SPECIAL ARTICLE

Academic Medical Centers' Standards for Clinical-Trial Agreements with Industry

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ABSTRACT

BACKGROUND

Although industry sponsors provide approximately 70 percent of the funding for clinical drug trials in the United States, little is known about the legal agreements that exist between industry sponsors and academic investigators. We studied institutional standards regarding contractual provisions that restrict investigators' control over trials.

METHODS

We used a structured, cross-sectional mail survey of medical-school research administrators responsible for negotiating clinical-trial agreements with industry sponsors.

RESULTS

Of 122 institutions approached, 107 participated. There was a high degree of consensus among administrators about the acceptability of several contractual provisions relating to publications. For example, more than 85 percent reported that their office would not approve provisions giving industry sponsors the authority to revise manuscripts or decide whether results should be published. There was considerable disagreement about the acceptability of provisions allowing the sponsor to insert its own statistical analyses in manuscripts (24 percent allowed them, 47 percent disallowed them, and 29 percent were not sure whether they should allow them), draft the manuscript (50 percent allowed it, 40 percent disallowed it, and 11 percent were not sure whether they should allow it), and prohibit investigators from sharing data with third parties after the trial is over (41 percent allowed it, 34 percent disallowed it, and 24 percent were not sure whether they should allow it). Disputes were common after the agreements had been signed and most frequently centered on payment (75 percent of administrators reported at least one such dispute in the previous year), intellectual property (30 percent), and control of or access to data (17 percent).

CONCLUSIONS

Standards for certain restrictive provisions in clinical-trial agreements with industry sponsors vary considerably among academic medical centers. Greater sharing of information about legal relationships with industry sponsors is desirable in order to build consensus about appropriate standards.

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In September 2000, Immune Response, a biopharmaceutical company, filed a $7 million legal action against the University of California at San Francisco after researchers published negative findings from a clinical trial of the company's experimental acquired immunodeficiency syndrome (AIDS) vaccine, Remune. The investigators had refused to allow the company to insert its own statistical analyses into the manuscript.[1] Immune Response demanded that the researchers not publish the article and withheld some of the data in an effort to dampen their publication prospects.[2] The investigators succeeded in publishing[3] but subsequently faced a legal battle that ended only after the university filed a counterclaim alleging that the contract between the parties gave the researchers permission to publish.[4]

The Remune case, other high-profile clashes between academic researchers and pharmaceutical sponsors,[5-7] and recent controversies concerning the disclosure of unfavorable findings in studies of antidepressants in children[8] and rofecoxib[9] have elevated concerns about industry-sponsored trials.[10-13] Because conflicts often turn on the language of the clinical-trial agreement, they illuminate the potential consequences of contractual provisions that restrict academic investigators' control over trials. Building on two previous studies,[14,15] we sought to obtain detailed data about academic medical centers' standards and policies concerning restrictive provisions in clinical-trial agreements.

METHODS

STUDY DESIGN

We selected a survey method after determining through conversations with research administrators at 12 medical schools that an analysis of the content of clinical-study agreements would not be possible because sponsors generally require that institutions keep them confidential. A survey questionnaire was designed and fielded with colleagues at the Center for Survey Research, University of Massachusetts, Boston.

STUDY POPULATION

The study population consisted of all 122 accredited medical schools in the United States, excluding Puerto Rico. We surveyed senior administrators in the offices of sponsored research at these institutions. Using the list of administrators approached for participation in a prior study[14] as a starting point, we used Internet and telephone research to identify the most knowledgeable person responsible for negotiating clinical-study agreements. Sometimes the questionnaire was completed by a senior administrator, and sometimes it was passed on to a frontline negotiator who was considered at least as knowledgeable about the survey topics.

SURVEY QUESTIONNAIRE

We convened a focus group of five research administrators, who were not among those selected for the main survey, for a 90-minute discussion of suitable survey questions. Participants received a $75 honorarium. We cognitively tested the draft instrument on seven research administrators selected to represent a range of institutions in terms of National Institutes of Health funding rank (a proxy for research intensity). Participants received $100 for participating in an audiotaped telephone interview in which they answered the survey questions aloud and responded to interspersed scripted cognitive questions. The final 12-page questionnaire contained 34 multipart questions, including queries about the appropriateness of 17 specific contractual provisions restricting investigators' control over multicenter clinical trials.

SURVEY ADMINISTRATION

After receiving clearance from the relevant institutional review boards, we mailed the survey to 122 medical schools in March 2004 along with a cover letter and fact sheet. The Center for Survey Research repeatedly contacted nonrespondents by mail, telephone, and e-mail during the next five months. A total of 107 administrators completed the survey. The adjusted response rate after the exclusion of four institutions determined to be ineligible because they did not conduct clinical trials was 91 percent.

STATISTICAL ANALYSIS

Professional survey coders double-entered and verified the data. We analyzed the data with the use of SPSS (version 12.0) and STATA (version 8.2) statistical software packages, testing subgroup differences using chi-square analysis and Cuzick's extension of the Wilcoxon rank-sum test for trend across ordered responses.[16] Reported P values are two-sided and uncorrected for multiple testing.

RESULTS

Respondents were experienced research administrators (Table 1), with a mean of 10.4 years of experience. Frontline negotiators and senior adminis-

Table 1. Characteristics of 107 Administrators and Their Institution or Office.*

Characteristic	No. (%)
Administrators	
Experience negotiating or administering study agreements	
0–3 yr	14 (13)
4–5 yr	21 (20)
6–10 yr	29 (28)
11–20 yr	32 (31)
>20 yr	9 (9)
Primary responsibility	
Frontline negotiator	41 (41)
Senior administrator	41 (41)
Other	19 (19)
Professional background	
Law	22 (21)
Business	54 (52)
Science	28 (27)
Medicine	10 (10)
Other academic	28 (27)
General administrative	56 (57)
Graduate degrees held	
J.D. or LL.B.	19 (18)
Ph.D. or M.D.	23 (22)
M.B.A.	15 (15)
M.S. or M.A.	16 (16)
Other	24 (24)
None	26 (26)
Institution or office	
Medical-school research intensity (NIH funding rank)	
Top 25th percentile	26 (25)
26th–50th percentile	31 (29)
51st–75th percentile	25 (24)
Bottom 25th percentile	24 (23)
Institutions represented by office	
Medical school	99 (93)
One hospital	21 (20)
Multihospital system	34 (32)
Types of agreements handled by office, other than clinical trials	
Other clinical research	93 (89)
Epidemiologic or population studies	81 (78)
Preclinical (laboratory or animal) studies	93 (89)
Technology-transfer agreements	41 (41)
Other	60 (57)
Annual no. of clinical-trial agreements handled by office	
1–10	7 (7)
11–20	6 (6)
21–50	11 (10)
51–100	27 (26)
>100	55 (52)
Change in volume of agreements in past 3 yr	
Large increase	45 (43)
Modest increase	34 (32)
No change	19 (18)
Decrease	7 (7)

* Percentages of completed responses are shown. Percentages may not total 100 because of rounding or because multiple responses were permitted. NIH denotes National Institutes of Health.

trators were equally represented in the data (Table 1). Fifty-two percent of the responding offices handled more than 100 clinical-trial agreements per year (defined as high-volume institutions), approximately a quarter handled 51 to 100, and the rest handled 50 or fewer.

Multicenter, sponsor-initiated trials accounted for 69 percent of all externally funded trials, on average, among all institutions, although there was wide institutional variation (range, 0 percent to 98 percent). Industry-sponsored trials accounted for 79 percent of all clinical trials, and 76 percent of all clinical-trial dollars, on average, across all institutions (range, 10 percent to 100 percent on both measures).

ACCEPTABILITY OF RESTRICTIVE CONTRACTUAL PROVISIONS

There was strong consensus (more than 85 percent agreement) about the unacceptability of several contractual provisions related to publication (Table 2). Provisions permitting the industry sponsor to revise a manuscript written by investigators (other than revisions relating to the protection of proprietary information) and allowing sponsors to decide that results should not be published were considered impermissible by 89 percent and 93 percent of respondents, respectively. On the other hand, virtually all respondents (96 percent) indicated that their office would accept a provision permitting the sponsor to review manuscripts for a limited time before publication. Most respondents named 60 days (44 percent) or 90 days (31 percent) as their institution's maximal acceptable time, although additional delays in connection with a patent application were generally considered acceptable.

For a second cluster of provisions, a dominant judgment (67 to 85 percent agreement) emerged, but a substantial minority of institutions held a different view. Eighty percent of institutions would permit a provision giving ownership of the research data to the sponsor, but 16 percent would not. Eighty percent would not approve a prohibition on independent publication by individual site investigators in a multicenter trial, but 15 percent would allow it. Sixty-eight percent of the respondents said their office would accept a provision barring investigators from altering the study design, whereas 15 percent said their office would not allow it and 18 percent were not sure. Similar views applied to a provision barring investigators from discussing research results while the trial was ongoing. There was majority agreement that restrictions on inves-

Table 2. Acceptability of Restrictive Provisions in Clinical-Trial Agreements.*

Question	Response		
	Yes	No	Not Sure
	percent		
Data ownership			
In your best judgment, would your office allow a clause in a multicenter clinical-trial agreement saying that:			
The sponsor will own the data produced by the research?	80	16	5
The sponsor will store the data and release portions to the investigators?	35	30	36
Study design			
In your best judgment, would your office allow a clause in a multicenter clinical-trial agreement saying that:			
The investigators (whether at your site or any other site) are not permitted to alter the study design after the agreement is executed?	68	15	18
The sponsor is permitted to alter the study design after the agreement is executed?	62	27	11
Dissemination of results			
In your best judgment, would your office allow a clause in a multicenter clinical-trial agreement saying that:			
The sponsor may review manuscripts written by the investigators for an agreed-on period before publication?	96	0	4
Maximum is 30 days	14		
Maximum is 45 days	4		
Maximum is 60 days	44		
Maximum is 90 days	31		
Maximum is 120 days	4		
Maximum is 180 days	2		
Maximum is 365 days	1		
In your best judgment, would your office allow a clause in a multicenter clinical-trial agreement saying that:			
The sponsor may decide that the results should not be published?	1	93	6
The sponsor may make revisions to a manuscript written by an investigator, other than revisions relating to the protection of proprietary information?	6	89	6
The sponsor may delay publication beyond the agreed-on time for manuscript review while a patent application is filed?	87	8	5
The sponsor may prohibit individual site investigators from publishing manuscripts independently of the sponsor or group?	15	80	6
The sponsor may include its own statistical analyses in manuscripts?	24	47	29
The sponsor will write up the results for publication and the investigators may review the manuscript and suggest revisions?	50	40	11
Other issues			
In your best judgment, would your office allow a clause in a multicenter clinical-trial agreement saying that:			
The investigators may not obtain funding from other sources for work in the same field of research as that funded by the industry sponsor?	12	82	7
While the trial is ongoing, the investigators may not discuss research results (including presentations at scientific meetings) with people not involved in the trial?	66	19	15
After the trial is over, the investigators may not discuss research results (including presentations at scientific meetings) until the sponsor consents to dissemination?	21	66	14
The terms of the clinical-trial agreement are confidential?	62	37	1
Any disputes relating to the clinical-trial agreement will be subject to mandatory arbitration?	26	60	14
After the trial is over, the industry sponsor may prohibit investigators from sharing raw research data with third parties?	41	34	24

* Data are from 107 administrators. Percentages of completed responses are shown. Because of rounding, percentages may not total 100.

tigators' rights to discuss results after the trial was over and to obtain funding from other sources for work in the same field as the sponsored trial were unacceptable, but 21 percent and 12 percent, respectively, of institutions would permit such restrictions.

For a third cluster of provisions, there was considerable variation in institutions' acceptability judgments, with a substantial number of institutions reporting uncertainty. Responses were nearly evenly split among approval, disapproval, and uncertainty regarding a clause providing that the industry sponsor would have custody of the data and would release portions to investigators. Twenty-four percent of the responding institutions would grant the sponsor the right to insert its own statistical analyses into manuscripts, 47 percent would prohibit it, and 29 percent were unsure what they would do. There was a marked split of opinion about whether sponsors could draft manuscripts reporting the research results, with the investigators' role limited to review and suggestions for revision (50 percent of responding institutions would allow it, and 40 percent would not). One in four respondents did not know whether the institution would approve a clause prohibiting the investigators from sharing data with third parties after the trial was over; the remainder were fairly evenly split (41 percent said their office would approve the provision, and 34 percent said their office would not approve it). There was also a substantial divergence in views about allowing the sponsor to make the terms of the trial agreement confidential and requiring that disputes over the agreement be submitted to arbitration.

There were some differences between acceptability ratings by administrators at high-volume institutions and those at low-volume institutions, but most of these differences were not statistically significant at conventional levels, and the direction of the relationship was not uniform. There were no significant differences in acceptability ratings between institutions with a high percentage and those with a low percentage of industry support.

We calculated an "approval score" representing the proportion of 15 restrictive provisions that the institution considered acceptable (with the exclusion of 2 that did not relate directly to the investigators' work). Approval scores ranged from 13 percent to 80 percent (mean ±SD, 44.1±13.5 percent), but the variation was not significantly associated with the volume of research or the percentage of industry support.

TENSIONS IN NEGOTIATIONS WITH INDUSTRY SPONSORS

A majority of administrators (56 percent) identified multicenter, sponsor-initiated trials as the type of trial most likely to give rise to differences between what the sponsor wanted and what the institution wanted in the clinical-trial agreement. For multicenter trials, the provisions most often identified by administrators as "very difficult" to negotiate were ownership of inventions and intellectual property (31 percent) and ownership of the data produced by

Table 3. Perceived Difficulty of Negotiating Provisions of Multicenter Trial Agreements with Industry Sponsors.*

Provision Negotiated	Response			
	Very Difficult	Somewhat Difficult	Not Difficult	Not Usually Negotiated
	percent			
Ownership of inventions and intellectual property	31	35	31	4
Ownership of the data produced by the research	25	38	32	5
Indemnification issues	17	51	31	2
Confidentiality of the data produced by the research	15	41	42	2
Rights to publish	15	54	30	1
Rights to disseminate study results	15	61	24	1
Confidentiality of trial participants' records and information	7	18	65	11

* Data are from 107 administrators. Percentages of completed responses are shown. Because of rounding, percentages may not total 100.

the research (25 percent) (Table 3). A high research volume (vs. a low volume) was predictive of greater perceived difficulty in negotiating provisions relating to the confidentiality of participants' records ($P<0.001$), the confidentiality of data ($P=0.03$), indemnification ($P<0.001$), and rights to publish ($P=0.005$). A low percentage of industry-sponsored trials (vs. a high percentage) predicted greater difficulty negotiating provisions concerning the confidentiality of participants' records ($P=0.04$) and indemnification ($P=0.04$). Tensions may be more likely to arise in negotiations in which the institution's desired contractual language is relatively strict, negotiations in which the institution considers the issue critical and nonnegotiable, or both types of negotiations.

DISPUTES WITH INDUSTRY SPONSORS

In the preceding five years, 82 percent of institutions had had one or more disputes or conflicts with an industry sponsor after a clinical-trial agreement had been signed. A mean of 1.8±1.7 types of disputes were reported, with 24 percent of institutions reporting 3 or more types of disputes in the preceding five years. The most common subject of disputes was payment (75 percent of institutions had had at least one such dispute in the preceding five years), followed by intellectual property (30 percent), control of or access to data (17 percent), content of publications (16 percent), and confidentiality of data or research results (16 percent).

Respondents were asked to describe the two most recent disputes with industry sponsors that had occurred at their institution after the agreement had been signed. A total of 65 first disputes and 48 second disputes were described. Payment, intellectual property, and control of data were the leading subjects of disputes (Table 4). Seven percent of the disputes resulted in litigation or arbitration, 55 percent resulted in extended negotiations, and 37 percent were resolved relatively quickly.

PERCEPTIONS OF THE RESEARCH ENVIRONMENT

Sixty-nine percent of administrators perceived that competition for research funds created pressure on administrators to compromise on the language in the contract, with 24 percent of those who perceived pressure describing it as great and 53 percent describing it as moderate. However, 67 percent rated their office's ability to maintain ethical standards when negotiating agreements with industry sponsors as very high; 25 percent rated it high, 7 percent medium, and only 1 percent low.

TOOLS AND PRACTICES USED TO FACILITATE NEGOTIATIONS WITH INDUSTRY SPONSORS

Institutions reported the development of five types of written policies or negotiation tools specifying standards for clinical-trial agreements; for each type, approximately two thirds of institutions reported use of it (Table 5). The type in widest use was a boilerplate agreement that administrators used as a starting point in negotiations with industry sponsors (84 percent). High-volume institutions were significantly more likely than low-volume institutions to have developed topic checklists ($P=0.006$), lists of unacceptable provisions ($P=0.04$), and boilerplate agreements ($P<0.001$). High proportions of respondents whose institutions had developed top-

Table 4. Prevalence of Disputes with Industry Sponsors of Clinical Trials.*

Subject of Dispute	No. (%)
Payment	62 (55)
Early termination	11 (10)
Timing of payment	9 (8)
Eligible expenses	7 (6)
Nonperformance by institution	4 (4)
Final payment	4 (4)
Appropriateness of budget amount	4 (4)
Other	5 (4)
Unspecified	18 (16)
Intellectual property	11 (10)
Data control	9 (8)
Indemnification	7 (6)
Publication	6 (5)
Personnel	5 (4)
Confidentiality	4 (4)
Misconduct	2 (2)
Enrollment of subjects	1 (1)
Control of study	1 (1)
Problem with IRB	1 (1)
Other	4 (4)

* The analyses included 113 disputes. The numbers of open-ended descriptions of the two most recent disputes with industry sponsors after execution of the contract are shown. Because of rounding, percentages may not total 100. IRB denotes institutional review board.

ic checklists (78 percent), lists of specific provisions that agreements should contain (83 percent), lists of unacceptable provisions (83 percent), general statements of principle (56 percent), and boilerplate agreements (52 percent) used these materials "a lot."

In addition to written policies, institutions frequently used review of clinical-trial agreements by lawyers, senior administrators, and other skilled personnel as a means of ensuring the integrity of agreements (Table 5). More than three quarters of administrators reported that they consulted with counterparts at other institutions regarding policies and standards.

Table 5. Policies, Tools, and Structures Used to Facilitate Negotiations Concerning Clinical-Trial Agreements.*

Variable	Overall (N=107)	High-Volume Institutions (N=55)	Low-Volume Institutions (N=51)
		percent	
Negotiation tools			
Written general statement of ethical or legal principles to which the institution adheres	65	74	57
Written checklist of topics that clinical-trial agreements should cover	77	89†	67
Written list of specific provisions that agreements should contain	75	82	69
Written list of specific provisions that are unacceptable	67	76‡	57
Written boilerplate agreement to use as a starting point in negotiations	84	100†	68
Negotiation practices			
Often or sometimes consult with counterparts in the offices of sponsored research at other schools or hospitals about policies and standards	78	87‡	67
All, most, or some frontline negotiators handling clinical-trial agreements have law degrees	41	54‡	29
Draft clinical-trial agreements always or usually signed or reviewed by a lawyer	34	34	35
Draft clinical-trial agreements always or usually signed or reviewed by a senior research administrator	79	70‡	88
Draft clinical-trial agreements always or usually signed or reviewed by the faculty principal investigator	91	89	92

* A high-volume institution was defined as one that handled more than 100 clinical-trial agreements annually. Data were missing for one respondent. Percentages of completed responses are shown.
† P<0.01 by the chi-square test.
‡ P<0.05 by the chi-square test.

DISCUSSION

The clinical-trial agreement defines the boundaries of researchers' and industry sponsors' rights and obligations. We identified a few areas of consensus and many differences among institutions in their views on what constitutes acceptable and unacceptable provisions in such agreements.

Our findings lend empirical support to concern expressed in previous commentary about the threat to academic freedom that restrictive contractual provisions may present.[8,11] They extend previous study findings that a substantial proportion of industry–academic research centers across a range of fields (including medicine) permitted sponsors to delete information from publications and delay publication[15] and that medical schools infrequently insisted that multicenter clinical-trial agreements contain specific protective provisions, such as data and safety monitoring boards, independent publications committees, and requirements that results be published.[14] Departing from an earlier study's focus on protective provisions,[14] we examined the acceptability of a wider range of restrictive provisions.

The heterogeneity of acceptability judgments among our respondents raises the possibility that industry sponsors could "forum shop," channeling their studies to relatively permissive institutions. However, the degree of heterogeneity was relatively small for some critical issues, such as whether sponsors could impose an absolute publications bar, and in general, the data did not demonstrate strong associations with observable institutional characteristics such as the volume of clinical research and the percentage of research funding obtained from industry. The lack of clear indicators of permissiveness may frustrate attempts to forum shop, although sponsors could still learn from experience, word of mouth, and institutional culture and leadership that countenanced permissive relationships with industry.

The lack of observable indicators undercuts the feasibility of a regulatory strategy focusing on "at risk" institutions. An alternative strategy would focus on issues that frequently give rise to disputes. Although most of the disputes reported by administrators in our study were superficially about money, the free-text descriptions of these conflicts suggest that many had embedded ethical issues. For

example, in one case, the sponsor refused to send the final payment because it did not approve the research report, "apparently because they didn't like the results of the study."

We identified a number of written negotiation tools that administrators consider helpful. Such tools enable negotiators to invoke "policy" in order to hold the line against a sponsor's demands and send a signal about the institution's standards to potential sponsors and the public. Medical schools that have not yet developed these tools are in the minority.

Increased information-sharing among institutions would help build consensus about appropriate standards for clinical-trial agreements.[17] Guidelines issued by the American Association of Medical Colleges (AAMC),[18] the International Committee of Medical Journal Editors (ICMJE),[19] and the Pharmaceutical Research and Manufacturers of America (PhRMA)[20] provide useful starting points. The ICMJE's broad statements of principle, although widely accepted, do not provide detailed guidance on specific contractual terms. PhRMA's statements are also general and may not reflect views within academia.[18] The AAMC offers more explicit advice, but on only a limited set of issues. Further work is required to develop comprehensive, useful standards for the academic community. The frequency with which our survey respondents reported being "not sure" about the acceptability of several contractual provisions suggests that many administrators may find additional guidance helpful.

Even when administrators are in agreement about particular provisions, their view may not reflect what investigators or ethicists regard as a "best practice." For example, most administrators would not accept a provision prohibiting individual site investigators in a multicenter trial from independently publishing their results, but in some trials, site-level publications could be scientifically inappropriate.[21] In addition, most administrators deemed it acceptable to keep the terms of agreements secret. This may seem eminently reasonable to industry sponsors, who may view research in the same way as they view other services they purchase on the open market and may wish to negotiate different agreements with various suppliers without letting other potential suppliers know the terms. But arguably, clinical research is special because of its implications for public health and safety, and transparency about the terms of study agreements would better serve the interests of public accountability.

Our study has limitations. We could not directly observe the willingness of institutions to approve various provisions by analyzing the content of trial agreements. Our questions elicited information about institutional policies and standards, but these responses do not provide estimates of actual approval rates. Some survey responses may have been untruthful; however, such bias would probably be in the direction of understating the degree of institutional permissiveness toward restrictive provisions. Finally, administrators' recall of previous disputes may have favored disputes that were especially important or protracted and omitted others.

The public benefits incalculably from industry funding of biomedical research.[22,23] The importance of nurturing academic–industry research relationships is clear, but so is the potential for problems if those relationships are not managed wisely. The clinical-trial agreement is the critical regulator of threats to academic freedom, with the potential to induce researchers' compliance with a sponsor's demands or to protect researchers from them. We have identified a number of issues on which institutional standards diverge significantly, as well as a few areas of accord. Further consensus-building among academic medical centers would help institutions structure research partnerships to be both ethical and productive.

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REFERENCES

1. Saltus R. AIDS drug researchers say firm pressured them: findings published, but fight goes to court. Boston Globe. November 1, 2000:A3.
2. Hilts PJ. Drug firm, scientists clash over HIV study. Chicago Tribune. November 1, 2000:N4.
3. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549x106/L CD4 cell counts: a randomized controlled trial. JAMA 2000;284:2193-202. [Erratum, JAMA 2001;285:2197.]
4. Lee N. UCSF, Immune Response drop countersuits. San Diego Bus J 2001;39:14.
5. Rennie D. Thyroid storm. JAMA 1997; 277:1238-43.
6. Shuchman M. Legal issues surrounding privately funded research cause furore in Toronto. CMAJ 1998;159:983-6.

7. Hailey D. Scientific harassment by pharmaceutical companies: time to stop. CMAJ 2000;162:212-3.
8. Meier B. Contracts keep drug research out of reach. New York Times. November 29, 2004:A1.
9. Topol EJ. Failing the public health — rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:1707-9.
10. Angell M. The truth about the drug companies: how they deceive us and what to do about it. New York: Random House, 2004.
11. Drazen JM. Institutions, contracts, and academic freedom. N Engl J Med 2002;347:1362-3.
12. Bodenheimer T. Uneasy alliance: clinical investigators and the pharmaceutical industry. N Engl J Med 2000;342:1539-44.
13. Nathan DG, Weatherall DJ. Academic freedom in clinical research. N Engl J Med 2002;347:1368-71.
14. Schulman KA, Seils DM, Timbie JW, et al. A national survey of provisions in clinical-trial agreements between medical schools and industry sponsors. N Engl J Med 2002;347:1335-41.
15. Cohen W, Florida R, Goe WR. University-industry research centers in the United States. Pittsburgh: Carnegie-Mellon University Press, 1994.
16. Cuzick JA. A Wilcoxon-type test for trend. Stat Med 1985;4:87-90.
17. Moses H III, Braunwald E, Martin JB, Thier SO. Collaborating with industry — choices for the academic medical center. N Engl J Med 2002;347:1371-5.
18. Baer I, Feiler ME, Regulski A, Switzer SS. Clinical trial contracts: a discussion of four selected provisions. Washington, D.C.: Association of American Medical Colleges, 2004. (Accessed May 2, 2005, at https://services.aamc.org/Publications/index.cfm?fuseaction=Product.displayForm&prd_id=76&prv_id=75.)
19. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals: updated October 2004. (Accessed May 2, 2005, at http://www.icmje.org.)
20. Pharmaceutical Research and Manufacturers of America. Principles on conduct of clinical trials and communication of clinical trial results. (Accessed May 2, 2005, at http://www.phrma.org/publications/publications//2004-06-30.1035.pdf.)
21. Schulman KA, Seils DM, Califf RM. Clinical-trial agreements between medical schools and industry. N Engl J Med 2003;348:476-7.
22. Blumenthal D. Academic-industry relationships in the life sciences: extent, consequences, and management. JAMA 1992;268:3344-9.
23. Gelijns AC, Thier SO. Medical innovation and institutional interdependence: rethinking university-industry connections. JAMA 2002;287:72-7.