Perelman School of Medicine
University of Pennsylvania

Conflicts of Interest

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Department of Medical Ethics & Health Policy

Ethical and Regulatory Aspects of Clinical Research
National Institutes of Health Clinical Center
October 23, 2013

Disclosure

I was a paid member of a Data & Safety Monitoring Committee for Genzyme/Sanofi until 11/2012

Goals

- Understand concerns about bias related to investigators' financial ties with industry
- Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions and productivity
- Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

Defining conflict of interest

"A COI is a set of *circumstances* that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest."

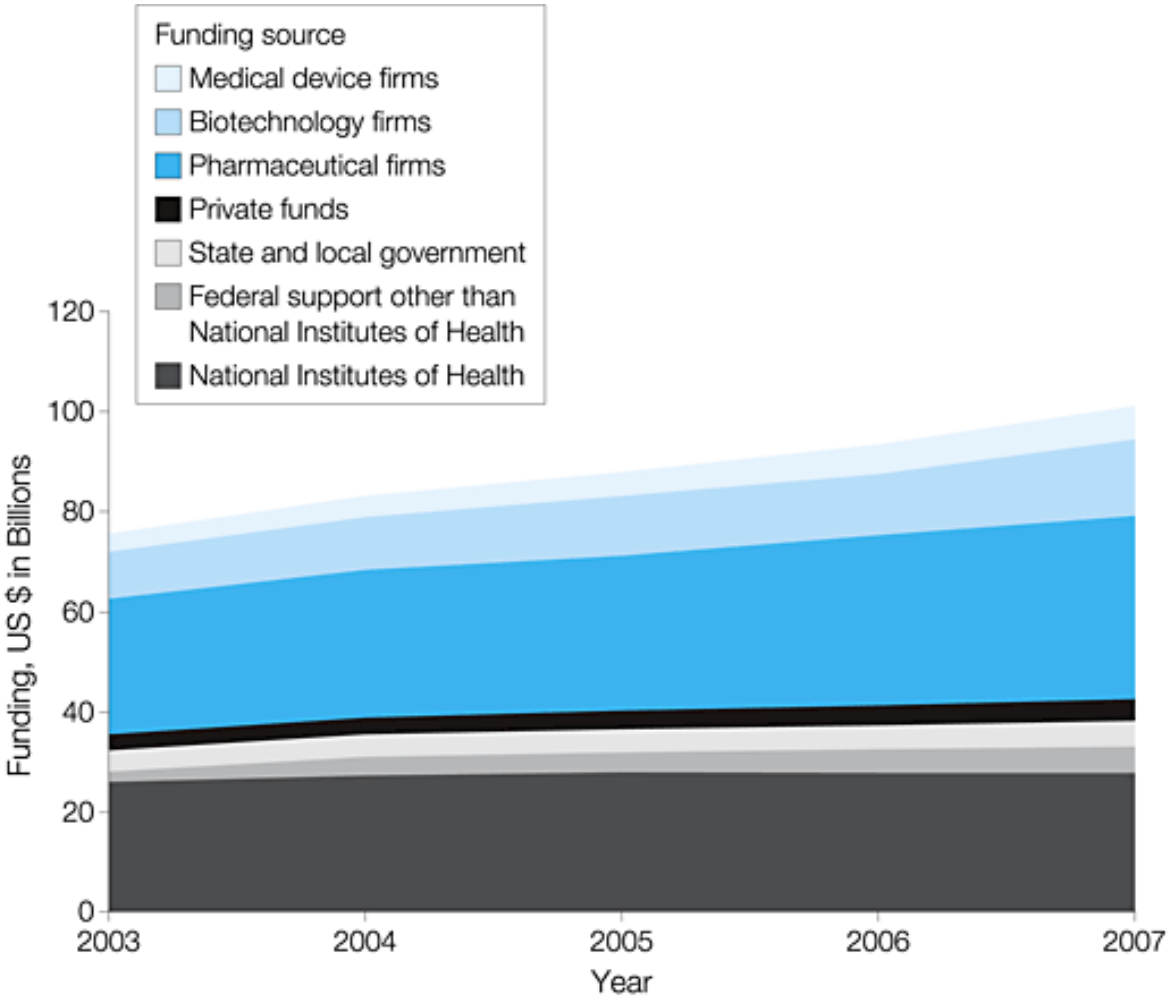
- Patient welfare
- Valid science
- Trainee education

Lo, B., M. J. Field, et al. (2009). *Conflict of interest in medical research, education, and practice.* Washington, D.C., National Academies Press.

Why do we care about conflicts of interest in research?

- Potential to influence investigators' judgments
  - Biased science
  - Increased risks to subjects(?)
- Potential to impede scientific openness
- Potential to undermine public trust

Industry supports a growing proportion of biomedical research



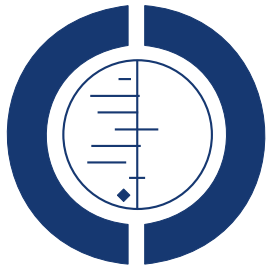
JAMA

JAMA 303:137, 2010

The “sponsor effect”: source of support predicts study outcome

Industry sponsorship and research outcome (Review)

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L

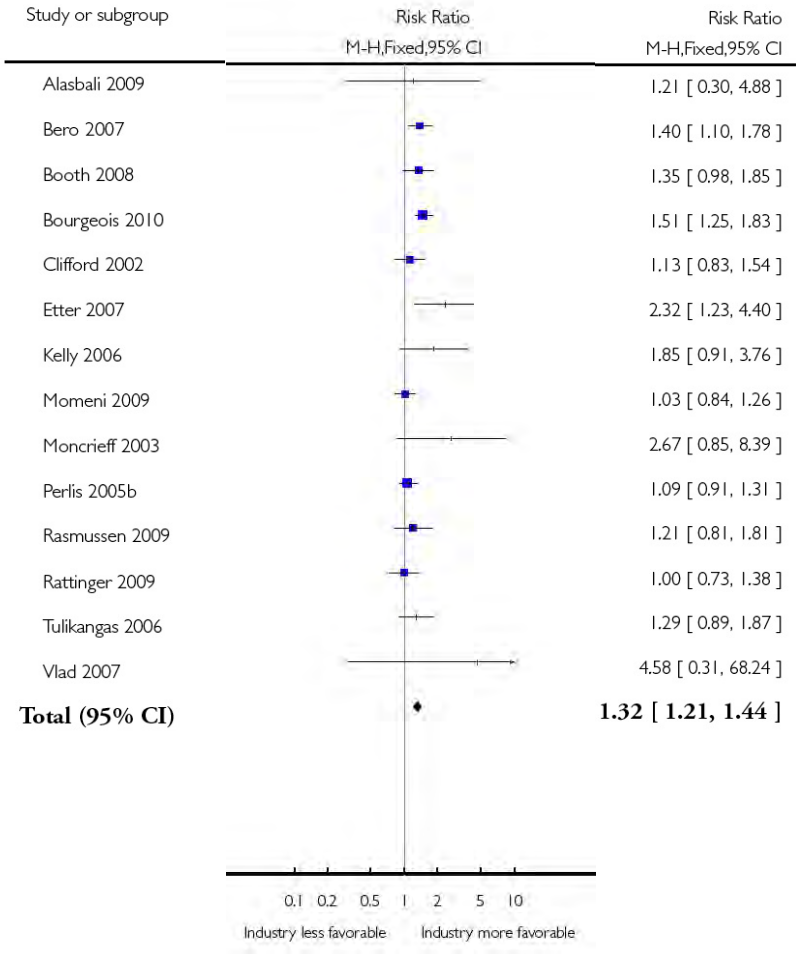


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 7

http://www.thecochranelibrary.com

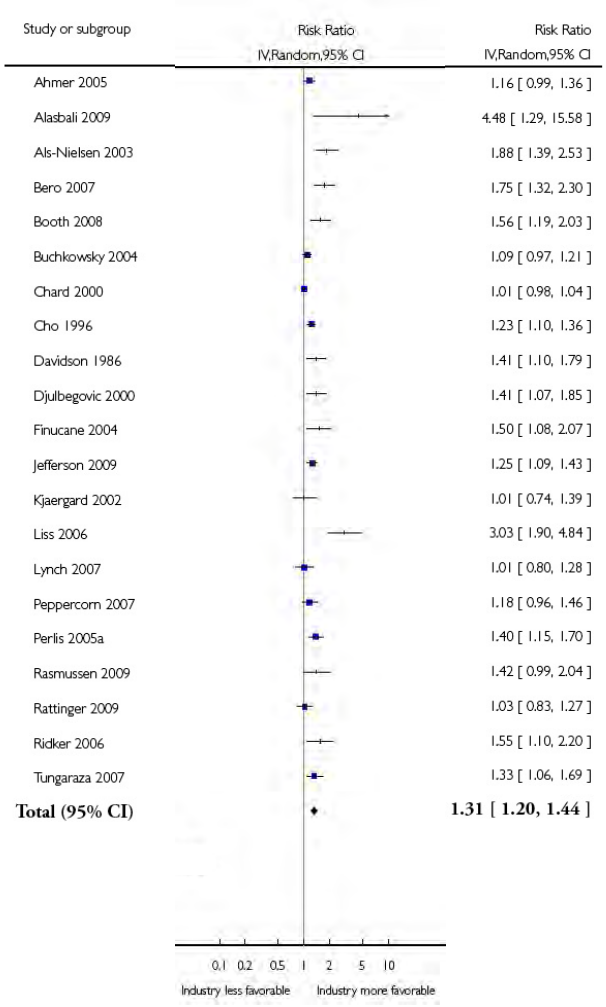
WILEY

Industry-sponsored studies are more likely to show favorable efficacy results



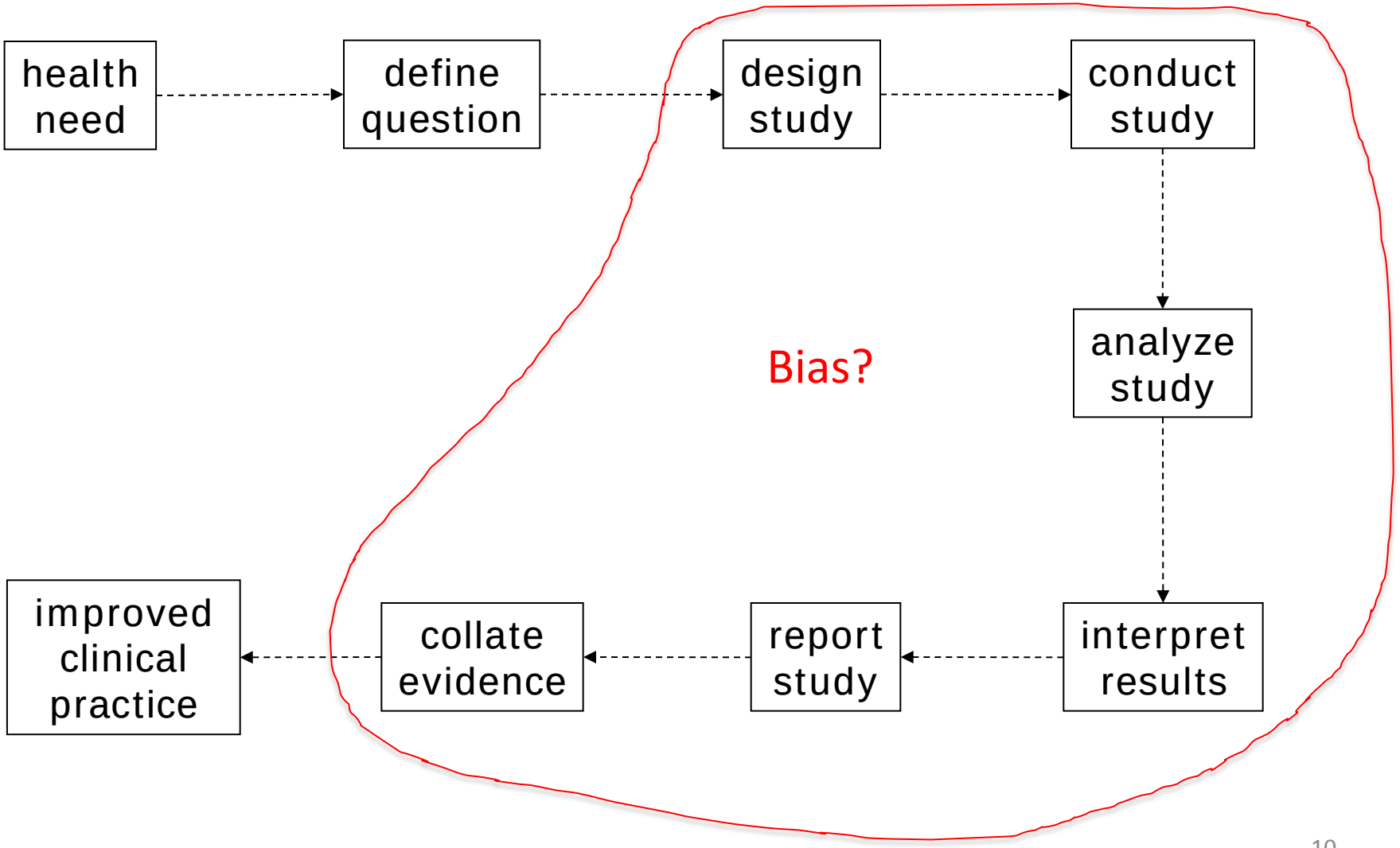
Cochrane Database Syst Rev. 2012;12:MR000033, Analysis 1.1

Industry-sponsored studies are more likely to draw favorable conclusions

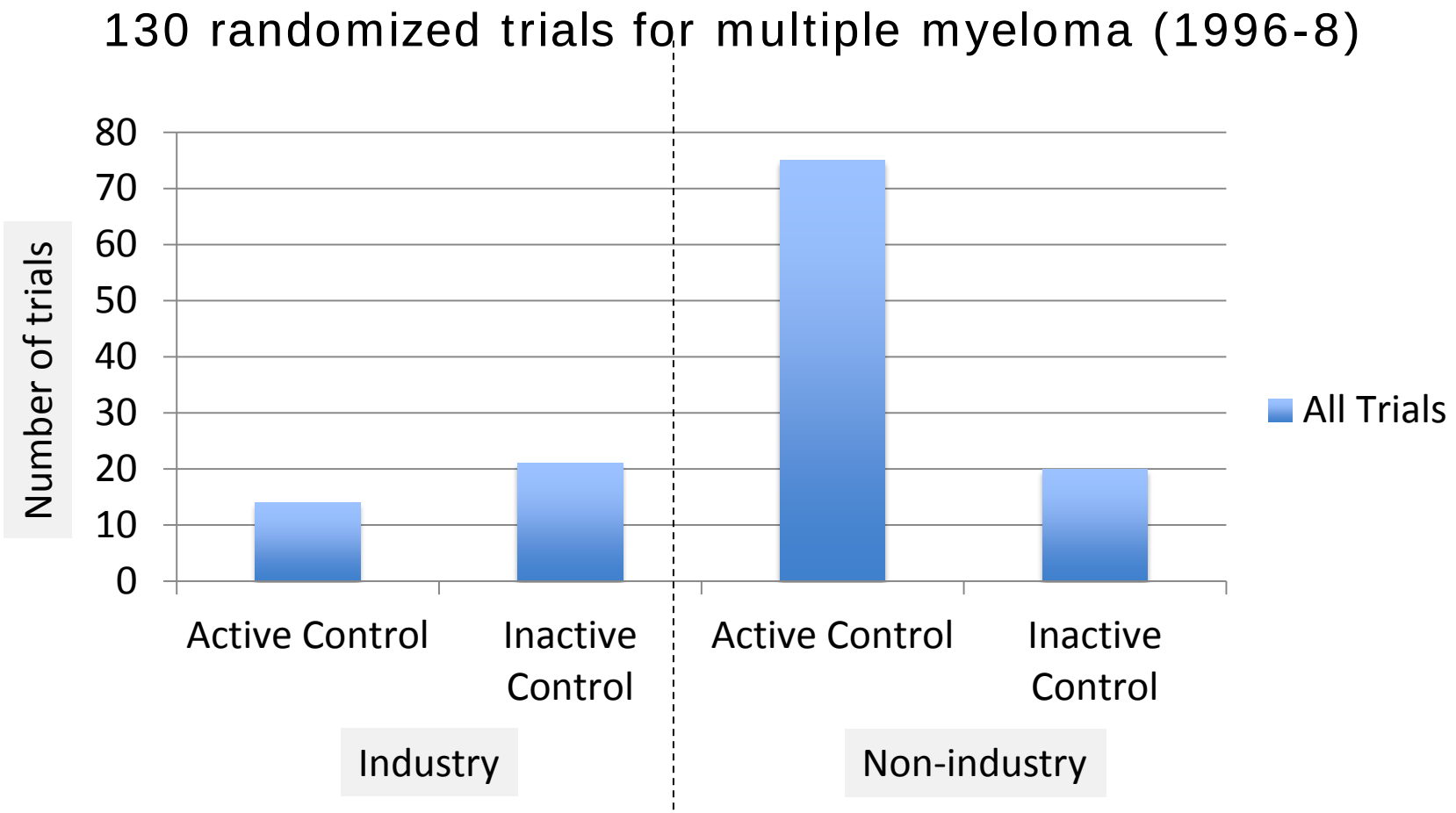


Cochrane Database Syst Rev. 2012;12:MR000033, Analysis 3.1

Various mechanisms may explain the more favorable results of industry trials



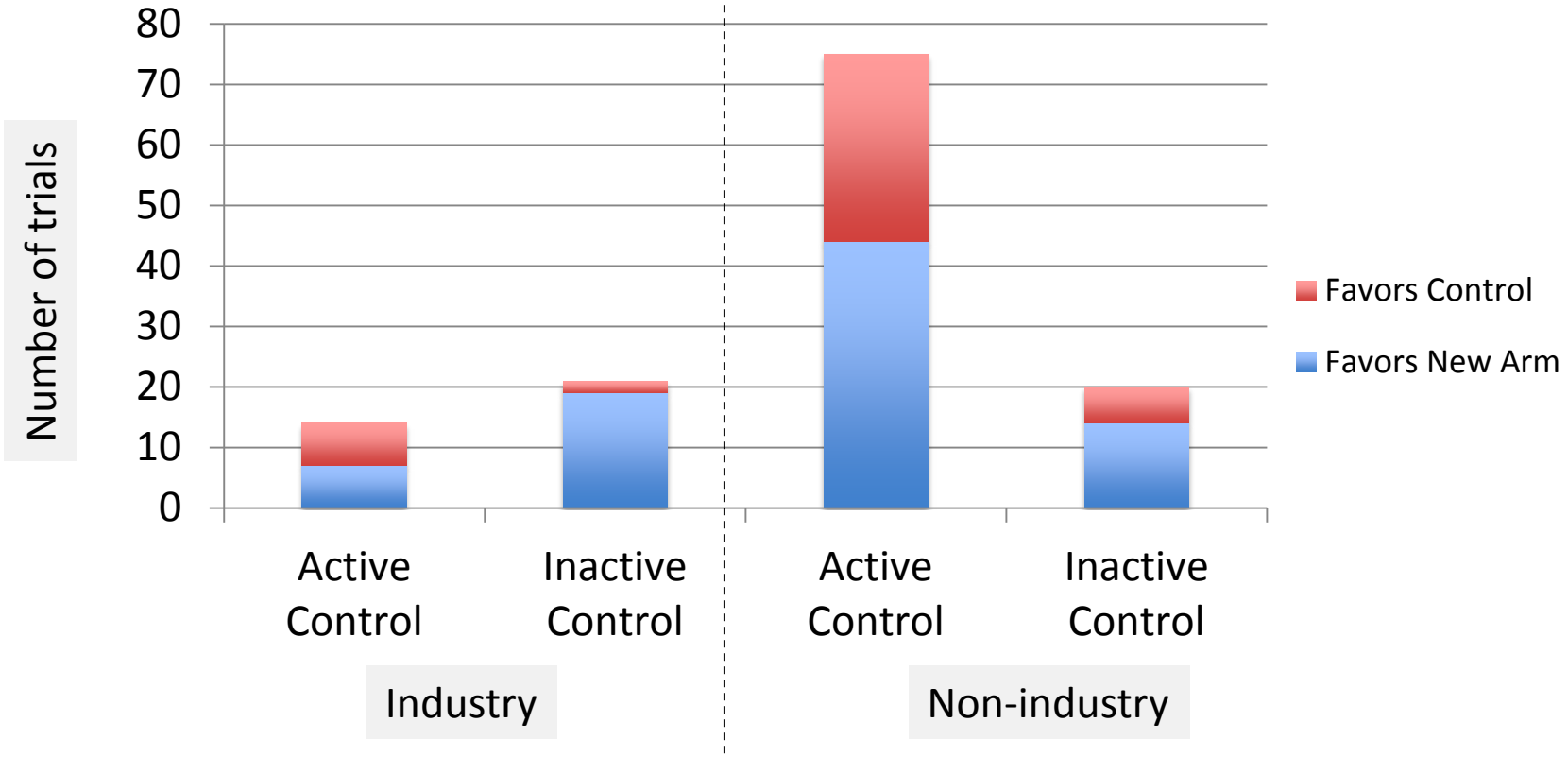
Industry-sponsored studies may be more likely to use inactive controls



Lancet 356:635, 2000

Use of inactive controls is associated with favoring new arm

- 130 randomized trials for multiple myeloma (1996-8)



Lancet 356:635, 2000

Published endpoints may differ from those in internal documents

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

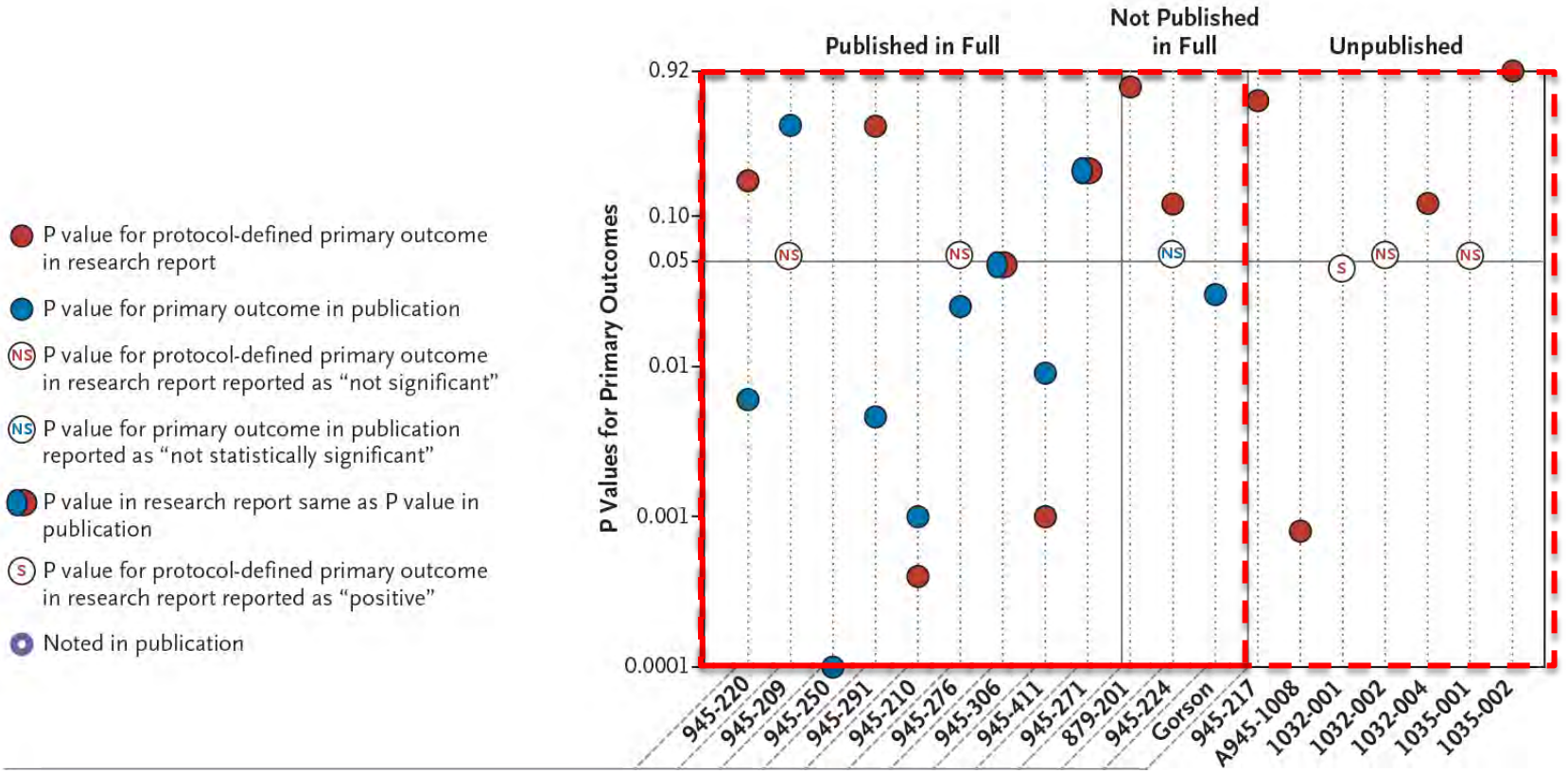
Outcome Reporting in Industry-Sponsored Trials of Gabapentin for Off-Label Use

S. Swaroop Vedula, M.D., M.P.H., Lisa Bero, Ph.D., Roberta W. Scherer, Ph.D., and Kay Dickersin, Ph.D.

- Authors reviewed 20 clinical trials of gabapentin for off-label indications
  - Compared outcomes of published reports to those in internal company documents
  - 12/20 trials published

NEJM 361:1963, 2009

Published endpoints may differ from those in internal documents



NEJM 361:1963, 2009

Conclusions may not reflect analytic results ("spin")

Als-Nielsen studied relationship between funding source & conclusion in 370 drug trials included in Cochrane meta-analyses

Table 3. Estimated Effect of Funding, Treatment Effect, and Double Blinding on Conclusions

Characteristic	Odds Ratio (95% Confidence Interval)	*P* Value
Funding		.005
Nonprofit organizations	1.0	
Not reported	2.4 (0.9-6.8)	.10
Nonprofit and for-profit organization	2.6 (0.9-7.9)	.09
For-profit organizations	5.3 (2.0-14.4)	.001
Treatment effect (*z* score)*	0.6 (0.5-0.7)	<.001
Double blinding	2.9 (1.4-6.0)	.004

*The likelihood of recommending the experimental drug as the treatment of choice decreased with higher *z* scores (the higher the score the smaller the benefit of the experimental drug).

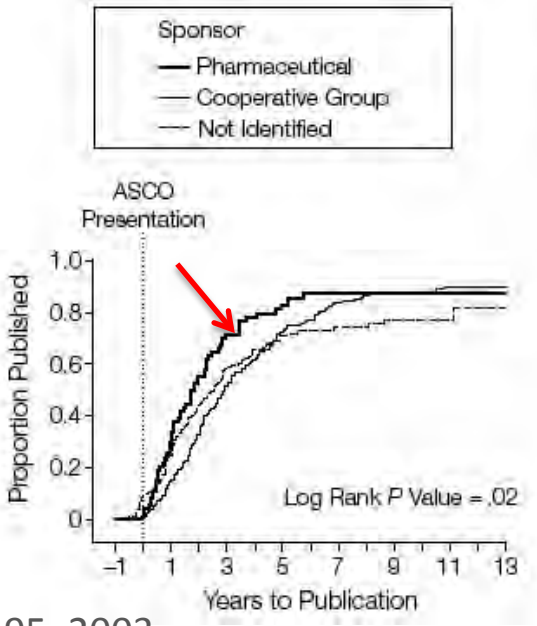
JAMA 290:921, 2003

Publication bias may be greater among industry-sponsored trials

Krzyzanowska et al reviewed publication outcomes of 510 large RCTs presented at an oncology meeting

Figure 3. Time to Publication by Sponsorship and by Type of Result and Sponsorship

A Time to Publication by Sponsorship



JAMA 290:495, 2003

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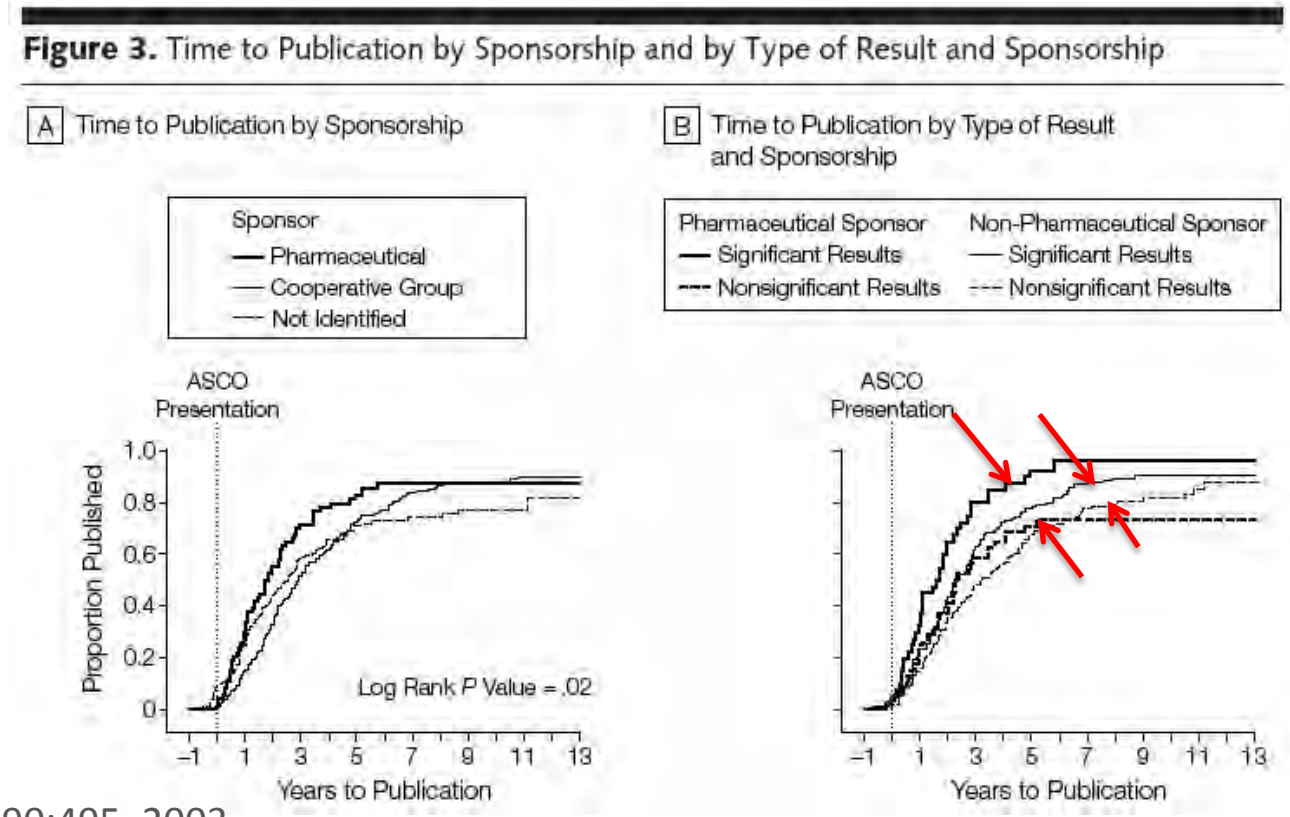


JAMA 290:495, 2003

Evidence syntheses may demonstrate a sponsor effect

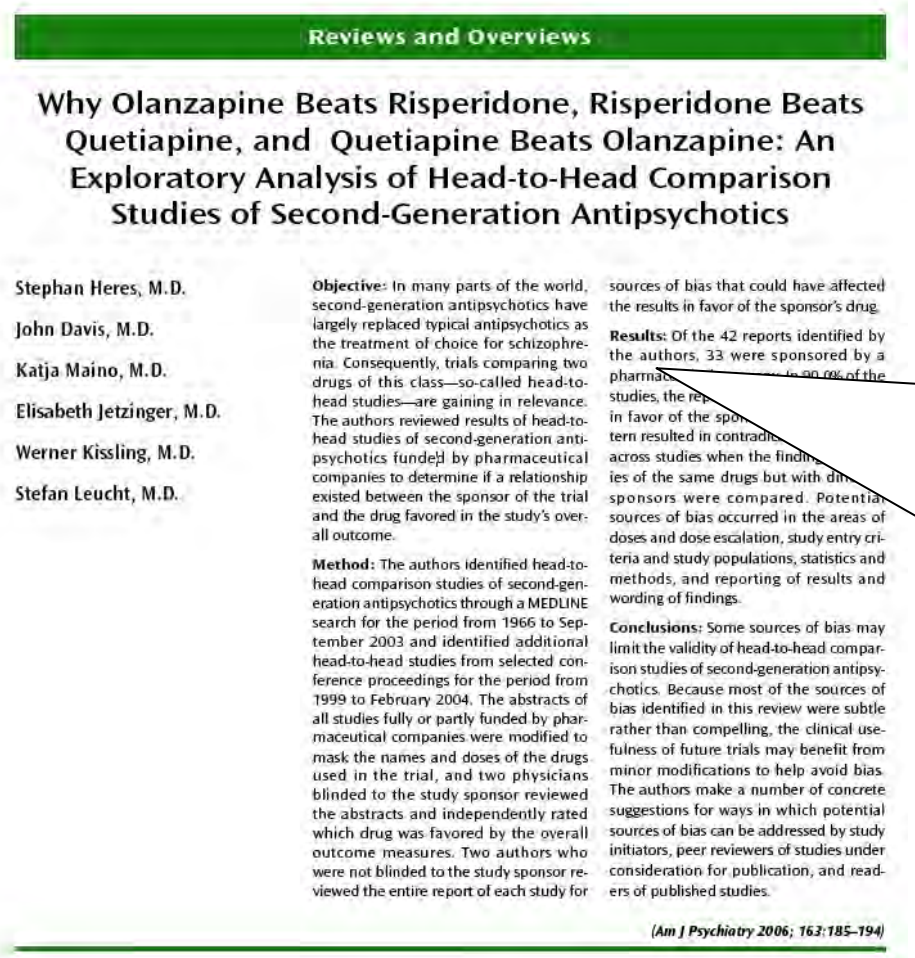
Jørgensen & colleagues compared Cochrane meta-analyses with industry-supported meta-analyses of same pairs of drugs

	Cochrane Reviews	Industry-supported Reviews
Overall quality, median (1-7)	7	2
Conclusions favor experimental drug*	0/8	7/8

* Despite overall similar effect sizes

BMJ 333:782, 2006

Bias may operate through multiple mechanisms



Reviews and Overviews

Why Olanzapine Beats Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation Antipsychotics

Stephan Heres, M.D.
John Davis, M.D.
Katja Maino, M.D.
Elisabeth Jetzinger, M.D.
Werner Kissling, M.D.
Stefan Leucht, M.D.

Objective: In many parts of the world, second-generation antipsychotics have largely replaced typical antipsychotics as the treatment of choice for schizophrenia. Consequently, trials comparing two drugs of this class—so-called head-to-head studies—are gaining in relevance. The authors reviewed results of head-to-head studies of second-generation antipsychotics funded by pharmaceutical companies to determine if a relationship existed between the sponsor of the trial and the drug favored in the study's overall outcome.

Method: The authors identified head-to-head comparison studies of second-generation antipsychotics through a MEDLINE search for the period from 1966 to September 2003 and identified additional head-to-head studies from selected conference proceedings for the period from 1999 to February 2004. The abstracts of all studies fully or partly funded by pharmaceutical companies were modified to mask the names and doses of the drugs used in the trial, and two physicians blinded to the study sponsor reviewed the abstracts and independently rated which drug was favored by the overall outcome measures. Two authors who were not blinded to the study sponsor reviewed the entire report of each study for sources of bias that could have affected the results in favor of the sponsor's drug.

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmac... ...in 90.0% of the studies, the rep... in favor of the spo... tern resulted in contradic... across studies when the findi... ies of the same drugs but with di... sponsors were compared. Potential sources of bias occurred in the areas of doses and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings.

Conclusions: Some sources of bias may limit the validity of head-to-head comparison studies of second-generation antipsychotics. Because most of the sources of bias identified in this review were subtle rather than compelling, the clinical usefulness of future trials may benefit from minor modifications to help avoid bias. The authors make a number of concrete suggestions for ways in which potential sources of bias can be addressed by study initiators, peer reviewers of studies under consideration for publication, and readers of published studies.

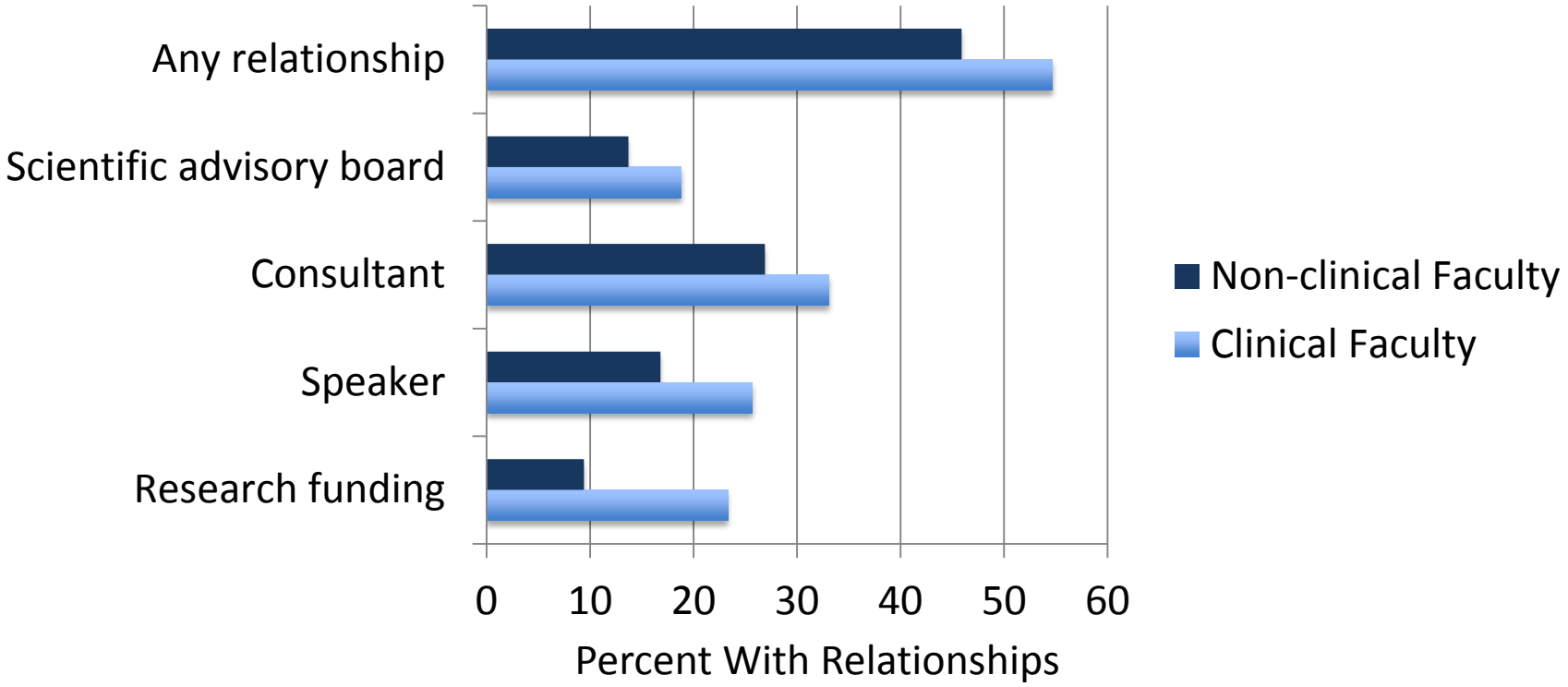
(Am J Psychiatry 2006; 163:185–194)

Results: Of the 42 reports identified by the authors, 33 were sponsored by a pharmaceutical company. In 90.0% of the studies, the reported overall outcome was in favor of the sponsor's drug. This pattern resulted in contradictory conclusions across studies when the findings of studies of the same drugs but with different sponsors were compared. Potential sources of bias occurred in the areas of doses and dose escalation, study entry criteria and study populations, statistics and methods, and reporting of results and wording of findings.

What about personal financial ties?

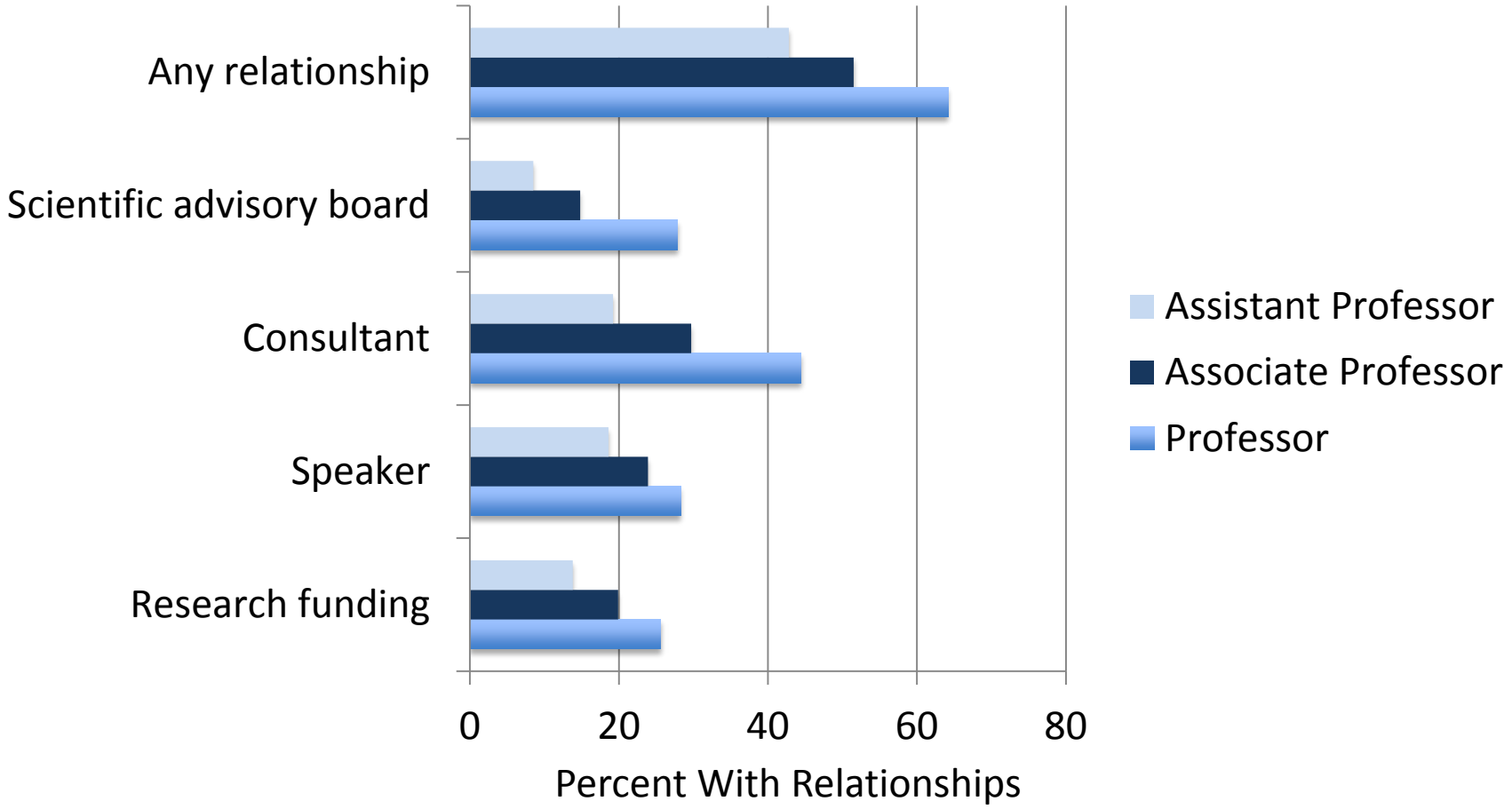
Personal financial ties are common

Zinner et al surveyed a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support



Health Affairs 28:1814, 2009

Personal financial ties vary by academic rank



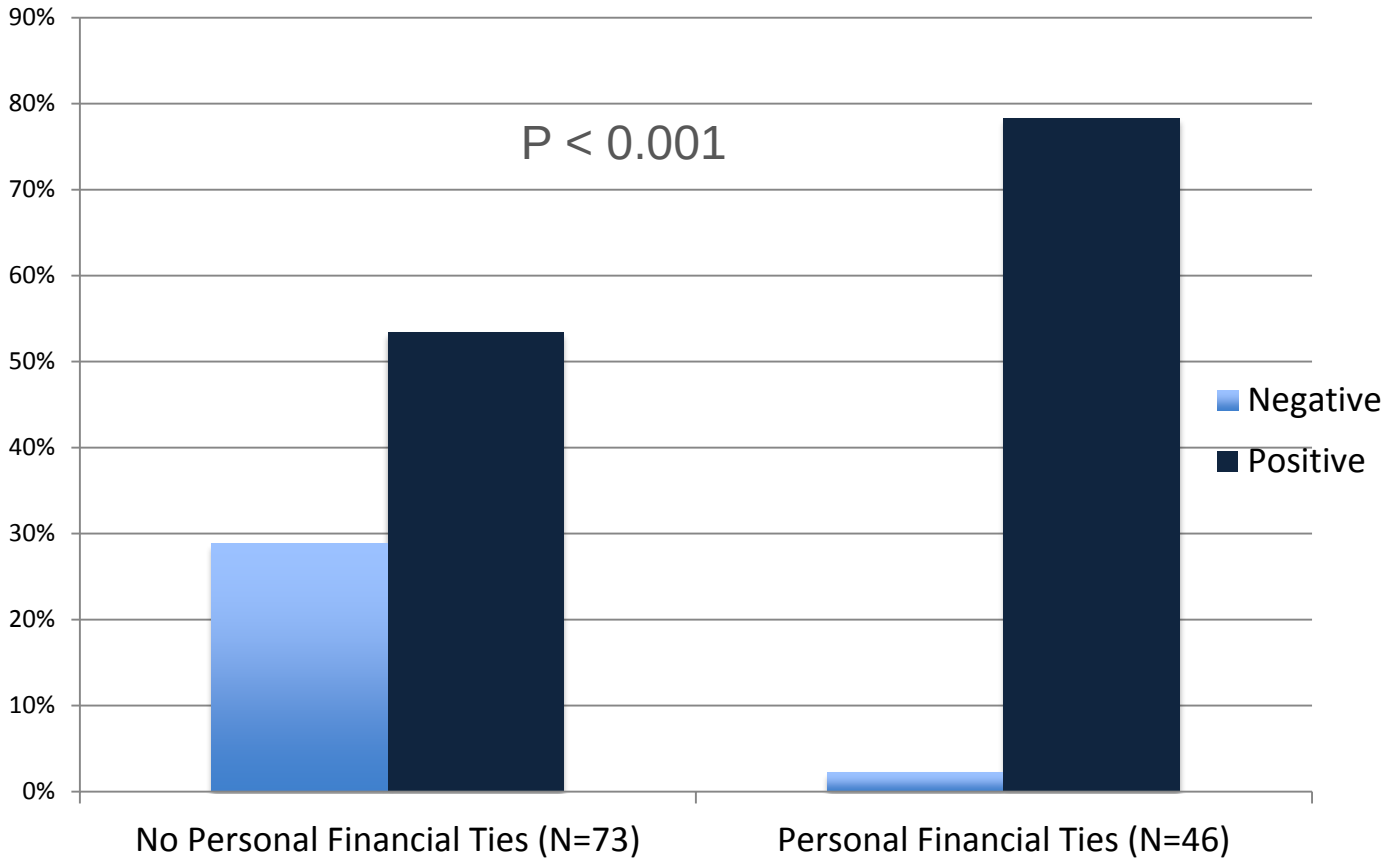
Health Affairs 28:1814, 2009

Do outcomes vary by presence or absence of personal financial ties?

- Few data
- Friedman & Richter reviewed all original reports published in NEJM or JAMA in 2001
  - 16-22% of articles (N=398) had at least one author who reported a personal financial tie to industry

JGIM 19:51, 2004; see also Am J Psychiatry 2005;162:1957

Do outcomes vary by presence or absence of personal financial ties?



*analysis does not control for source of study funding

JGIM 19:51, 2004

Authors' positions on controversial questions may vary by financial ties

- Wang et al reviewed articles that commented on rosiglitazone and the risk of myocardial infarction
  - 108/202 articles included a COI statement
  - 90 authors (45%) reported a financial COI

BMJ 340:1344, 2010

Authors' positions on controversial questions may vary by financial ties

BMJ 340:1344, 2010

Goals

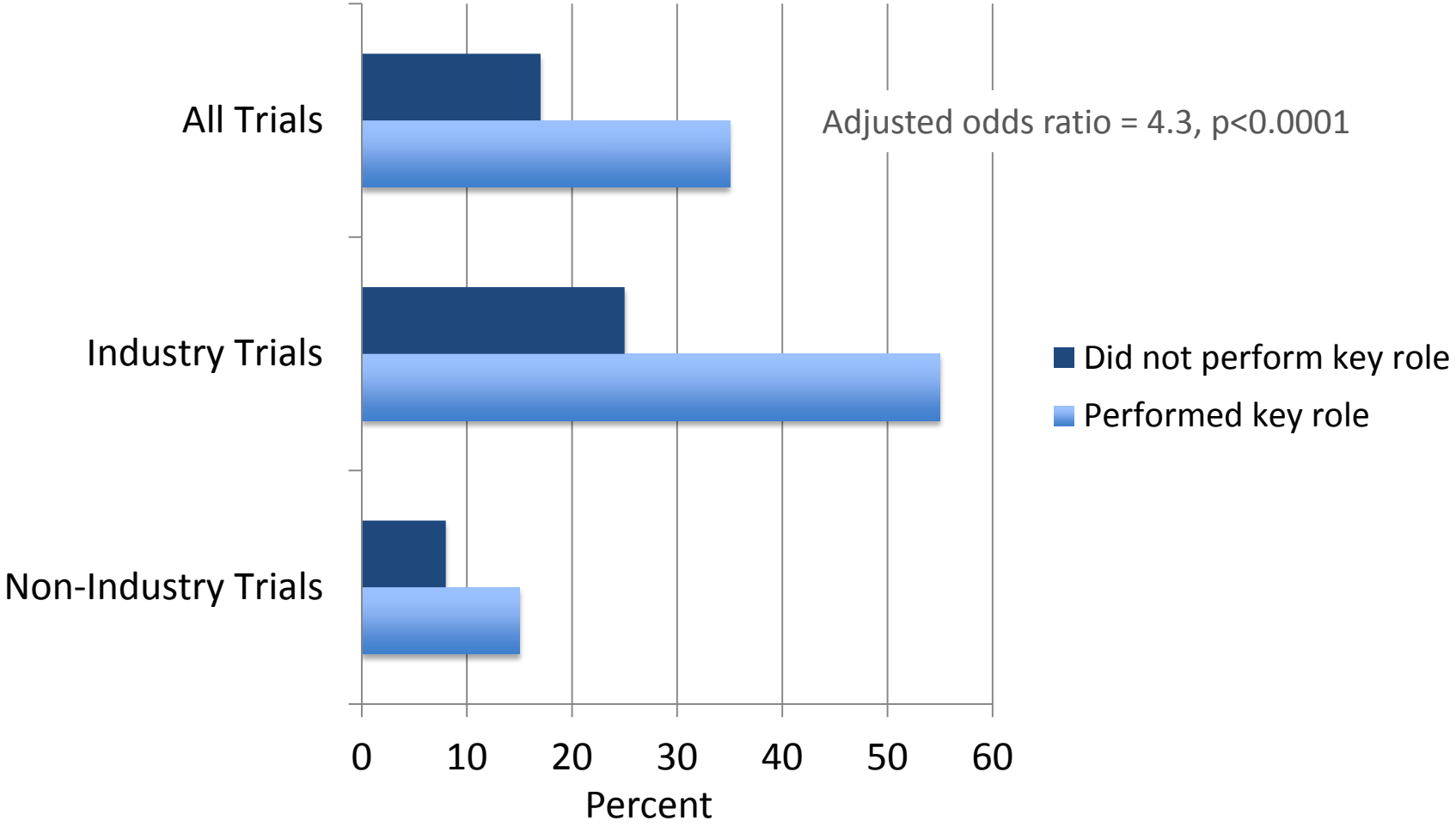
- ✓ Understand concerns about bias related to investigators' financial ties with industry
- Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions
- Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

Authors who play key scientific roles in clinical trials have more ties

- We identified all reports of clinical trials of drugs or biologics published in the *Journal of Clinical Oncology* between January 2006 & June 2007 (N=235)
  - We abstracted financial disclosures and authorship contributions of all authors (N=2927)
  - We asked whether authors who reported performing key scientific roles (conception & design, analysis & interpretation, or drafting of manuscript) were more likely than other authors to report financial ties

J Clin Oncol 28:1316, 2010

Authors who play key scientific roles in clinical trials have more ties



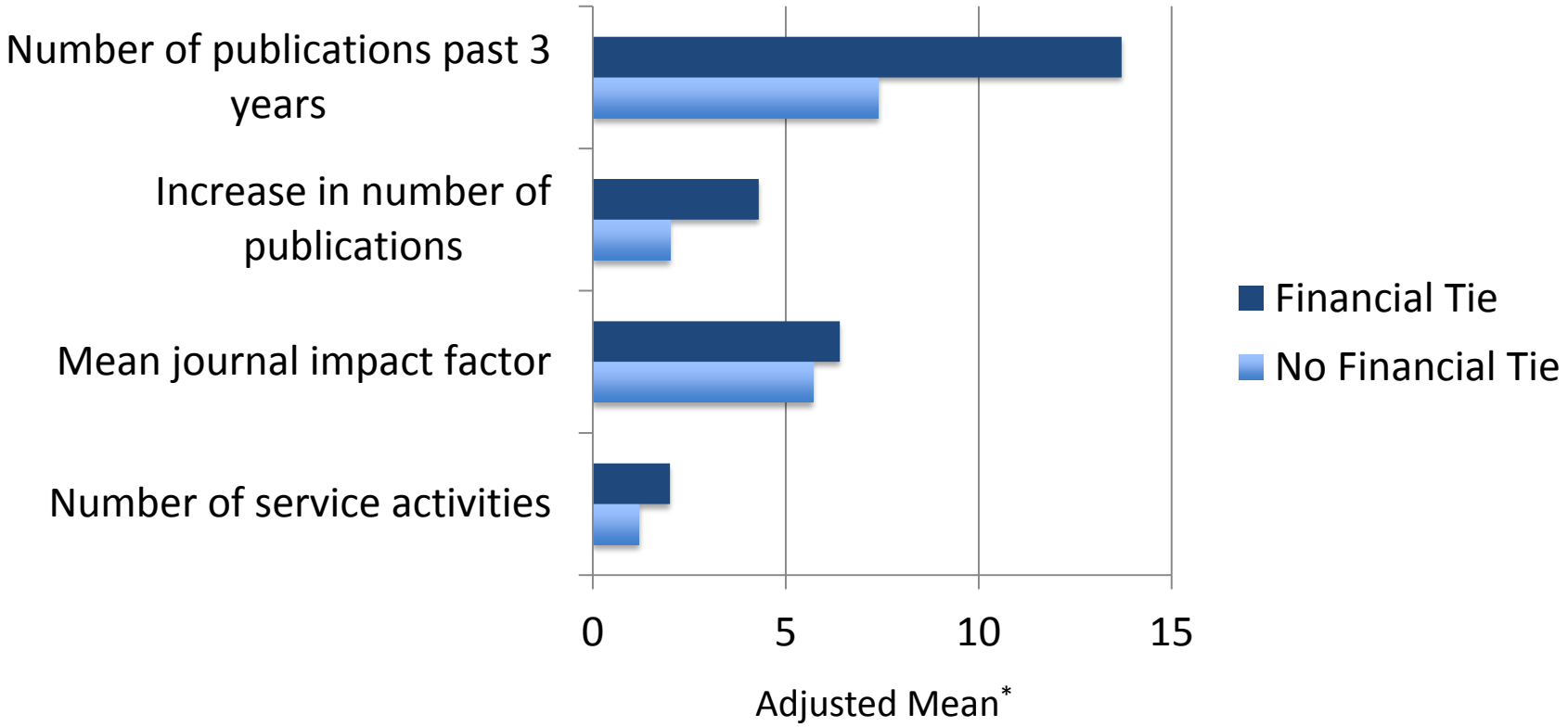
J Clin Oncol 28:1316, 2010

Financial ties are positively correlated with scientific productivity

- Recall Zinner et al survey of a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support

Health Affairs 28:1814, 2009

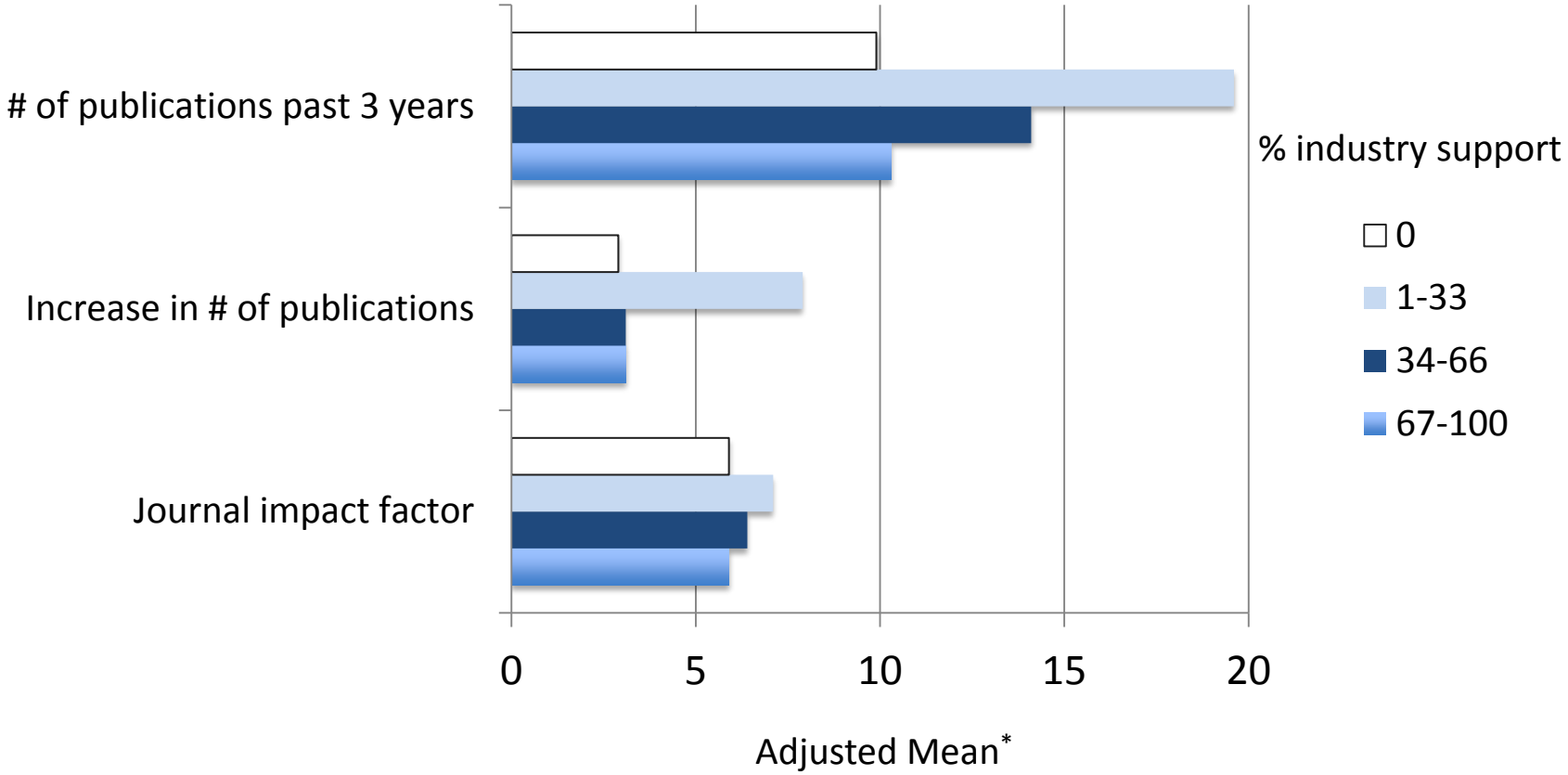
Financial ties are positively correlated with scientific productivity…



*Adjusted for rank, years in profession, sex, total research funding, clinical department

Health Affairs 28:1814, 2009

…within the context of a balanced research portfolio



*Adjusted for rank, years in profession, sex, total research funding, clinical department

Health Affairs 28:1814, 2009

Productivity and financial ties: take-home points

- Academic authors with financial ties make greater scientific contributions than their peers without ties
- Industry support, at least within a balanced research portfolio, correlates with greater scientific productivity
- Mechanisms behind these relationships are unknown
- Unclear how increased restrictions on academic-industry collaboration might affect scientific output and translation

Goals

- ✓ Understand concerns about bias related to investigators' financial ties with industry
- ✓ Consider implications of recent data regarding associations between investigators' financial ties and their scientific contributions
- • Review potential policy solutions to the problem of academic-industry financial ties, along with their limitations

Policy context

- Much attention
  - Congress
  - State legislatures
  - Federal funders
  - Universities, academic medical centers, & their organizations
  - Institute of Medicine
  - Company & trade association policies
  - Journals

Several strategies are available for addressing financial COI

- Manage
- Prohibit
- Disclose

NIH recently adopted new rules for extramural grantees

- Definition of Significant Financial Interest (SFI) changed from $10000 to $5000
- Grantees must disclose *all* SFI to institution
  - Institution then determines which SFI constitute COI
  - Institution must develop management plans for all identified financial COI
  - Institution must disclose nature of COI and key elements of management plan to PHS funder
  - Institution must post COI information on public website, or make available on written request within 5 business days

http://grants.nih.gov/grants/policy/coi/

NIH rules offer guidance re: management

- Disclosure
- Appointment of an independent monitor capable of taking measures to protect the design, conduct, and reporting of the research against bias
- Modification of the research plan
- Recusal, reduction/elimination of financial interest, severance of relationship

http://grants.nih.gov/grants/policy/coi/coi_faqs.htm#3202

Prohibition

Institute of Medicine

- "Academic medical centers and other research institutions should establish a policy that individuals generally may not conduct research with human participants if they have a significant financial interest in an existing or potential product or a company that could be affected by the outcome of the research. Exceptions to the policy should be made public and should be permitted only if the conflict of interest committee (a) determines that an individual's participation is essential for the conduct of the research and (b) establishes an effective mechanism for managing the conflict and protecting the integrity of the research."

Lo, B., M. J. Field, et al. (2009). *Conflict of interest in medical research, education, and practice.* Washington, D.C., National Academies Press.

Disclosure

- To whom?
  - Sponsors?
  - IRBs?
  - Institutions/COI committees?
  - Journals, readers, meeting attendees?
  - Research subjects?

Many (most?) patients & subjects favor disclosure of financial ties

REVIEW ARTICLE

HEALTH CARE REFORM

The Impact of Disclosing Financial Ties in Research and Clinical Care

A Systematic Review

Adam Licurse, BA; Emma Barber, BS; Steve Joffe, MD; Cary Gross, MD

Background: Despite increased demand for disclosure of physician and researcher financial ties (FTs) to industry, little is known about patients', research participants', or journal readers' attitudes toward FTs.

Methods: We systematically reviewed original, quantitative studies of patients', research participants', or journal readers' views about FTs to pharmaceutical and medical device companies. The MEDLINE, Scopus, and Web of Knowledge databases were searched for English-language studies containing original, quantitative data on attitudes toward FTs. We screened 6561 citations and retrieved 244 potentially eligible abstracts. Of these, 20 met inclusion criteria.

Results: Eleven studies assessed FTs and perceptions of quality. In clinical care, patients believed FTs decreased the quality and increased the cost of care. In research, FTs affected perceptions of study quality. In 2 studies, readers' perceptions of journal article quality [illegible] after disclosure of FTs. Eight studies assesse[illegible] ability of FTs. Patients were more likel[illegible] sonal gifts to physicians as unacceptabl[illegible] professional gifts. In 6 of the 10 studi[illegible] importance of disclosure, most pati[illegible] participants believed FTs should be disclosed; in the other 4, approximately one-quarter believed FTs should be disclosed. Among the 7 studies assessing willingness to participate in research, approximately one-quarter of participants reported less willingness after disclosure of FTs.

Conclusions: Patients believe that FTs influence professional behavior and should be disclosed. Patients, physicians, and research participants believe FTs decrease the quality of research evidence, and, for some, knowledge of FTs would affect willingness to participate in research.

Arch Intern Med. 2010;170(8):675-682

In 6 of the 10 studies that assessed the importance of disclosure, most patients and research participants believed FTs should be disclosed; in the other 4, approximately one-quarter believed FTs should be disclosed. Among the 7 studies assessing willingness to participate in research, approximately one-quarter of participants reported less willingness after disclosure of FTs.

Physicians discount studies that disclose industry sponsorship

- Kesselheim et al sent abstracts describing trials of 3 hypothetical agents to a random sample of Board-certified internists (N=269 respondents)
  - Abstracts varied systematically by level of methodological rigor and by funding disclosure (industry, none, NIH)
  - Respondents' perceptions of rigor, confidence in findings, and willingness to prescribe drug varied by both rigor of trial and by type of disclosure

NEJM 367:1119, 2012

Physicians discount studies that disclose industry sponsorship

	Industry funding vs. none OR (95% CI)	Industry funding vs. NIH OR (95% CI)
Perception of rigor	0.63 (0.46-0.87)	0.50 (0.36-0.69)
Confidence in results	0.71 (0.51-0.98)	0.51 (0.36-0.70)
Willingness to prescribe drug	0.68 (0.49-0.94)	0.52 (0.37-0.71)

NEJM 367:1119, 2012

Affordable Care Act promotes disclosure of physicians' ties to industry

- US manufacturers of drugs, devices, biologics, and medical supplies covered under federal programs must report payments to *physicians and teaching hospitals* to DHHS on an annual basis
  - DHHS makes data publicly available
- Covers all types of payments worth $10 or more, including research funding
- Substantial fines for noncompliance, esp. if knowing

http://www.prescriptionproject.org/tools/initiatives_factsheets/files/Sunshine-fact-sheet-3.23.10.pdf

Caveat emptor: disclosure may have undesirable effects

Effect	Mechanism	
	Researcher	Prospective Subject
Mitigate problem of COI		
Exacerbate problem of COI		

Sah S et al, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1970961
JAMA 307:669, 2012
J Pers Social Psychol 104:289, 2013

Caveat emptor: disclosure may have undesirable effects

Effect	Mechanism	
	Researcher	Prospective Subject
Mitigate problem of COI	• Decreased willingness to enter conflicted arrangements	
Exacerbate problem of COI		

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Sah S et al, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1970961
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Sah S et al, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1970961
JAMA 307:669, 2012
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Several techniques may decrease adverse effects of disclosure

- Reduce social pressure of disclosure
  - Route disclosure through third party
  - Give advisee time & space to make decision
- Minimize need for disclosure within relationships, esp. trust-based relationships
  - Vs. arms-length contexts, where less problematic

Sah S et al, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1970961
JAMA 307:669, 2012
J Pers Social Psychol 104:289, 2013

How well do these rules accomplish their major goals?

- Minimize risks to human subjects
- Reduce risk of bias in science
- Protect the reputations of academic faculty and institutions
- Preserve public trust in research

Summary

- Substantial evidence base for bias in industry-funded research
- Weaker, but growing, evidence base that personal financial ties pose additional risk
- New evidence that financial ties correlate with scientific contributions & productivity
- Much policy activity, but unclear how well policies accomplish key goals