

Perelman
School of Medicine
UNIVERSITY of PENNSYLVANIA

Conflicts of Interest

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Ethical and Regulatory Aspects of Clinical Research
National Institutes of Health Clinical Center
October 28, 2015

Disclosure

I have no financial relationships to disclose

Goals

- Understand concerns about bias related to industry funding and investigators' financial ties
- Consider implications of recent data regarding associations between investigators' financial ties and scientific contributions
- Review potential policy responses to academic-industry financial ties & their limitations

Defining conflict of interest

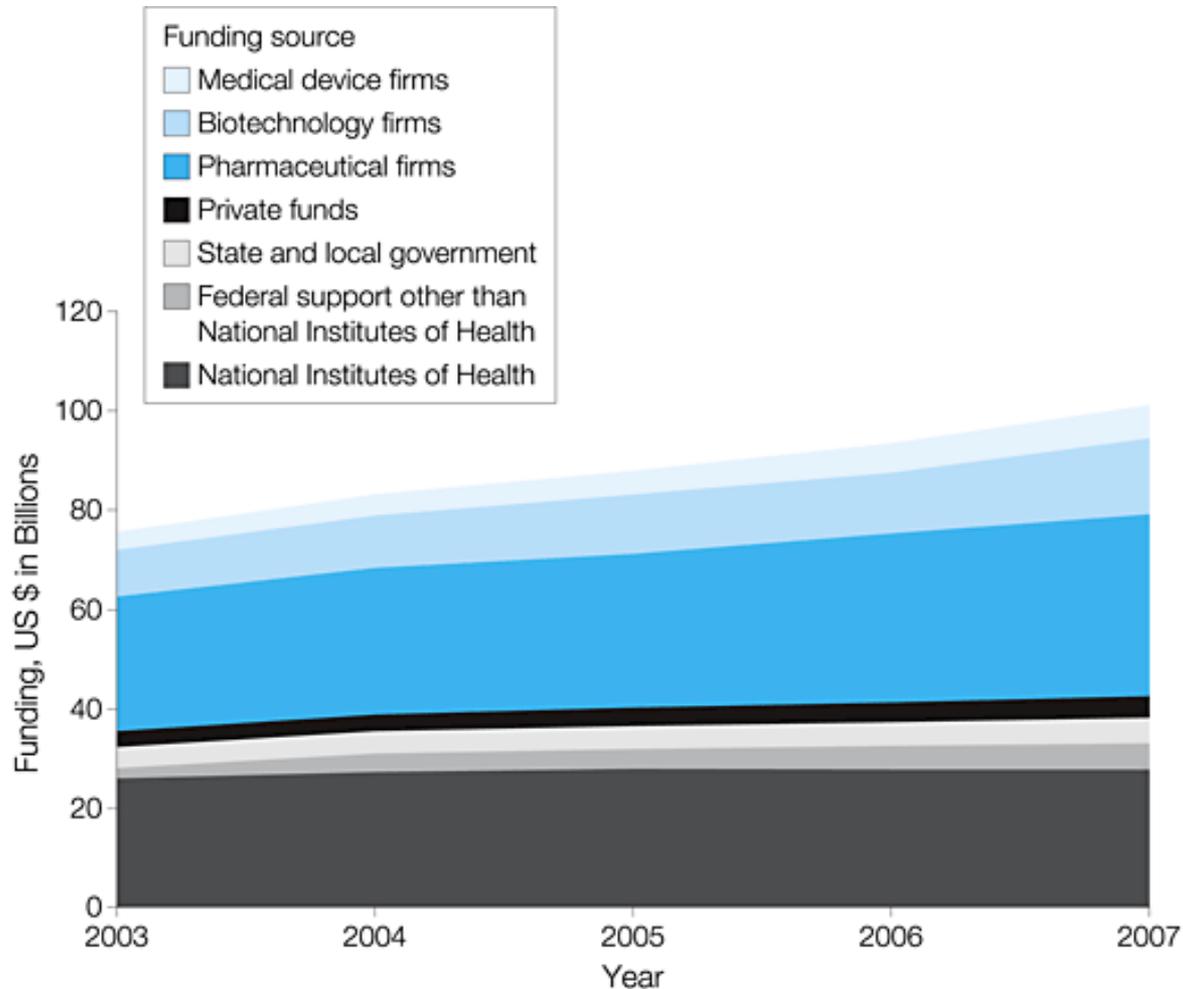
“A COI is a set of *circumstances* that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest.”

- Patient welfare
- Valid science
- Trainee education

Why do we care about conflicts of interest in research?

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

Industry supports a growing proportion of biomedical research



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

Industry sponsorship and research outcome (Review)

Lundh A, Sisondo S, Lexchin J, Busuioac OA, Bero L

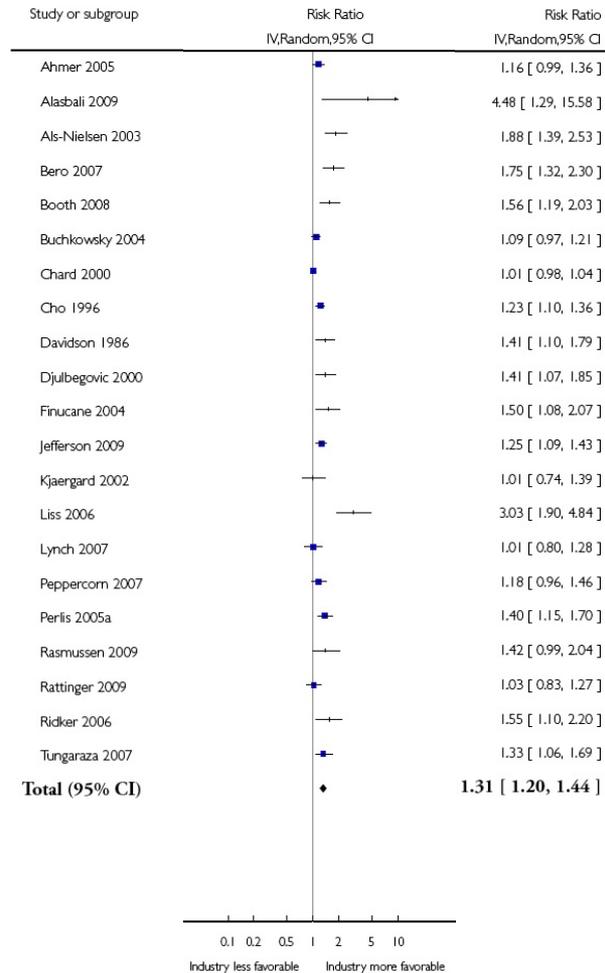


This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 7

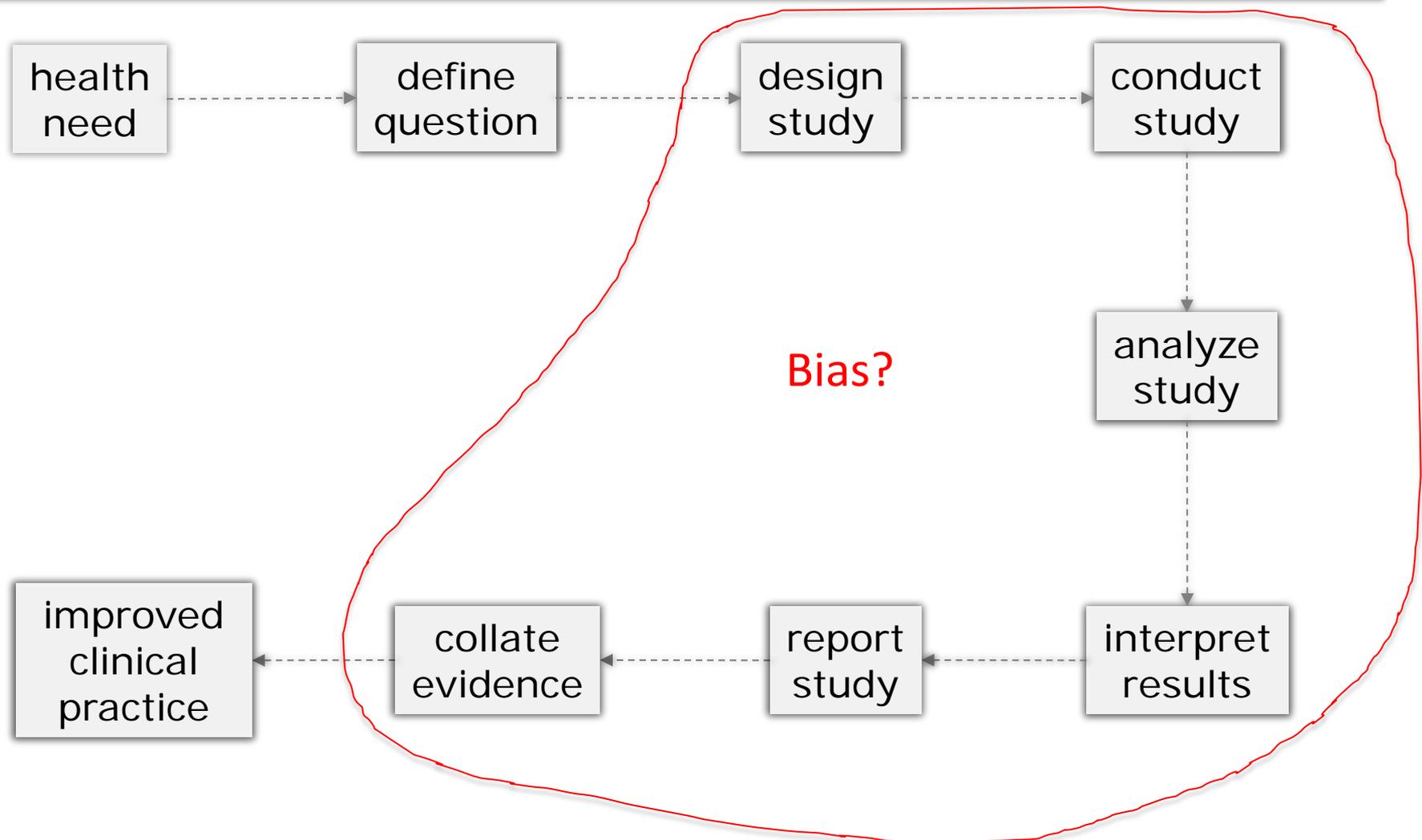
<http://www.thecochranelibrary.com>

WILEY

Industry-sponsored studies are more likely to draw favorable conclusions

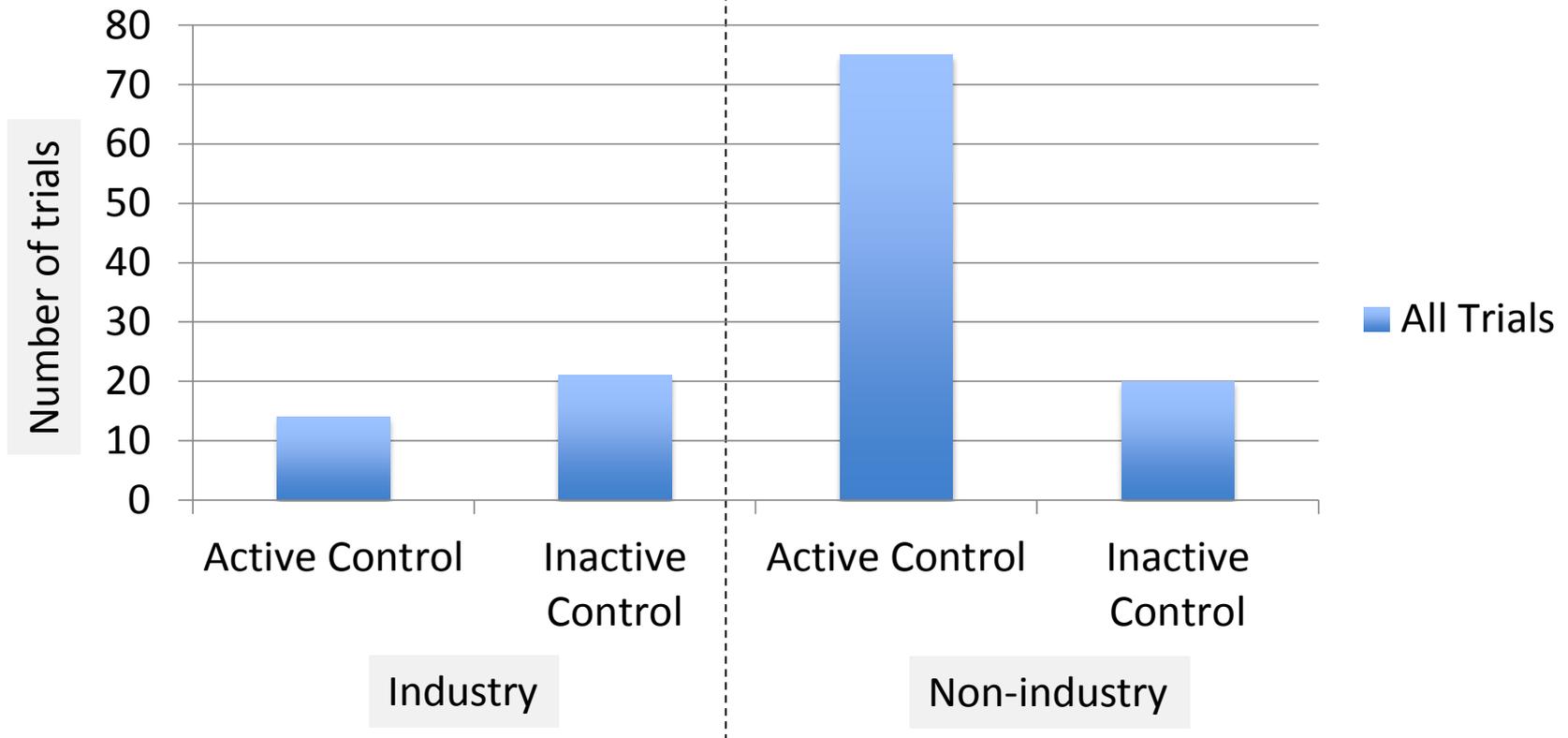


Various mechanisms may explain the more favorable results of industry trials



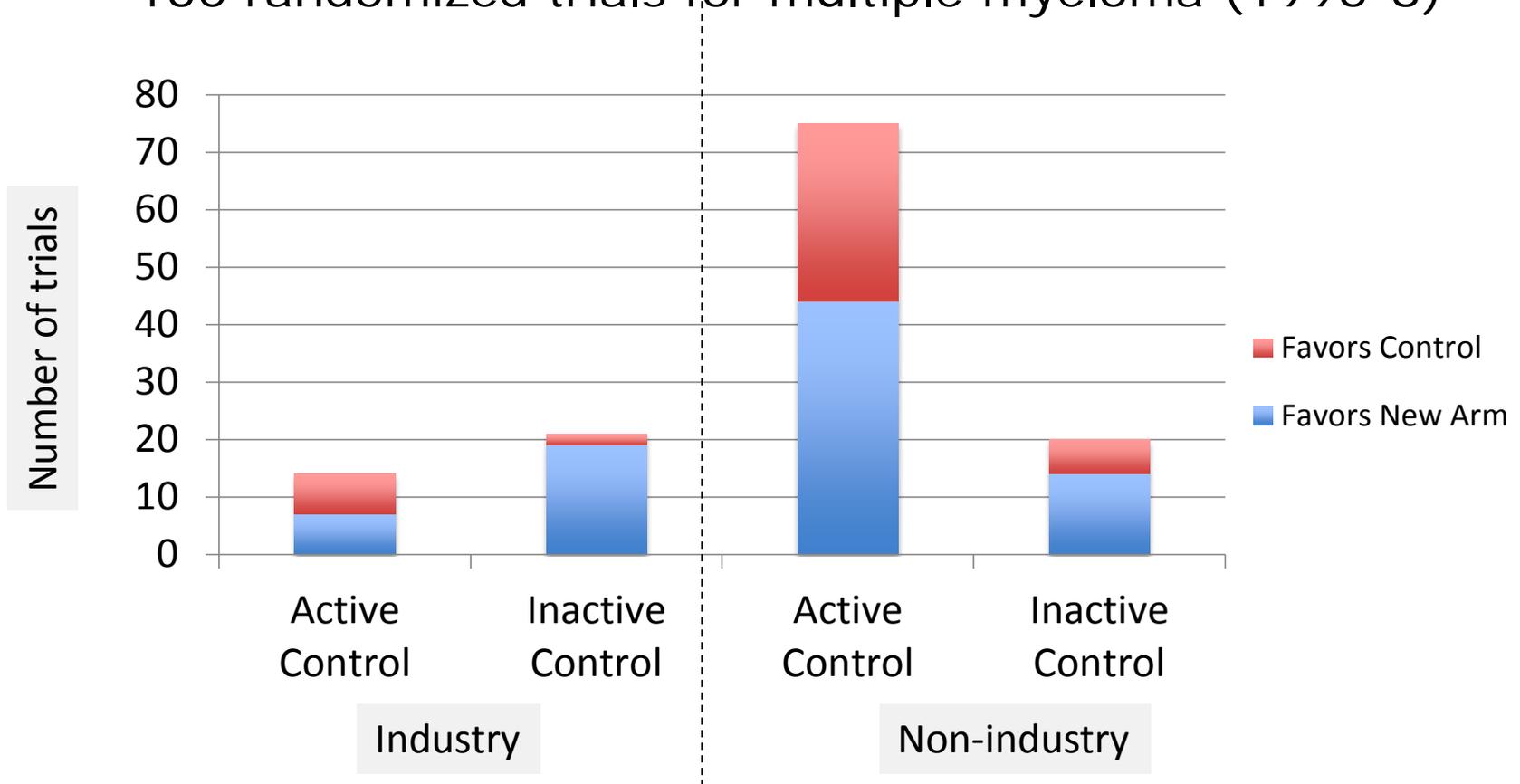
Industry-sponsored studies may be less likely to use active controls

130 randomized trials for multiple myeloma (1996-8)



Use of inactive controls is associated with favoring new arm

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



Published endpoints may differ from those in internal documents

The NEW ENGLAND JOURNAL *of* MEDICINE

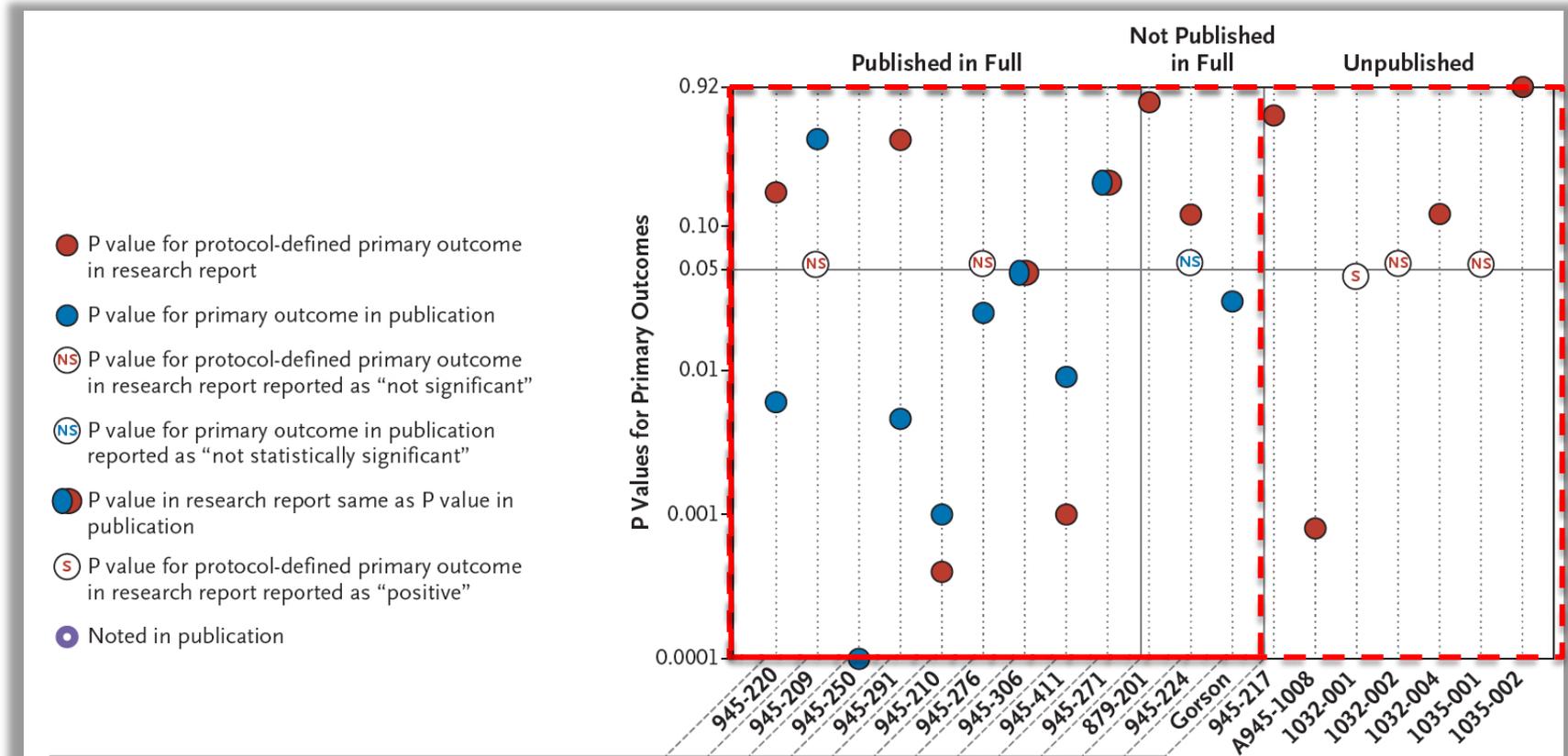
SPECIAL ARTICLE

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

Published endpoints may differ from those in internal documents



Spin: conclusions may stray from quantitative results

Als-Nielsen studied relationship between funding source & conclusion in 370 randomized 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

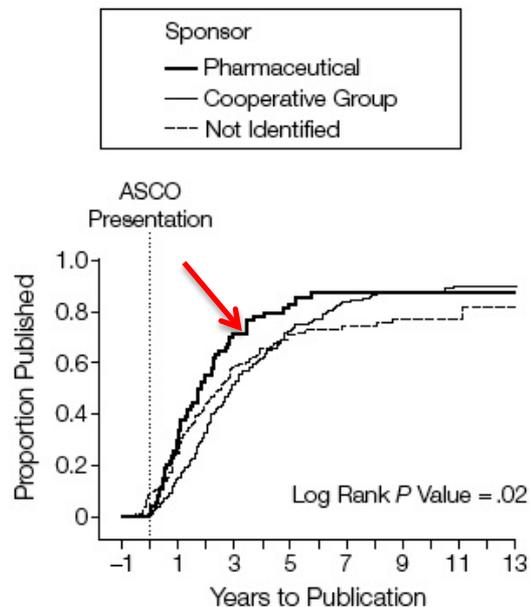
*The likelihood of recommending the experimental drug as the treatment of choice decreased with higher z scores (the higher the score the smaller the benefit of the experimental drug).

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

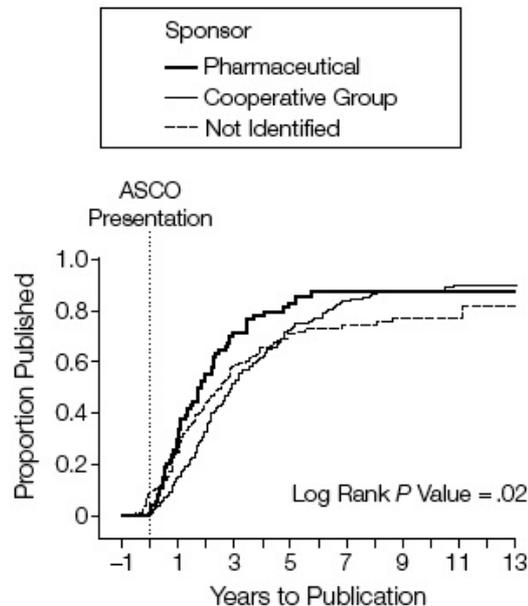


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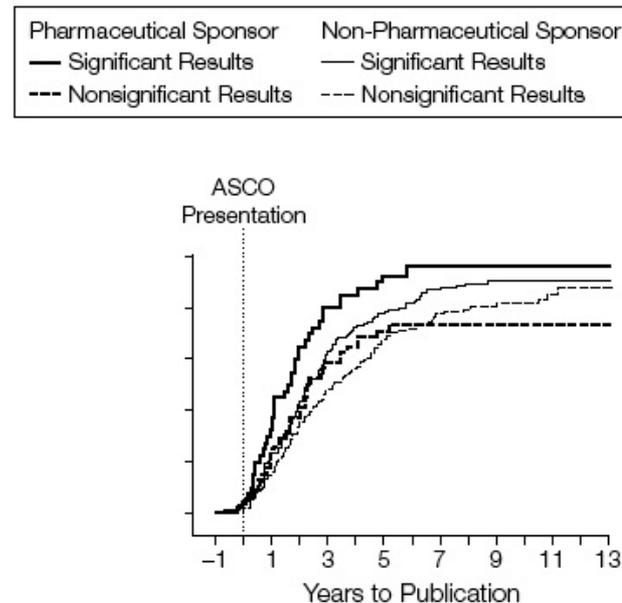
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Figure 3. Time to Publication by Sponsorship and by Type of Result and Sponsorship

A Time to Publication by Sponsorship



B Time to Publication by Type of Result and Sponsorship



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

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 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.

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.

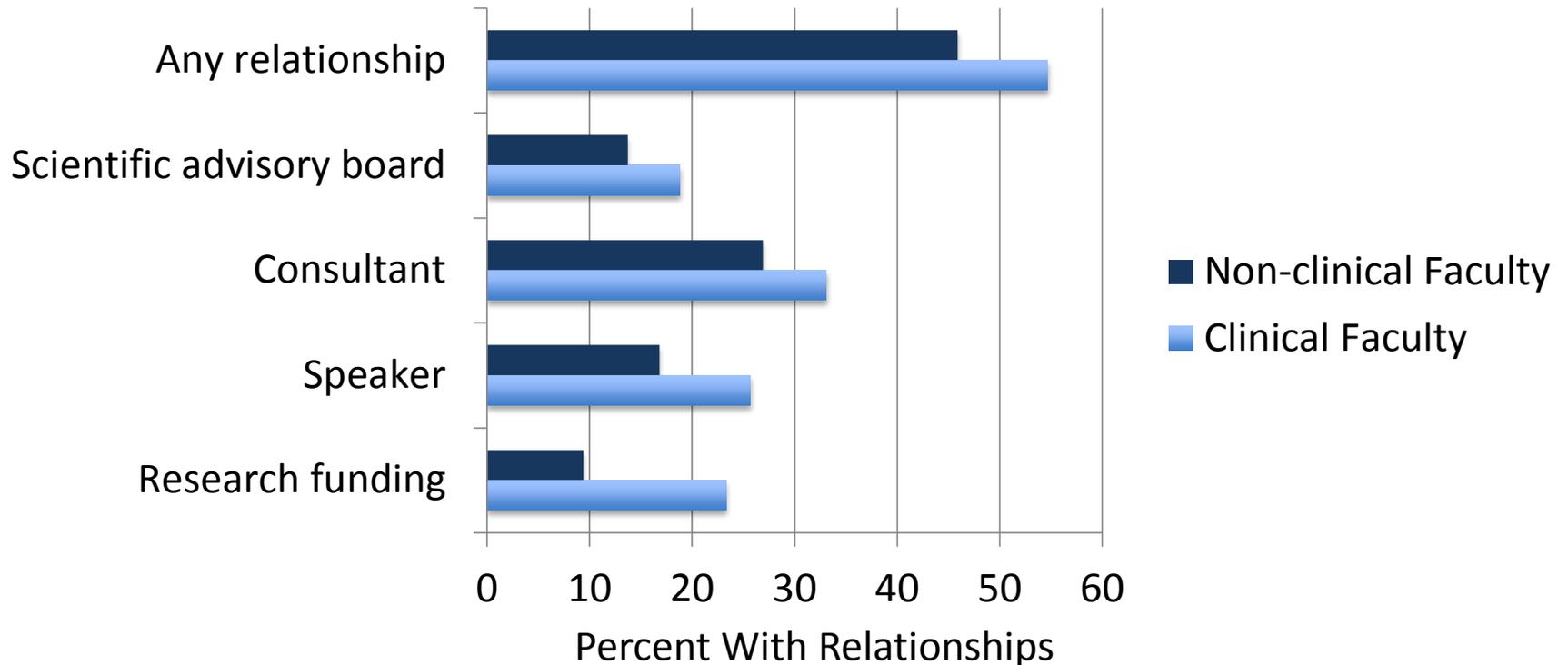
(*Am J Psychiatry* 2006; 163:185–194)

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**What about personal
financial ties?**

Personal financial ties are common

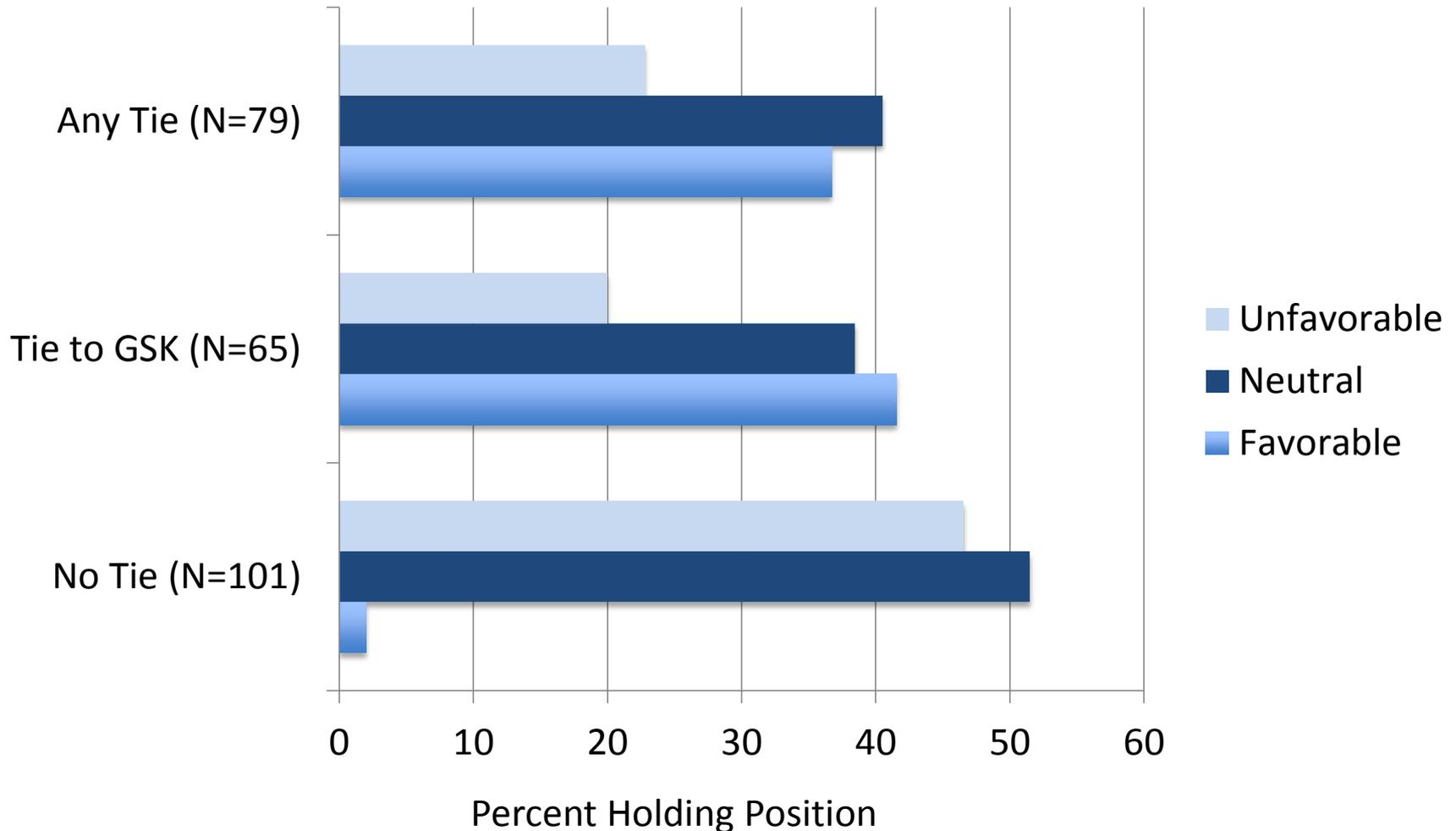
Zinner et al surveyed a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support



Authors' positions may vary according to their 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

Authors' positions may vary according to their financial ties



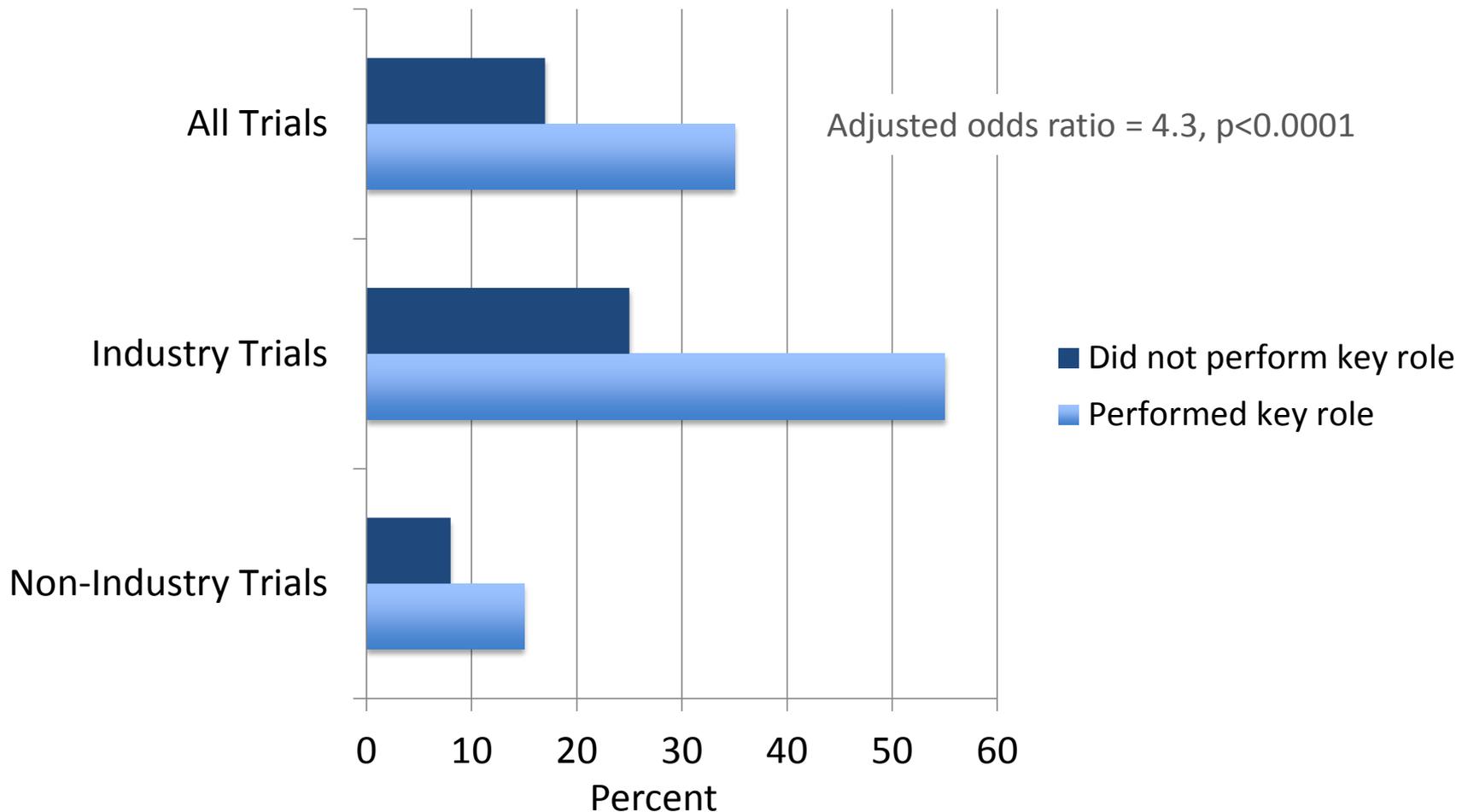
Goals

- ✓ 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

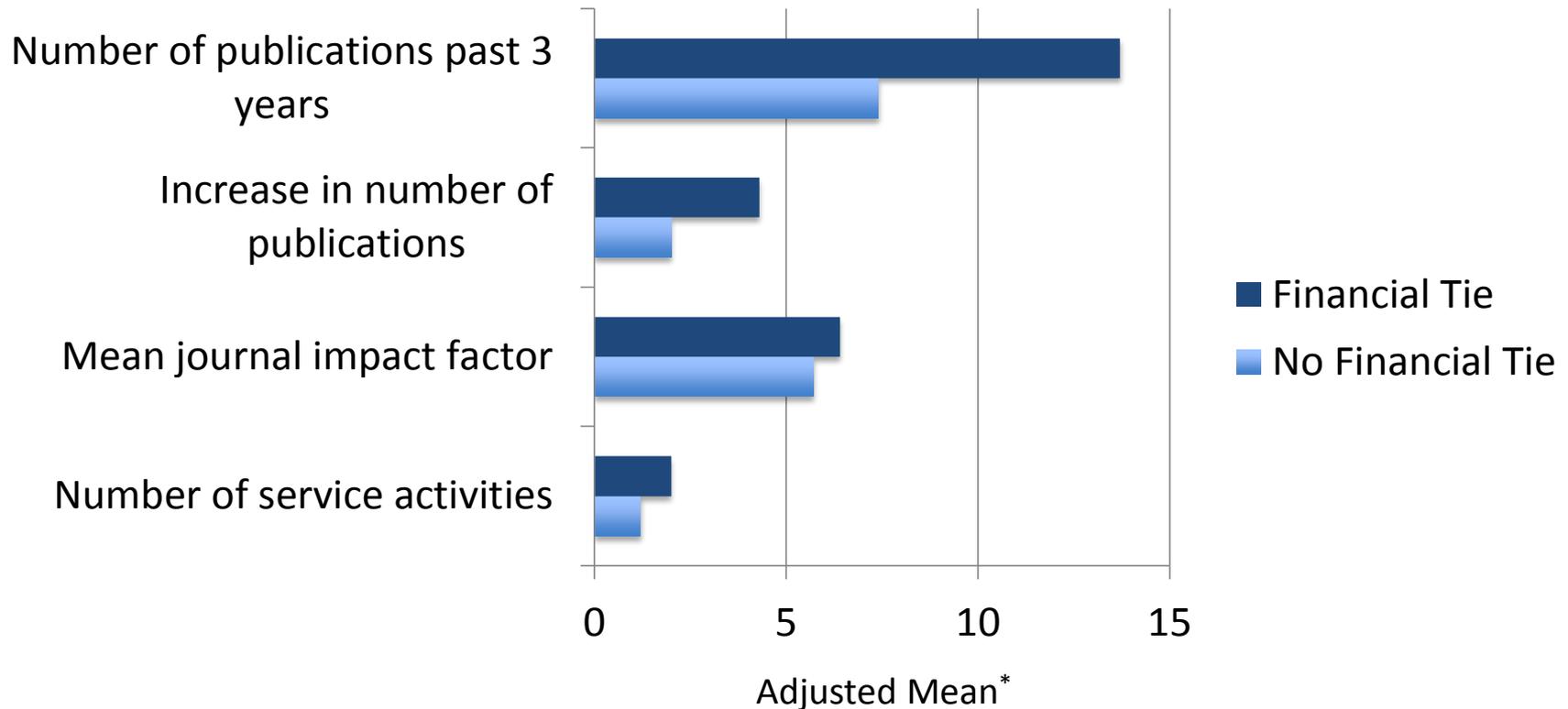
Authors who play key scientific roles in clinical trials have more ties



Financial ties correlate *positively* with scientific productivity

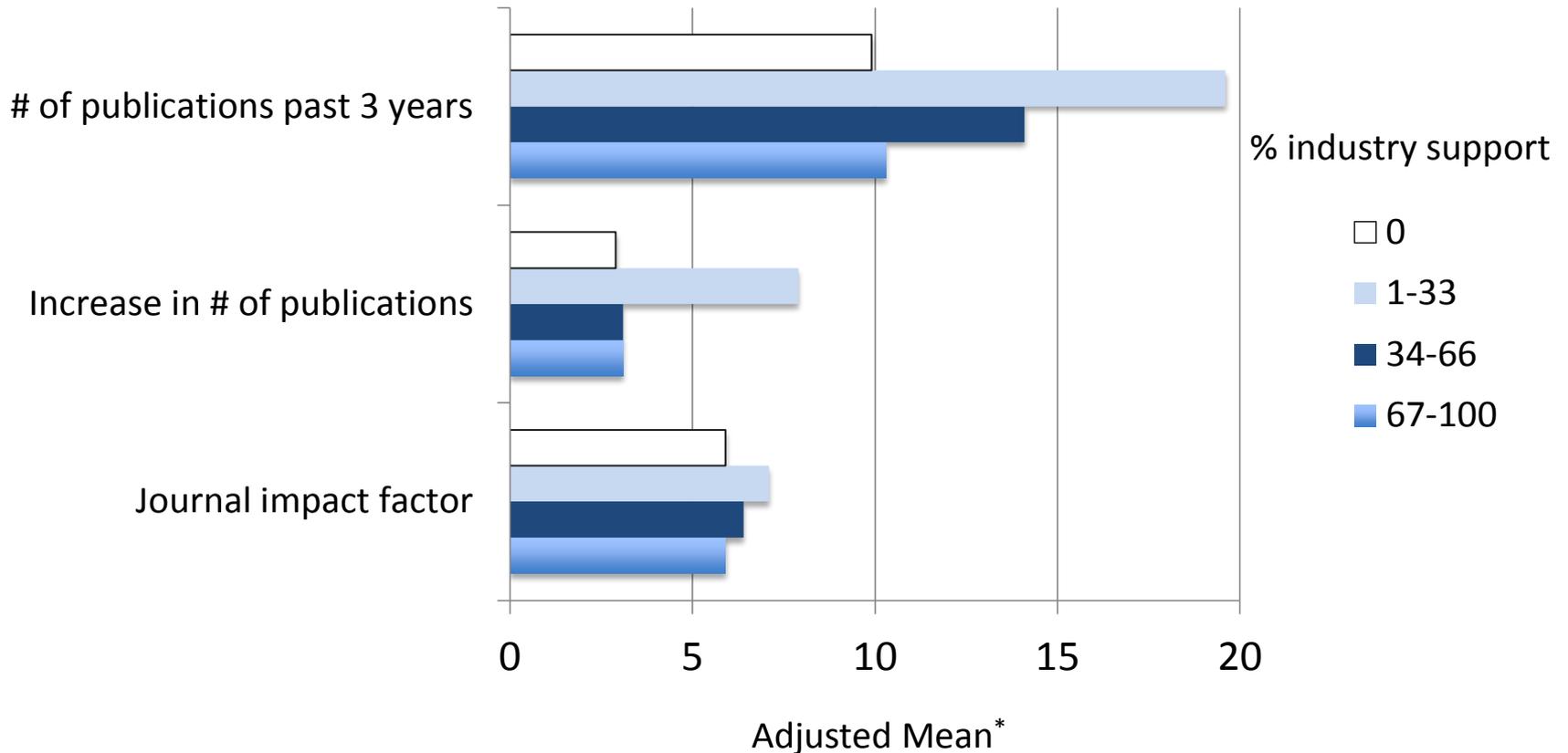
- Recall Zinner et al survey of a stratified random sample of life-sciences faculty at the 50 U.S. universities with the most NIH support

Financial ties correlate *positively* with scientific productivity...



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

...within the context of a balanced research portfolio



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

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/oversee
- 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

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

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.”

Disclosure

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

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

Affordable Care Act promotes disclosure of physicians' ties to industry

Open Payments - Centers f... x +

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View Summary Data
Search the Data
Create Charts and Graphs with the Data Explorer
Download Open Payments Datasets

Open Payments

Sometimes, doctors and hospitals have financial relationships with health care manufacturing companies. These relationships can include money for research activities, gifts, speaking fees, meals, or travel. The Affordable Care Act requires CMS to collect information from applicable manufacturers and group purchasing organizations (GPOs) in order to report information about their financial relationships with physicians and hospitals. Open Payments is the federally run program that collects the information about these financial relationships and makes it available to you. [View the summary data dashboard](#) for an overview of the published data.

Search & Explore Open Payments Data

Use the [search tool](#) to look up a doctor or hospital, or a company that's made payments. Download all Open Payments data in detail. [Interact](#) with all the data sets. States can [create and download](#) custom reports.

Open Payments Data in Context

What is a conflict of interest? What is nature of payment? [Learn about](#) Open Payments and what it may mean for physicians, industry, and you.

Program Participants: Access the System

Learn more about system registration requirements:

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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 decreased after disclosure of FTs. Eight studies assessed the acceptability of FTs. Patients were more likely to view personal gifts to physicians as unacceptable, compared with professional gifts. 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.

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

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)

Caveat emptor: disclosure may have undesirable effects

Effect	Mechanism	
	Researcher	Prospective Subject
Mitigate problem of COI	<ul style="list-style-type: none">Decreased willingness to enter conflicted arrangements	
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	<ul style="list-style-type: none">Decreased willingness to enter conflicted arrangements	<ul style="list-style-type: none">Decreased trust in researcher
Exacerbate problem of COI		

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Caveat emptor: disclosure may have undesirable effects

Effect	Mechanism	
	Researcher	Prospective Subject
Mitigate problem of COI	<ul style="list-style-type: none">• Decreased willingness to enter conflicted arrangements	<ul style="list-style-type: none">• Decreased trust in researcher
Exacerbate problem of COI	<ul style="list-style-type: none">• <i>Strategic exaggeration</i> (more biased advice due to expected discounting)• <i>Moral licensing</i> (feeling that bias is justified because advisee has been warned)	

Sah S et al, http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1970961

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Exacerbate problem of COI	<ul style="list-style-type: none"> <i>Strategic exaggeration</i> (more biased advice due to expected discounting) <i>Moral licensing</i> (feeling that bias is justified because advisee has been warned) 	<ul style="list-style-type: none"> <i>Insinuation anxiety</i> (desire not to offend adviser by suggesting that s/he is biased) <i>Panhandler effect</i> (feeling of pressure to give adviser what s/he wants)

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

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

Questions remain about how well 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

Is the pendulum swinging back?

VIEWPOINT

Confluence, Not Conflict of Interest Name Change Necessary

Anne R. Cappola, MD, ScM
Institute for Translational Medicine and Therapeutics, Simlow Center for Translational Research, University of Pennsylvania Perelman School of Medicine, Philadelphia; and Associate Editor, JAMA.

Garret A. FitzGerald, MD, FRS
Institute for Translational Medicine and Therapeutics, Simlow Center for Translational Research, University of Pennsylvania Perelman School of Medicine, Philadelphia.

The primary interest of the biomedical scientific endeavor is to benefit patients and society. Frequently, this primary interest coincides with secondary interests, most commonly financial in nature, at the interface of the investigator's relationship with a private sponsor, typically a drug or device company or, increasingly, venture capital firms. Academia and the public have become sensitive to how such a secondary interest might be unduly influential, biasing the interpretation of results, exposing patients to harm, and damaging the reputation of an institution and investigator. This concern has prompted efforts to minimize or "manage" such "conflicts of interest" resulting in a plethora of policies at both the local and national level. Although these policies are often developed in reaction to a limited number of investigators, once introduced, they apply to all. Given the broad array of stakeholders, the diversity of approaches, and the concern that such policies might restrain innovation and delay translation of basic discoveries to clinical benefit, the Institute for Translational Medicine

may be even more seductive come of a study may influence impact journal, invitations to motion, salary, and space. E may publicly eschew any direct sponsor, such fiscal and procure to them indirectly from tract clinical trials with their timation of how fame—w institutions, funders, and jou is a considerable challenge. of monetary gain, which can is complex.² A possible strat mapping approach to potent a heat map of gene express press and give weight to ele on the y-axis, charted agains the x-axis that are likely to g perience would refine the a sure of such information or its provision in consent for

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MEDICINE AND SOCIETY

CONFLICTS OF INTEREST — PART 1
Debra Malina, Ph.D., Editor

Reconnecting the Dots — Reinterpreting Industry–Physician Relations

Lisa Rosenbaum, M.D.

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MEDICINE AND SOCIETY

CONFLICTS OF INTEREST — PART 3
Debra Malina, Ph.D., Editor

Beyond Moral Outrage — Weighing the Trade-Offs of COI Regulation

Lisa Rosenbaum, M.D.

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MEDICINE AND SOCIETY

CONFLICTS OF INTEREST — PART 2
Debra Malina, Ph.D., Editor

Understanding Bias — The Case for Careful Study

Lisa Rosenbaum, M.D.

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