnology *companies to publicly report payments* to physicians and other


CONFLICT OF INTEREST
IN MEDICAL RESEARCH,
EDUCATION, AND PRACTICE
INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Reasons for not publishing…

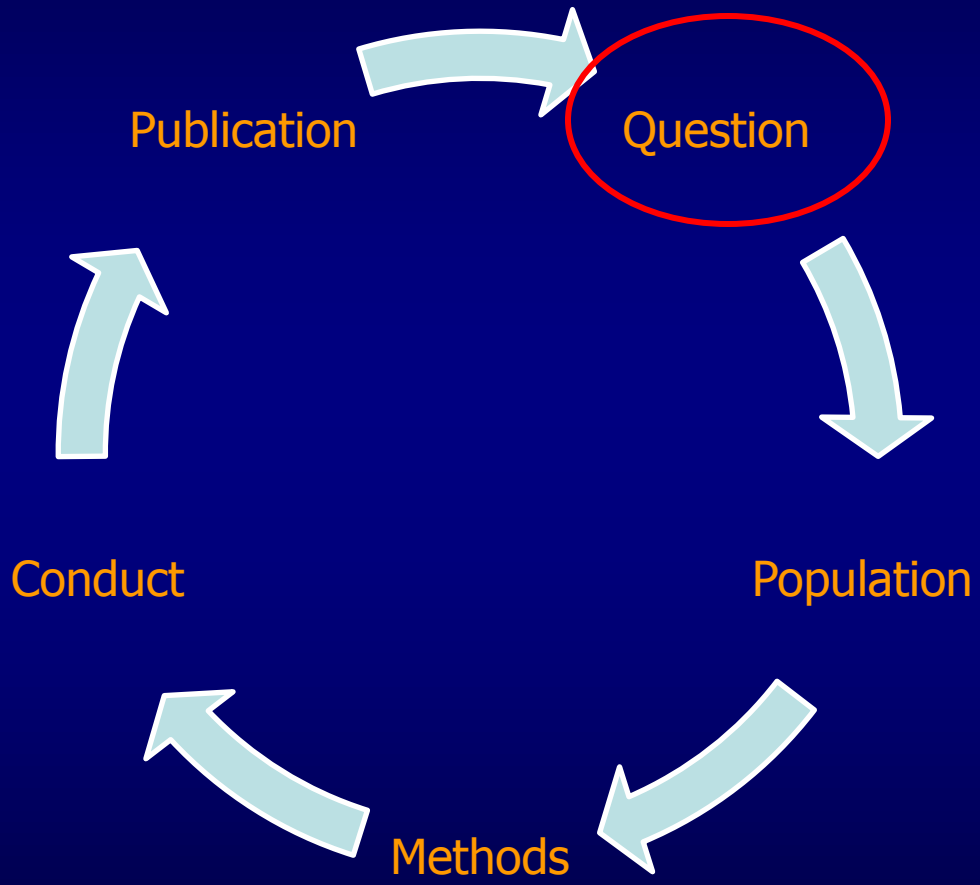
"The data are in my opinion very worthwhile. Efforts were made a number of times to work on publishing the data, but *it was never possible to find a time when both the PI and the company simultaneously had time* available to commit."

"Unfortunately I do not think this complete study has ever been published. *It is clearly important that this should be published*. I have been and continue to be in contact with [company name] to see how this can be published."

Assessing bias in drug studies

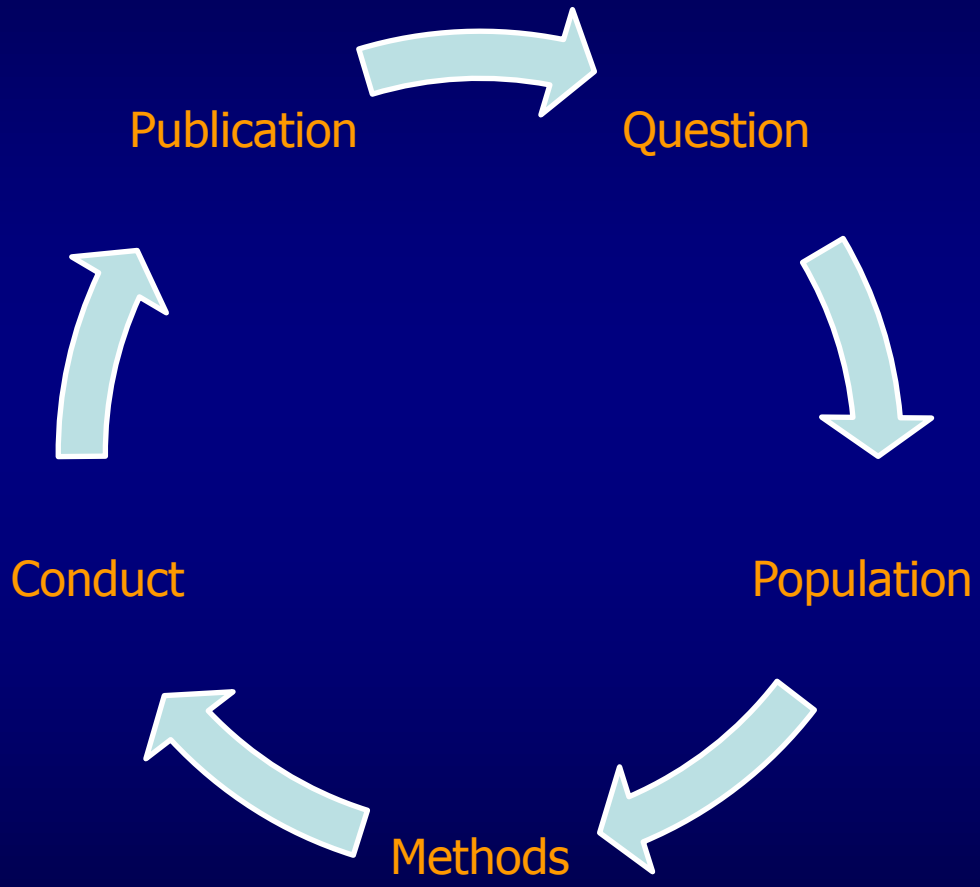
- Who paid for the study?
- Was the question clinically important?
- What drugs and doses were studied?
- Were the outcomes relevant? Too many of them?
- Were the results clinically significant?
- Do you know if all the data were published?

So what is going on?



Odierna DH , Forsyth SR, White J, Bero LA (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

Cycle of Bias



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Asking the right question
"Disease Mongering"

- **Turning the ordinary processes of life into medical illnesses**
- **Exaggerating the extent and severity of disease**
- **Widening the definitions of disease and illness?**
  - » **Raymond Moynihan, Selling Sickness, 2005**

Selling sickness: the pharmaceutical industry and disease mongering

Ray Moynihan, Iona Heath, David Henry

A lot of money can be made from healthy people who believe they are sick. Pharmaceutical companies sponsor diseases and promote them to prescribers and consumers. Ray Moynihan, Iona Heath, and David Henry give examples of "disease mongering" and suggest how to prevent the growth of this practice

“Statin mongering”

- National Cholesterol Education Program updated the Adult Treatment Panel III (ATP III) guidelines in 2004.
  - recommend a LDL cholesterol level below 100 mg/dL in patients at risk for coronary heart disease.
- 40 million Americans should be on statins in higher doses and for a longer period (up from 13 million)
- New ATP III guidelines were based on evidence from 5 published randomized controlled trials (RCTs)
  - ALL received funding from industry
- 8 of the 9 members of the panel had financial ties with pharmaceutical companies manufacturing statin drugs

Consequences of “Statin Mongering”

- Drug-drug comparisons are important for formulary / purchaser decisions
- Examine associations between study design characteristics aimed at reducing bias, research funding source, and other factors with results and conclusions of 192 published statin-drug comparisons.

Why do some statins appear more efficacious than others ?

- 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)

Multivariate analysis: industry funded (n = 95)

Characteristic	Results Favor OR (95% CI)	Conclusions Favor OR (95% CI)
Impact factor		
Highest Quartile	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		
Largest Quartile	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)**

Statistical Significance of Reported Outcomes Changed

- 43 outcomes in the NDAs did not favor the test drug
  - 20 were not included in the papers
  - 5 changed statistical significance, with 4 changing to favor test drug in the paper

- Changes in outcomes occurred in 36 (22%) trials found in 19 (58%) NDAs

Open access to drug trial data

POLICY

Drug-company data vaults to be opened

European agency will publish firms' clinical-trial results

420 | NATURE | VOL 495 | 28 MARCH 2013 | CORRE

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Case 6: Diagnostic criteria

- A guideline review panel is considering a recommendation that changes the diagnostic criteria for a disease. The result is that pharmacological treatments will be recommended for more people.
- A guideline panel member has financial ties (consulting fees, research funding) from a company that makes one of the pharmacological treatments.

Effect of unpublished FDA data on meta-analytic estimates for drug safety in RCTs

Drug class	# of Meta-Analyses	# of Meta-Analyses with no change in meta-analytic estimate for drug safety	Meta-Analyses with an meta-analytic estimate for showing MORE HARM		Meta-Analyses with an meta-analytic estimate for showing LESS HARM	
			# of meta-analyses	Range of Increase	# of meta-analyses	Range of Decrease
Topical Anti-inflammatory	1	-	1	49%	-	-
TOTAL	**1**	**-**	**1**	**49%**	**-**	**-**

Hart, B, Lundh, A and Bero, L. The effect of reporting bias on meta-analyses of drug trials: Re-analysis of meta-analyses. BMJ, 2011;343:d7202. doi: 10.1136/bmj.d7202

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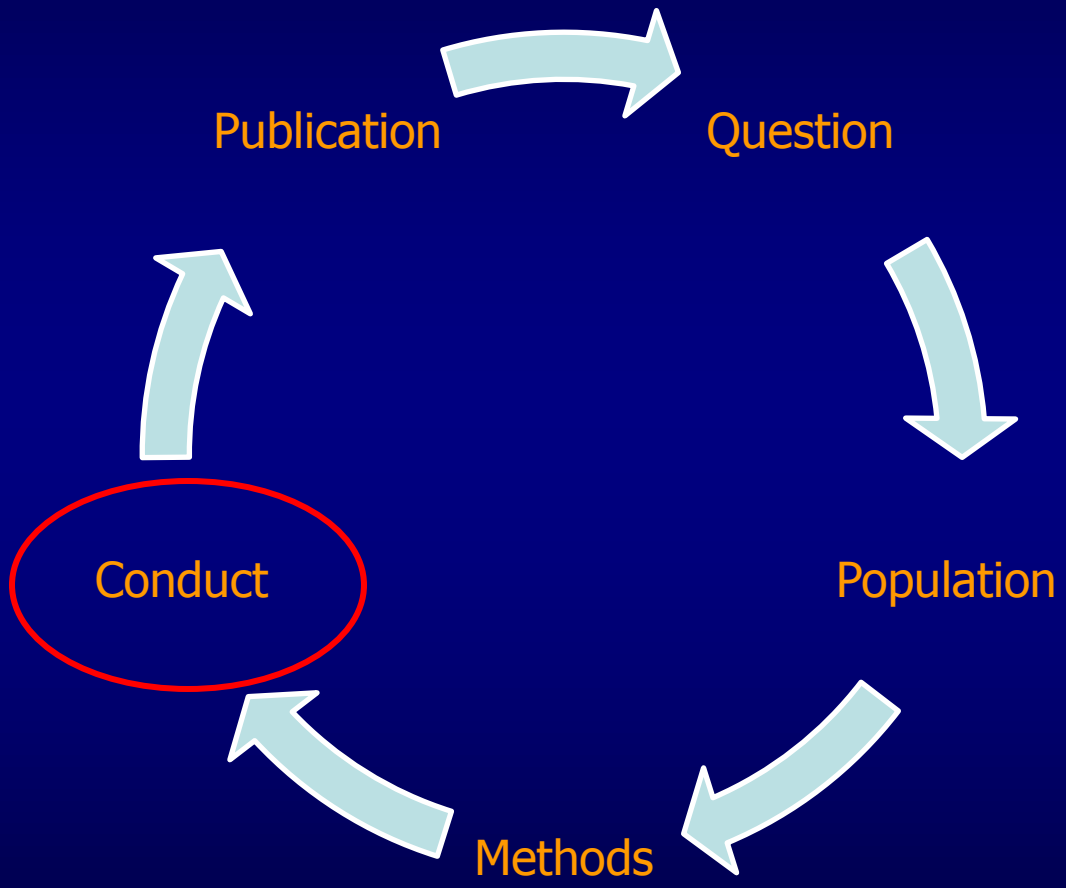

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Research sponsorship as a risk of bias

- The reporting of Cochrane Reviews: now requires 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 Table"
  - Debate on this topic for 2013 Cochrane Colloquium

- Cochrane Plain Language Summaries: 'highly desirable" that all funding sources of included studies be disclosed in the Plain Language Summary