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Scope and Impact of Financial Conflicts of Interest in Biomedical Research

A Systematic Review

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INDUSTRY SUPPORT OF BIOMEDICAL research in the United States increased dramatically in the last 2 decades. Industry's share of total investment in biomedical research and development grew from approximately 32% in 1980 to 62% in 2000, while the federal government's share fell.^{1,2} During this period, the relationship between academic institutions and industry flourished, spawning medical advances, creating new biotechnology markets, and providing needed support for further discovery. However, an entanglement of relationships among industry, investigators, and academic institutions also emerged.

Conflicts of interest are "a set of conditions in which professional judgment concerning a primary interest (such as a patient's welfare or the validity of research) tends to be unduly influenced by a secondary interest (such as financial gain)."³ Financial interests are not the only, or necessarily the most powerful, secondary interests faced by investigators and academic institutions. For investigators, other pressures, including the desire for professional recognition and the need to compete successfully for research funding, are intrinsic to the research process.⁴ Institutions also confront myriad pressures arising from balancing the needs of diverse departments and con-

Context Despite increasing awareness about the potential impact of financial conflicts of interest on biomedical research, no comprehensive synthesis of the body of evidence relating to financial conflicts of interest has been performed.

Objective To review original, quantitative studies on the extent, impact, and management of financial conflicts of interest in biomedical research.

Data Sources Studies were identified by searching MEDLINE (January 1980–October 2002), the Web of Science citation database, references of articles, letters, commentaries, editorials, and books and by contacting experts.

Study Selection All English-language studies containing original, quantitative data on financial relationships among industry, scientific investigators, and academic institutions were included. A total of 1664 citations were screened, 144 potentially eligible full articles were retrieved, and 37 studies met our inclusion criteria.

Data Extraction One investigator (J.E.B.) extracted data from each of the 37 studies. The main outcomes were the prevalence of specific types of industry relationships, the relation between industry sponsorship and study outcome or investigator behavior, and the process for disclosure, review, and management of financial conflicts of interest.

Data Synthesis Approximately one fourth of investigators have industry affiliations, and roughly two thirds of academic institutions hold equity in start-ups that sponsor research performed at the same institutions. Eight articles, which together evaluated 1140 original studies, assessed the relation between industry sponsorship and outcome in original research. Aggregating the results of these articles showed a statistically significant association between industry sponsorship and pro-industry conclusions (pooled Mantel-Haenszel odds ratio, 3.60; 95% confidence interval, 2.63–4.91). Industry sponsorship was also associated with restrictions on publication and data sharing. The approach to managing financial conflicts varied substantially across academic institutions and peer-reviewed journals.

Conclusions Financial relationships among industry, scientific investigators, and academic institutions are widespread. Conflicts of interest arising from these ties can influence biomedical research in important ways.

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stituencies. However, financial interests related to biomedical research are nonobligatory and often unrecognized unless disclosed. They are the focus of current national discussion because they induce public anxiety about the influence of money on the research process.^{3,5,6}

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Several reports suggest that financial ties pose a threat to scientific integrity.⁷⁻¹¹ In 1999, the tragic death of a participant in an industry-sponsored clinical trial in which investigators and the academic institution held significant financial stakes focused national attention on financial conflicts of interest and safeguards for human participants.¹² The nation's medical leadership warned that public trust in research might falter if action were not taken.^{13,14} However, attempts to develop new conflict of interest policies have encountered substantial controversy. For example, one member of the Association of American Medical Colleges task force charged with developing new guidelines on conflicts of interest believed that the proposed guidelines were too limited.¹⁵ Another member, representing industry, refused to support the guidelines, suggesting that they would only serve to impede innovation.¹⁶

Consensus for reform may only arise from a full understanding of the nature and influence of financial conflicts of interest. In the context of disagreement, a synthesis of evidence may strengthen the bond between impassioned debate and optimal policy.^{17,18} Meta-analyses, which combine the results of several studies, can also derive more definitive conclusions than primary studies alone.¹⁹

We therefore performed a systematic review to answer the following 3 questions: (1) How common are financial relationships among industry, scientific investigators, and academic institutions; (2) What is the impact of these financial relationships; and (3) How are these financial relationships managed? We aimed to develop an objective framework within which more informed policy decision making can occur.¹⁷

METHODS

Data Sources

Data sources included studies that contained original, quantitative data addressing financial relationships among industry, investigators, and academic institutions. The MEDLINE database was searched from January 1980 through Oc-

tober 2002, using the free text "conflict of interest" and the exploded Medical Subject Heading terms *conflict of interest* or *conflict (psychology)* and *research support with clinical trials, commerce, or industry*, and *schools* in all possible combinations. Three experts (David Blumenthal, MD, Jerome Kassirer, MD, and David Korn, MD) identified additional studies. Further articles were identified from the reference sections of relevant studies, letters, editorials, comments, and books. This strategy was supplemented by using the Web of Science database to generate a list of articles that cited identified original quantitative studies.

Study Selection

A study was included if it met the following criteria: (1) its stated primary or secondary purpose was to assess the extent, impact, or management of financial relationships among industry, investigators, or academic institutions; (2) it contained a section describing study methods; (3) it was written in English; and (4) it was published following the passage of the Bayh-Dole Act of 1980,²⁰ which encouraged academic institutions and scientific investigators to seek industry partnerships. A study was excluded if it did not contain data pertaining to any of the 3 objectives, or if it was a commentary, letter, editorial, abstract, dissertation, or case study. Two investigators (J.E.B. and C.P.G.) reviewed 1664 citations and selected appropriate studies.

After the initial MEDLINE search, we retrieved a total of 144 articles identified as potentially containing original quantitative data on financial relationships among industry, investigators, and academic institutions. Of these, 21 studies met our inclusion criteria. An additional 16 studies were identified by other sources (8 from other articles' references, 5 from Web of Science, and 3 from experts). Hence, a total of 37 studies were included.

Data Extraction

One investigator (J.E.B.) extracted the following unambiguous data for each study: design, data source, type of fi-

nancial interaction studied (ie, industry sponsorship, consultantship, employment, technology transfer, new venture formation, gifts, or personal funds), and results. For studies assessing the extent of financial relationships, the main outcome was the prevalence of specific types of industry relationships (eg, industry sponsorship, new venture formation, etc). For studies assessing the impact of financial relationships, the main outcomes were the proportion of industry-sponsored and nonindustry-sponsored studies with a certain outcome (ie, pro-industry conclusion) or characteristic (ie, study design or study quality).

Criteria used to appraise methodological quality varied according to study design. To appraise the methodological quality of cross-sectional surveys, we extracted sample size and response rate. For systematic reviews, we extracted how industry sponsorship was defined, whether the outcome or characteristic was defined, and blinding (ie, whether the outcome or characteristic was assessed independently of study sponsorship). For systematic reviews on study quality, we also extracted how the quality assessment instrument was defined or validated. For content analyses and secondary data analyses, we extracted whether the assessment instruments were predesigned, pilot tested, or validated.

Synthesis of Evidence

Evidence was integrated into tabular displays, drawing from the balance sheet model for integrating and interpreting multiple types of evidence.^{21,22} We presented original data from studies assessing the relation between industry sponsorship and study outcome in a common format: the proportion of industry-sponsored vs nonindustry-sponsored studies that yielded a pro-industry conclusion. We used the authors' published data to calculate these proportions when available. We contacted authors directly if data were not reported.

A pro-industry conclusion was defined as a study outcome that was fa-

avorable to industry sponsors. For example, if an industry-sponsored study concluded that a new therapy produced by the sponsoring entity was superior, this was considered a pro-industry conclusion. If a study examined whether an industry product was harmful, we considered a negative result to be a pro-industry conclusion. Neutral studies were classified as neither positive nor negative, and were not considered pro-industry.

We applied meta-analytic techniques to the subset of studies addressing the association between industry sponsorship and outcome in original research. Before pooling the results of these different studies, we determined that the data were not significantly different by testing for data homogeneity.^{23,24} The homogeneity test evaluates whether different odds ratios (ORs) across studies can be explained by the random variation of a common underlying OR.^{23,24} The homogeneity test showed that the ORs for these studies were not significantly different ($P = .75$) and could therefore be pooled. We then used Mantel-Haenszel techniques to calculate a summary OR.^{25,26} Analyses were performed by using STATA version 6.0 (Stata Corp, College Station, Tex) and $P < .05$ was considered statistically significant.

RESULTS

Of the 37 studies eligible for inclusion, 10 addressed the extent of financial relationships, 23 addressed the impact of financial relationships, and 8 addressed the management of financial relationships. Four studies addressed more than 1 objective.

Extent of Financial Relationships

Ten studies²⁷⁻³⁶ documented the extent of financial relationships among industry, scientific investigators, and academic institutions. Eight of these studies were cross-sectional surveys and reported response rates of about 60% or more, which approximates the mean response rate among surveys in medical journals (TABLE 1).³⁷

Studies suggest that 23% to 28% of academic investigators in biomedical re-

search receive research funding from industry.^{27,33} A 1998 survey found that 43% of investigators also receive research-related gifts, including biomaterials and discretionary funds.³⁵ Approximately one third of investigators at academic institutions have personal financial ties with industry sponsors. Earlier studies have shown that 37% of investigators in the National Academy of Sciences had "dual affiliations" with both universities and companies.²⁸ A 1992 analysis of 789 articles from major medical journals found that 34% were written by lead authors with relevant personal financial interests in their research (ie, company patents, equity, or advisory board, or director positions).²⁹ An analysis of disclosure forms at a single institution found that 7.6% of investigators had personal financial ties with sponsors of their research, including paid speaking engagements (34%), consulting arrangements (33%), positions on advisory boards (32%), or equity (14%).³⁶ A range of financial interactions clearly exists.

It also appears that life science companies are increasingly involved with academia. A 1986 survey³⁰ reported that 46% of firms supported academic research, while a 1996 survey³¹ found that 92% supported academic research.

Only 1 study investigated the prevalence of industry involvement (defined as equity ownership) among academic institutions. The Association of University Technology Managers reported in 1999 that 124 of its 183 member institutions (68%) in the United States and Canada held equity in businesses that sponsor research performed at the same institutions.³² Some institutions were heavily involved; 27 institutions reportedly held equity in 10 or more start-ups.³²

Impact of Financial Relationships

Relation Between Industry Sponsorship and Study Conclusion. Eleven studies concluded that industry-sponsored research tends to yield pro-industry conclusions (TABLE 2).³⁸⁻⁴⁸ The quality of these studies was relatively

strong, as all 11 explicitly defined study outcome a priori, although only 7 used a blinded review.^{38,40,41,45-48}

The FIGURE demonstrates the OR and 95% confidence interval (CI) for each of the 8 articles that compared the outcome of industry-sponsored vs nonindustry-sponsored original research studies.^{38-44,48} The summary OR for all 8 articles, which together evaluated 1140 original studies, was 3.60 (95% CI, 2.63-4.91). When the studies were stratified into groups involving only randomized controlled trials (RCTs)^{38-40,48} (OR, 4.14; 95% CI, 2.72-6.32) and other study types⁴¹⁻⁴⁴ (OR, 3.00; 95% CI, 1.89-4.77), the findings did not differ significantly ($P = .31$).

Another study⁴⁵ analyzed 61 nonsteroidal anti-inflammatory drug (NSAID) RCTs, all of which were industry-sponsored, and found that the investigational therapy was comparable with (71.4% of studies) or superior to (28.6% of studies) the comparison therapy. No studies found that the comparison therapy was superior.⁴⁵

Two studies evaluated the relation between industry sponsorship and authors' published positions. A 1998 study⁴⁶ compared authors' financial relationships with industry with their published positions about the safety of calcium channel blockers (Table 2). Authors who had financial relationships with pharmaceutical companies were significantly more likely to reach supportive conclusions than authors without such industry affiliations (51% vs 0%; $P < .001$).⁴⁶ Similarly, a 1998 analysis⁴⁷ of 106 review articles on the health effects of second-hand smoking showed that industry-sponsored reviews were significantly more likely to yield pro-industry conclusions than nonindustry-sponsored studies (94% vs 13%; $P < .001$).

Four studies investigated the relation between sponsorship and study design (Table 2). In an analysis of multiple myeloma RCTs, industry-sponsored studies were substantially more likely to use inactive controls (ie, placebo or no-therapy controls) than were nonindustry-sponsored studies

Table 1. Extent of Financial Relationships Among Industry, Scientific Investigators, and Academic Institutions

Source	Study Design	Study Population	No. of Respondents (Response Rate, %)	Financial Interaction	Results, No. (%)
Prevalence of Industry Involvement Among Academic Investigators					
Blumenthal et al, ²⁷ 1996	Cross-sectional survey	Faculty members in the life sciences at the 50 US universities receiving the most funding from the NIH	2052 (65)	Industry sponsorship	28% of faculty received industry-research funds*
Blumenthal et al, ³³ 1986	Cross-sectional survey	Same as above	1238 (68)	Industry sponsorship, consultantship	23% of faculty received industry-research funds
Blumenthal et al, ³⁴ 1997	Cross-sectional survey	Same as above	2167 (64)	Industry sponsorship	149 of 585 genetics faculty (25) received industry-research funds 440 of 1529 nongenetics faculty (28) received industry-research funds
Campbell et al, ³⁵ 1998	Cross-sectional survey	Same as above	2167 (64)	Gifts, personal funds	920 of 2140 faculty (43) received research-related gifts, including biomaterials (24), discretionary funds (15), research equipment (11), travel (11), and educational (9) support
Krimsky and Ennis, ²⁸ 1991	Secondary data analysis and cross-sectional survey	Database of US and Canadian biotechnology firms and associated scientists	359 (NA)	Technology transfer, new venture formation	132 of 359 biomedical scientists (37) in the National Academy of Sciences had "dual affiliations" at both a university and a biotechnology firm
Krimsky et al, ²⁹ 1998	Secondary data analysis	Database of 789 published manuscripts and authors' affiliations, patent applications	789 (NA)	Technology transfer, new venture formation	267 of 789 articles (34) had at least 1 author with a personal financial interest in the results
Boyd and Bero, ³⁶ 2000	Secondary data analysis	Positive disclosure forms submitted from 1980 to 1999 by faculty at the University of California, San Francisco	896 (NA)	Consultantship, gifts, personal funds, equity interest	68 of 896 faculty investigators (7.6) reported financial ties with sponsors, including speaking fees (34), consulting (33), advisory board positions (32), or equity (14)
Prevalence of Academic Involvement Among Life Science Companies					
Blumenthal et al, ³⁰ 1986	Cross-sectional survey	Senior executives of life science firms	293 (84)	Contract research, consultantship, employment, gifts, personal funds	46% of firms in the biotechnology industry support research at universities
Blumenthal et al, ³¹ 1996	Cross-sectional survey	Senior executives of life science firms	210 (69)	Industry sponsorship, consultantship, employment, gifts, personal funds	91.8% of firms in the biotechnology industry support research at universities
Prevalence of Equity Ownership Among Academic Institutions					
Pressman, ³² 2000†	Cross-sectional survey	Members of the Association of University Technology Managers	183 (59)	Technology transfer, new venture formation	124 of 183 institutions (68) held equity in businesses engaged in research performed at the same institutions 27 of 183 institutions (15) held equity in 10 or more start-ups engaged in research performed at the same institutions

Abbreviations: NA, not applicable; NIH, National Institutes of Health.

*The 1996 study surveyed a broader sample of investigators than the 1986 study. Therefore, the authors reanalyzed data for comparison and found no difference in the extent of industry sponsorship over time (21% in 1995; 23% in 1985; $P > .05$).

†This study was not published in a peer-reviewed journal.

Table 2. Relation Between Industry Sponsorship and Study Conclusion and Study Design

Source	Study Design	Study Sample	No. of Studies*	Definition of Industry Sponsorship	Study Outcome Defined*	Blinded Review†	Findings		P Value‡
							No. (%) With Pro-industry Conclusion		
							Industry	Nonindustry	
Industry Sponsorship vs Study Conclusion									
Davidson, ³⁸ 1986	Systematic review	RCTs published in 5 general medical journals	107	A, B	Yes	Yes	33 of 37 (89)	43 of 70 (61)	.002
Djulgovic et al, ⁴⁰ 2000	Systematic review	RCTs involving multiple myeloma	136	A, C	Yes	Yes	26 of 35 (74)	50 of 95 (53)	.03
Yaphe et al, ³⁹ 2001	Systematic review	RCTs published in 5 general medical journals	314	A, C, D, H	Yes	No	181 of 209 (87)	62 of 96 (65)	<.001
Kjaergard and Als-Nielsen, ⁴⁸ 2002	Systematic review	RCTs published in <i>BMJ</i>	159	§	Yes	Yes	25 of 27 (93)	71 of 105 (68)	.009
Friedberg et al, ⁴³ 1999	Systematic review	Economic analysis of oncology drugs	44	A	Yes	No	12 of 20 (60)	10 of 24 (42)	.23¶
Cho and Bero, ⁴¹ 1996	Systematic review	Original clinical drug articles	152	A, C, D	Yes	Yes	39 of 40 (98)	89 of 112 (79)	.01
Turner and Spilich, ⁴² 1997	Systematic review	Articles investigating nicotine and cognitive performance	91	A, D	Yes	No	27 of 35 (77)	29 of 56 (52)	.02
Swaen and Meijers, ⁴⁴ 1988	Systematic review	Retrospective cohort studies	179	D	Yes	No	34 of 72 (47)	28 of 107 (26)	.001
Rochon et al, ⁴⁵ 1994	Systematic review	RCTs of NSAIDs	61	A, C, D, E	Yes	Yes	15 of 52 (29)	No studies reported	NA
Stelfox et al, ⁴⁶ 1998	Systematic review and survey	Authors of articles on calcium channel blockers	69	A, D, F	Yes	Yes	24 of 47 (51)	0 of 22 (0)	<.001
Barnes and Bero, ⁴⁷ 1998	Systematic review and secondary data analysis	Review articles on the health effects of passive smoking	106	A, E, G	Yes	Yes	29 of 31 (94)	10 of 75 (13)	<.001
Industry Sponsorship vs Study Design									
Djulgovic et al, ⁴⁰ 2000	Systematic review	RCTs involving multiple myeloma	113	A, C	Yes	Yes	Industry-sponsored studies used inactive controls more than nonindustry-sponsored studies		
Kjaergard and Als-Nielsen, ⁴⁸ 2002	Systematic review	RCTs published in <i>BMJ</i>	159	§	Yes	Yes	Industry-sponsored studies used inactive controls more than nonindustry-sponsored studies, although this did not explain the positive association between industry sponsorship and study design		
Rochon et al, ⁴⁵ 1994	Systematic review	RCTs of NSAIDs	61	A, C, D, E	Yes	Yes	In 27 trials (48), the dose of the industry-associated drug was higher than that of the comparison drug		
Johansen and Gotsche, ⁴⁹ 1999	Systematic review	RCTs of antifungal agents	12	A, D, H	Yes	No	Inappropriate comparison agents favored the success of fluconazole		

Abbreviations: A, grant support; B, author funding; C, author affiliation with sponsor; D, drug supplied to investigators; E, publication in industry-sponsored supplement; F, honorarium, travel/educational support, or participation in symposia; G, submission of statements to the Environmental Protection Agency on behalf of the tobacco industry; H, industry involvement in study design or analysis; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; RCTs, randomized controlled trials.

*The total number of studies in some reviews is greater than the number assessed for the relation between funding source and outcome because in some instances the funding source could not be ascertained. An explicit predefined method was used to classify study outcome.

†Study outcome, study design, or authors' published positions were assessed independently of study sponsorship.

‡P value using χ^2 for comparison between groups.

§Did not report how industry sponsorship was defined.

||Compared positive results from studies sponsored by industry alone with those from nonindustry-sponsored studies (93% vs 68%; $P = .009$). Studies cosponsored by industry and nonprofit organizations are excluded in this comparison. If positive results from studies sponsored by industry alone plus cosponsored studies are compared with positive results from nonindustry-sponsored studies, the comparison is not statistically significant (72% vs 68%; $P = .55$).

¶Authors did find a significant difference in the proportion of studies that reached a negative conclusion (ie, anti-industry) that were sponsored by industry vs nonindustry (5% vs 38%; $P = .04$).

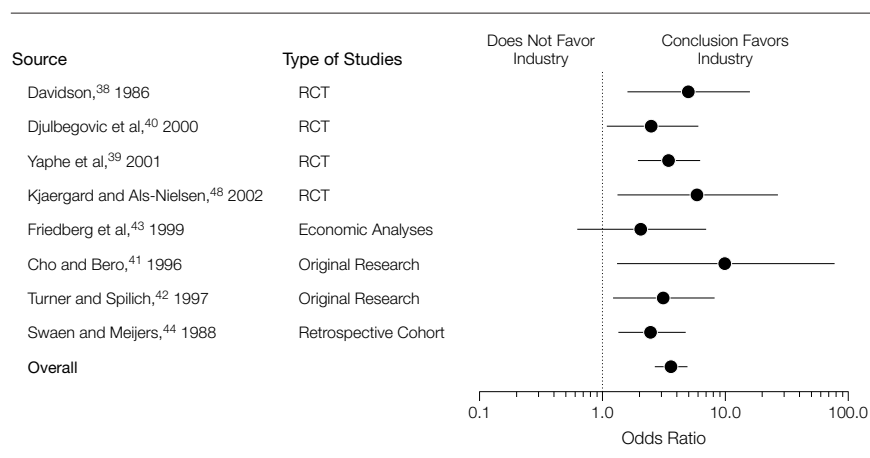
(60% vs 21%; $P < .001$).⁴⁰ The authors also found that the use of inactive controls increased the likelihood of positive study results.⁴⁰ An analysis of 159 RCTs also reported that trials funded by for-profit organizations were more likely to use an inactive control.⁴⁸ In the analysis of NSAID RCTs, the dose of the industry-associated drug was higher than that of the comparison drug in 27 trials (48%), although the dosing was comparable in 23 trials (41%).⁴⁵ Another study⁴⁹ found that industry-sponsored RCTs of oral fluconazole for systemic fungal infections tended to use poorly absorbed oral drugs as comparison agents, thus favoring the success of fluconazole, which is well absorbed from the gastrointestinal tract.

Relation Between Industry Sponsorship and Study Quality. Five analyses reported that industry-sponsored studies were of comparable quality to nonindustry-sponsored studies^{40,41,50-52} (TABLE 3). Four of these studies^{40,41,50,52} used validated quality-assessment tools and 3 studies^{40,41,52} used a blinded review. Two other studies^{53,54} found that RCTs published in industry-sponsored supplements were generally of lower quality compared with RCTs published in parent journals. These findings were ascribed to a difference in peer-review process between industry-sponsored supplements and parent journals.

Relation Between Industry Sponsorship and Restrictions on Investigator Behavior. Seven studies^{27,31,33,55-58} investigated whether industry ties prohibit open collaboration or delay publication of results (TABLE 4). All of these studies were cross-sectional surveys and reported response rates more than 60%. In a 1994 survey³¹ of 210 life science companies, 58% indicated that they typically require investigators to keep information confidential for more than 6 months in order for industry to file a patent. Another analysis⁵⁵ found that industry-sponsored faculty were more likely than other faculty to report delays in the publication of their research results.

Other surveys have suggested that 12% to 34% of academic researchers

Figure. Relation Between Industry Sponsorship and Study Outcome in Original Research Studies



RCT indicates randomized controlled trial. Error bars indicate 95% confidence intervals.

have requested and been denied access to research results.^{55,56} Controlling for other variables, 2 studies^{55,57} found that participation in commercial activities (ie, patenting or start-up companies) was significantly associated with data withholding, although industry sponsorship alone was not.

Industry sponsorship may be associated with a shift in research emphasis from basic research to clinical research.^{27,33,58} Faculty members with industry relationships are more than twice as likely as those without such funding to take commercial considerations into account when choosing research topics (35% vs 14%; $P < .001$).²⁷ In addition, 50% of respondents to a 1995 survey of recombinant DNA researchers believed that industry sponsorship shifts the emphasis of research programs.⁵⁸

Management of Financial Relationships

Eight studies^{36,59-65} addressed the management of financial relationships among industry, scientific investigators, and academic institutions (TABLE 5). A 2000 analysis of 17 federal agencies sponsoring human participant research reported that only 4 had policies explicitly governing extramural researchers.⁵⁹ Similarly, 4 surveys of major US academic institutions found substantial vari-

ability of policies governing conflicts of interest. A survey of 250 institutions found that management of conflicts and penalties for nondisclosure were almost universally discretionary.⁵⁹ A survey of 10 research-oriented medical schools reported that only 1 institution prohibited investigators from having equity, consulting agreements, or decision-making positions in a company sponsoring their research.⁶¹ Another survey found that only 19% of institutions had specific limits on their faculties' research-related financial interests.⁶⁰ A survey of 122 medical schools reported poor compliance with recently revised guidelines for trial design, access to data, and control over publication in contractual agreements with industry sponsors of clinical research.⁶⁵

Although peer-reviewed journals have taken a role in managing conflicts of interest, journal policies also vary considerably. An analysis of 47 high-impact biomedical journals published in 2000 found that 43% had policies requiring disclosure of conflicts of interest.⁵⁹ A more extensive analysis in 1997 found that 157 of 474 medical journals (33%) and 24 of 922 science journals (3%) had conflict of interest policies in effect.⁶² However, even among journals with stated disclosure policies, few articles contained financial conflict disclosures.^{62,64}

Table 3. Relation Between Industry Sponsorship and Study Quality

Source	Study Design	Study Sample	No. of Studies	Definition of Industry Sponsorship	Description of Quality Assessment Instrument	Quality Assessment Instrument Validated*	Blind Interpretation†	Findings	P Value
Djulbegovic et al, ⁴⁰ 2000	Systematic review	RCTs for multiple myeloma	113	A, D	3-Item assessment of randomization, blinding, and follow-up	Yes	Yes	Industry-sponsored RCTs had a trend toward higher quality scores than nonindustry-sponsored RCTs	.06
Knox et al, ⁵² 2000	Systematic review	Economic analyses of oncology drugs	44	A	9-Item assessment including randomization, generalizability of data, statistical significance tests, perspective statement, description of costs, description of cost differences, time horizon, limitations, and comparison with other studies	Yes	Yes	Industry-sponsored studies were more likely to provide information on key components of the methods section and less likely to report on study generalizability than nonindustry-sponsored studies	NR
Kjaergard et al, ⁵⁰ 1999	Systematic review	RCTs published in <i>Hepatology</i>	234	A‡	5-Item assessment of randomization, blinding, follow-up, randomization concealment, and sample size calculations	Yes	No	Quality of industry and nonindustry funded RCTs did not differ significantly	.68
Cho and Bero, ⁴¹ 1996	Systematic review	Original clinical drug articles	127	A, C, D	24-Item "methodologic" scale 7-Item "clinical relevancy" scale	Yes	Yes	Articles in industry-sponsored symposia were similar in methodological quality and relevance scores to articles published in parent journals	>.02
Anderson et al, ⁵¹ 1991	Systematic review	RCTs of second-line agent in rheumatoid arthritis	105	A, C, D, E, F	10-Item assessment of patient eligibility criteria, randomization, reporting of randomization method, blinding of patients and evaluators, follow-up, reporting of adverse effects, statistical methods, and power analysis	No	No	No difference was found in the qualitative standards of industry-sponsored studies compared with nonindustry-sponsored studies	NR
Bero et al, ⁵⁴ 1992	Systematic review	Symposia published as separate issues or sections of journals	625	E	3-Item assessment of misleading titles, brand names, and peer-review status	No	No	Articles published in industry-sponsored symposia were more likely to have misleading titles and to use brand names and less likely to be peer reviewed in the same manner as articles in parent journals	<.001
Rochon et al, ⁵³ 1994	Systematic review	RCTs in cardiology journals	242	A, C, D, E, F	6-Item assessment of control regimen, randomization, blinding, follow-up, statistical analyses, and reporting of adverse effects	Yes	Yes	Quality scores were lower in RCTs published in journal supplements than in those published in parent journals	.01

Abbreviations: A, grant support; B, author funding; C, author affiliation with sponsor; D, drug supplied to investigators; E, publication in industry-sponsored supplement; F, industry involvement in study design; NR, not reported; RCTs, randomized controlled trials.

*Quality assessment instrument validated through empirical evidence.

†Study quality assessed independently of study sponsorship.

‡Did not report how industry sponsorship was defined.

Table 4. Relation Between Industry Sponsorship and Restrictions on Investigator Behavior

Source	Study Design	Study Population	No. of Respondents (Response Rate, %)	Financial Interaction	Results, No. (%)
Blumenthal et al, ³¹ 1996	Cross-sectional survey	Senior executives of life science firms	210 (69)	Industry sponsorship, consultantship, employment, gifts, personal funds	58% of firms require academic institutions to keep information confidential longer than is necessary to file a patent
Blumenthal et al, ⁵⁵ 1997	Cross-sectional survey	Faculty members in the life sciences at 50 US universities receiving the most funding from the NIH	2167 (64)	Industry sponsorship, technology transfer, new venture formation	691 of 2032 researchers (34) have been denied access to research results Industry sponsorship was independently associated with publication delay (OR, 1.34; 95% CI, 1.07-1.59; $P < .05$) Commercialization (ie, patenting or start-up companies) was independently associated with publication delay and data withholding (OR, 3.15; 95% CI, 2.88-3.41; $P < .001$; OR, 2.45; 95% CI, 2.08-2.82; $P < .01$, respectively)
Campbell et al, ⁵⁶ 2000	Cross-sectional survey	Same as above	2366 (62)	Industry sponsorship	12% of medical school researchers have been denied access to research results
Campbell et al, ⁵⁷ 2002	Cross-sectional survey	Same as above	1849 (64)	Industry sponsorship, technology transfer, new venture formation	Commercialization (ie, patenting or start-up companies) was independently associated with data withholding (OR, 1.72; 95% CI, 1.06-2.81; $P < .03$)
Blumenthal et al, ³³ 1986	Cross-sectional survey	Faculty members in the life sciences at 40 of 50 US universities receiving the most funding from the NIH	1238 (68)	Industry sponsorship, consultantship	Industry-sponsored faculty were more likely to report restrictions on publication than researchers without such support (24% vs 5%; $P < .001$) Industry-sponsored faculty were more likely to take commercial considerations into account when selecting research projects (30% vs 7%; $P < .001$)
Blumenthal et al, ²⁷ 1996	Cross-sectional survey	Faculty members in the life sciences at 50 US universities receiving the most funding from the NIH	2052 (65)	Industry sponsorship	Industry-sponsored faculty were significantly more likely than nonindustry-funded faculty to refuse to share research results or biomaterials (11% vs 6%, respectively; $P = .008$) and to take commercial considerations into account when choosing research topics (35% vs 14%, respectively; $P < .001$)
Rabino, ⁵⁸ 1998	Cross-sectional survey	Members of the American Society for Microbiology	1267 (63)	Industry sponsorship	50% of respondents believed that industry sponsorship shifts the emphasis of research programs toward commercial interests

Abbreviations: CI, confidence interval; NIH, National Institutes of Health; OR, odds ratio.

Table 5. Management of Financial Relationships Among Industry, Scientific Investigators, and Academic Institutions

Source	Study Design	Sample Size	Study Sample	Methodology Comment	Results, No. (%)
McCrary et al, ⁵⁹ 2000	Content analysis	250 47 17	COI policies at US institutions receiving more than \$5 million from the NIH or NSF Biomedical journals Federal agencies	Explicit content analysis instrument predesigned, pilot tested Interrater reliability assessed	215 of 235 institutions (91) had policies that adhered to the federal threshold for disclosure 20 of 47 journals (43) required disclosure 4 of 17 federal agencies sponsoring human subjects research had policies explicitly governing extramural researchers
Lo et al, ⁶¹ 2000	Content analysis	10	COI policies at 10 medical schools with largest research funding in the United States	Policies analyzed "in accordance with established legal principles for the interpretation of contracts and statutes"	Significant variability among institutions regarding policies on equity ownership
Cho et al, ⁶⁰ 2000	Content analysis	89	COI policies at US institutions with the most funding from the NIH in 1998	Explicit content analysis instrument predesigned, pilot tested Interrater reliability assessed	32 of 89 COI policies (36) specifically described activities that were allowed 17 of 89 institutions (19) specified limits on faculty equity interests
Schulman et al, ⁶⁵ 2002	Cross-sectional survey	108	Officials at medical schools engaged as sites for industry-sponsored multicenter clinical trials A subset engaged as coordinating centers	Response rate: 108 of 122 multicenter sites (88%) and 14 of 20 coordinating center sites (70%)	Limited compliance with revised guidelines for trial design, access to data, and control over publication For example, 1% of institutions' contractual agreements with industry sponsors ensured author access to all trial data; 40% explicitly addressed editorial control of publications
Boyd and Bero, ³⁶ 2000	Secondary data analysis	225	Positive disclosure forms submitted from 1980 to 1999 by clinical, basic, or social science faculty at the University of California, San Francisco	Explicit data extraction instrument	Institution banned acceptance of any income from firms funding clinical trials during the course of the trial In 128 of 488 disclosures (26), the institution recommended strategies to manage potential conflicts of interest
Krimsky and Rothenberg, ⁶² 2001	Systematic review and cross-sectional survey	61 134 138	Original research articles in top journals ranked by the ISI in 1997 Editors of journals with COI policies	COI policy interpretation defined Unblinded interpretation Response rate: 138 of 181 editors (76%)	157 of 474 medical journals (33%) and 24 of 922 science journals (3%) had policies requiring disclosure of conflicts of interest 357 of 61 134 articles (0.5) published in these journals contained financial disclosures 98 of 135 editors (72) of journals with COI policies reported that they always or almost always publish disclosures
Hussain and Smith, ⁶⁴ 2001	Systematic review	3642	Articles from 6 sample issues of 5 leading medical journals from 1989, 1994, 1996, and 1999	Inclusion/exclusion criteria undefined Unblinded interpretation	Found a small but increasing proportion of articles with disclosure declarations, from 2 declarations in 1989 to 38 in 1999 Only 2% of the 791 articles published in 1999 contained disclosures
Dorman et al, ⁶³ 1999	Systematic review	154	Acute stroke RCTs identified in the Cochrane Register	Inclusion/exclusion criteria defined Unblinded interpretation	Reporting of the extent of industry involvement was generally poor Industry-sponsored trials did not report any details on the financial reimbursement of clinical investigators

Abbreviations: COI, conflict of interest; ISI, Institute for Scientific Information; NIH, National Institutes of Health; NSF, National Science Foundation; RCTs, randomized controlled trials.

COMMENT

This comprehensive review of the literature confirms that financial relationships among industry, scientific investigators, and academic institutions are pervasive. About one fourth of biomedical investigators at academic institutions receive research funding from industry.^{27,33} One study²⁹ reported that lead authors in 1 of every 3 articles published hold relevant financial interests, while another³² reported that approximately two thirds of academic institutions hold equity in “start-up” businesses that sponsor research performed by their faculty.

Despite the prevalence of these relationships and the broad concerns they have generated, a relative paucity of data has been published describing the impact of financial ties on biomedical research. Although only 37 articles met inclusion criteria, evidence suggests that the financial ties that intertwine industry, investigators, and academic institutions can influence the research process. Strong and consistent evidence shows that industry-sponsored research tends to draw pro-industry conclusions. By combining data from articles examining 1140 studies, we found that industry-sponsored studies were significantly more likely to reach conclusions that were favorable to the sponsor than were nonindustry studies.

There are several possible reasons for this finding. It is possible that, given limited resources, industry only funds potentially winning therapies. However, we found 4 studies that empirically demonstrated that industry preferentially supports trial designs that favor positive results, such as the use of placebo as the comparison therapy in controlled trials.⁴⁰ Comparisons of new therapies to placebo may be appropriate in some cases, although such comparisons are likely to favor the new therapy.^{66,67} The frequent use of placebo controls in clinical trials is often attributed to Food and Drug Administration regulations; however, the Food and Drug Administration does not require the use of placebo and is supportive of trials that incorporate active con-

trols.⁶⁸⁻⁷⁰ Use of active controls does not eliminate the potential for bias; indeed, evidence from NSAID and fluconazole RCTs has revealed that inappropriate administration and dosing disparities decrease the effectiveness of active controls.^{45,49}

Publication bias, or the phenomenon of positive results being published more frequently than negative results, may also play a role in the relation between industry sponsorship and study outcome.⁶⁶ The review of 61 published industry-sponsored RCTs involving NSAIDs, none of which reported a negative conclusion, is consistent with this hypothesis.⁴⁵ This finding is inconsistent with the ethical principle of equipoise, which holds that, over time, there should be no difference in the number of results that favor investigational therapies vs comparison therapies.^{40,71} In addition, some have suggested that industry sponsorship may be associated with multiple reporting of studies with positive outcomes, further compounding publication bias and potentially swaying review articles toward more positive results.^{49,72}

Several studies found that industry-sponsored research appears to be of similar quality to other research.^{40,41,50-52} However, studies addressing the quality of industry-sponsored clinical trials used assessment instruments based on selected methodological criteria, such as randomization and blinding. These criteria are important components of high-quality clinical trials, but fall short of determining a study's overall quality.⁷³ Other important considerations should include the relevance of the question being asked and the use of appropriate control therapies.^{66,74}

Consistent evidence also demonstrated that industry ties are associated with both publication delays and data withholding. These restrictions, often contractual in nature, serve to compound bias in biomedical research. Anecdotal reports suggest that industry may alter, obstruct, or even stop publication of negative studies.^{7,8} Such restrictions seem counterproductive to the arguments in favor of academic-

industry collaboration, namely encouraging knowledge and technology transfer. Evidence shows, however, that industry sponsorship alone is not associated with data withholding.⁵⁵ Rather, such behavior appears to arise when investigators are involved in the process of bringing their research results to market.⁵⁵

The extensive equity holdings of academic institutions are particularly concerning. In many ways, these equity arrangements are simply extensions of the increase in university patent licensing activity encouraged by the Bayh-Dole Act.³² However, institutional ownership of equity is different from accrual of patent royalties because ownership carries the responsibility of business stewardship. Equity ownership has created a new revenue model for academic institutions and has induced a dramatic increase in institutional medical entrepreneurialism, further blurring the lines between academic and commercial values. A shift in institutional priorities could potentially affect the distribution of scarce resources.⁷⁵ More research is required to elucidate the extent of these institutional equity holdings and their precise role in realizing the promise of academic research or fostering a shift in the academic mission.

This review identified uneven adherence to methodologic standards. Cross-sectional surveys were almost universally successful in reporting high response rates, and systematic reviews defined outcome measures a priori. However, substantial heterogeneity was found in the use of blinding in systematic reviews. In addition, the potential hazards of financial conflicts of interest should be assessed in light of the potential benefits of academic-industry collaboration. These include significant advances in scientific knowledge and public health, wellness, and productivity.⁷⁶ Future studies should be performed to better understand how collaboration and technology transfer contribute to these benefits.^{76,77}

Current management of financial conflicts of interest is in a state of flux.

Several studies in this review reported substantial variability among academic institutions and peer-reviewed journals in their policies governing financial conflicts.⁵⁹⁻⁶² Efforts to respond to these shortcomings by professional societies and journals have also differed substantially, reflecting the controversy underlying the proposals for reform. Some policies call for the prohibition of certain financial relationships,⁷⁸⁻⁸⁰ while others suggest only strict disclosure and monetary limits.^{16,81-85} Journals also have made an attempt to ensure that investigators retain control of and full access to their study data.^{86,87} Despite these efforts, overall compliance of academic institutions and peer-reviewed journals with these guidelines appears poor.^{62,64,65}

An effective policy approach to financial conflicts of interest in biomedical research must tread a delicate path. The safety of human participants must remain the paramount concern, bias in the research process must be minimized, and appropriate incentives for research innovation must be preserved. Policy must also take into account the industrialization of clinical research.⁸⁸ Academic institutions are no longer central to research involving human participants. For-profit contract research organizations now consume more than 60% of clinical research funding from industry, leveraging their ability to complete trials more rapidly and less expensively than academic institutions.⁸ In addition, management of financial interests at the institutional level is particularly challenging, as it is questionable whether institutions that stand to gain substantial benefits from research commercialization can still police themselves.^{75,89,90}

The variety of proposals for reform likely stems from lack of consensus about the gravity of the problem and the optimal approach for a solution. This review shows that financial relationships are pervasive and problematic. A convergence of pressures, including increasing industry financing of biomedical research and development, encouragement of technology transfer by the federal gov-

ernment, and erosion of academic medical center revenue, will likely lead to increased reliance on industry financing in the future. Lasting and balanced reform may emerge when all stakeholders in the research process build consensus around a system of checks and balances to promote medical innovation while improving oversight and transparency. As a first step in this process, all investigators and sponsors undertaking human participant research should not only fully disclose the nature and extent of their relationships but also make available all research results from completed clinical trials in a comprehensive, publicly accessible registry.^{66,72,89,91,92} To preserve lasting benefits and enable future advances, close scrutiny will be required to understand and monitor the unintended consequences of academic-industry collaboration.

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REFERENCES

- Moses H, Martin JB. Academic relationships with industry: a new model for biomedical research. *JAMA*. 2001;285:933-935.
- National Institutes of Health Extramural Data and Trends. Bethesda, Md: National Institutes of Health; 2000.
- Thompson D. Understanding financial conflicts of interest. *N Engl J Med*. 1993;329:573-576.
- Levinsky N. Nonfinancial conflicts of interest in research. *N Engl J Med*. 2002;347:759-761.
- Korn D. Conflict of interest in biomedical research. *JAMA*. 2000;284:2234-2237.
- Kassirer J, Angell M. Financial conflicts of interest in biomedical research. *N Engl J Med*. 1993;329:570-571.
- Rennie D. Thyroid storm. *JAMA*. 1997;277:1238-1243.
- Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. *N Engl J Med*. 2000;342:1539-1544.
- Wilson D, Heath D. Uninformed consent. *The Seattle Times*. March 11-14, 2001:1-14.
- Hilts PJ. Company tried to block report that its HIV vaccine failed. *New York Times*. September 1, 2000:26.
- Gillis J. A hospital's conflict of interest: patients weren't told of stake in cancer drug. *Washington Post*. June 30, 2002:A1.
- Weiss R, Nelson D. Teen dies undergoing experimental gene therapy. *Washington Post*. September 29, 1999:A1.
- Cohen JJ. Trust us to make a difference: ensuring public confidence in the integrity of clinical research. *Acad Med*. 2001;76:209-214.
- Shalala D. Protecting research subjects: what must be done. *N Engl J Med*. 2000;343:808-810.
- Blumenstyk G. Association announces guidelines on conflicts of interest in research involving people. *Chronicle of Higher Education*. December 18, 2001.
- Task Force on Financial Conflicts of Interest in Clinical Research. *Protecting Subjects, Preserving Trust, Promoting Progress: Policy and Guidelines for the Oversight of Individual Financial Interests in Human Subjects Research*. Washington, DC: Association of American Medical Colleges; 2001.
- Bero L, Jasad A. How consumers and policymakers can use systematic reviews for decision making. *Ann Intern Med*. 1997;127:37-42.
- Slavin R. Best evidence synthesis: an intelligent alternative to meta-analysis. *J Clin Epidemiol*. 1995;48:9-18.
- Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med*. 1997;126:376-380.
- The Bayh-Dole Act of 1980, 35 USC §200-212 (2000).
- Mulrow C, Langhorne P, Grimshaw J. Integrating heterogeneous pieces of evidence in systematic reviews. *Ann Intern Med*. 1997;127:989-995.
- Eddy D. Comparing benefits and harms: the balance sheet. *JAMA*. 1990;263:2493-2505.
- Gart J. The comparison of proportions: a review of significance tests, confidence intervals and adjustments for stratification. *Rev Int Statist Inst*. 1971;39:148-169.
- Breslow N, Day N. *Statistical Methods in Cancer Research*. Lyon, France: International Agency for Research on Cancer; 1987.
- Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22:719-748.
- Robins J, Breslow N, Greenland S. Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics*. 1986;42:311-323.
- Blumenthal D, Campbell EG, Causino N, Louis KS. Participation of life-science faculty in research relationships with industry. *N Engl J Med*. 1996;335:1734-1739.
- Krimsky S, Ennis JG. Academic-corporate ties in biotechnology: a quantitative study. *Sci Technol Hum Val*. 1991;16:275-287.
- Krimsky S, Rothenberg LS, Stott P, Kyle G. Scientific journals and their authors' financial interests: a pilot study. *Psychother Psychosom*. 1998;67:194-201.
- Blumenthal D, Gluck M, Louis KS, Wise D. Industrial support of university research in biotechnology. *Science*. 1986;231:242-246.
- Blumenthal D, Causino N, Campbell E, Louis KS. Relationships between academic institutions and industry in the life sciences: an industry survey. *N Engl J Med*. 1996;334:368-373.
- Pressman L. *AUTM Licensing Survey, FY 1999: Survey Summary*. Northbrook, Ill: Association of University Technology Managers; 2000.
- Blumenthal D, Gluck M, Louis KS, et al. University-industry research relationships in biotechnology: implications for the university. *Science*. 1986;232:1361-1366.
- Blumenthal D, Causino N, Campbell EG. Academic-industry research relationships in genetics: a field apart. *Nat Genet*. 1997;16:104-108.

35. Campbell EG, Louis KS, Blumenthal D. Looking a gift horse in the mouth: corporate gifts supporting life sciences research. *JAMA*. 1998;279:995-999.
36. Boyd EA, Bero LA. Assessing faculty financial relationships with industry. *JAMA*. 2000;284:2209-2214.
37. Asch D, Jedrzejewski M, Christakis N. Response rates to mail surveys published in medical journals. *J Clin Epidemiol*. 1997;50:1129-1136.
38. Davidson RA. Source of funding and outcome of clinical trials. *J Gen Intern Med*. 1986;1:155-158.
39. Yaphe J, Edman R, Knishkowsky B, Herman J. The association between funding by commercial interests and study outcome in randomized controlled drug trials. *Fam Pract*. 2001;18:565-568.
40. Djulbegovic B, Lacey M, Cantor A, et al. The uncertainty principle and industry-sponsored research. *Lancet*. 2000;356:635-638.
41. Cho MK, Bero LA. The quality of drug studies published in symposium proceedings. *Ann Intern Med*. 1996;124:485-489.
42. Turner C, Spillich GJ. Research into smoking or nicotine and human cognitive performance: does the source of funding make a difference? *Addiction*. 1997;92:1423-1426.
43. Friedberg M, Saffran B, Stinson TJ, et al. Evaluation of conflict of interest in economic analyses of new drugs used in oncology. *JAMA*. 1999;282:1453-1457.
44. Swaen G, Meijers J. Influence of design characteristics on the outcome of retrospective cohort studies. *Br J Ind Med*. 1988;45:624-629.
45. Rochon PA, Gurwitz JH, Simms RW, et al. A study of manufacturer-supported trials of nonsteroidal anti-inflammatory drugs in the treatment of arthritis. *Arch Intern Med*. 1994;154:157-163.
46. Stelfox HT, Chua G, O'Rourke K, Detsky AS. Conflict of interest in the debate over calcium-channel antagonists. *N Engl J Med*. 1998;338:101-106.
47. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA*. 1998;279:1566-1570.
48. Kjaergard L, Als-Nielsen B. Association between competing interests and authors' conclusions: epidemiological study of randomised clinical trials published in the BMJ. *BMJ*. 2002;325:249-253.
49. Johansen HK, Gotzsche PC. Problems in the design and reporting of trials of antifungal agents encountered during meta-analysis. *JAMA*. 1999;282:1752-1759.
50. Kjaergard LL, Nikolova D, Gluud C. Randomized clinical trials in hepatology: predictors of quality. *Hepatology*. 1999;30:1134-1138.
51. Anderson JJ, Felson DT, Meenan RF. Secular changes in published clinical trials of second-line agents in rheumatoid arthritis. *Arthritis Rheum*. 1991;34:1304-1309.
52. Knox K, Adams J, Djulbegovic B, et al. Reporting and dissemination of industry versus non-profit sponsored economic analyses of six novel drugs used in oncology. *Ann Oncol*. 2000;11:1591-1595.
53. Rochon PA, Gurwitz JH, Cheung CM, et al. Evaluating the quality of articles published in journal supplements compared with the quality of those published in the parent journal. *JAMA*. 1994;272:108-113.
54. Bero LA, Galbraith BA, Rennie D. The publication of sponsored symposiums in medical journals. *N Engl J Med*. 1992;327:1135-1140.
55. Blumenthal D, Campbell EG, Anderson MS, et al. Withholding research results in academic life science: evidence from a national survey of faculty. *JAMA*. 1997;277:1224-1228.
56. Campbell EG, Weissman JS, Causino N, Blumenthal D. Data withholding in academic medicine: characteristics of faculty denied access to research results and biomaterials. *Res Policy*. 2000;29:303-312.
57. Campbell EG, Clarridge BR, Gokhale NN, et al. Data withholding in academic genetics: evidence from a national survey. *JAMA*. 2002;287:473-480.
58. Rabino I. Societal and commercial issues affecting the future of biotechnology in the United States: a survey of researchers' perceptions. *Naturwissenschaften*. 1998;85:109-116.
59. McCrary SV, Anderson CB, Jakovljevic J, et al. A national survey of policies on disclosure of conflicts of interest in biomedical research. *N Engl J Med*. 2000;343:1621-1626.
60. Cho MK, Shohara R, Schissel A, Rennie D. Policies on faculty conflicts of interest at US universities. *JAMA*. 2000;284:2203-2208.
61. Lo B, Wolf LE, Berkely A. Conflict-of-interest policies for investigators in clinical trials. *N Engl J Med*. 2000;343:1616-1620.
62. Krinsky S, Rothenberg L. Conflict of interest policies in science and medical journals: editorial practices and author disclosures. *Sci Eng Ethics*. 2001;7:205-218.
63. Dorman PJ, Counsell C, Sandercock P. Reports of randomized trials in acute stroke, 1955 to 1995: what proportions were commercially sponsored? *Stroke*. 1999;30:1995-1998.
64. Hussain A, Smith R. Declaring financial competing interests: survey of five general medical journals. *BMJ*. 2001;323:263-264.
65. Schulman K, Seils D, Timbie J, et al. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. *N Engl J Med*. 2002;347:1335-1341.
66. Bero LA, Rennie D. Influences on the quality of published drug studies. *Int J Technol Assess Health Care*. 1996;12:209-237.
67. Rothman K, Michels K. The continuing unethical use of placebo controls. *N Engl J Med*. 1994;331:394-398.
68. Temple R, Ellenberg SS. Placebo-controlled trials and active-control trials in the evaluation of new treatments. *Ann Intern Med*. 2000;133:455-463.
69. Adequate and Well-controlled Studies, 21 CFR §314.126 (2001).
70. *Guidance for Industry: Choice of Control Group and Related Issues in Clinical Trials*. Washington, DC: Food and Drug Administration; 2001.
71. Edwards SJ, Lilford RJ, Brauholtz DA, et al. Ethical issues in the design and conduct of randomized controlled trials. *Health Technol Assess*. 1998;2:1-132.
72. Rennie D. Fair conduct and fair reporting of clinical trials. *JAMA*. 1999;282:1766-1768.
73. Berk PD, Sacks HS. Assessing the quality of randomized controlled trials: quality of design is not the only relevant variable. *Hepatology*. 1999;30:1332-1334.
74. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary. *Control Clin Trials*. 1996;17:1-12.
75. Emanuel E, Steiner D. Institutional conflict of interest. *N Engl J Med*. 1995;332:262-267.
76. Blumenthal D. Growing pains for new academic/industry relationships [see comments]. *Health Aff (Millwood)*. 1994;13:176-193.
77. Gelijns A, Thier S. Medical innovation and institutional interdependence: rethinking university-industry connections. *JAMA*. 2002;287:72-77.
78. American Society of Gene Therapy. Policy of the American Society of Gene Therapy on financial conflict of interest in clinical research [adopted April 5, 2000]. Available at: <http://www.asgt.org/policy/index.html>. Accessed June 5, 2002.
79. Healy B, Campeau L, Gray R, et al. Conflict of interest guidelines for a multicenter clinical trial of treatment after coronary-artery bypass-graft surgery. *N Engl J Med*. 1989;320:949-951.
80. Topol E, Armstrong P, Werf FV, et al. Confronting the issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion. *J Am Coll Cardiol*. 1992;19:1123-1128.
81. *Report on Individual and Institutional Financial Conflict of Interest*. Washington, DC: American Association of Universities; 2001.
82. Coyle S. Physician-industry relations, Part 1: individual physicians. *Ann Intern Med*. 2002;136:396-402.
83. Coyle S. Physician-industry relations, Part 2: organizational issues. *Ann Intern Med*. 2002;136:403-406.
84. Morin K, Rakatansky H, Riddick F, et al. Managing conflicts of interest in the conduct of clinical trials. *JAMA*. 2002;287:78-84.
85. Task Force on Financial Conflicts of Interest in Clinical Research. *Protecting Subjects, Preserving Trust, Promoting Progress II: Principles and Recommendations for Oversight of an Institution's Financial Interests in Human Subjects Research*. Washington, DC: Association of American Medical Colleges; 2002.
86. DeAngelis C, Fontanarosa P, Flanagan A. Reporting financial conflicts of interest and relationships between investigators and research sponsors. *JAMA*. 2001;286:89-91.
87. Davidoff F, DeAngelis C, Drazen J, et al. Sponsorship, authorship, and accountability. *JAMA*. 2001;286:1232-1234.
88. Rettig RA. The industrialization of clinical research. *Health Aff (Millwood)*. 2000;19:129-146.
89. Press E, Washburn J. The kept university. *Atlantic Monthly*. March 2000:39-54.
90. Kassirer J. Pseudoaccountability. *Ann Intern Med*. 2001;134:587-590.
91. Horton R, Smith R. Time to register randomised trials. *Lancet*. 1999;354:1138-1139.
92. McCrary AT. Better access to information about clinical trials. *Ann Intern Med*. 2000;133:609-614.