

HEALTH LAW, ETHICS, AND HUMAN RIGHTS

Compact versus Contract — Industry Sponsors' Obligations to Their Research Subjects

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Public unease about industry's influence over clinical research has never been greater. Recent events have elevated concerns about financial ties among investigators, academic medical centers, and industry sponsors,¹⁻⁴ and disquieting findings have emerged about the legal relationships these entities form to conduct clinical trials.⁵⁻⁸ Tort litigation brought by injured research subjects has accentuated the legal dimensions of clinical research relationships.⁹⁻¹¹

These areas of focus converged in *Abney v. Amgen*, an important case decided in March 2006 by the U.S. Court of Appeals for the Sixth Circuit.¹² The dispute centered on the legal obligation of an industry sponsor to provide clinical-trial participants with an investigational medication after the termination of a study. The court held that despite a provision in the consent form stating that subjects could elect to continue taking the study drug for up to 2 years after the trial ended, the sponsor had no obligation to provide the drug. It grounded this conclusion in a determination that the plaintiffs had not entered into a legal relationship with the sponsor that would bind Amgen to fulfill this promise.

The *Abney* case raises weighty legal issues for academic medical centers and their research faculty, as well as troublesome ethical questions.¹³ The case underscores that notwithstanding the advantages of an arms-length relationship between academic investigators and industry sponsors, such an arrangement has undesirable legal consequences.

THE GDNF CLINICAL TRIAL

Edward Abney and his seven fellow plaintiffs were patients with Parkinson's disease who enrolled in a phase 2 trial of a synthetic protein called glial cell line–derived neurotrophic factor

(GDNF) at the University of Kentucky Medical Center in 2003.¹⁴ The drug was delivered by direct infusion into the putamen, a region deep in the brain, through a surgically placed catheter. The multicenter trial was sponsored by Amgen, which had spent \$150 million to acquire the biotechnology company that developed GDNF. As is customary, Amgen executed a clinical-trial agreement with the university to set up the trial and submitted the study protocol to the university's institutional review board (IRB).

The protocol and consent form stated that at the end of the trial, the subjects “may elect to continue treatment for up to an additional 24 months.” The consent form also stated that subjects could be withdrawn from the study if the investigators deemed that the risk to them outweighed the benefits, if they were noncompliant with instructions, or “if the agency funding the study decides to stop the study early for a variety of reasons.”

The trial showed disappointing results based on analysis of the primary efficacy end point (percent change in the baseline motor score at 6 months). Though the improvement among those receiving GDNF was slightly greater than among those receiving placebo, the difference did not achieve statistical significance.¹⁴ Nevertheless, Amgen decided to continue the trial, with all 34 subjects receiving open-label GDNF. However, in September 2004, Amgen informed the university that it had decided to stop the trial, citing three concerns. First, neutralizing antibodies that could also attack naturally occurring GDNF had developed in several subjects. Second, brain lesions had been discovered in studies of GDNF in primates. Third, the drug apparently lacked efficacy. Before making its announcement, Amgen consulted with Food and Drug Administration (FDA) officials, who agreed that termination of the

study would be reasonable but said the decision was entirely Amgen's.¹⁵

Many subjects, however, believed that their conditions had improved and wanted to continue receiving GDNF. Amgen met with FDA officials to discuss whether "compassionate use" of GDNF would be appropriate. The FDA granted its permission but gave Amgen discretion to decide whether it would provide the drug. The company declined, and the subjects sued, alleging that the termination decision was financially motivated.¹⁶

PLAINTIFFS' CLAIMS
AND COURT'S FINDINGS

The plaintiffs advanced three legal arguments, all variants on the theme that Amgen had broken a promise to subjects to provide post-trial access to the drug. First, they claimed that Amgen had breached its contract with subjects. Second, they alleged "promissory estoppel." This legal doctrine proposes that if Person A reneges on a promise on which Person B has reasonably relied, to B's detriment, fairness may require that A make B whole, even if the promise was not set forth in a valid contract. Finally, they argued that Amgen violated its fiduciary duty to them.

A federal district court rejected these arguments and denied the plaintiffs' motion for a preliminary injunction to compel Amgen to continue providing GDNF. The plaintiffs then appealed to the Sixth Circuit, which affirmed the lower court's holding. (A plaintiff's burden of proof to obtain a preliminary injunction is more onerous than his or her burden at trial; denial of a preliminary injunction does not necessarily indicate that a claim will ultimately fail.)

The district court made three key findings, drawing on precedent in a similar case.¹⁵ First, no contract existed between the research subjects and Amgen. The subjects had a contract with the university (and through it, the investigators): the consent form. The university and the investigators had a contract with Amgen: the clinical study agreement. But neither of these documents created a contractual obligation between Amgen and the subjects or gave the investigators authority to make promises that would bind Amgen. That might have been the case if Amgen and the investigators had had a principal-agent relationship, but such a relationship requires a high degree of

control by the principal over the agent's work that rarely (if ever) applies to research faculty. Rather, as outlined in the clinical-trial agreement signed by Amgen and the university, the investigators were independent contractors, working outside Amgen's control. The court specifically rejected the theory of "apparent authority," through which an independent contractor may be treated as a legal agent if the principal holds the contractor out as having the authority to act on the principal's behalf. Although subjects may have believed the investigators were authorized to speak for Amgen when they promised access to the drug, Amgen itself never gave them specific reason to think so.

Similarly, the court found, the estoppel claim would not succeed because Amgen had made no direct promises to the subjects. The promise came from the investigators, not the sponsor, and again the investigators had no authority to speak for Amgen. In addition, the court held that the consent-form provision regarding extended treatment was subject to the caveat (found elsewhere in the form) that the sponsor could decide to terminate the study "for a variety of reasons."

Finally, the court held that Amgen did not have a fiduciary duty to the subjects "to ameliorate their pain and treat their illness with the best medicine available."¹² A fiduciary duty may be inferred from a relationship in which one party reposes trust in the integrity of another party who has agreed to act primarily for his or her benefit.¹⁷ The court found no such relationship between Amgen and the subjects because the company's reasons for sponsoring the study were not primarily to benefit the subjects.

The court noted, however, that Abney might have a viable lawsuit against the University of Kentucky's IRB and investigators. It observed that "it was the University that was legally bound by the Informed Consent Document and thus arguably legally obligated to continue to administer the treatment to the plaintiffs." Citing the Maryland Court of Appeals' holding in *Grimes v. Kennedy Krieger Institute*,⁹ the court opined that investigators owe a duty to subjects that goes beyond the statements in the consent form. It further found that the university had done a poor job of informing subjects about the circumstances under which the trial might be stopped and how that might affect their access to the drug.

LEGAL CONTEXT

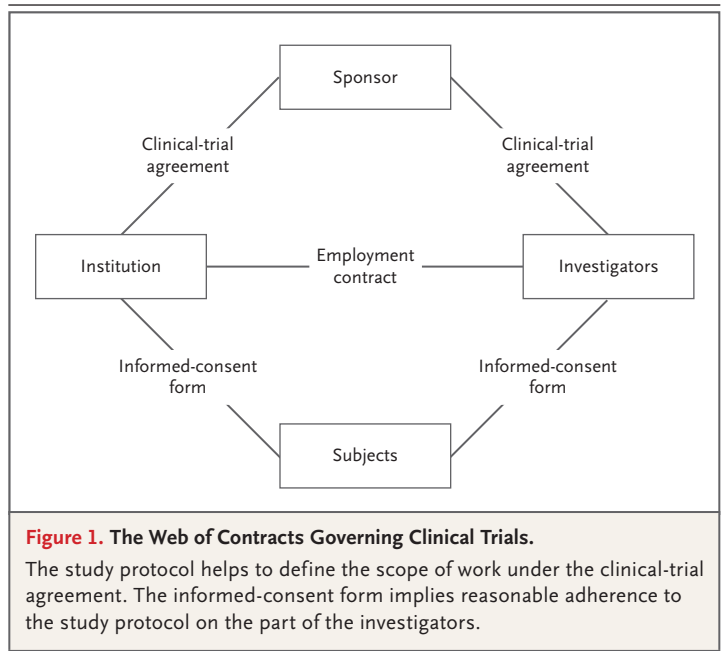
Abney highlights the complexity of legal relationships among the parties to clinical trials. We briefly review the relevant law before turning to ethical and policy considerations surrounding the question of industry sponsors' obligations to subjects.

Clinical trials are governed by a web of contracts (Fig. 1). First, academic medical centers execute clinical-trial agreements with industry sponsors, in which institutions accept money in exchange for providing research services and facilities and (along with investigators) commit to certain responsibilities. When investigators are signatories to these agreements, they become bound by them as well. The study protocol, which may be explicitly referenced in the clinical-trial agreement, helps define the scope of work under this contract.

Second, the nature of investigators' relationship with the institution (including the general rights and responsibilities that accompany it) is established by an employment contract or affiliation agreement. There are diverse models for this relationship; frequently, the employment contract will not address the conduct of research, but the nature of the relationship will dictate the degree of control that the institution has over the investigators' research activities.

Third, the consent agreement sets the parameters of the relationship between the research subjects and the investigators and the institution. The institution is considered a party to this agreement because it has responsibility for monitoring the integrity of the research conducted by its employees and affiliates. In addition, it generally approves the consent form through its IRB. Because the consent form typically mentions that the IRB has approved the study, it implicitly represents that the investigators will adhere to the study protocol (with approved modifications). Most courts have characterized the consent form as creating a "unilateral contract," in which a promise (by the investigators and institution) is exchanged for a "performance" (the subject's participation in a trial). This kind of contract does not bind the subjects to go through with the performance, but if they do, the promisor must fulfill the promise.

Conspicuously absent from this web is a strand



directly connecting subjects to sponsors. In theory, it might be possible to draft a consent form so as to bind the sponsor to certain obligations,¹⁵ but this does not happen in practice. Circumstances exist in which courts will find a quasicontractual or fiduciary relationship between two parties even when no explicit contract exists; however, *Abney* suggests that the sponsor–subject relationship does not call for this type of intervention.

The finding of a fiduciary relationship between two parties carries great legal significance. A fiduciary relationship creates two legal duties: a duty of care, which requires diligence in making decisions on the beneficiary's behalf, and a duty of loyalty, which requires the fiduciary to promote the beneficiary's best interests.¹⁸ Examples of fiduciary relationships include those of physician and patient, trustee and beneficiary, guardian and ward, director and shareholder, and attorney and client.

The courts have rarely considered the legal obligations that research sponsors owe to subjects, but some precedent exists. According to the district court in *Abney*, no court has found a fiduciary relationship between a clinical-trial sponsor and the subjects, nor can such a relationship be inferred from the Common Rule or other regulations.¹⁶ A Massachusetts court held that although investigators in a gene-transfer trial had duties

to subjects that could give rise to a negligence suit, the industry sponsor did not have such duties, because it did not conduct the trial.¹⁹ A North Carolina court dismissed claims for negligence and breach of fiduciary duty against an industry sponsor of a trial of a psoriasis drug, holding that only health care providers could have fiduciary duties.²⁰ As the *Abney* court suggested, there appears to be no precedent supporting the notion that sponsors of research conducted at academic medical centers have direct legal duties — of any kind — to subjects. (Although subjects conceivably could file fraud claims against sponsors who misrepresented information to them or product liability claims alleging that an investigational product was defective, more general claims grounded in negligence or breach of contract appear precluded.)

In contrast, several courts have held that research institutions and investigators have a “special relationship” to subjects that creates legal duties, including a duty to seek informed consent and a general duty of care in the conduct of research that could give rise to a negligence action.^{9,21-25} The special relationship arises from both the informed-consent agreement and the Common Rule. However, the relationship does not constitute a fiduciary relationship.^{9,23}

The *Abney* decision appears faithful to these precedents and to principles of contract law. Although not binding on other jurisdictions, other courts would probably hold similar views. The subjects’ relationship with the investigators and the university may have involved a duty of care, but there is little basis for concluding that Amgen owed the subjects anything. Only a few courts^{9,26-28} have ruled on whether a research consent form can constitute a legal contract that binds the investigators and institution, but their answer has nearly always been yes²⁹ (and Lynch HF: personal communication). Regardless of whether the investigators and institution were themselves contractually bound, however, neither was authorized to make representations that would bind Amgen.

Legal precedent supports the general proposition that a consent form can create a binding obligation on an industry sponsor to provide the investigational medication after the trial is over.²⁶ However, this precedent emanates from a case in which the company conducted the trial itself, rather than contracting with academic investigators. In that case, the company was unquestion-

ably a party to the consent agreement. Thus, the legal rules may be different for research conducted “in house” and perhaps also by contract research organizations if the sponsor tightly controls their work.

A legal theory under which investigators or sponsors stand in a fiduciary relationship to subjects would be fundamentally at odds with the nature of the research enterprise. The foremost duty of the investigators and the sponsor cannot be to maximize the interests of subjects, because that could conflict with the dictates of the study protocol and sound science in a range of circumstances.^{18,30-32} Their mission is scientific, not therapeutic; investigators may not, for example, deviate from the protocol to take actions that they think will better serve the interests of particular subjects.¹⁰ Furthermore, industry sponsors cannot have fiduciary relationships with subjects, because corporations have fiduciary duties to their shareholders that preclude their giving subjects’ interests the “undivided loyalty” that fiduciary relationships require.³³

ETHICAL CONSIDERATIONS

Though a plausible reading of the law, *Abney* raises troubling ethical questions. First, how far do sponsors’ and investigators’ obligations to research subjects extend after completion of a trial, and what grounds those obligations? According to the Declaration of Helsinki, when a study ends, every subject “should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.”³⁴ This requirement might be criticized as too onerous, given the open-ended obligations it potentially imposes.³⁵ It is also unhelpful in most early-phase trials, in the clarification of obligations to subjects before study data are mature, and in cases in which trials are terminated too early to determine whether the investigational drug is the “best proven” therapy. In the present case, given legitimate concerns about safety and efficacy, Amgen’s refusal to provide GDNF after the trial ended did not violate Helsinki’s mandate.

However, even if general principles of research ethics would not require provision of the drug in this case, the consent agreement arguably created additional obligations by promising subjects that they could decide whether to continue taking the drug. Where this representation was ma-

terial to their decision to participate, then regardless of whether a legal contract existed, a compact, or covenant, did — and the company has an ethical duty to keep its end of the bargain. Although the consent form gave Amgen the right to stop the trial “for a variety of reasons,” it was unclear whether this clause qualified the promise of continued access to GDNF after trial closure. Given subjects’ relative lack of sophistication, it is reasonable to construe ambiguities in the consent form in their favor. Furthermore, although nonmaleficence concerns suggest that strong evidence of serious toxicity should overcome the presumption of continued access, without appropriate qualification of the promise in the consent agreement, an apparent lack of efficacy triggers no such concerns.

Second, what are the implications of viewing the academic investigators’ relationship with the sponsor as that of an independent contractor? The facts of the *Abney* case suggest that academic medical centers, IRBs, and investigators may misunderstand the limits that clinical-trial agreements place on their ability to make promises to research subjects. The decision and its precedents imply that the law will offer little help to subjects seeking to enforce those promises insofar as they require resources from sponsors. This outcome is unsettling.

Commentators have generally advocated an arms-length relationship between industry sponsors and academic investigators, because such a relationship is believed to protect investigators’ freedom, reduce conflicts of interest, and promote scientific integrity. By setting up academic investigators as independent contractors, however, sponsors evade direct liability to subjects and create a legal immunity that seems unfair. Nevertheless, the alternative — making academic investigators the legal agents of pharmaceutical companies — is unappealing because it would place investigators’ work in clinical trials under the direct control of the companies. The arms-length relationship is appropriate, then, but academic medical centers must take measures to protect subjects from its potential consequences.

Finally, *Abney* raises questions about whether the nature of the industry–academic relationship and its implications for the terms of clinical-trial participation are sufficiently clear to research subjects. Specifically, is a typical participant in an industry-funded trial likely to understand the

limitations of the investigators’ authority to make binding commitments? Surely most subjects will infer that if investigators are promising access to the drug after trial completion, they have secured the sponsor’s agreement to provide it. Should not subjects’ perspectives matter in construing ethical obligations, particularly if sponsors are aware of how the arrangement will look to subjects? Although the *Abney* court signaled that (without a bona fide “apparent authority” relationship) the subject’s perspective will not matter in construing legal obligations, we should think differently about ethical obligations.

If research subjects routinely misunderstand the authority of investigators and institutions to make promises that implicate sponsors, this suggests the need for greater transparency. One question is whether clinical-trial agreements, which are typically confidential,^{5,8} should be made available to subjects. Such agreements are clearly pivotal in defining important obligations and relationships that affect subjects’ rights and well-being. However, most subjects are unlikely to comprehend these complex documents. We should instead seek a way to evaluate the promises investigators make in light of the authority granted them in the clinical-trial agreement and then distill the relevant information for subjects. At present, clinical-trial agreements are not routinely reviewed by IRBs, and research administrators report that such documents are poorly understood by investigators.⁵

RECOMMENDATIONS FOR ACADEMIC MEDICAL CENTERS

Academic medical centers must recognize the substantial risk of conflicts and contradictions within the web of contracts governing research relationships. They face liability exposure if they fail to monitor these conflicts and make promises to subjects that cannot be fulfilled. Because of sponsors’ legal immunity and investigators’ obligations to safeguard the welfare of subjects, the burden of ensuring that agreements and promises are consistent and transparent falls on academic medical centers and their programs for human research protection.

Given their central role in ensuring that clinical trials at an institution are conducted in an ethical manner, IRBs may be best positioned to accept responsibility for ensuring consistency

among clinical-trial agreements, protocols, and consent forms.³⁶ As currently constituted, however, most IRBs are probably incapable of performing this function. An alternative would be to create an administrative liaison between IRBs and offices that administer grants and contracts.

Three goals should guide efforts to reconcile clinical-trial agreements, protocols, and consent forms. First, any promises to subjects that are articulated in the consent process or form must be backed either by the legal authority to bind the sponsor or by the institution's ability to satisfy the promise independently. Academic medical centers and investigators must realize that they are not passively conveying a sponsor's promise to potential subjects through the consent form; rather, they are themselves making a promise and must therefore be able to fulfill it. Second, they must clearly communicate any limits on promises to prospective subjects. Finally, any aspects of the study design that the institution views as necessary to the ethical justification of the trial must be legally enforceable, typically by incorporation into the clinical-trial agreement. For example, if the institution views access to the study drug after conclusion of study participation as ethically required, that obligation must be enforceable through appropriate contract language. Much of the problem highlighted by *Abney* can be avoided through more careful drafting of contracts.

Some observers may object that our proposal contributes to the lawyerization of clinical research, which many perceive as imposing bureaucracy on the research enterprise with little benefit to subjects.³⁷ A greater focus on legal issues may lead IRBs to orient consent forms more toward exculpatory provisions, an undesirable result. But as *Abney* shows, clinical trials are already intimately governed by legal relationships, and the implications of these arrangements can go to the heart of what matters to participants. Whatever the wisdom of treating consent forms as contracts, that is the current state of the law. To ignore this reality not only exposes academic medical centers to potential liability but also compromises their ability to understand and fulfill their ethical obligations to subjects.

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1. Armstrong D. Financial ties to industry cloud major depression study. *Wall Street Journal*. July 11, 2006:A1.
2. Medical journal says it was again misled. *New York Times*. July 13, 2006:A19.
3. Washburn J. Rent-a-researcher: did a British university sell out to Procter & Gamble? *New York: Slate*, December 22, 2005. (Accessed June 7, 2007, at <http://www.slate.com/id/2133061/>.)
4. DeAngelis CD. The influence of money on medical science. *JAMA* 2006;296:996-8.
5. Mello MM, Clarridge BR, Studdert DM. Academic medical centers' standards for clinical-trial agreements with industry. *N Engl J Med* 2005;352:2202-10.
6. *Idem*. Researchers' views of the acceptability of restrictive provisions in clinical trial agreements with industry sponsors. *Account Res* 2005;12:163-91.
7. Steinbrook R. Gag clauses in clinical-trial agreements. *N Engl J Med* 2005;352:2160-2.
8. 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.
9. *Grimes v. Kennedy Krieger Institute, Inc.*, 782 A.2d 807 (Md. 2001).
10. Morreim EH. Litigation in clinical research: malpractice doctrines versus research realities. *J Law Med Ethics* 2004;32:474-84.
11. Mello MM, Studdert DM, Brennan TA. The rise of litigation in human subjects research. *Ann Intern Med* 2003;139:40-5.
12. *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006).
13. GDNF poses troubling questions for doctors, drug maker: toxicity, negative outcome raise doubts. *Ann Neurol* 2006;59:A5-A6.
14. Lang AE, Gill S, Patel NK, et al. Randomized controlled trial of intraputamenal glial cell line-derived neurotrophic factor infusion in Parkinson disease. *Ann Neurol* 2006;59:459-66. [Erratum, *Ann Neurol* 2006;60:747.]
15. *Suthers v. Amgen, Inc.*, 372 F. Supp. 2d 416 (S.D.N.Y. 2005).
16. *Abney v. Amgen, Inc.*, 2005 U.S. Dist. LEXIS 14258 (E.D. Ky. 2005).
17. *Layne v. Bank One*, 395 F.3d 271 (6th Cir. 2005).
18. Coleman CH. Duties to subjects in clinical research. *Vanderbilt Law Rev* 2005;58:387-449.
19. *Darke v. Estate of Isner*, 20 Mass. L. Rep. 419 (Mass. Super. Ct. 2005).
20. Complaint, *Hamlet v. Genentech, Inc.*, No. 03 CVS 1161 (N.C. Super. Ct. 2004).
21. Resnik DB. Liability for institutional review boards: from regulation to litigation. *J Leg Med* 2004;25:131-84.
22. *Greenberg v. Miami Children's Hospital Research Institute, Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003).
23. *Moore v. Regents of University of California*, 793 P.2d 479 (Cal. 1990), *cert. denied*, 499 U.S. 936 (1991).
24. *In re Cincinnati Radiation Litigation*, 874 F. Supp. 796 (S.D. Ohio 1995).
25. *Kernke v. Menninger Clinic, Inc.*, 172 F. Supp. 2d 1347 (D. Kan. 2001).
26. *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993), *aff'd*, 76 F. 3d 385 (9th Cir. 1996).
27. *Washington University v. Catalonia*, 437 F. Supp. 2nd 985 (E.D. Mo. 2006).
28. *Harden v. University of Cincinnati Med. Ctr.*, 2004 WL 2341713 (Ohio App. 10 Dist. 2004).
29. *Saver RS*. Medical research and intangible harm. *Univ Cinci Law Rev* 2006;74:941-1012.

30. Morreim EH. Medical research litigation and malpractice tort doctrines: courts on a learning curve. *Houst J Health Law Policy* 2003;4:1-86.
31. *Idem*. The clinical investigator as fiduciary: discarding a misguided idea. *J Law Med Ethics* 2005;33:586-98.
32. Miller FG, Brody H. A critique of clinical equipoise: therapeutic misconception in the ethics of clinical trials. *Hastings Cent Rep* 2003;33(3):19-28.
33. *Meinhard v. Salmon*, 164 N.E. 545 (N.Y. 1928).
34. World Medical Association. Declaration of Helsinki, 5th revision. 2000. (Accessed June 7, 2007, at <http://www.wma.net/e/policy/b3.htm>.)
35. Wanerman RE. It ain't over till it's over: rights and obligations when a clinical trial ends. *Medical Research Law & Policy Report*. Vol. 5. 2006:439. (Washington, DC: Bureau of National Affairs.)
36. DuVal G. Institutional ethics review of clinical study agreements. *J Med Ethics* 2004;30:30-4.
37. Gunsalus CK, Bruner EM, Burbules NC, et al. Mission creep in the IRB world. *Science* 2006;312:1441.

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