

Conflicts of Interest in Clinical Studies

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ASGCT Clinical Trials Training Course

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Disclosure Information

I have the following financial relationship to disclose:

- Data and Safety Monitoring Board: Genzyme Corp.

Questions

- What is a conflict of interest (COI)?
- Why do we care about COI?
- How might COIs affect biomedical research?
- How can we deal with COIs?

Definition of COI

- A COI occurs when “a professional judgment concerning a primary interest...tends to be unduly influenced by a secondary interest...”
 - Or better: “risks being induly influenced...”

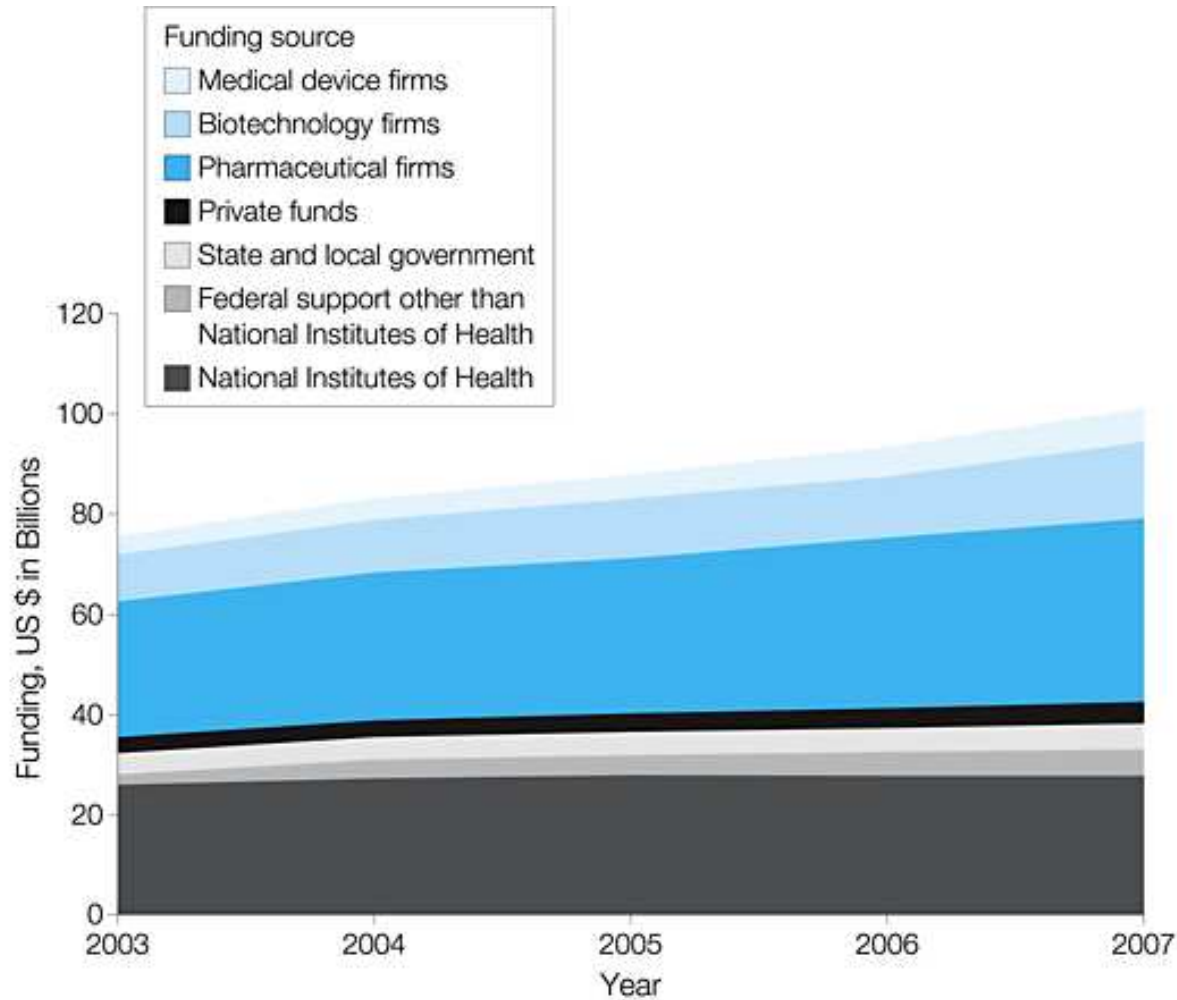
Types of COI

- Clinical vs. research (vs. educational)
- Financial vs. non-financial
- Individual vs. institutional

Why Do We Care About COI in Research?

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

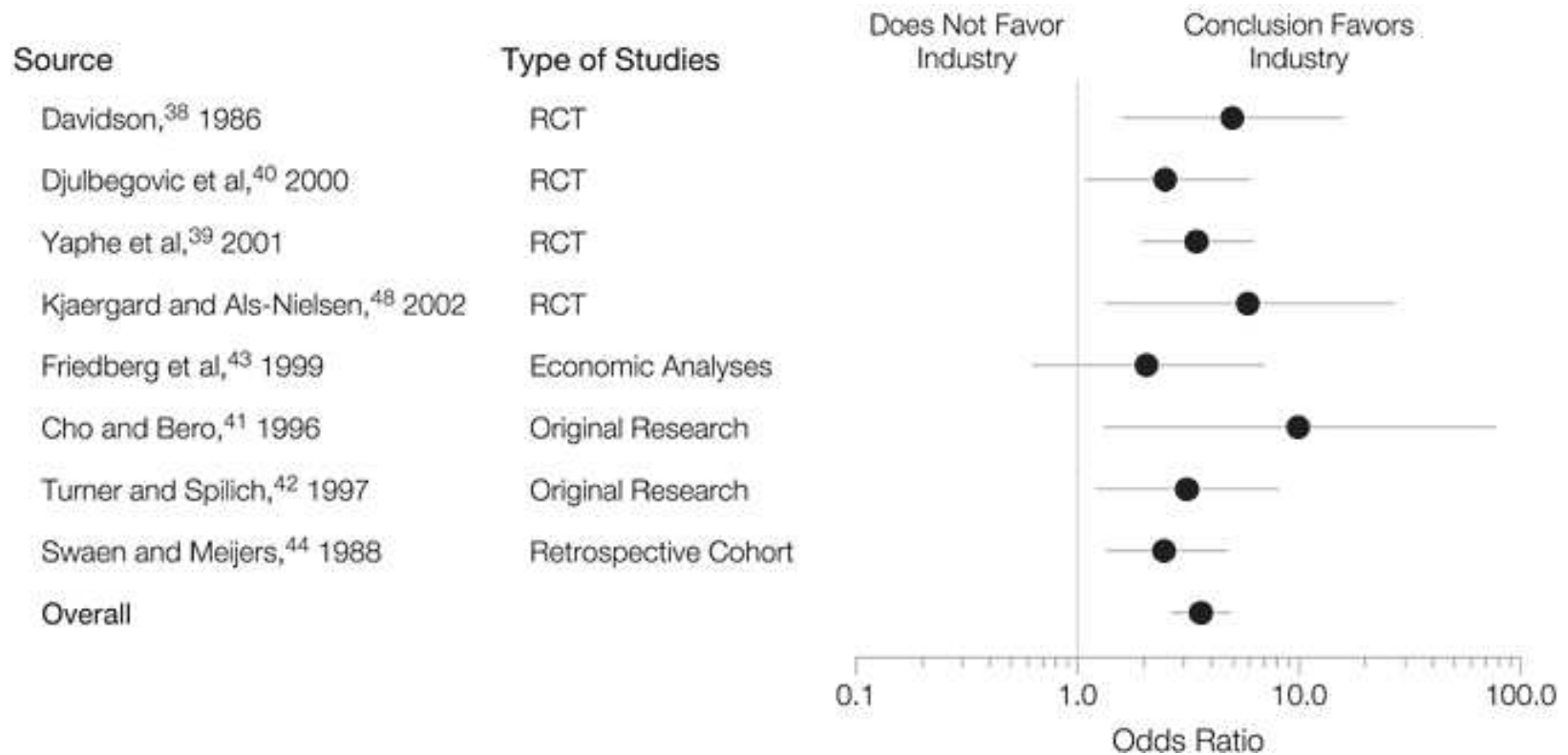
National Biomedical Research Expenditures



Prevalence of Personal Financial Ties

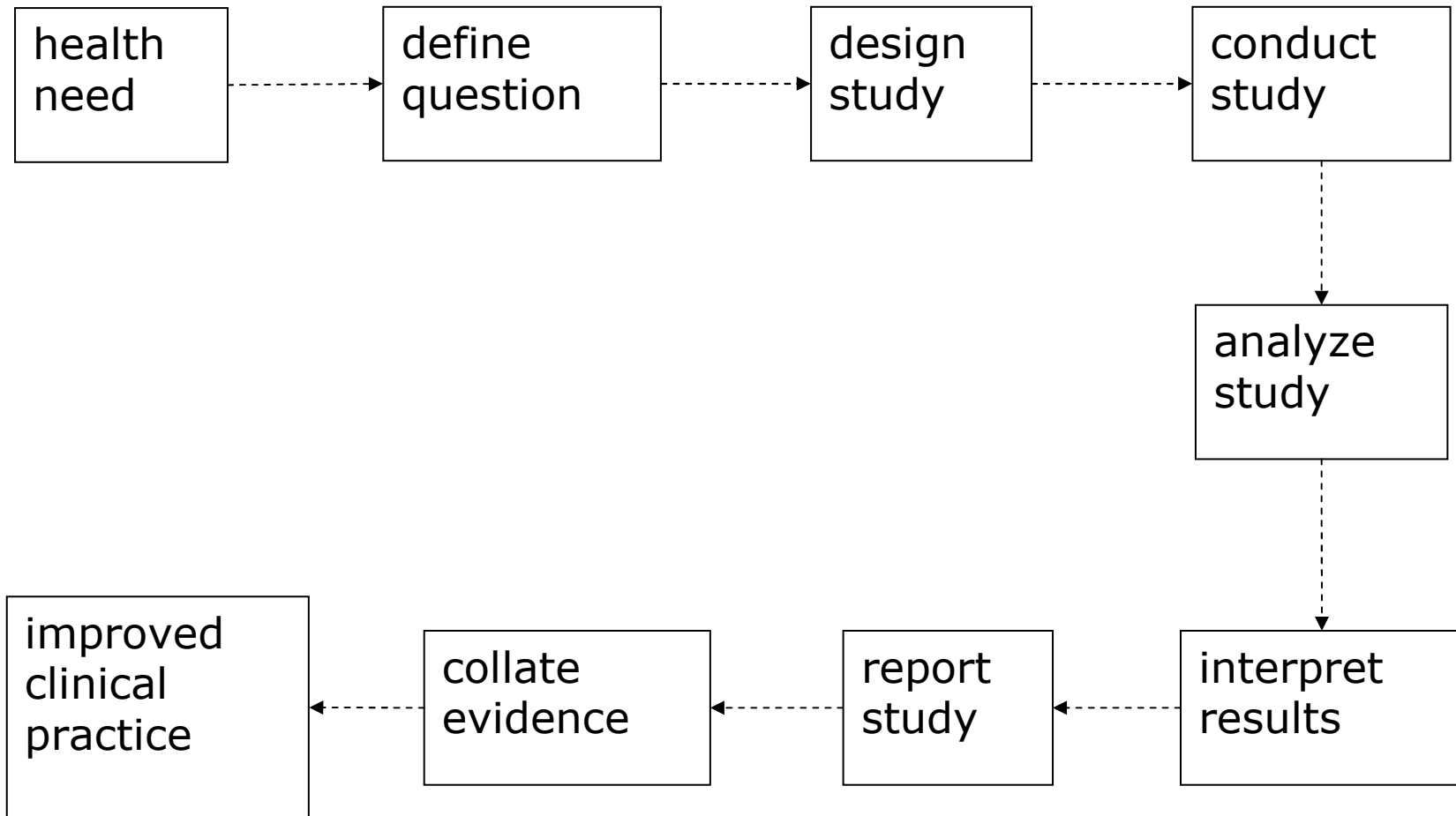
<u>Article</u>	<u>Population</u>	<u>% With Ties</u>	<u>Type of Tie</u>
Blumenthal 1986	Life science faculty at major AHCs	23%	Sponsorship, consultants
Blumenthal 1996	"	28%	Industry sponsorship
Blumenthal 1997	"	25-28%	Industry sponsorship
Campbell 1998	"	43%	Gifts, personal funds
Krimsky 1991	Members of NAS	37%	Tech transfer, venture formation
Krimsky 1998	Authors	34%	" (at least one author)
Boyd 2000	UCSF faculty	8%	Personal ties to industry research sponsors

Relation Between Industry Sponsorship & Study Outcome

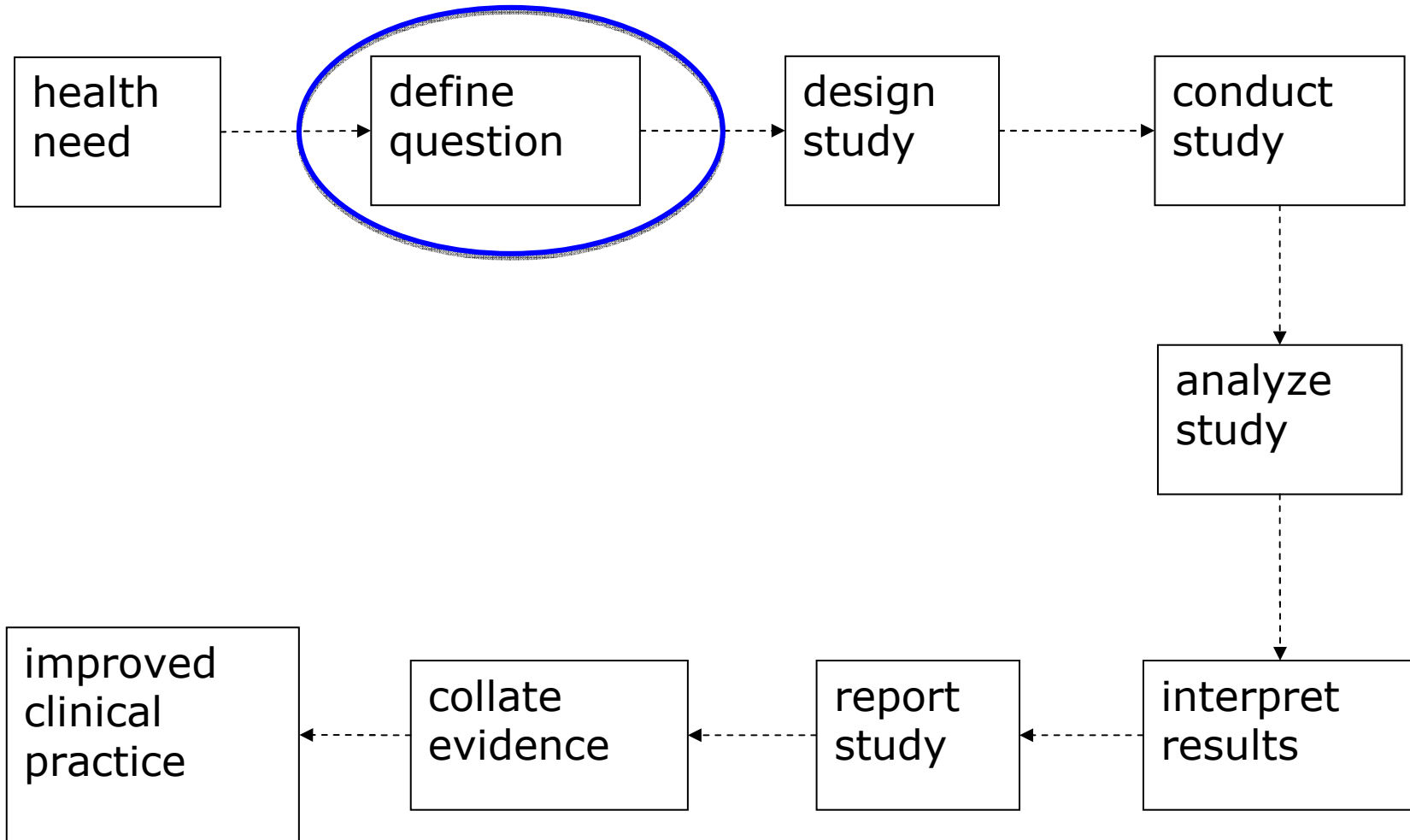


JAMA 289:454, 2003

Model of Research Process



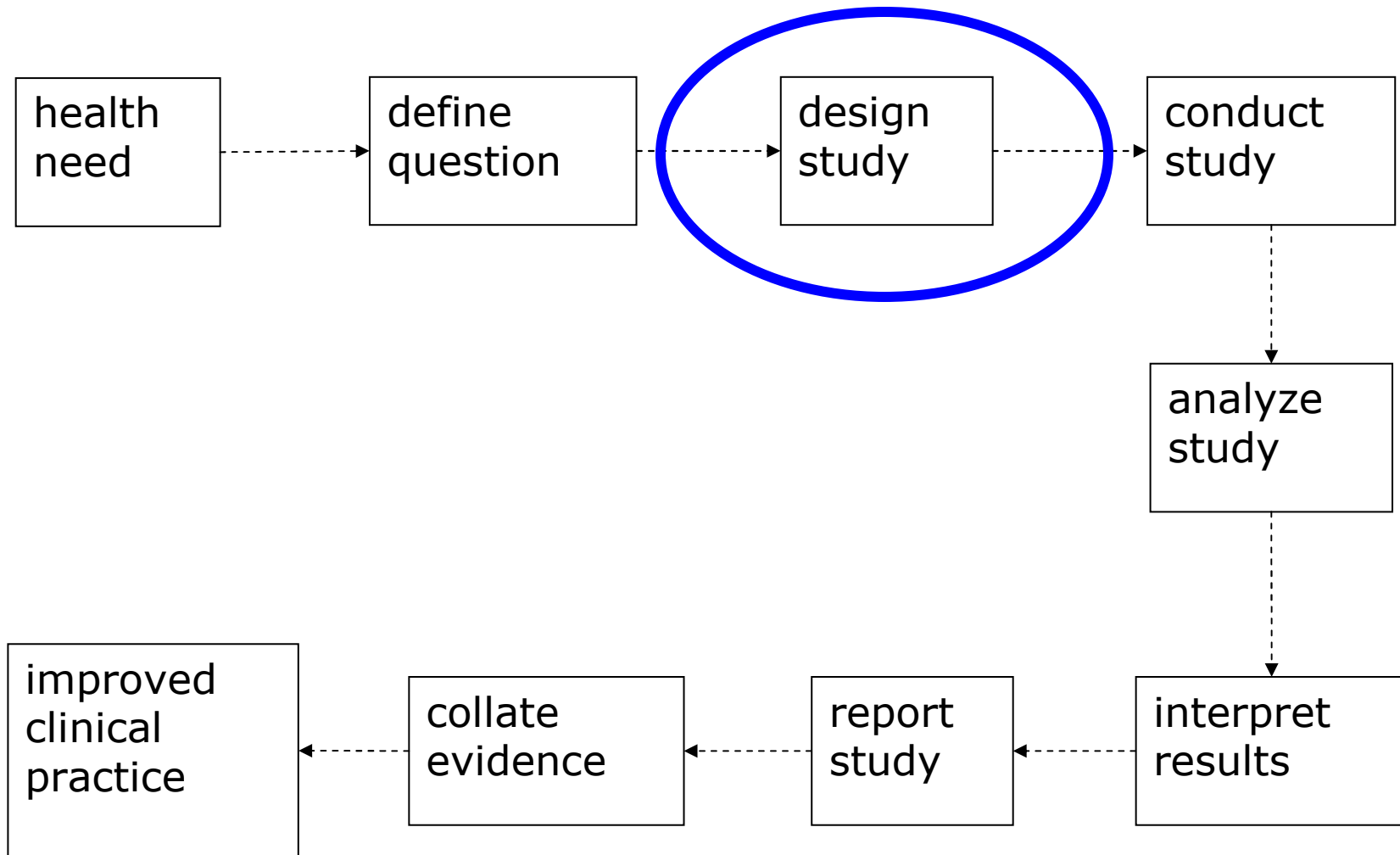
Model of Research Process



Defining Question

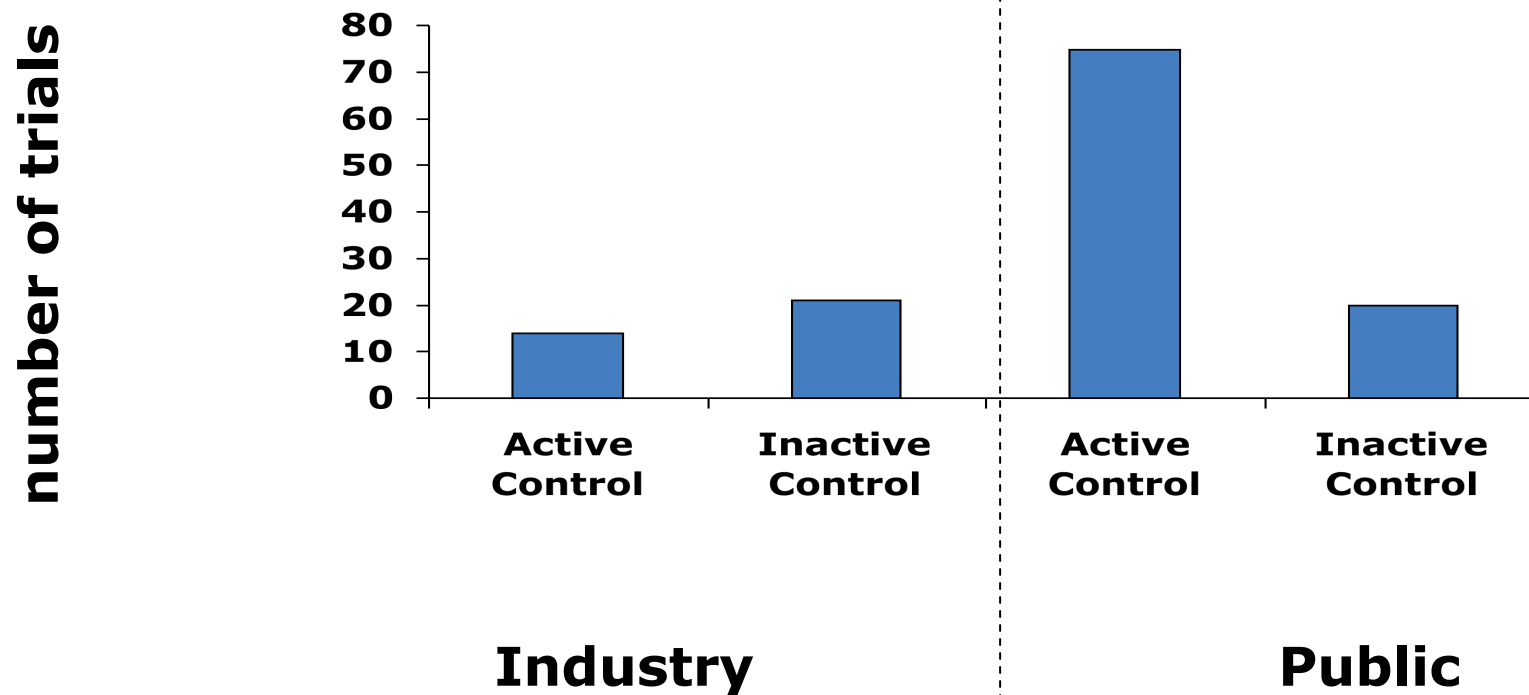
- “Picking the winner”
- Choosing not to study clinically important but financially risky questions
 - e.g., cardiac risks of COX-2 inhibitors

Model of Research Process

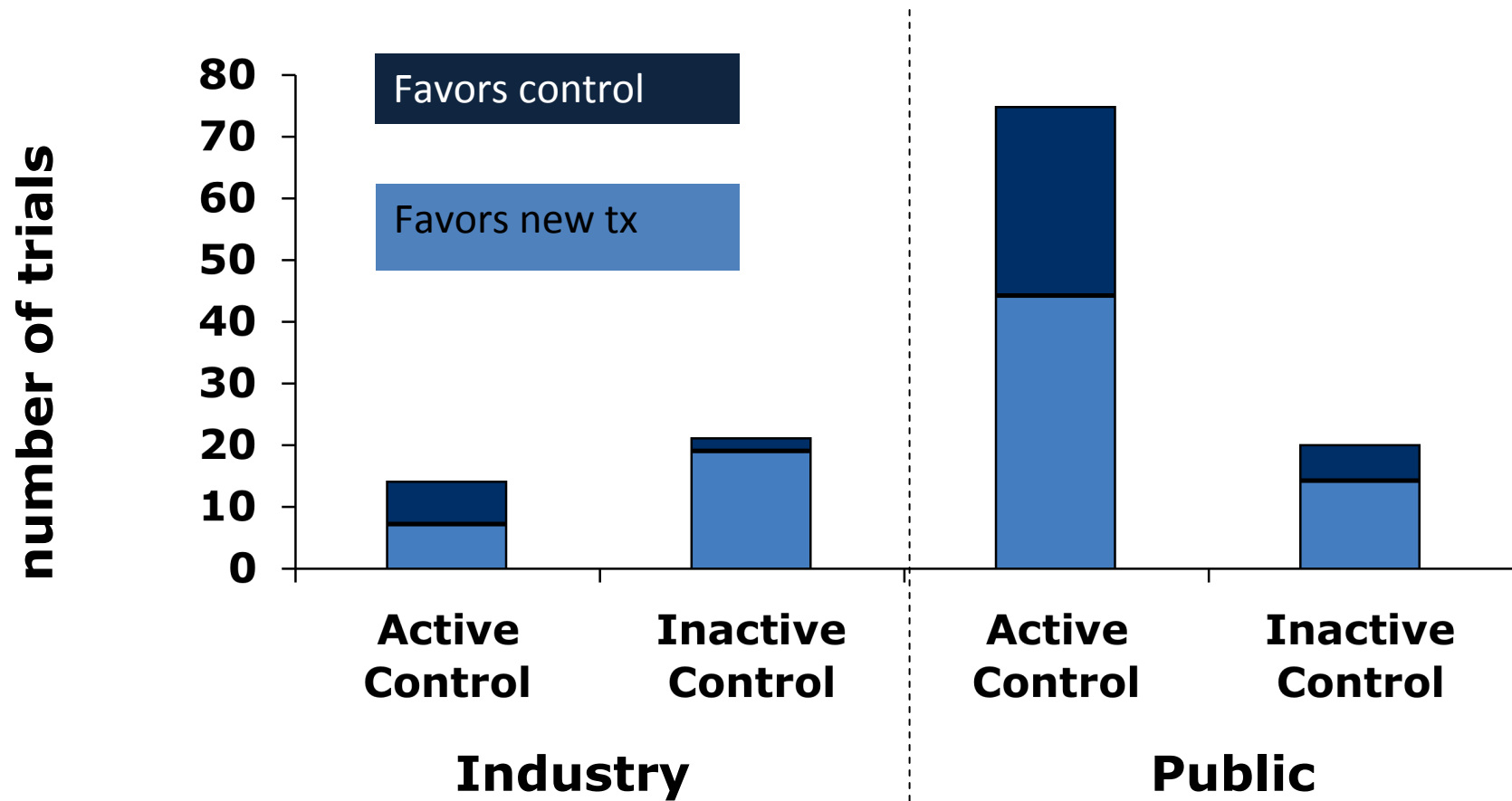


Choice of Control

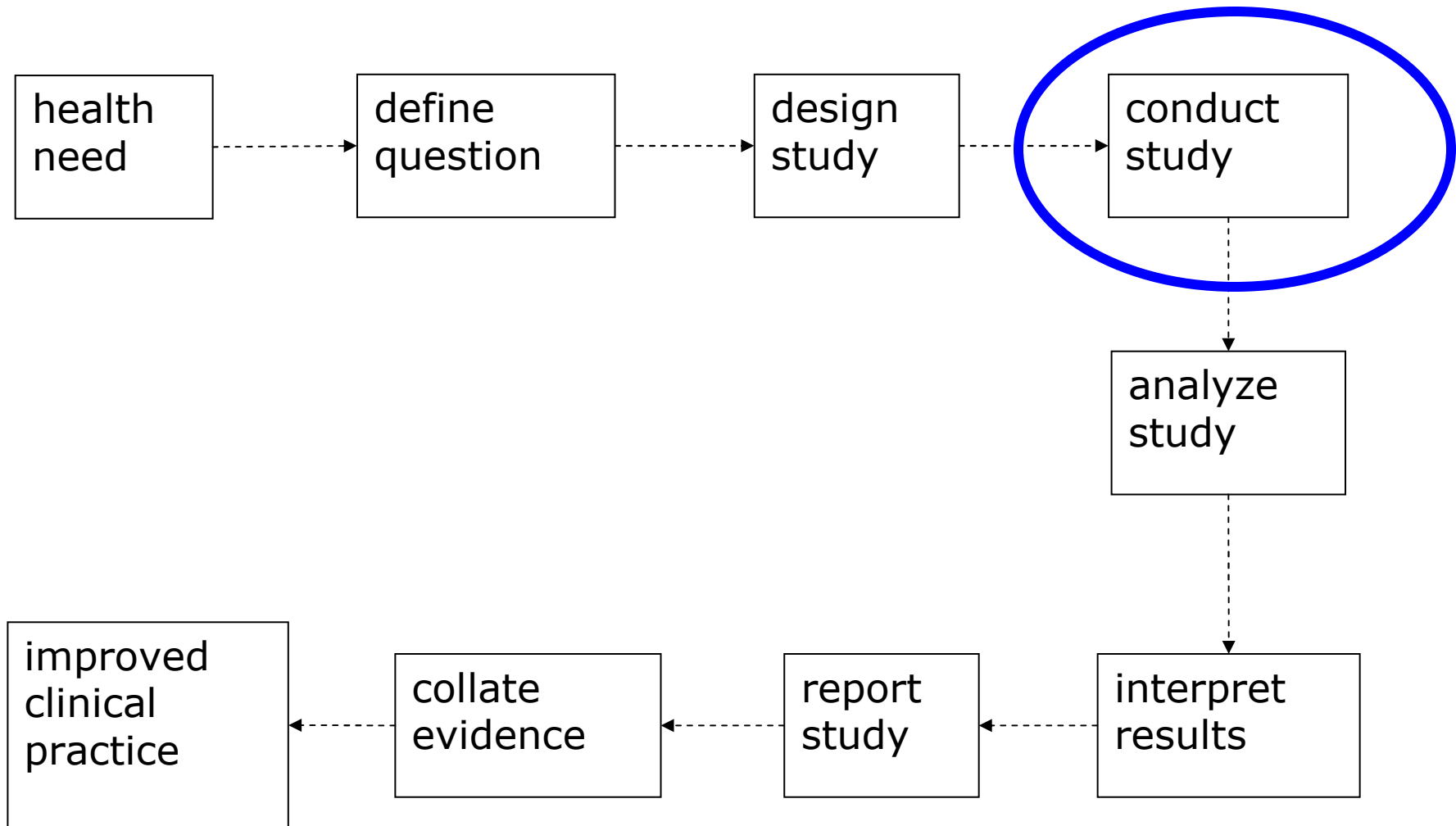
- 130 randomized trials for multiple myeloma (1996-8)



Choice of Control



Model of Research Process



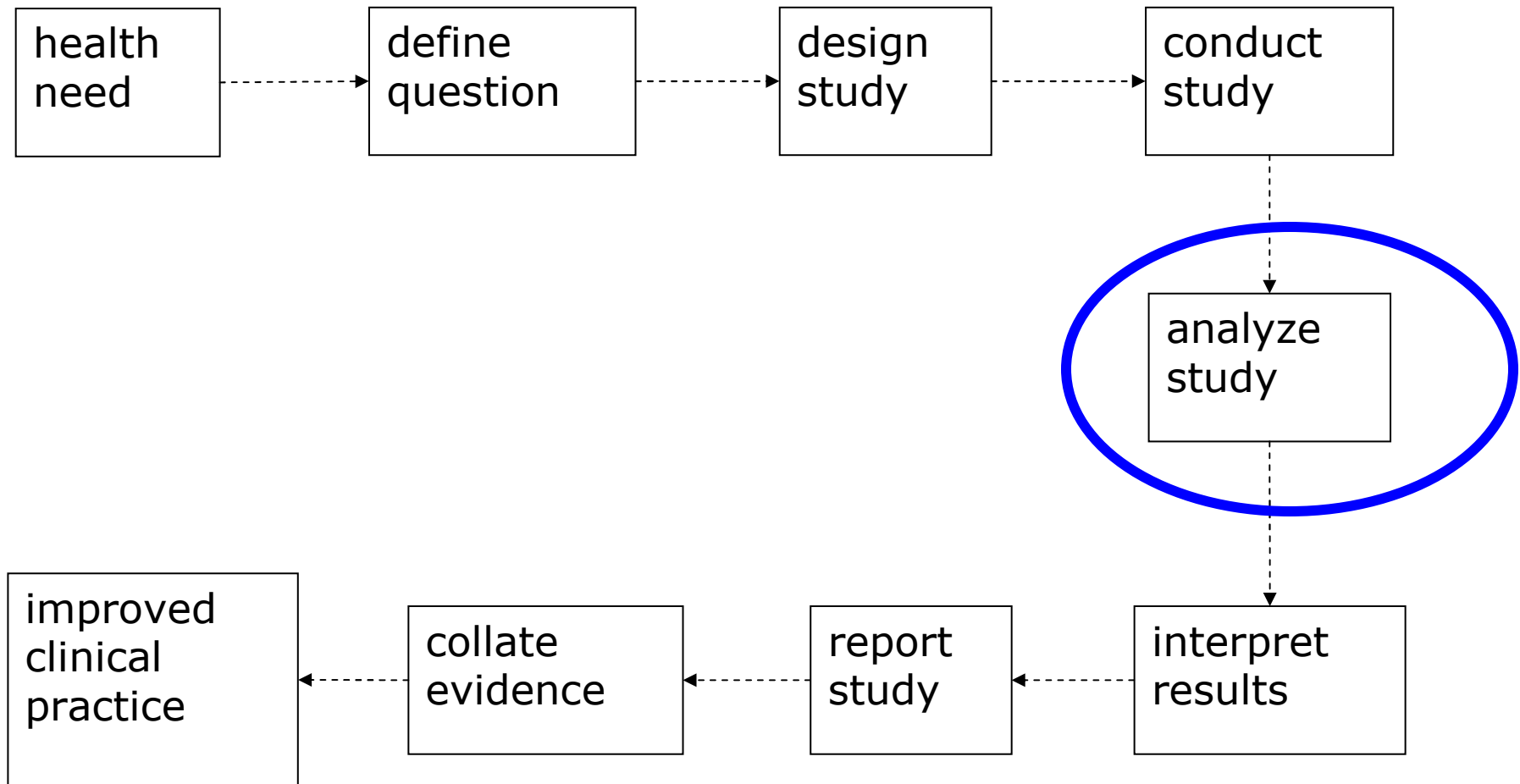
Study Conduct

- Possible ways to influence conduct of trial
 - Biased assessment of outcomes
 - Biased selection or assignment of subjects
 - Biased reporting of adverse events

Study Conduct: Anecdote

- 73 yr-old woman dies suddenly during a Merck-sponsored trial of rofecoxib vs. naproxen
- According to the New York Times:
 - “Dr. Eliav Barr, a Merck scientist, initially judged that the woman had probably died of a heart attack.
 - “‘Common things being common, the clinical scenario is likely to be MI,’ Dr. Barr wrote in an e-mail message in November 2000 to Dr. [Alice] Reicin, the clinical research executive... ‘Certainly, it is not definitive. I just used my clinical judgment.’
 - “Dr. Reicin quickly responded, ‘I think this should be called an unknown cause of death.’ A few hours later, she wrote, ‘I would prefer unknown cause of death so we don't raise concerns.’”

Model of Research Process



Study Analysis

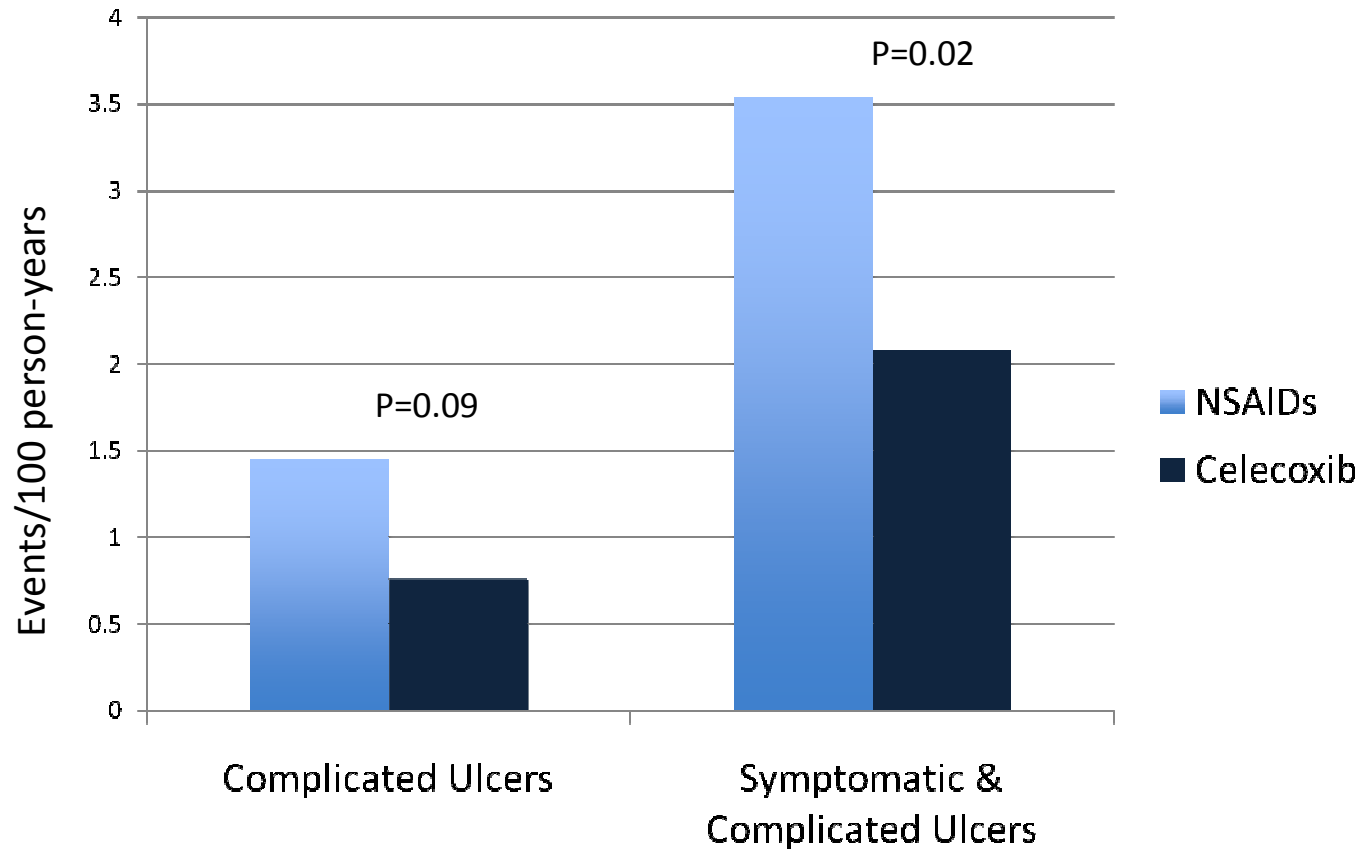
- Possible ways to influence trial results during the analysis
 - Reporting of endpoints that were not pre-specified
 - Post hoc subgroup analyses (“data mining”)
 - Inappropriate inclusion or exclusion of cases

Celecoxib Long-term Arthritis Safety Study (CLASS)

- Parallel Double-Blinded RCTs
 - Celecoxib Vs. Ibuprofen
 - Celecoxib Vs Diclofenac
- Endpoints:
 - 1°: Complicated Ulcer at 12 months
 - 2°: Complicated/Symptomatic Ulcer

CLASS Study

Incidence of complicated & of symptomatic ulcers at 6 months



Sources: Silverstein et al, JAMA; 2000; 284; 1247-55

FDA Arthritis Advisory Panel, February 7, 2001

Study Conclusions in JAMA

Manuscript:

“Celecoxib associated with lower incidence of symptomatic and ulcer complications combined”

Silverstein et al, JAMA; 2000; 284; 1247-55

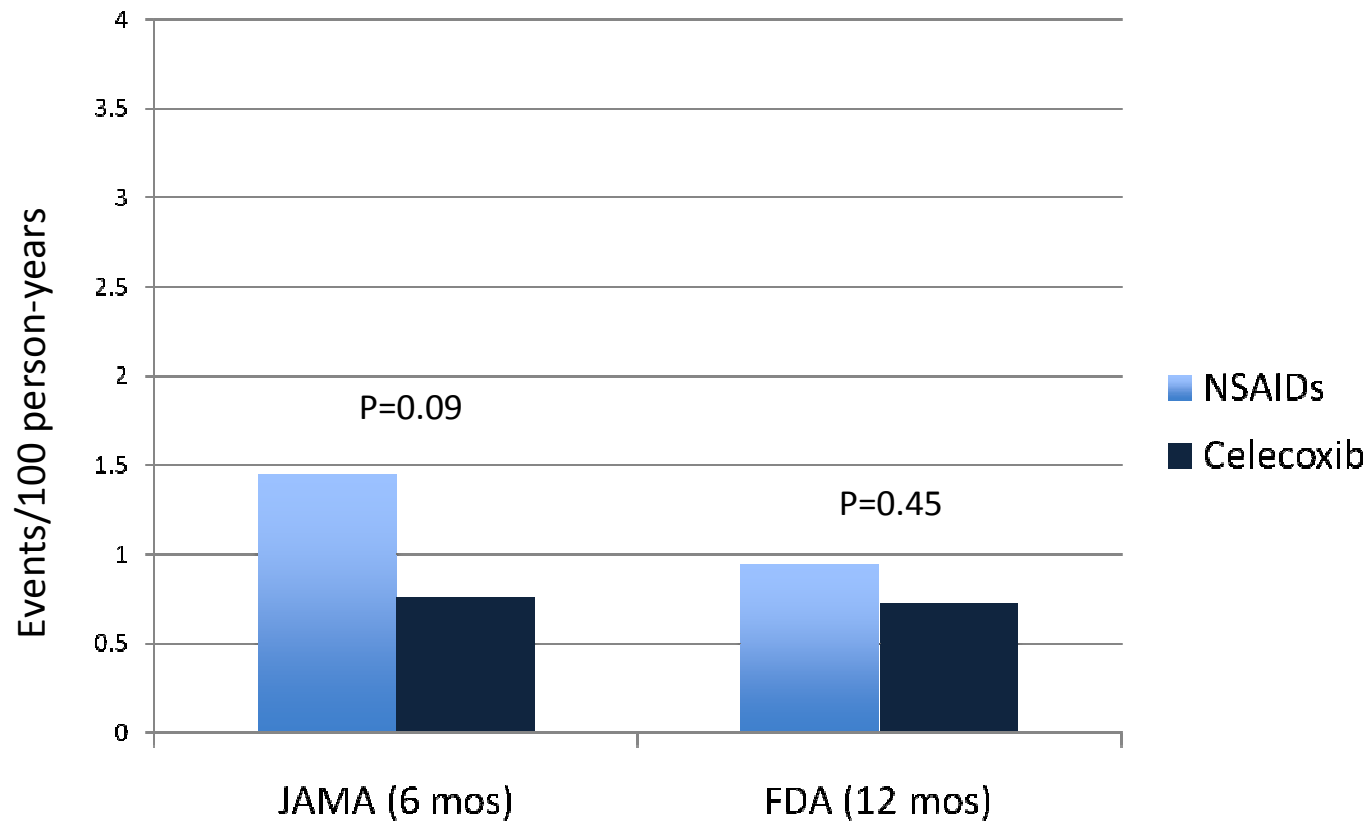
Editorial:

“....suggests that Celecoxib is effective at reducing the risk of symptomatic ulcers.....However, because this prospective analysis was limited to six months, careful future analysis will be required....”

M Wolfe, JAMA; 2000; 284; 1297-9

CLASS Study

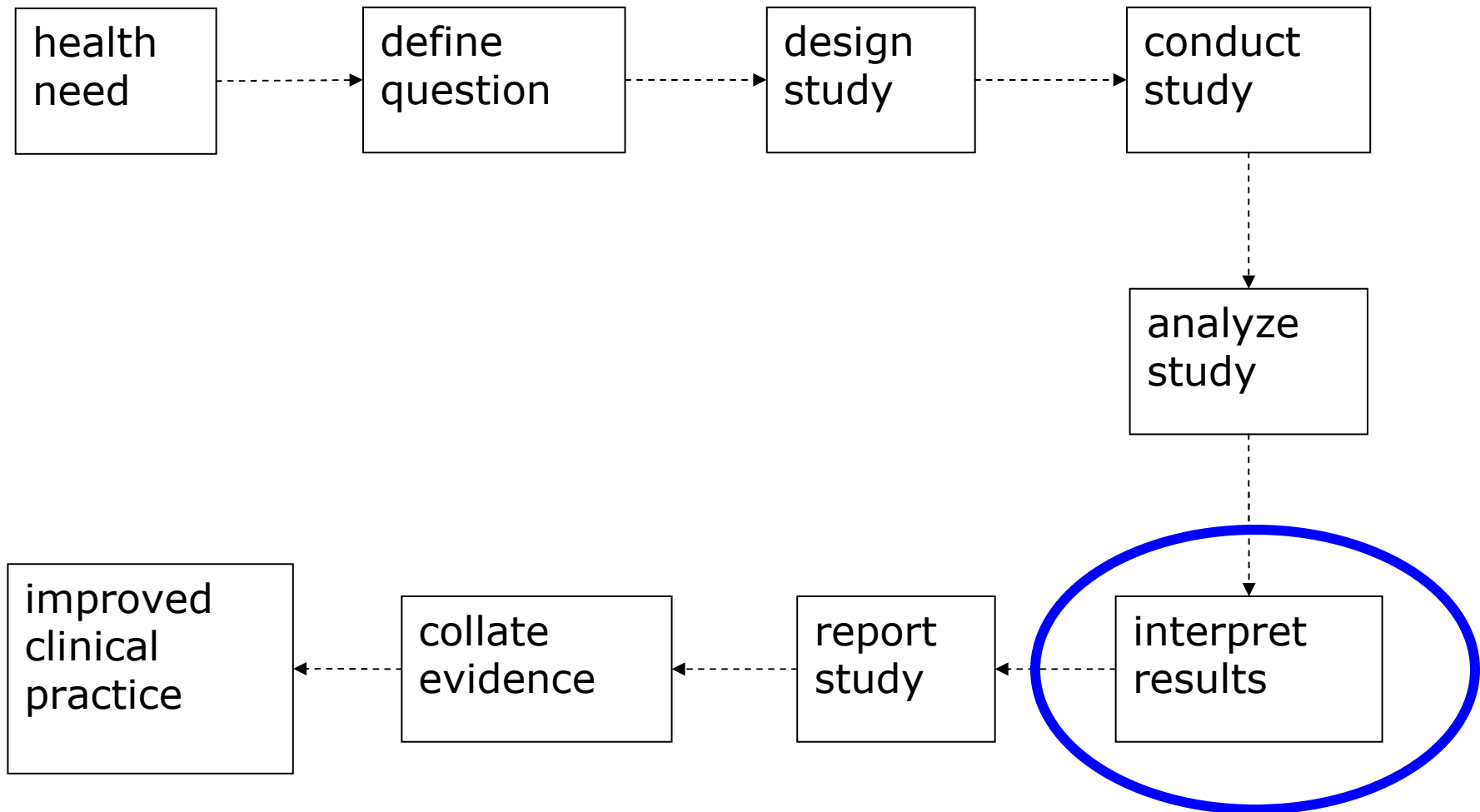
Incidence of complicated ulcers at 6 & 12 months



Sources: Silverstein et al, JAMA; 2000; 284; 1247-55

FDA Arthritis Advisory Panel, February 7, 2001

Model of Research Process



Study Interpretation

- “Spin”
 - Overstate results or their implications
 - Understate toxicities

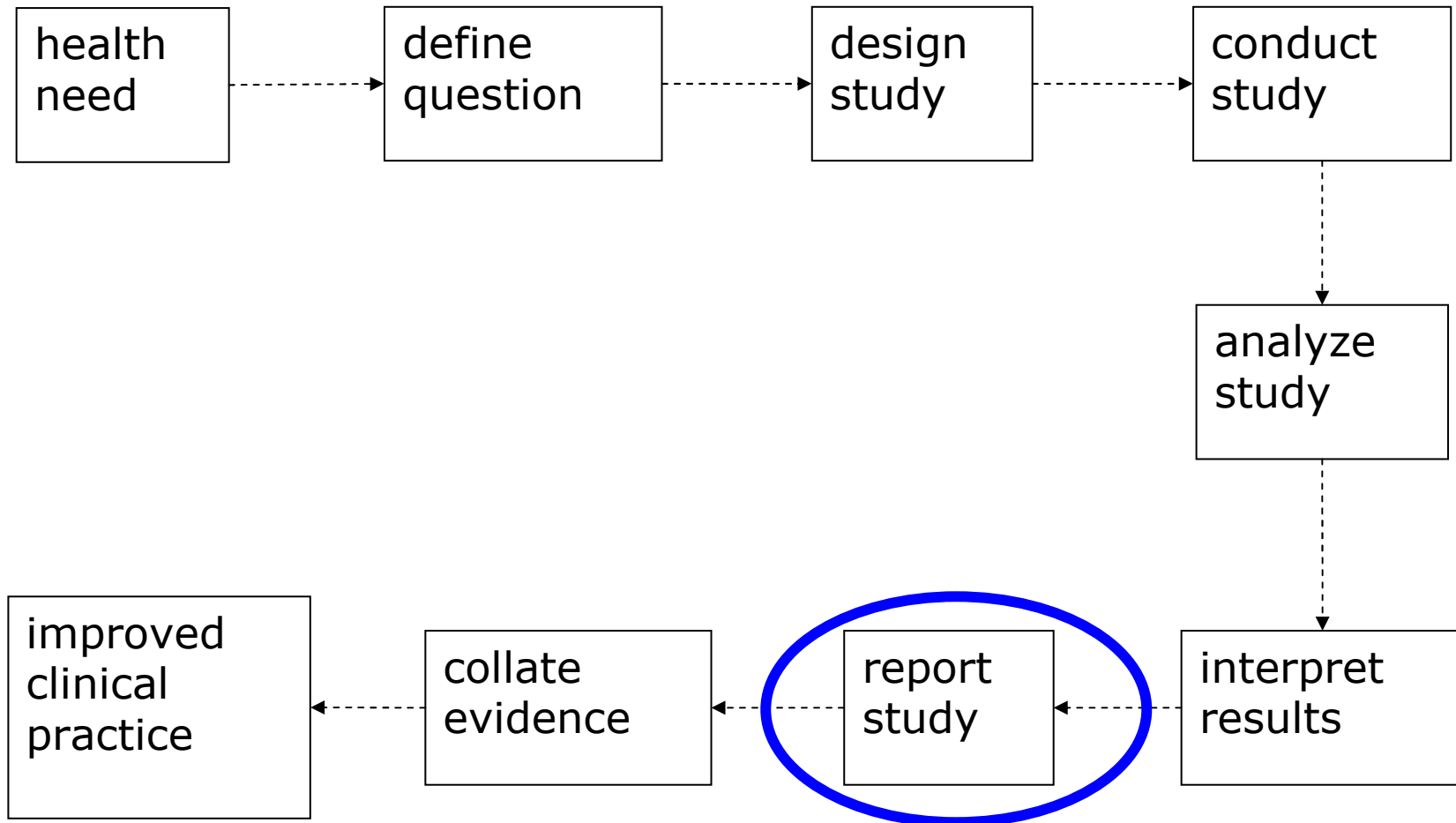
Predictors of Recommending the Experimental Drug

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).

Model of Research Process



Study Reporting

- Delayed or non-publication of negative articles
 - “publication bias”
- Contracts with restrictive publication clauses

Publication Bias & Industry-Funded Trials

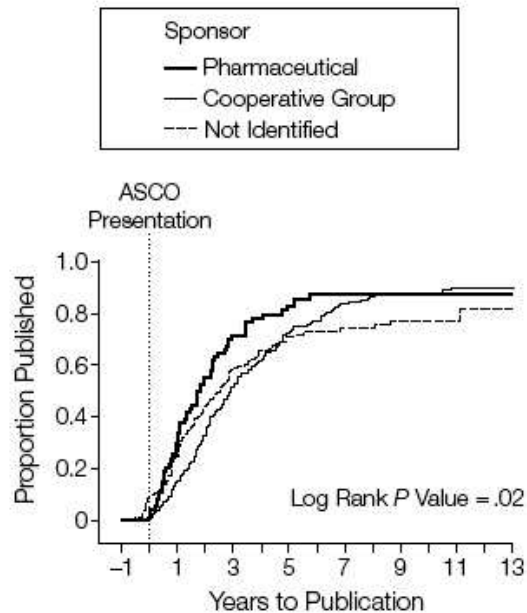
- Data on differential publication bias between industry-sponsored & other trials are mixed
- 2 of 6 meta-analyses reviewed by Lexchin et al found longer times to publication among industry-funded trials
 - One additional analysis found that industry-funded trials were more likely than other trials to be published in symposia rather than in peer reviewed publications

Publication Bias & Industry-Funded Trials

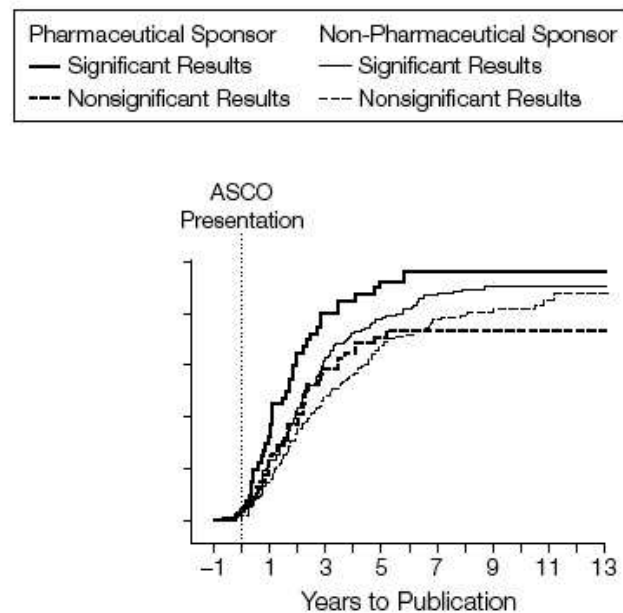
- Krzyzanowska et al reviewed publication outcomes of 510 large RCTs presented at an oncology meeting

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

A Time to Publication by Sponsorship



B Time to Publication by Type of Result and Sponsorship



Restrictions on Reporting: Industry-Academic Contracts

Item	% of Contracts Containing Item (Median)	
	All	
Access to all data for authors of reports	1	
Requirement for independent writing committee	0	
Requirement for publication of results	0	
Addresses editorial control of reports on trial results	40 *	

*in validation study, 0/10 contracts contained this item

Restrictions on Reporting: Industry-Academic Contracts

Item	% of Contracts Containing Item (Median)	
	All	Coord Center
Access to all data for authors of reports	1	50
Requirement for independent writing committee	0	6
Requirement for publication of results	0	5
Addresses editorial control of reports on trial results	40 *	75

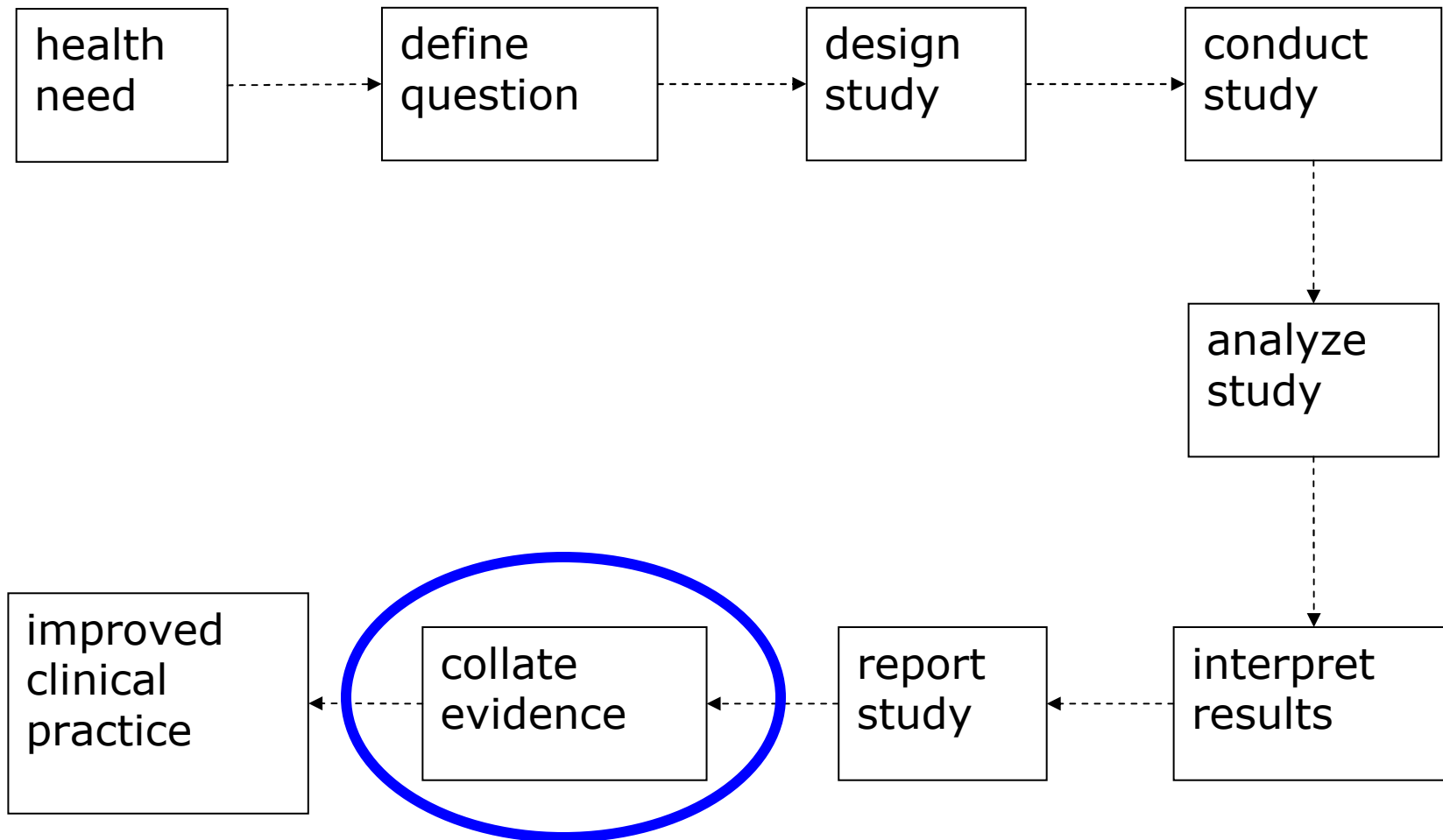
*in validation study, 0/10 contracts contained this item

NEJM 347:1335, 2002
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Secrecy In Science

- Survey of 2167 life science faculty at major universities
 - 20% reported publication delay ≥ 6 months during past 3 years
 - 9% reported refusing to share results w/ university scientists during past 3 years
 - Participation in academic-industry research relationship & engagement in commercialization of university research correlated with delays & withholding

Model of Research Process



Industry Support in Meta-Analyses

- Comparison of 24 Cochrane reviews of drugs with matched meta-analyses in paper journals
 - 8 declared industry support
 - 9 did not declare support
 - 7 declared no support or non-profit support

Industry Support in Meta-Analyses

- Compared with Cochrane reviews:
 - Paper reviews (regardless of funding) had lower methodological quality
 - All 7 industry funded reviews with conclusions supported the drug without reservations, vs. none of the Cochrane reports
 - Despite similar estimated treatment effects

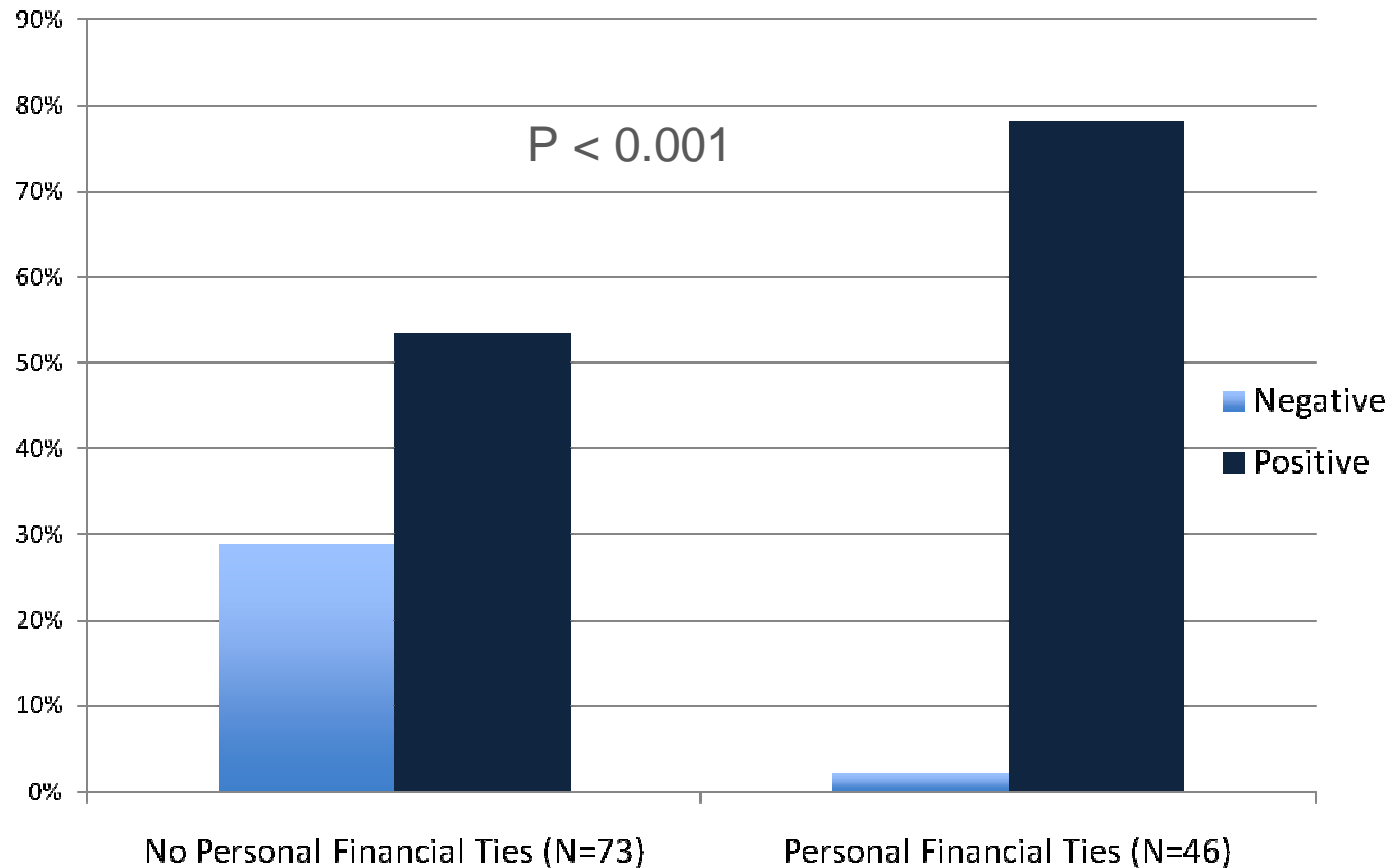
Relationship Between Personal Financial Ties & Study Results

- 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 with a personal financial tie to a private corporation

JGIM 19:51, 2004

See also Am J Psychiatry 2005;162:1957

Outcomes among Drug Trials, by Presence or Absence of Personal Financial Ties



JGIM 19:51, 2004

See also Am J Psychiatry 2005;162:1957

Putting It All Together

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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Strategies For Addressing Financial COI

- Ignore
- Disclose
- Manage
- Avoid/Prohibit

Disclosure

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

What Are the Practical Effects of Disclosure?

- Can alert prospective subjects, institutions, sponsors, reviewers, & readers to the issue
- However:
 - How should peer reviewers, journal editors, readers, etc. respond?
 - Not clear that most research subjects want this information, nor that it would alter their decisions

Management

- Periodic reports
- Oversight by institutional official
- Appointment of special monitor
- Independent review of data

Prohibition

- Association of American Medical Colleges (AAMC) guidelines:
 - “presumption that, in the absence of compelling circumstances, a financially interested individual may not conduct human subjects research”

Public Policy Outlook

- Increasing public concern
 - Recent revelations by Sen. Grassley of undisclosed industry ties

The New York Times
nytimes.com

September 28, 2008

EDITORIAL

Whose Best Interest?

Two drug companies have announced that they will publicly disclose some of their payments to doctors starting next year. But the two companies fell short of complete disclosure, and the industry as a whole lags far behind. Legislation to establish a wide-ranging nationwide reporting system is still needed.

These pledges are a step in the right direction and ought to be emulated by all other pharmaceutical companies. But voluntary piecemeal disclosures are not enough. A sound Senate bill, the Physician Payments Sunshine Act, would establish a mandatory national registry of payments to physicians.

Non-financial COI

“Many academic colleagues working in...basic biological research would run over their grandmothers to claim priority for a discovery, impose their pet theory on the field, obtain a research grant, win an award or garner a promotion. ...for relatively modest remuneration we compete for scarce resources and labor in obscurity to achieve small advances few understand or appreciate. We exercise our ambitions by publishing research papers in high-profile journals.”

--T. Stossel, Wall St. Journal, December 30, 2005

Summary

Financial ties to industry are common

- In research, raise concerns about harm to subjects, secrecy in science, and biased results
- Evidence that industry funding is assoc. with favorable outcomes is compelling
 - Little evidence on mechanisms
 - Little evidence on role of *personal* financial ties
- Strategies for dealing with COI exist but are imperfect