

## Special Article

## A NATIONAL SURVEY OF PROVISIONS IN CLINICAL-TRIAL AGREEMENTS BETWEEN MEDICAL SCHOOLS AND INDUSTRY SPONSORS

KEVIN A. SCHULMAN, M.D., DAMON M. SEILS, M.A., JUSTIN W. TIMBIE, B.A., JEREMY SUGARMAN, M.D., M.P.H., LAUREN A. DAME, J.D., M.P.H., KEVIN P. WEINFURT, PH.D., DANIEL B. MARK, M.D., M.P.H., AND ROBERT M. CALIFF, M.D.

**ABSTRACT**

**Background** Concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) has issued revised guidelines for investigators' participation in the study design, access to data, and control over publication. It is unclear whether research conducted at academic institutions adheres to these new standards.

**Methods** From November 2001 through January 2002, we interviewed officials at U.S. medical schools about provisions in their institutions' agreements with industry sponsors of multicenter clinical trials. A subgroup of the respondents were also asked about coordinating-center agreements for such trials.

**Results** Of the 122 medical schools that are members of the Association of American Medical Colleges, 108 participated in the survey. The median number of site-level agreements executed per institution in the previous year was 103 (interquartile range, 50 to 210). Scores for compliance with a wide range of provisions — from ensuring that authors of reports on multicenter trials have access to all trial data (1 percent [interquartile range, 0 to 21]) to addressing the plan for data collection and monitoring (10 percent [interquartile range, 1 to 50]) — demonstrated limited adherence to the standards embodied in the new ICMJE guidelines. Scores for coordinating-center agreements were somewhat higher for most survey items.

**Conclusions** Academic institutions routinely engage in industry-sponsored research that fails to adhere to ICMJE guidelines regarding trial design, access to data, and publication rights. Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed. (N Engl J Med 2002;347:1335-41.)

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**T**HE integrity of industry-sponsored clinical research has come under increasing scrutiny. Until recently, criticism focused on investigators' financial conflicts of interest with industry sponsors<sup>1-6</sup> and the publication bias arising from pressure by sponsors to withhold negative research results.<sup>7-11</sup> Some of these concerns culminated in the publication in 2001 of guidelines by the Association of American Medical Colleges for the management of individual financial interests in biomedical research.<sup>12</sup> However, recommendations for dealing with conflicts of interest do not address other potential sources of bias in industry-sponsored research, including the role of the sponsor in the study design, investigators' access to data, and control over publication.

Also in 2001, concerned about threats to the integrity of clinical trials in a research environment increasingly controlled by private interests, the International Committee of Medical Journal Editors (ICMJE) revised its "Uniform Requirements for Manuscripts Submitted to Biomedical Journals."<sup>13,14</sup> The revisions call for full disclosure of the sponsor's role in the research, as well as assurances that the investigators are independent of the sponsor, are fully accountable for the design and conduct of the trial, have independent access to all trial data, and control all editorial and publication decisions.<sup>14</sup> The aim of the guidelines is to promote integrity in the hope of preserving public trust in the clinical research enterprise.<sup>13</sup>

It is unclear whether research conducted at academic institutions adheres to the standards embodied in the ICMJE guidelines. Research at academic institutions is governed not only by federally mandated institutional review boards but also by legal agreements between the sponsor and the institution, and medical centers are responsible for determining whether

From the Center for Clinical and Genetic Economics (K.A.S., D.M.S., J.W.T., K.P.W.), the Outcomes Research and Assessment Group (D.B.M.), Duke Clinical Research Institute (R.M.C.), and the Center for the Study of Medical Ethics and Humanities (J.S., L.A.D.), Duke University Medical Center; and the Duke University School of Law (L.A.D.) — all in Durham, N.C. Address reprint requests to Dr. Schulman at the Center for Clinical and Genetic Economics, Duke Clinical Research Institute, P.O. Box 17969, Durham, NC 27715, or at kevin.schulman@duke.edu.

and under what conditions clinical research is conducted at their institutions.<sup>9</sup> To our knowledge, there have been no national surveys of the provisions in agreements between academic institutions and industry sponsors of clinical trials. We surveyed U.S. medical schools to determine whether their agreements described the parties' roles in the design and conduct of trials, access to data, and commitment to publication, including publication rights and responsibilities.

## METHODS

### Survey Respondents

From November 2001 through January 2002, we contacted officials at 122 medical schools about their agreements with industry sponsors of multicenter clinical trials. The schools were members of the Association of American Medical Colleges.<sup>15</sup> Only institutions in the 50 states and the District of Columbia that were engaged in clinical trials were included in the survey. We identified respondents by contacting officials in offices of research administration (or in the most closely related offices) and asking if they were responsible for the content of research agreements. Depending on the administrative structure at each institution, the interviewer was referred to the person whom the initial contact thought would be the most appropriate respondent. Before each interview, the interviewer verified that the identified respondent was the person at the institution who was most knowledgeable about the content of agreements with industry sponsors. The institutional review board of Duke University Medical Center determined that the study was exempt from the requirement for approval.

### Interviews

The structured telephone survey was conducted by two of us, both of whom were involved in the development of the questionnaire. Respondents were asked questions about agreements in which the institutions acted as sites, rather than coordinating centers, for industry-sponsored, multicenter clinical trials. For these trials, a sponsor or coordinating center typically circulates a standard agreement to participating sites. A site may accept the agreement or request modifications (Smith HG, Duke University: personal communication). Executed agreements are the only legally binding mechanism between the sponsor and the sites — aside from regulatory requirements governing the conduct of the trial — and are therefore an important tool for defining the rights and responsibilities of the parties.

A subgroup of respondents was asked similar questions about agreements in which their institutions acted as coordinating centers for industry-sponsored, multicenter trials. The subgroup consisted of the 20 medical schools with the largest amount of funding from the National Institutes of Health in fiscal year 2000,<sup>16</sup> as an approximation of the institutions most likely to serve as coordinating centers.

The survey questions are listed in the Appendix. Several questions were directly related to the ICMJE guidelines. We asked what percentage of agreements explicitly addressed data collection, monitoring, and analysis; what percentage required that authors of reports on multicenter trials have access to all data; and what percentage addressed editorial control of such reports.

The survey included additional questions about provisions that might indicate the degree to which agreements were consistent with the spirit of integrity assumed in the ICMJE guidelines. We asked whether agreements contained explicit language about publication of the results of multicenter trials, authorship criteria for reports on multicenter trials, and use of site data that was independent of the use of overall trial data. Since some of these issues may be covered in trial protocols, we asked about the relation between the agree-

ments and the protocols governed by those agreements. We also sought information about provisions regarding the confidentiality of trial materials (e.g., protocols and case-report forms), confidentiality provisions that might affect publication rights, and provisions for the review of agreements by local institutional review boards. Since the subsequent use of stored biologic materials is a subject of continuing debate,<sup>17</sup> we asked about trials in which institutions collected biologic materials that might be used in subsequent research and whether agreements governing such trials included a commitment to publish the results of any subsequent studies involving these materials.

Respondents were asked to give their best estimate in answering each question. If a respondent did not know the answer to a question and was not comfortable offering an estimate, the response was documented as "don't know." Although respondents were allowed to view the questions before the interview, they were not asked to review their agreements beforehand.

For most questions, respondents were asked to estimate the percentage of their agreements in the previous year that contained the item addressed by the question. For convenience, we refer to the reported percentage as the institution's compliance score for that item. We summarize the distribution of compliance scores among the institutions using medians and interquartile ranges. Responses to other types of questions are summarized with the use of medians and interquartile ranges for continuous responses and percentages for categorical responses.

### Validation Study

To estimate the concordance between responses and actual agreements, we asked selected institutions to provide access to or copies of up to 20 site agreements executed between August and October 2001. The selected institutions reflected a range of characteristics, including the number of agreements, the seniority of the respondent, and the number of outlying responses. Of the 36 institutions invited to participate in the validation study, 10 agreed to do so. Two of us audited the collected agreements using the survey items. For each item, we calculated the median compliance score among the institutions.

## RESULTS

### Participants

We excluded 2 of the 122 medical schools that are members of the Association of American Medical Colleges because they did not participate in clinical trials, and we excluded 4 institutions that contracted with private research organizations or local hospitals to conduct trials without exercising institutional oversight of the agreements. Two schools fell administratively under the same institution, so a single respondent participated. Of the remaining 115 institutions, 1 could not participate because of recent personnel changes, 2 were excluded because they had executed no new agreements in the previous year, and 4 refused to participate. Thus, we obtained responses from 108 of 122 institutions.

We excluded 1 of the 20 schools selected for the coordinating-center survey because it did not coordinate industry-sponsored trials. We excluded two institutions because they had executed no new coordinating-center agreements in the previous year. Three institutions refused to participate. Thus, we administered the coordinating-center survey to 14 institutions.

Forty-eight percent of respondents (52) were in

offices of grants and contracts or sponsored programs, 40 percent (43) in research-administration offices, 7 percent (8) in industry-liason offices, and 5 percent (5) in legal-affairs offices.

**Survey Responses**

The median number of site agreements executed in the previous year was 103 (interquartile range, 50 to 210). The median proportion of site agreements that involved an academic coordinating center was 10 per-

cent (interquartile range, 5 to 20). In the coordinating-center survey, the median number of agreements was 10 (interquartile range, 5 to 28). Tables 1 and 2 show the median compliance scores for items in the surveys of site agreements and coordinating-center agreements, respectively.

**Trial Design**

Site agreements rarely required the presence of an independent executive committee or data and safety

**TABLE 1. COMPLIANCE SCORES FOR SITE AGREEMENTS BETWEEN MEDICAL SCHOOLS AND INDUSTRY SPONSORS OF MULTICENTER CLINICAL TRIALS.\***

ITEM†	SURVEY		VALIDATION STUDY	
	NO.	MEDIAN SCORE (INTERQUARTILE RANGE)	NO.	MEDIAN SCORE (INTERQUARTILE RANGE)
		%		%
Design of trial				
Agreement addresses plan for data collection and monitoring	108	10 (1–50)	10	0
Agreement addresses plan for data analysis and interpretation	108	5 (0–12)	10	0
Agreement requires an independent steering or executive committee	108	2 (0–10)	10	0
Agreement requires an independent data and safety monitoring board	108	1 (0–13)	10	0
Access to data				
Agreement requires access to all data for authors of reports on multicenter trials	108	1 (0–21)	10	0
Agreement allows site investigators to analyze and publish site data	108	100 (75–100)	10	100 (95–100)
Agreement allows use of site data for other educational or research purposes	107	85 (35–100)‡	10	45 (7–56)
Publication of results				
Agreement requires publication of trial results	107	0 (0–10)	10	0
Agreement requires an independent writing or publications committee	108	0 (0–5)	10	0
Agreement addresses criteria for authorship of reports on trial results	108	20 (5–60)	10	0 (0–17)
Agreement addresses editorial control of reports on trial results	108	40 (5–95)‡	10	0
Agreement addresses decisions about where to submit manuscripts	108	0 (0–5)	10	0
Agreement includes a commitment to publication of the results of subsequent genetic research	94	0	10	0
Other issues				
Agreement contains provision that prevents confidentiality clause from restricting investigators' publication rights	107	98 (50–100)	10	47 (26–58)
Agreement named as superseding document in case of conflict between agreement and protocol	103	70 (25–98)	10	65 (46–87)
Agreement explicitly requires institution to follow protocol	108	100 (90–100)	10	100
Agreement explicitly requires sponsor to follow protocol	107	0 (0–25)	10	9 (1–22)

\*The compliance score for each item is the percentage of the institution's agreements that addressed the item.

†See the Appendix for the complete list of survey items.

‡The responses had a bimodal distribution.

**TABLE 2.** COMPLIANCE SCORES FOR COORDINATING-CENTER AGREEMENTS BETWEEN MEDICAL SCHOOLS AND INDUSTRY SPONSORS OF MULTICENTER CLINICAL TRIALS.\*

ITEM†	No.	MEDIAN SCORE (INTERQUARTILE RANGE)
Design of trial		
Agreement addresses plan for data collection and monitoring	14	83 (55–100)
Agreement addresses plan for data analysis and interpretation	13	80 (20–100)
Agreement requires an independent steering or executive committee	14	3 (0–50)
Agreement requires an independent data and safety monitoring board	13	1 (0–50)
Access to data		
Agreement requires access to all data for authors of reports on multicenter trials	13	50 (10–95)
Agreement allows use of trial data for other educational or research purposes	14	88 (16–100)
Publication of results		
Agreement requires publication of trial results	13	5 (0–75)
Agreement requires an independent writing or publications committee	14	6 (0–23)
Agreement addresses criteria for authorship of reports on trial results	13	50 (0–90)
Agreement addresses editorial control of reports on trial results	13	75 (20–100)
Agreement addresses decisions about where to submit manuscripts	13	0 (0–20)
Agreement includes a commitment to publication of the results of subsequent genetic research	10	0
Other issues		
Agreement contains provision that prevents confidentiality clause from restricting investigators' publication rights	14	100 (75–100)
Agreement named as superseding document in case of conflict between agreement and protocol	10	63 (20–90)
Agreement explicitly requires institution to follow protocol	13	100 (99–100)
Agreement explicitly requires sponsor to follow protocol	13	50 (1–100)‡

\*The compliance score for each item is the percentage of the institution's agreements that addressed the item.

†See the Appendix for the complete list of survey items.

‡The responses had a bimodal distribution.

monitoring board as a condition of the institution's participation in multicenter trials (Table 1). For example, with regard to the percentage of agreements that required a data and safety monitoring board, the median compliance score was 1 percent (interquartile range, 0 to 13). Also, agreements infrequently addressed the collection and monitoring of data or the analysis and interpretation of data. Coordinating-center respondents gave similar responses; however, a greater percentage of their agreements addressed, in some fashion, the collection, monitoring, analysis, and interpretation of data (Table 2). Only 17 respondents in the site survey (16 percent) and none in the coordinating-center survey reported that the institutional review board routinely reviewed agreements.

#### Access to Data

The compliance score for the requirement that authors of reports on multicenter studies have access to all data was 1 percent (interquartile range, 0 to 21) for site agreements (Table 1) and 50 percent (interquartile range, 10 to 95) for coordinating-center agreements (Table 2). Site agreements tended to secure the inves-

tigator's access to site-level data for analysis and possible publication, and both site agreements and coordinating-center agreements tended to ensure access to data for other educational and research purposes.

#### Publication of Results

Compliance scores for addressing criteria for authorship of reports on multicenter studies were low for site agreements but were higher for coordinating centers. Site and coordinating-center agreements rarely required an independent publications committee, and they rarely required publication of trial results. The scores for a commitment to publish the results of subsequent research on stored biologic materials were also low. Also, only eight institutions in the site survey (7 percent) and only one in the coordinating-center survey (7 percent) determined whether the results of multicenter trials had been published.

#### Other Issues

The median duration of confidentiality was five years (interquartile range, five to seven) in both site and coordinating-center agreements. Only 18 institu-

tions in the site survey (17 percent) and 5 in the coordinating-center survey (36 percent) had a policy dictating the limits of the duration of confidentiality, although many respondents mentioned that they try to negotiate as short a duration as possible. Responses to other questions about confidentiality and the relation between agreements and their respective protocols are shown in Tables 1 and 2.

#### Validation

Ten institutions participated in the validation study, with a total of 102 agreements. As shown in Table 1, when respondents misestimated their compliance substantially, they tended to overestimate rather than underestimate it.

### DISCUSSION

Our findings suggest that academic institutions routinely participate in clinical research that does not adhere to ICMJE standards of accountability, access to data, and control of publication.<sup>13,14</sup> These standards address long-standing concern about the integrity of research published in biomedical journals.<sup>7-10,18-22</sup> We found that academic institutions rarely ensure that their investigators have full participation in the design of the trials, unimpeded access to trial data, and the right to publish their findings. Even when a site investigator does not wish to engage in trialwide activities, it is the obligation of the institution to ensure that the research in which its faculty members participate is properly conducted and that their rights as investigators are protected.<sup>9</sup> It is not clear, however, that institutions have succeeded in doing so.

Moreover, the institutions participating in our survey rarely required the presence of an independent executive committee, data and safety monitoring board, or publications committee as a condition of their participation in multicenter trials. Such bodies can be important safeguards of integrity and safety in clinical trials.<sup>23,24</sup> Likewise, we found that site agreements rarely addressed important elements of the right to publish, including editorial control and criteria for authorship of reports on multicenter trials.

Although the institutions secured their investigators' access to site-level data, they rarely required that authors of reports on multicenter studies have independent access to all trial data, an explicit requirement of the ICMJE guidelines. This requirement was also missing in a substantial percentage of coordinating-center agreements. Data from an individual site are not an adequate surrogate for the entire trial data base. In multicenter trials, analysis of an individual site's data is scientifically unsound. Yet this is the contractual provision most often relied on by institutions to provide evidence of investigators' independence. A recent report from Toronto proposes that sites should request

assurances from industry sponsors that the publication rights of the authors of multicenter reports will be protected.<sup>25</sup>

When institutions serve as coordinating centers rather than sites, they may be more likely to strike a balance between the interests of industry sponsors and scientific goals.<sup>26</sup> However, even coordinating-center agreements often do not fully protect the rights of investigators or address important issues of trial design and conduct that would help ensure the integrity of the research.

The current research environment may impede institutions' attempts to negotiate contract provisions that secure investigators' rights.<sup>9,13,25,26</sup> In response to some survey items, particularly those addressing publication and confidentiality, several respondents said that they felt powerless in contract negotiations with sponsors. One respondent stated that although some institutions may be able to negotiate provisions that ensure investigators' rights, her institution was "just a small medical school." These sentiments, coupled with our findings, suggest that the academic community may need to reevaluate its approach to contracting for sponsorship of clinical trials in order to ensure that research is conducted in a manner consistent with the ICMJE standards and the ethical obligations of research institutions.

The ethical obligations of investigators to protect the rights and interests of research participants have been articulated repeatedly.<sup>27,28</sup> Patients participate in clinical research for a variety of reasons, and although many participate with the hope of personal medical benefit, they tend to endorse the notion that they are contributing to scientific knowledge and helping others through eventual improvements in medical care.<sup>29-31</sup> Indeed, part of the ethical justification for exposing patients to the risks of research that may not offer a personal benefit hinges on the benefit of gaining generalizable knowledge and the assumption that participants understand this.<sup>32</sup> If institutions and sponsors fail to ensure publication of the knowledge obtained from the research, they arguably fail to honor their implicit commitment to participants. Our results suggest that many academic institutions do not guarantee that this commitment will be fulfilled.

Research findings can be disseminated in various ways, including publication in peer-reviewed journals and posting on the Internet or in public electronic archives. The latter may be an important outlet for trials that failed because of inadequate enrollment or other factors unrelated to efficacy or toxicity.<sup>33</sup> In any case, compliance with the ICMJE guidelines requires that such decisions about publication be left to authors who are independent of the sponsor and accountable for the research.<sup>14,33</sup>

Although ethical considerations provide the strong-

est support for an obligation to ensure the dissemination of research findings, case law suggests that there may also be a legal obligation to participants in clinical research. In two cases brought by research participants, trial courts found that sponsors and investigators have a legal obligation to follow through on certain commitments made to participants and that promises of benefits offered to them become contractually binding on sponsors once the participants have fulfilled their obligations.<sup>34,35</sup> In both these cases, the agreements were explicit, and the respective obligations were clear. Whether courts would make a similar decision in cases in which the promises were not as explicit, as in the conduct of clinical research and the publication of research findings, is uncertain.

Some caveats should be considered in interpreting the results of our study. First, the survey relied on recollections of institutional officials. In the validation study, we reviewed agreements from a subgroup of institutions to validate the survey responses, thus somewhat mitigating this concern. Second, although we sought to interview the person at each institution who was most knowledgeable about the issues addressed by the survey, other persons may have had knowledge that we were unable to obtain. Finally, we were unable to address the possibility that compliance rates varied according to whether an institution's investigators were potential authors of reports on multicenter trials or were simply participating investigators.

Academic institutions routinely engage in research that fails to adhere to ICMJE guidelines for trial design, access to data, and publication rights. Our findings suggest that a reevaluation of the process of contracting for clinical research is urgently needed.

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#### APPENDIX. SURVEY QUESTIONS.

1. Approximately how many new clinical-trial site agreements for multicenter trials does your institution sign each year? (Please give a number, rather than a range.)
  - a) What percentage of these trials are coordinated by academic institutions?
2. What percentage of your agreements with the sponsor explicitly address the overall trial's plan for data collection and monitoring?
3. What percentage of your agreements with the sponsor explicitly address the overall trial's plan for data analysis and interpretation?
4. What percentage of your agreements with the sponsor explicitly address the criteria for authorship of the overall trial's results?
5. What percentage of your agreements with the sponsor explicitly address editorial control of the overall trial's manuscripts?
6. What percentage of your agreements with the sponsor explicitly address the decisions about where the overall trial's manuscripts will be submitted for publication?
7. What percentage of your agreements with the sponsor require that the overall trial have an independent steering or executive committee?
8. What percentage of your agreements with the sponsor require that the overall trial have an independent data and safety monitoring board?

9. What percentage of your agreements with the sponsor require that the overall trial have an independent writing or publications committee?

10. What percentage of your agreements with the sponsor require that the authors of the overall trial's manuscripts have access to all trial data?

11. What percentage of your agreements with the sponsor require that the overall trial's results be published?

a) Of the agreements that require the overall trial's results to be published, what percentage specify a time frame for publication, such as from the time of data-base lock or another defined time?

12. What percentage of your agreements with the sponsor allow your institution to conduct and publish analyses of site-specific data independently of the overall trial?

13. What percentage of your agreements with the sponsor allow you to use your site's data for other educational or research purposes independently of the overall trial?

14. How long, on average, do the confidentiality clauses in your agreements remain in effect?

15. Are limits on the duration of confidentiality dictated by university policy?

16. What percentage of your agreements include a provision that prevents the confidentiality clause from restricting investigators' publication rights?

17. What percentage of your agreements with the sponsor contain explicit language that names the agreement as the controlling document in the case of a conflict between the agreement and the protocol?

18. What percentage of your clinical-trial site agreements state explicitly that your institution must follow the study protocol?

19. What percentage of your clinical-trial site agreements state explicitly that the sponsor must follow the study protocol?

20. Does your institution's institutional review board routinely review the content of your industry-sponsored site agreements?

21. Does your institution routinely evaluate its completed multicenter studies to determine whether the overall results were published?

22. In some clinical trials, sponsors ask investigators to collect blood or other specimens from subjects for possible use in future genetic research. In these types of trials, what percentage of your clinical-trial site agreements include a commitment to publish the results of such research?

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