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# AT THE END OF THE CLINICAL TRIAL: DOES ACCESS TO INVESTIGATIONAL TECHNOLOGY END AS WELL?

RICHARD S. SAVER\*

*Medical research subjects increasingly are demanding (and litigating about) continued access to investigational technology after the clinical trial has concluded. This Article undertakes a critical review of the legal, ethical, and policy issues that arise in post-trial access disputes. The regulatory and reimbursement objectives of many key stakeholders affected by the clinical trial testing process—research subjects, drug companies, device manufacturers, investigators, payers, and regulatory agencies—are not always aligned, leading to difficult tensions. Post-trial access disputes deserve greater regulatory and scholarly attention, and remain quite difficult to resolve, precisely because these distinct stakeholder perspectives become particularly salient and the differences pragmatically all the more important at the end of the clinical trial. A study's conclusion is a critical juncture and can become a flashpoint for general conflict. At the end of a study, many of the stakeholders have already invested and committed significant resources (both personal and financial) to the clinical trial, yet now may find their expectations for what should happen next abruptly frustrated or overridden by other interests. This Article considers the primary legal and ethical arguments, as well as policy considerations, for offering subjects greater post-trial access to investigational technology and also explores important reasons for rejecting such access demands. An incremental reform approach is recommended, one that moves beyond the status quo—where subjects have generally weak rights to post-trial access—yet avoids the dangers and possible counterproductive effects of unbounded post-trial access. Two preliminary suggestions are offered to help move in this direction: (1) requiring more detailed regulatory review of plans and budgets for post-trial access before clinical trial protocols are approved; and (2) providing subjects, in certain situations,*

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*other benefits as an alternative to continued access to the study technology.*

## INTRODUCTION

Investigational medical technology presents difficult questions for health law and policy regarding access. Patients and health care providers often want to use experimental drugs, new medical devices, and other investigational technology before these products have completed testing in clinical trials and received final regulatory approvals for regular clinical care.<sup>1</sup> Indeed, when conventional treatments are not working, critically ill patients may perceive investigational technology as their only hope. Expanded access respects patient and provider autonomy, responds to individual health needs, and diffuses medical advances more rapidly to clinical practice. Yet these objectives often run up against equally important regulatory and population health considerations favoring restricted access. Risks to the population are minimized by ensuring that investigational technology undergoes sufficient safety and efficacy testing, usually through formal clinical trials, before the technology is approved for marketing and public distribution. In addition, unrestricted utilization of still unproven and possibly cost-ineffective technology adds additional cost pressures to a health care financing system already straining under limited resources.

Until now, access disputes have typically concerned whether patients must participate in medical research in order to receive investigational technology. Consider the example of experimental drugs not yet approved for general commercial use by the Food and Drug Administration (FDA).<sup>2</sup> Under FDA law, pharmaceutical companies generally cannot supply experimental drugs unless in connection with clinical trials that are testing the medication and gathering data for the FDA-approval process.<sup>3</sup> Litigation efforts by patients to demand non-approved technology outside of a clinical trial have generally met with limited success, dating from the

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1. See, e.g., Judy Foreman, *For Some, Untested Drug Is a Last Chance*, BOSTON GLOBE, Sept. 23, 2003, at C3.

2. Experimental medical devices and other investigational technology are subject to different regulatory approval procedures and usage rules than experimental drugs. This discussion uses experimental drugs as an example of the more general pattern of restricting access to investigational technology outside of a clinical trial.

3. See 21 C.F.R. § 312.7(b) (2008); see also *id.* § 312.34 (describing limited opportunities for “treatment use” of investigational new drugs even when outside of clinical trial participation).

Laetrile battles of earlier decades to the more recent *Abigail Alliance* litigation concerning access to experimental cancer drugs.<sup>4</sup>

The other typical access battle involves reimbursement. Even after investigational medical technology has obtained full regulatory approval for commercial use and health care providers can legally prescribe it in ordinary clinical practice, patients may not have health care coverage for it. Private health care payers typically exclude coverage in their insurance contracts for experimental or medically unnecessary services; an exclusion that can be applied to all sorts of investigational and newly approved technology.<sup>5</sup> Payment rules under governmental health care programs such as Medicare and Medicaid similarly restrict reimbursement for investigational technology.<sup>6</sup> A great deal of litigation has involved patients challenging such coverage exclusions.<sup>7</sup>

This Article concerns a different type of access dispute that has not received equivalent attention to date, yet is emerging as a continuing problem, especially as the amount of experimentation with human subjects steadily increases: what should happen at the end of a clinical trial? Medical research subjects increasingly are demanding (and litigating about) continued access to investigational technology after the clinical trial has concluded.<sup>8</sup> Unfortunately, there

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4. See *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), *cert. denied*, 128 S. Ct. 1069 (2008) (Eribitux); *United States v. Rutherford*, 442 U.S. 544 (1979) (Laetrile).

5. See Richard S. Saver, *Reimbursing New Technologies: Why Are the Courts Judging Experimental Medicine?*, 44 STAN. L. REV. 1095, 1098 (1992); see also *Rollo v. Blue Cross/Blue Shield of N.J.*, No. 90-597, 1990 WL 312647 (D.N.J. Mar. 22, 1990) (involving a claim against a health insurance plan for an exclusion of experimental medicine).

6. See 42 U.S.C. § 1395y(a)(1)(A)-(B) (2000).

7. See, e.g., *Rollo*, 1990 WL 312647. See generally Mark A. Hall & Gerard F. Anderson, *Health Insurers' Assessment of Medical Necessity*, 140 U. PA. L. REV. 1637 (1992); Saver, *supra* note 5.

8. A related form of access dispute, beyond the scope of this Article, concerns subjects seeking access to investigational technology during the trial, as opposed to at the end. During the trial not all participating subjects enjoy access to the investigational technology. In randomized studies, comparing "control" standard treatment groups against groups receiving the investigational technology, some subjects will be assigned the standard treatment even when they wanted access to the investigational technology. This also can lead to access conflict. For example, in *Stewart v. Cleveland Clinic Foundation*, 736 N.E.2d 491 (Ohio Ct. App. 1999), the plaintiff was assigned to the standard treatment arm of a cancer study and received radiation and surgery but no preoperative chemotherapy (the investigational intervention). The plaintiff sued, raising various informed consent claims including that he had not been told about the possibility of receiving the investigational intervention outside of the clinic trial. An Ohio appellate court ruled that the plaintiff's informed consent claim was sufficient to survive summary judgment, but there was no ruling on the merits, and the case eventually set-

does not appear to be a firm consensus regarding how best to respond to such access demands. Many difficult questions arise for health law and policy: Do the subjects who participated in the research have any valid claims, legally or ethically, for continued access to the study technology? Should they have priority access over others? Should sponsors and investigators have discretion to inform subjects during the consent process that the trial may be terminated at any time and, if so, that there will be no opportunity for continued access to the investigational technology? If there are obligations to provide subjects with continued access, are they borne equally by the clinical investigators, trial sponsors, and medical centers where the research is conducted? And does ensuring access mean only providing subjects an opportunity to continue receiving the technology or also paying for it?

In some respects, post-trial access disputes are merely new variations on the more traditional problem of patients demanding access to investigational technology without participating in a clinical trial at all. Both types of disputes—post-trial and sans-trial—implicate many common themes: tensions between patient and provider freedom of choice versus the governmental public health interest in controlled access and systematic testing; difficulties health care payers encounter in deciding whether and when to reimburse new health care technology of uncertain efficacy, safety, and cost-effectiveness; and the often unclear distinctions between truly experimental medicine, innovative therapy, and ordinary clinical care.

Yet, as this Article explores, post-trial access disputes arise in a special context, one that provides provocative new perspectives on the access conundrum. To start, the legal status and reasonable expectations of a clinical trial subject who has already participated in medical research seem very different from the status and expectations of the ordinary patient. Also, consistent with the general theme of this symposium—regulation and reimbursement of health care technology—post-trial access disputes have important, perhaps somewhat unappreciated, implications regarding oversight and financing of health care technology.

The clinical trial serves as the primary gateway for new medical technology to diffuse into general clinical practice.<sup>9</sup> Successful

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tled. *See id.* at 501-02; *see also* Jerry Menikoff, *The Hidden Alternative: Getting Investigational Treatments Off-Study*, 361 LANCET 63, 64, 66 (2003).

9. *See* Phases of an Investigation, 21 C.F.R. § 312.21 (2008).

completion of clinical trial testing is usually required for investigational technology to obtain full regulatory approval.<sup>10</sup> Accordingly, the clinical trial becomes a critical step as a matter of regulation and reimbursement. From a regulatory perspective, required clinical trial testing serves a risk management function, ensuring that potentially dangerous new technology is monitored and adverse exposure is limited until better consensus about the technology emerges.<sup>11</sup> From a reimbursement perspective, clinical trial testing generates preliminary efficacy and (sometimes) cost-effectiveness data, assessment information that is quite important to governmental and private payers deciding whether, and under which conditions, to offer coverage for a new medical technology.<sup>12</sup> However, the regulatory and reimbursement objectives of the many key stakeholders affected by the clinical trial testing process—research subjects, drug companies, device manufacturers, investigators, payers, and regulatory agencies—are not always aligned, leading to difficult tensions.

Post-trial access disputes are quite difficult to resolve because these distinct stakeholder perspectives become particularly salient, and the differences more important, at the end of the clinical trial. A study's conclusion is a critical juncture and can become a flashpoint for general conflict and for inconsistent regulatory and reimbursement agendas to surface. By the end of a study many of the stakeholders have already invested and committed significant resources—both personal and financial—to the clinical trial, yet may find their expectations for what should happen next abruptly frustrated or overridden by other interests.

For example, after the research study ends, subjects may highly value continued access to an investigational technology, even if it seemingly offers only marginal therapeutic improvement.<sup>13</sup> Subjects who have risked harm or experienced other research-related burdens for the good of the clinical trial will likely feel entitled to recoup any possible treatment benefit suggested by the study. But an investigator may have less regard for subjects' post-trial access needs and place more value on ensuring that the trial continues to a

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10. *See id.*

11. *See* Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach, 495 F.3d 695, 705-06 (D.C. Cir. 2007) (en banc) (“Current law bars public access to drugs undergoing clinical testing on safety grounds.”), *cert denied*, 128 S. Ct. 1069 (2008).

12. *See* 21 C.F.R. § 312.21.

13. *See, e.g.,* Michael D. Lemonick & Andrew Goldstein, *At Your Own Risk*, *TIME*, Apr. 22, 2002, at 46 (noting that when one clinical trial was terminated for safety reasons, twelve participants fought to be allowed to continue the trial).

valid statistical stopping point, or even that altogether new trials are conducted with different subjects to resolve the research issue presented to a reasonable degree of scientific acceptability. A pharmaceutical company sponsoring the clinical trial may also have less regard for subjects' post-trial access needs and conclude, for business reasons, such as likely unfavorable reimbursement from health care payers, that the new technology is no longer worth developing, even if it showed some benefit in the medical study. The FDA, meanwhile, may focus its regulatory review on whether the trial data justifies approving the technology for commercial use with clinical patients generally, as opposed to concern for what happens to individual subjects once a particular trial shuts down.

Despite the important and often conflicting interests implicated, post-trial access disputes have generally received insufficient regulatory and scholarly attention. Part of this is because, as noted, the more frequent access battles have typically occurred with patients (as opposed to already enrolled research subjects). Also, long-standing concerns about protecting research subjects from physical harm, deception, and exploitation have meant that law and ethics pay a great deal of attention to the beginning stages of a clinical trial,<sup>14</sup> including what goes on in subject recruitment, what needs to be disclosed during the informed consent process, how study risks and benefits are evaluated, and how protocols get initially approved. What happens once the trial is over has simply been much farther off the radar screen. Moreover, to the extent that post-trial access disputes have attracted attention, much of the focus has been on international research, including HIV and hepatitis studies. In these clinical trials, concerns have been raised about possible exploitation of subjects in developing countries because the subjects do not have access to the study technology, or affordable health care more generally, once their study participation ends.<sup>15</sup> While these subjects will rarely enjoy the benefits of post-

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14. See generally Carl H. Coleman, *Duties to Subjects in Clinical Research*, 58 VAND. L. REV. 387 (2005); Richard Delgado & Helen Leskovic, *Informed Consent in Human Experimentation: Bridging the Gap Between Ethical Thought and Current Practice*, 34 UCLA L. REV. 67 (1986); Robert Gatter, *Walking the Talk of Trust in Human Subjects Research: The Challenge of Regulating Financial Conflicts of Interest*, 52 EMORY L.J. 327 (2003).

15. See, e.g., Christine Grady, *The Challenge of Assuring Continued Post-Trial Access to Beneficial Treatment*, 5 YALE J. HEALTH POL'Y L. & ETHICS 425, 431-32 (2005) (explaining that an HIV prevention study that would have involved almost 1000 Cambodian sex workers fell through because of demands to provide the participants health care following the conclusion of the research); see also *The Participants in the*

trial access, the technology, once testing is completed, will be made commercially available to benefit patients in richer countries.<sup>16</sup> Yet the basic problem of access after research participation ends is not limited to international studies. Domestic research subjects also may face quite limited access opportunities post-trial.

In an attempt to address the neglect of post-trial access disputes, this Article undertakes a critical review of the key legal, ethical, and policy issues that arise. The Article purposefully avoids making definitive conclusions about whether and when to accommodate subjects' demands for expanded post-trial access. Instead, it aims to provide a more complete, balanced, and nuanced framework for thinking about post-trial access claims, and to highlight the difficult questions that will likely emerge for health law and policy.

Part I briefly explains what drives research subjects' access demands, discusses representative post-trial access disputes, and explains how investigators and sponsors have considerable discretion to limit subjects' post-trial access to investigational technology. Part II reviews how current law and ethics guidance is sufficiently "grey," often offering unclear direction regarding what obligations are owed to subjects at the end of the study. Part III analyzes, at a more theoretical level, the primary legal and ethical arguments, as well as policy considerations, for offering subjects greater post-trial access to investigational technology. This section also considers important reasons for rejecting such access demands. Part IV advocates moving beyond the status quo—where subjects generally have weak rights to post-trial access—yet suggests an incremental reform approach that is sensitive to the dangers and possible counterproductive effects of unbounded post-trial access. It offers two preliminary suggestions to help move in this direction: (1) more required regulatory review of plans and budgets for post-trial access before clinical trial protocols are approved; and (2) providing subjects, in certain situations, other benefits as an alternative to continued access to the study technology.

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2001 Conference on Ethical Aspects of Research in Developing Countries, *Moral Standards for Research in Developing Countries: From "Reasonable Availability" to "Fair Benefits"*, HASTINGS CENTER REP., May-June 2004, at 17 [hereinafter *Moral Standards for Research in Developing Countries*].

16. See, e.g., Peter Lurie & Sidney M. Wolfe, *Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries*, 337 NEW ENG. J. MED. 853 (1997) (discussing HIV trials); *Moral Standards for Research in Developing Countries*, *supra* note 1515, at 24-26 (discussing clinical trials of Havrix, a hepatitis A vaccine, in northern Thailand).



## I. POST-TRIAL ACCESS—WHAT DRIVES THESE DISPUTES AND REPRESENTATIVE CASES

### A. *Access Demands and Expectations of Research Subjects*

Research subjects certainly deserve praise and respect for volunteering for experiments that contribute to the progress of medical knowledge and likely help future patients more than themselves. But the altruistic aspect of research participation should not be overstated. Subjects volunteer for trials for a variety of complex reasons. Apart from altruism, subjects may enroll in clinical trials because of a sense of hopelessness, general optimism about new technology and medical innovation, or a seeming need to take action rather than face their illness more passively through only comfort care and monitoring.<sup>17</sup> Quite clearly, some degree of self-interest may be involved as well. Participation in medical research enables subjects to enjoy access to investigational technology perceived as cutting-edge, the best available, or the last shot at improving their health.

Access concerns of subjects may be acute because of the limited opportunities patients have to receive investigational technology outside of clinical trials. Consider, again, the example of experimental medication. FDA rules allow investigational new drugs to be prescribed, in applicable situations, for treatment purposes (so-called “treatment INDs”).<sup>18</sup> FDA procedures also allow for accelerated approval of certain drugs and biological products used to treat serious or life-threatening illnesses.<sup>19</sup> Nonetheless, ac-

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17. See Nancy E. Kass & Jeremy Sugarman, *Trust: The Fragile Foundation of Contemporary Biomedical Research*, 26 HASTINGS CENTER REP., SEPT.-OCT. 1996, AT 25; David T. Stern, *Future Challenges From the U.S. Perspective: Trust as the Key To Clinical Research*, 15 J. CLINICAL ETHICS 87, 88-89 (2004).

18. See Treatment Use of an Investigational New Drug, 21 C.F.R. § 312.34(b) (2008). The regulations generally allow treatment use of an investigational new drug if: (1) the medication will be used to treat a “serious or immediately life-threatening disease”; (2) “no comparable or satisfactory alternative drug or other therapy” is available; (3) the drug is being tested in a controlled clinical trial or all trials have concluded; and (4) the sponsor “is actively pursuing marketing approval” for the drug (i.e., the sponsor is taking the necessary regulatory steps in order to offer the drug on the market for regular clinical care). *Id.*

19. See 21 C.F.R. §§ 314.500-.510, 601.40-41 (allowing for fast-track approval of drugs and biological products providing meaningful therapeutic benefit compared to existing treatments); see also Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration’s Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503 (1995).

cess through these channels remains quite narrow.<sup>20</sup> In the recent *Abigail Alliance* litigation, plaintiffs challenged FDA rules that generally prevent access to Phase I drugs<sup>21</sup> if the patient is not participating in or eligible for a clinical trial.<sup>22</sup> The eventual en banc decision of the United States Court of Appeals for the District of Columbia Circuit held that the FDA's restricted access rules did not violate constitutionally protected liberty interests of terminally ill patients.<sup>23</sup> Although the FDA won the case, the agency has been developing its own proposal to expand access to unapproved drugs.<sup>24</sup> Yet, even under the new agency approach, access to investigational drugs for patients not participating in clinical trials will likely remain limited.<sup>25</sup>

Reimbursement issues further influence access demands of research subjects. In a clinical trial, the study technology is typically paid for by the trial sponsor.<sup>26</sup> Also, subjects in clinical trials are

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20. The FDA rarely allows treatment INDs and when allowed, this access is typically only for drugs undergoing later stages of clinical trial testing (Phase III trials or after). See Meghan K. Talbott, *The Implications of Expanding Access to Unapproved Drugs*, 35 J.L. MED. & ETHICS 316 (2007). For an explanation of the differing phases of clinical trial testing, see note 2121 *infra*. Even for drugs involving immediately life-threatening diseases, the FDA has generally restricted INDs to drugs that have already completed Phase I testing. See 21 C.F.R. § 312.34(a).

21. Investigational new drugs typically undergo different phases of clinical trial testing. Phase I studies establish levels of tolerance to determine safe dosage levels. The typical Phase I study involves a small group of subjects (in the range of twenty to eighty) compared to later phase trials. If deemed nontoxic, a drug passes into Phase II, where it is tested to demonstrate efficacy and relative safety. Phase III studies involve expanded controlled and uncontrolled clinical trials and further, more comprehensive evaluations of efficacy and safety. See 21 C.F.R. § 312.21.

22. See *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc), *cert. denied*, 128 S. Ct. 1069 (2008).

23. *Id.* at 713.

24. Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147 (Food & Drug Admin. Dec. 14, 2006) (to be codified at 21 C.F.R. pt. 312).

25. For example, under the FDA's new proposal, expanded access outside of a clinical trial is available only after the FDA determines that there is no comparable or satisfactory alternative therapy. Also, the FDA must determine that expanded access outside of a clinical trial does not impede the ability to enroll subjects in research studies needed to further evaluate the technology for efficacy and safety. See *id.* at 75,150-151. Further, it is not clear whether sponsors will have strong enough incentives to offer their experimental drugs outside of clinical trials given the potential costs involved and the complications that expanded access can create regarding sponsors' ability to conduct further clinical trial testing. See, e.g., Judy Vale, Note, *Expanding Expanded Access: How the Food and Drug Administration Can Achieve Better Access to Experimental Drugs For Severely Ill Patients*, 96 GEO. L.J. 2143, 2160 (2008).

26. See Gina Kolata & Kurt Eichenwald, *For the Uninsured, Drug Trials Are Health Care*, N.Y. TIMES, June 22, 1999, at A1 (explaining that drug trials are particularly attractive to the uninsured because of the chance to obtain free treatment).

monitored for the accrual of study data and so enjoy more regular contact with health care providers and more opportunities for ancillary health care that the sponsor may also pay for.<sup>27</sup> Thus, patients lacking good (or any) health insurance may look to continued clinical trial participation as a way to obtain coverage for basic health care services, let alone investigational technology.<sup>28</sup>

In addition, powerful advocacy groups, including organizations for persons with HIV/AIDS and breast cancer, have influenced public perceptions about medical research, likely fueling research subjects' access demands. These groups have lobbied vigorously for increased research opportunities and for loosening the perceived rigidity on clinical trial eligibility.<sup>29</sup> Unfortunately, these groups may also be conveying unrealistic expectations of benefits from investigational technology, while glossing over the inherent risks of using experimental interventions.<sup>30</sup>

## B. *Recent Representative Disputes*

In recent litigation, subjects' post-trial access claims have met with very limited success. It appears that investigators, and particularly trial sponsors, enjoy considerable discretion in offering subjects access to the investigational technology after the research is over.

### 1. *The Amgen Cases*

The recent litigation involving the pharmaceutical company Amgen demonstrates this pattern.<sup>31</sup> Amgen sponsored multicenter studies of an investigational drug for treating Parkinson's Disease.

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27. See generally Roger Brownsword, *The Ancillary-Care Responsibilities of Researchers: Reasonable But Not Great Expectations*, 35 J.L. MED. & ETHICS 679 (2007).

28. See Kolata & Eichenwald, *supra* note 2626; see also Grady, *supra* note 1515, at 435 ("If patients everywhere had better access to needed treatments, continued access to treatment at the end of a trial would be primarily a temporary issue. Research is only one way of contributing to improved access to health care.").

29. See generally REBECCA DRESSER, *WHEN SCIENCE OFFERS SALVATION: PATIENT ADVOCACY AND RESEARCH ETHICS* (2001).

30. See *id.* at 58-60 ("Advocacy literature often refers to investigational agents and procedures as 'new treatments' and calls studies on terminal conditions 'life saving research.' The possibility that research interventions might prove ineffective or more risky than standard therapy is seldom broached. Instead, advocates equate clinical trials and medical treatment.").

31. See *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006); *Suthers v. Amgen, Inc. (Suthers II)*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006) (ruling on motion to dismiss plaintiffs' claims); *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416 (S.D.N.Y. 2005) (preliminary injunction ruling).

The study medication, a synthetic protein called glial cell line-derived neurotrophic factor (GDNF), was tested in a series of Phase I and Phase II studies, beginning in 2000-2001, at different medical centers around the country. Amgen had strong hopes for commercializing GDNF after having acquired the biotechnology company that initially developed it in a multimillion dollar acquisition. But the initial trial results proved disappointing. Some subjects showed improvement in mobility, but not by large enough degrees to be statistically significant. Meanwhile, safety concerns emerged. Monitoring revealed that some subjects had developed neutralizing antibodies that could attack naturally occurring GDNF in their bodies and could make their conditions worse. Also, brain lesions and related potential neurotoxic responses were found in primates undergoing animal studies of GDNF. In 2004, Amgen announced that it would end all clinical trials of GDNF. Amgen based this decision on safety concerns combined with an apparent lack of efficacy shown in the trial results. The FDA stated that it would allow Amgen to continue to provide the drug post-trial to certain subjects under its limited “compassionate use” program.<sup>32</sup> But the agency also said the decision to do so was up to Amgen, and Amgen declined.

Some subjects were fiercely convinced that the study drug worked and wanted to continue taking it notwithstanding the new safety concerns.<sup>33</sup> Individuals enrolled in multicenter studies at New York University Medical Center and the University of Kentucky Medical Center brought separate federal lawsuits against the pharmaceutical company, seeking to compel Amgen to continue providing them access to GDNF.<sup>34</sup> Each lawsuit asserted nearly identical legal claims: breach of contract, promissory estoppel, and breach of fiduciary duty. Both the Southern District Court of New York (*Suthers v. Amgen, Inc.*)<sup>35</sup> and the Court of Appeals for the Sixth Circuit (*Abney v. Amgen, Inc.*)<sup>36</sup> ruled against the subjects.

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32. *Suthers I*, 372 F. Supp. 2d at 423. Under “compassionate use” programs, the FDA gives special approval for a drug not approved for any use to be administered to a limited number of patients with serious and life-threatening illnesses. *See id.* at 423 n.6; Benjamin R. Rossen, *FDA’s Proposed Regulations to Expand Access to Investigational Drugs for Treatment Use: The Status Quo in the Guise of Reform*, 64 *FOOD & DRUG L.J.* 183, 194 (2009).

33. *Abney*, 443 F.3d at 544-45; *Suthers I*, 372 F. Supp. 2d at 422.

34. *Abney*, 443 F.3d at 545; *Suthers I*, 372 F. Supp. 2d at 419.

35. *Suthers I*, 372 F. Supp. 2d at 430.

36. *Abney*, 443 F.3d at 553.

Both of the *Amgen* courts followed very similar reasoning in finding that the subjects had properly been denied post-trial access. Several plaintiffs argued that they had been promised in the informed consent documents that they could elect to continue with GDNF for another twenty-four months at the study's conclusion.<sup>37</sup> Several plaintiffs further contended that an investigator had made representations that if the treatment was at all successful, Amgen would keep them on the drug for an indefinite period.<sup>38</sup> Yet both courts rejected the breach of contract claims, finding that Amgen did not enter into any contract with the subjects.<sup>39</sup> The courts reasoned that the informed consent document was between the universities/investigators and the subjects, while the contract for conducting the research (a distinct Clinical Trial Agreement) was entered into between the universities/investigators and Amgen.<sup>40</sup> In this complex web of contractual relationships, there were, importantly, no direct agreements between Amgen and the subjects, and so the subjects' breach of contract claims against Amgen failed.<sup>41</sup>

Similarly, the courts held that any promissory estoppel claims could not succeed against Amgen.<sup>42</sup> The courts found that Amgen made no direct promises to the subjects. All enrollment discussions were between the investigators and the subjects and did not include Amgen. The courts further indicated that even if a contract or enforceable promise had been formed between Amgen and the subjects, the informed consent documents and Clinical Trial Agreements did not make an unconditional promise to provide the study drug *ad infinitum*.<sup>43</sup> Instead, these documents informed subjects that the study could be terminated at any time by notice from Amgen and that the study could be terminated for scientific reasons, such as the safety and efficacy issues asserted by Amgen.<sup>44</sup>

Both courts likewise rejected the claims that Amgen had a fiduciary duty to provide a potentially beneficial study drug to the

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37. *Id.* at 544.

38. *See Suthers I*, 372 F. Supp. 2d at 424-25.

39. *Abney*, 443 F.3d at 548-49; *Suthers I*, 372 F. Supp. 2d at 425-26.

40. *See Abney*, 443 F.3d at 547; *Suthers I*, 372 F. Supp. 2d at 424.

41. *Abney*, 443 F.3d at 547-49; *Suthers I*, 372 F. Supp. 2d at 424-26; *see also* *Vinion v. Amgen, Inc.* 272 Fed. Appx. 582 (9th Cir. 2008) (affirming dismissal of breach of contract claim and various agency claims against Amgen for failing to provide the study drug following termination of the clinical trial).

42. *Abney*, 443 F.3d at 550; *Suthers I*, 372 F. Supp. 2d at 426.

43. *Abney*, 443 F.3d at 547 n.5; *Suthers I*, 372 F. Supp. 2d at 424.

44. *Abney*, 443 F.3d at 547 n.5; *Suthers I*, 372 F. Supp. 2d at 424.

subjects.<sup>45</sup> The courts found no special duties arising between Amgen and the trial subjects. The courts reasoned that the trial sponsor stood in an indirect position too far removed from the subjects to have formed a fiduciary relationship with them.<sup>46</sup>

The *Amgen* cases illustrate the difficulties that subjects have in asserting cognizable legal claims, especially against trial sponsors, for post-trial access. It remains unclear whether the subjects' claims failed primarily because Amgen had serious safety and efficacy reasons for denying continued access. Some of the principal investigators at different research sites vigorously disagreed with Amgen's conclusions and wanted to continue the trial or implement some form of compassionate use for enrolled subjects.<sup>47</sup> It is also not clear to what extent the safety and efficacy issues raised by Amgen were a pretext for the sponsor's more bottom-line financial reasons for terminating the study. The plaintiffs claimed that Amgen simply decided to terminate the trials because GDNF was not likely to turn a profit.<sup>48</sup> The plaintiffs contended that Amgen might have been concerned about diminishing revenue margins because its patent on the drug was soon to expire, only a limited number of patients would likely use the drug because of the invasive means used to deliver it, and the drug had a short shelf life.<sup>49</sup> Nonetheless, Amgen vigorously denied that it had decided to end the studies primarily due to financial reasons.<sup>50</sup> However, as a doctrinal matter, given the courts' views that the trial sponsor had no clear contractual obligations or fiduciary duties to the subjects, it is highly debatable what constraints the courts would have been willing to impose, if any, on Amgen's ability to terminate the study and block continued access abruptly, even if the trial sponsor lacked valid safety and efficacy reasons.

## 2. Other Representative Disputes

Clinical trial testing often yields data that is neither clearly positive nor clearly negative. Instead, the results suggest that the investigational technology offers limited efficacy, marginal improvement, or, at best, performs no worse than existing treatments. Such ambiguous data can be interpreted very differently by

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45. *Abney*, 443 F.3d at 550; *Suthers I*, 372 F. Supp. 2d at 429.

46. *See Abney*, 443 F.3d at 550-51; *Suthers I*, 372 F. Supp. 2d at 426-29 & n.9.

47. *See, e.g., Suthers I*, 372 F. Supp. 2d at 422.

48. *See Abney*, 443 F.3d at 545.

49. *Id.*

50. *Id.*

stakeholders with distinct agendas. Not surprisingly, trials involving ambiguous study results frequently lead to post-trial access conflicts. These tensions were evident in *Pollack v. Rosalind Franklin University*, litigation involving subjects who had participated in a longstanding breast cancer vaccine study at Rosalind Franklin University of Medicine and Science (Chicago Medical School).<sup>51</sup> The subjects alleged that the medical school improperly terminated the investigation.<sup>52</sup> Among other claims, they contended that the consent forms and oral representations made by the researchers indicated that the vaccine treatment would be continued *ad infinitum*. The study's initial principal investigator, Dr. Georg Springer, died in 1998 and left a bequest to Chicago Medical School, allegedly to help continue funding the study. However, in 2004, the University terminated the study after its Institutional Review Board (IRB) raised efficacy concerns that the data was too inconclusive to show if the vaccine worked.<sup>53</sup> The University IRB determined that it was not in the subjects' best interests to continue with such unproven therapy.<sup>54</sup>

Yet many subjects, enrolled in the trial for years, felt the vaccine had clearly benefited them and firmly wanted to continue with it.<sup>55</sup> The plaintiffs included women with stage three breast cancer whose advanced disease stages likely precluded them from many other clinical trial opportunities and for whom standard treatments offered little promise.<sup>56</sup> The lawsuit alleged breach of fiduciary duty, breach of contract, unjust enrichment, common law fraud, and negligence, among other counts.<sup>57</sup>

The University eventually settled the case so there was no ruling on the merits.<sup>58</sup> Although the settlement terms were confiden-

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51. *Pollack v. Rosalind Franklin Univ.*, No. 04C5613, 2006 WL 3783418, at \*1 (N.D. Ill. Dec. 20, 2006).

52. Complaint, *Pollack v. Rosalind Franklin Univ.*, No. 04C5613, 2006 WL 3783418 (N.D. Ill. Dec. 20, 2006) (on file with the author).

53. See Natasha Korecki, *Women Go to Court for Breast Cancer Vaccine*, CHI. SUN-TIMES, Oct. 26, 2004, at 12.

54. See *id.*

55. See *id.* (explaining that despite doubts about the vaccine's effectiveness, at least one woman, Catherine Moloney, believed that she was alive today because of the vaccine). Indeed, the lack of clear efficacy data was a longstanding problem with the clinical trial. Specifically, the study's effectiveness was hard to establish because there were no control groups. See *id.*

56. See Complaint, *supra* note 52.

57. See *id.*

58. *Pollack v. Rosalind Franklin Univ.*, No. 04C5613, 2006 WL 3783418, at \*1 (N.D. Ill. Dec. 20, 2006).

tial, the University apparently agreed to fund a new vaccine program for the women at another institution.<sup>59</sup> However, the settlement provided the subjects incomplete relief, and the victory was somewhat empty in terms of vindicating their clear preferences for continued post-trial access.<sup>60</sup> The settlement only called for the University to help fund the study at another yet-to-be-named institution, with no guarantee that another institution would actually agree to take over a study involving a vaccine of already questionable efficacy.<sup>61</sup> Also it was not clear after the passage of time if a key ingredient for producing the vaccine was still readily available, making transition of the vaccine study to another institution all the more difficult.<sup>62</sup> The *Pollack* litigation reveals the difficult remedy problems subjects can encounter in enforcing claims to post-trial access.

Post-trial access disputes often result from poor planning by the trial sponsors and investigators about what will happen when the study concludes. For example, in a recent clinical trial of an experimental vaccine to treat shingles, the study results demonstrated that subjects who received the study vaccine were far less likely to develop shingles or long-lasting pain from the condition than subjects who received a placebo.<sup>63</sup> Despite such strong evidence that the investigational technology worked, Merck, the drug company sponsoring the trial, was unable to switch the placebo subjects over to the experimental vaccine when the trial concluded.<sup>64</sup> The drug maker did not have enough vaccine available for all subjects once the trial ended.<sup>65</sup> Indeed, it was unclear whether the placebo subjects would ever have access before Merck received full FDA approval for the vaccine.<sup>66</sup> This frustrated access occurred

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59. See Nataska Korecki, *Breast Cancer Vaccines Return With Settlement*, CHI. SUN-TIMES, Oct. 30, 2004, at 6.

60. In 2006, a federal magistrate judge determined that the court did not have subject matter jurisdiction to enforce the settlement agreement and vacated an earlier order that acted to enforce a critical clause of the agreement. *Pollack*, 2006 WL 3783418, at \*8. One plaintiff told the press, “[w]e wanted our vaccine, that was our main thing.” Korecki, *supra* note 59.

61. See *Pollack v. Rosalind Franklin Univ.*, No. 04C5613, 2006 WL 2868921, at \*1 (N.D. Ill. Oct. 4, 2006), *vacated*, 2006 WL 3783418.

62. Kelly Field, *Medical School Settles Allegations of Fraud*, CHRON. OF HIGHER EDUC., Nov. 12, 2004, at A34.

63. Todd Ackerman, *Promising Drug Test, Unfulfilled Promise*, HOUS. CHRON., June 15, 2005, at A1.

64. See *id.*

65. *Id.*

66. *Id.*



even as the subjects alleged that they had been promised the vaccine at the end of the trial if it was proven effective.<sup>67</sup> Although Merck likely knew how many placebo subjects were participating and could have anticipated their post-trial access demands, the trial sponsor apparently did very little in the planning stages to address this.<sup>68</sup> Nor is it clear whether the IRBs that approved the shingle vaccine protocol sufficiently considered and discussed Merck's limited plans for post-trial access.<sup>69</sup>

## II. POST-TRIAL OBLIGATIONS UNDER CURRENT LAW AND ETHICS GUIDANCE

As the representative disputes indicate, investigators and trial sponsors enjoy considerable discretion in deciding when to terminate a clinical trial and whether to offer subjects any post-trial access to the investigational technology. Decisions about post-trial access seem largely driven by clinical research norms and industry practices. Current law and ethics guidance, unfortunately, offers little clear direction on these matters. In short, “[u]ntil recently, regulations and codes of research ethics have been silent about what should happen at the conclusion of a clinical study.”<sup>70</sup>

### A. *Current Law*

#### 1. Federal Research Regulations

The federal research regulations governing medical research say very little regarding when a trial may be terminated and the post-trial obligations to subjects that may arise. The regulations also do very little to address the many possible adverse consequences arising from terminating a study.<sup>71</sup> The informed consent provisions require that subjects be told about “the expected duration of the subject’s participation”<sup>72</sup> and reminded that they have the ability to “discontinue participation at any time.”<sup>73</sup> Also, sub-

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67. *Id.*

68. *See id.*

69. *See id.*

70. Grady, *supra* note 15, at 425.

71. *See* Jesse A. Goldner, *An Overview of Legal Controls on Human Experimentation and the Regulatory Implications of Taking Professor Katz Seriously*, 38 ST. LOUIS U. L.J. 63, 131-32 (1993) (discussing proposed amendments to the regulations that would clarify and remedy the current situation).

72. Elements of Informed Consent, 21 C.F.R. § 50.25(a)(1) (2008); General Requirements for Informed Consent, 45 C.F.R. § 46.116(a)(1) (2008).

73. 21 C.F.R. § 50.25(a)(8); 45 C.F.R. § 46.116(a)(8).

jects are to be informed of the “[a]nticipated circumstances under which the subject’s participation may be terminated by the investigator without regard to the subject’s consent,”<sup>74</sup> but such information is to be disclosed only “when appropriate.”<sup>75</sup>

In any event, the regulations do not expressly require disclosure to subjects of detailed information about the myriad reasons unrelated to safety, such as lack of financing or changed business prospects, that may lead to discontinuation of the study and a denial of post-trial access. Indeed, in *Suthers v. Amgen, Inc.*, some of the informed consent documents simply stated that a subject might be withdrawn from the clinical trial due to “termination or cancellation of the study by the sponsor.”<sup>76</sup> Although this terse statement placed no conditions or limitations on why the sponsor might be allowed to terminate the trial, and did not even make clear that a termination might still arise even if the technology was beneficial, the court implicitly found that the narrow disclosure was sufficient.<sup>77</sup> The court relied on this statement to find that subjects were adequately put on notice about the possibility of interrupted access to the study medication.<sup>78</sup>

Apart from informed consent, the federal research regulations also require that most applicable clinical trial protocols obtain the approval of an IRB before subjects can be enrolled in the study.<sup>79</sup> Yet the regulations do not discuss in any detail to what extent IRBs should consider post-trial access plans as part of their protocol review process or what IRBs should ask and require of sponsors and investigators regarding post-trial access.

Even if an IRB imposes post-trial access requirements as part of its conditions for protocol approval, the requirements would be difficult to monitor and enforce. IRBs may not even be able to gather sufficient information and data on what is happening to the subjects after the clinical trial is over to even become aware of a brewing post-trial access dispute.

More importantly, IRBs simply have little authority or clear jurisdiction to compel a sponsor or investigator to offer post-trial access, or even to require that a trial be continued to a reasonable

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74. 21 C.F.R. § 50.25(b)(2); 45 C.F.R. § 46.116(b)(2).

75. 21 C.F.R. § 50.25(b); 45 C.F.R. § 46.116(b).

76. *Suthers v. Amgen, Inc. (Suthers II)*, 441 F. Supp. 2d 478, 481, 484 (S.D.N.Y. 2006).

77. *Id.* at 485.

78. *Id.*

79. *See* 21 C.F.R. § 56.103; 45 C.F.R. § 46.109.

stopping point before the sponsor or investigator can terminate it. A sponsor or investigator can often unilaterally stop a trial simply with adequate notice to the IRB. The IRB's enforcement powers at that point are quite limited even if it becomes aware of problematic conduct by the sponsor in blocking post-trial access. The IRB cannot terminate or withhold approval for a trial that has already ended. It may only be able to deter sponsors indirectly by threatening not to approve their future protocols at the institutions.

## 2. Common Law Contract/Informed Consent

The traditional common law's general emphasis on individualism and self-reliance would suggest that subjects are free to decide whether to enroll in trials that offer limited or no post-trial access to investigational technology.<sup>80</sup> Absent clear promises or contractual obligations made to subjects about post-trial access, the common law is unlikely to require it.<sup>81</sup>

Yet proving the existence of express agreements or promises about post-trial access can become difficult for subjects. First, there is the question whether any binding contracts even exist in the medical research context. Although subjects sign written informed consent documents when enrolling in a study,<sup>82</sup> some courts have been reluctant to find binding contractual obligations in the research setting, treating the informed consent documents as merely notice of the subjects' consent rather than an enforceable contract.<sup>83</sup>

Even if viewed as contracts, the informed consent documents typically are carefully worded to avoid express commitments to post-trial access and yet to provide flexibility in allowing for when and why the trial may be terminated.<sup>84</sup> Some sponsors do offer to

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80. Cf. Brownsword, *supra* note 27, at 687 (contrasting the classic common law approach to contracts and torts, which focused on self-reliance and individualism, with current approaches, which focus on reliance on others).

81. See, e.g., *Vinion v. Amgen, Inc.*, 272 Fed. Appx. 582 (9th Cir. 2008) (affirming a dismissal of a subject's breach of contract and tort claims against Amgen for failing to provide the study drug following the termination of the clinical trial).

82. See 21 C.F.R. § 50.25; 45 C.F.R. § 46.116.

83. See, e.g., *Harden v. Univ. of Cincinnati Med. Ctr.*, No. 04AP-154, 2004 WL 2341713 (Ohio Ct. App. Oct. 19, 2004). In *Harden*, the court rejected a subject's breach of contract claim that the defendants had promised the subject medical care for life. *Id.* at \*6. The court reasoned that the informed consent document merely served as notice of the subject's consent to the investigational procedure. *Id.* at \*5. It was not a legally binding contract involving bargained-for promises with sufficient consideration. *Id.* at \*7-8.

84. See, e.g., *Abney v. Amgen, Inc.*, 443 F.3d 540, 547 n.6 (6th Cir. 2006) ("Even if the Informed Consent Document or the Clinical Trial Agreement created a contract

provide continued post-trial access for a limited time after the trial formally ends, but these developments are ad hoc rather than common practice.<sup>85</sup>

Further complicating matters, as demonstrated in the *Amgen* cases,<sup>86</sup> is the fact that even if the informed consent document makes express promises to subjects about post-trial access, the sponsor is typically not a signatory to this document. Thus, promises made in the informed consent document may not bind the sponsor. Yet the sponsor, not the investigator or medical center, usually controls access to the study technology, at least with privately funded studies involving an external sponsor. It is especially revealing that the United States Court of Appeals for the Sixth Circuit in *Abney v. Amgen, Inc.*, although unwilling to find liability against the defendant trial sponsor, nonetheless took the unusual step in its opinion of openly lamenting the poor state of informed consent about post-trial access.<sup>87</sup> The court called on parties not even involved in the litigation (and therefore not subject to the court's immediate jurisdiction) to work harder to ensure that subjects were better informed about what would happen at the end of a clinical trial:

Moreover, the litigation in this case indicates that the University, through its Informed Consent Document, and its other representations to the plaintiffs did a poor job informing the plaintiffs as to the grounds upon which the study would terminate and their access to GDNF would be denied. We urge the University's Institutional Review Board, and other review boards throughout the Circuit, to take additional measures to ensure that patients fully understand that even if they or their physicians believe an experimental treatment to be safe and efficacious there may be circumstances under which they will be denied continued access to treatment. If this fact had been properly explained to the plaintiffs in this case prior to the outset of the clinical trial (and

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between Amgen and the plaintiffs, Amgen would still have no duty to provide the plaintiffs with [the drug]. . . . [T]he Clinical Trial Agreement specifically allowed Amgen to terminate the agreement 'immediately upon written notice.'"); *supra* note 76 and accompanying text (discussing the Amgen informed consent document's phrasing on when the trial could be terminated).

85. See Grady, *supra* note 15, at 429-30.

86. See *Abney*, 443 F.3d 540; *Suthers v. Amgen, Inc. (Suthers II)*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006); *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416 (S.D.N.Y. 2005); see also discussion *supra* Part I.B.1.

87. *Abney*, 443 F.3d at 551 n.6.

spelled out clearly in the Informed Consent Document) perhaps the litigation in this case could have been avoided.<sup>88</sup>

The fact that the court took this extraordinary step of issuing an open call urging change throughout the circuit regarding how IRBs conduct their protocol reviews and what subjects are told reveals the current limited reach of the common law. However bothered the court may have been about Parkinson's Disease trial subjects' possible misunderstanding and detrimental reliance on a belief that they could continue with GDNF, the court was unable to find the informed consent problems actionable against Amgen, the actual defendant in the case.<sup>89</sup> Amgen was not a party to the Informed Consent Document and did not enroll the subjects, yet as the trial sponsor it controlled access to the technology.<sup>90</sup>

### 3. Unclear Legal Duties in the Investigator-Subject Relationship and Limited Duties Between Sponsors and Subjects

A further reason that the law provides unclear direction as to any post-trial access obligations owed to research subjects is because the more general duties of care that are owed to research subjects remain legally uncertain. The common law views many aspects of the physician-patient relationship as fiduciary in nature and often imposes heightened duties of care and loyalty on the physician.<sup>91</sup> But fiduciary principles may not apply to the investigator-

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88. *Id.*

89. *Id.* at 551.

90. It should be noted that despite the court's implied suggestion that the plaintiffs' real grievance was with the investigators and the University, not the sponsor Amgen, even an informed consent claim against these other parties would likely run into problems. Even if misleading statements about post-trial access were made, for a viable informed consent claim to succeed, plaintiffs would typically have to prove the additional elements of causation and damages. In other words, plaintiffs would have to show that any negligent information disclosure caused them tangible, physical harm. This proof can be especially hard for research subjects to satisfy. Often in a medical study the technology in question is investigational and its risks and benefits are still largely unknown, making it quite speculative and difficult to prove through litigation that deprived access to the investigational technology made subjects therapeutically worse off. *See generally* Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 963-65 (2006).

91. Even in regular doctor-patient relationships, courts have found physicians liable for breach of fiduciary duty in only limited scenarios, such as failure to secure informed consent or to maintain confidentiality. *See* Maxwell J. Mehlman, *Fiduciary Contracting: Limitations on Bargaining Between Patients and Health Care Providers*, 51 U. PITT. L. REV. 365, 401-14 (1990) (finding inconsistency in how courts apply fiduciary principles to different health care relationships); Marc A. Rodwin, *Strains in the Fidu-*

subject relationship. The classic fiduciary has undivided loyalty to and acts in the best interest of the principal.<sup>92</sup> But an investigator cannot have undivided loyalty to and always act in the best interest of the subject.<sup>93</sup> The protocol will demand that consistent study procedures be followed in order to yield generalizable data. This limits the ability of the investigator to provide individually tailored care and to act solely in the best interest of the subject.<sup>94</sup> Also, the principal aim of a study is to benefit future patients, not the immediate subject, through the knowledge gained. Because of the researcher's experimentation goals rather than clinical care focus, the principal-investigator relationship fits quite awkwardly into the fiduciary framework.<sup>95</sup>

On the other hand, some commentators urge imposing full fiduciary or fiduciary-like duties upon investigators.<sup>96</sup> The relationship between investigator and subject features power and informational asymmetries, the vulnerability and potential for exploitation by one party, conflicts of interest affecting the more powerful party, and significant trust, dependence, and expectations of confidence. These factors are typically found in fiduciary relationships and arguably support requiring investigators to meet heightened duties of care and loyalty to subjects.<sup>97</sup>

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*ciary Metaphor: Divided Physician Loyalties and Obligations in a Changing Health Care System*, 21 AM. J.L. & MED. 241, 247-51 (1995) (discussing the application of fiduciary standards to physicians).

92. See Rodwin, *supra* note 91, at 243 ("The law defines a fiduciary as a person entrusted with power or property to be used for the benefit of another and legally held to the highest standard of conduct.").

93. See Kurt Eichenwald & Gina Kolata, *Drug Trials Hide Conflicts for Doctors*, N.Y. TIMES, May 16, 1999, at A1. Dr. David S. Schimm is quoted as stating: "What the patients are not seeing is that the clinical investigator is really a dual agent with divided loyalties between the patient and the pharmaceutical company." *Id.*

94. See ROBERT J. LEVINE, *ETHICS AND REGULATION OF CLINICAL RESEARCH* 10 (2d ed. 1986) ("The deprivation of the experimentation ordinarily done to enhance the well-being of a patient is one of the burdens imposed on the patient-subject . . .").

95. See E. Haavi Morreim, *The Clinical Investigator as Fiduciary: Discarding a Misguided Idea*, 33 J.L. MED. & ETHICS 586 (2005). Indeed, in the first *Suthers v. Amgen, Inc.* case, the District Court for the Southern District of New York, in finding that the trial sponsor had no fiduciary duties, questioned whether even the investigators or academic medical centers with more direct connection to research subjects had clear fiduciary duties to the subjects. *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416, 427 n.9 (S.D.N.Y. 2005).

96. See, e.g., Delgado & Leskovic, *supra* note 14, at 109-10; Angela R. Holder, *Do Researchers and Subjects Have a Fiduciary Relationship?*, IRB: ETHICS & HUM. RES., Jan. 1982, at 6.

97. See Holder, *supra* note 96; see also Coleman, *supra* note 14, at 431-32.

A somewhat in-between position urges application of a “partial entrustment” model to the investigator-subject relationship.<sup>98</sup> Under this view, investigators have special responsibilities toward subjects because subjects have given investigators permission to access and collect confidential health information, perform tests, obtain samples, and undertake other procedures. Investigators enjoy considerable discretionary power because of this grant of permission. Subjects are seen as partially entrusting their health to investigators, suggesting that investigators have accompanying responsibilities for the subjects’ health.<sup>99</sup> These duties of care may not be as strong as those in the ordinary doctor-patient relationship but should involve some limited responsibilities to protect subjects from harm.<sup>100</sup>

While academic commentators have supported the partial entrustment model,<sup>101</sup> it has yet to be clearly adopted in the limited case law involving medical research. Indeed, there is very little in the way of controlling precedent that helps determine the legal nature of the investigator-subject relationship.<sup>102</sup> Thus, the question remains whether researchers and subjects are in a classic fiduciary relationship, a quasi-fiduciary relationship, a special relationship, fall under the partial entrustment model, or are simply parties interacting at arms length. Because the individualized care and loyalty obligations that investigators may owe to subjects are not well defined, understandable confusion exists about whether the investigator has any duty to ensure a subject’s post-trial access to the investigational technology.

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98. See, e.g., Henry S. Richardson & Leah Belsky, *The Ancillary-Care Responsibilities of Medical Researchers*, HASTINGS CENTER REP., Jan.-Feb. 2004, at 25, 27.

99. See *id.* at 27-32.

100. See *id.* at 28.

101. See, e.g., *id.*

102. In *Grimes v. Kennedy Krieger Institute*, 782 A.2d 807, 849-52 (Md. 2001), which involved research on lead-paint abatement in homes rented to families with children, the Maryland Court of Appeals held that the researchers had heightened obligations toward the subjects. The court’s reasoning, however, remains ambiguous as it identified several possible sources for imposing heightened obligations, including the “special relationship” that might exist between researcher and subject, the special quasi-contract between the parties established by the informed consent document, duties derived from the federal research regulations, and duties implied from international ethics standards such as the Nuremberg Code. See *id.* Thus, *Grimes* does not provide clear answers to whether an investigator has heightened obligations premised solely on special relationship/fiduciary duty theories. Moreover, *Grimes* has not been widely followed to date.

As for trial sponsors, existing precedent suggests that the duties that sponsors owe to subjects are quite narrow and perhaps even more limited than the duties that investigators owe subjects. Recall that in both *Amgen* cases the courts were unwilling to find that the trial sponsor had a fiduciary relationship with the subjects that triggered heightened duties of care.<sup>103</sup> The courts reasoned that the sponsor had no contact with the subjects and imposing a fiduciary duty would be inconsistent with sponsors' loyalties to the protocol as a whole and their need to maintain sufficient distance to pursue legitimate research ends.<sup>104</sup> Moreover, a sponsor, even more than an investigator, has more plainly apparent loyalties to the scientific protocol. Thus, the fiduciary paradigm of undivided loyalty to subjects seems particularly ill-fitting when applied to the trial sponsor.

### B. *Ethics Guidance*

Current ethics guidance similarly remains underdeveloped. Closest on point is the Declaration of Helsinki, adopted by the World Medical Association (WMA).<sup>105</sup> As revised by the WMA in 2008, the Helsinki Declaration now states that “[a]t the conclusion of the study, patients entered into the study are entitled . . . to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.”<sup>106</sup> In 2004, after much debate over an earlier provision regarding post-trial access, the WMA issued a clarification stating that it was

reaffirm[ing] its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care.

Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.<sup>107</sup>

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103. *Abney v. Amgen, Inc.*, 443 F.3d 540, 551 (6th Cir. 2006); *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416, 429 (S.D.N.Y. 2005).

104. *Abney*, 443 F.3d at 550-551; *Suthers I*, 372 F. Supp. 2d at 426-29.

105. See WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ¶ 33 (2008), <http://www.wma.net/e/policy/pdf/17c.pdf> [hereinafter WMA Ethical Principles].

106. *Id.*

107. See Press Release, World Medical Association, Clarification on Declaration of Helsinki (Oct. 11, 2004), [http://www.wma.net/e/press/2004\\_24.htm](http://www.wma.net/e/press/2004_24.htm).



The Declaration of Helsinki revisions were undertaken in response to concerns about international HIV trials and exploitation of subjects in developing countries.<sup>108</sup> Many of the subjects, because of cost barriers and limited sponsor plans for distribution, were unlikely to receive the investigational technologies once they were approved for commercial use in the United States and other developed countries. Yet these subjects bore much of the risk of clinical trial testing.<sup>109</sup>

The revisions to the Declaration of Helsinki appropriately highlight the importance of anticipating post-trial access needs of research subjects.<sup>110</sup> Further, the Declaration revisions implicitly recognize that it is inequitable and ethically troubling to deny subjects access to beneficial study technology at the end of a trial when their efforts involved risk and were critical for generating the research data that demonstrated the technology's efficacy. Nonetheless, the Declaration revisions unfortunately leave many important questions unanswered.

First, what level of benefit must a study technology offer to trigger an ethical obligation of ensuring that subjects have post-trial access? The Declaration states the obligation as only to offer subjects access to interventions "identified as beneficial in the study."<sup>111</sup> But many clinical trials fail to generate data that unambiguously shows that the study technology offers clear improvement over existing treatments. Instead, the data can be murky. Is there still a strong ethical obligation to provide willing subjects continued access to investigational technology shown to be only marginally more effective than existing treatments? What if the technology requires further stages of testing before issues of comparative benefit can be more definitively resolved? Do subjects who participated in now completed trials still have a meritorious claim to post-trial access pending further testing? Indeed, for such reasons, the Declaration of Helsinki's provisions become particularly hard to apply to early stages of clinical trial testing such as Phase I studies that pri-

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108. See Press Release, World Medical Association, WMA to Continue Discussion on Declaration of Helsinki (Sept. 14, 2003), [http://www.wma.net/e/press/2003\\_19.htm](http://www.wma.net/e/press/2003_19.htm).

109. See Editorial, *One Standard, Not Two*, 362 LANCET 1005 (2003); MORAL STANDARDS FOR RESEARCH IN DEVELOPING COUNTRIES, *supra* note 15.

110. See WMA Ethical Principles, *supra* note 105.

111. *Id.* ¶ 33.

marily evaluate toxicity, not efficacy.<sup>112</sup> After a technology has completed Phase I testing, or even after limited Phase II trials, there still may not be enough useful data generated to determine whether the “identified as beneficial in the study” standard applies and triggers a post-trial access obligation.

Second, if there is a legitimate claim by subjects for post-trial access, must access be offered for unlimited duration? It is possible that subjects may want to continue with investigational technology long after the study has ended, especially for treatment of chronic diseases. Does the case for continued post-trial access weaken over time? Third, the Declaration of Helsinki has very little to say about who has the responsibility to ensure that a subject has post-trial access—the investigator, the sponsor, the academic medical center where the research is conducted? Or is the responsibility shared jointly?

Apart from the Declaration of Helsinki, other ethical guidance on post-trial access remains quite limited. For example, the International Ethical Guidelines of the Council for International Organizations of Medical Sciences (CIOMS) initially advised that agencies sponsoring medical research “should agree in advance . . . that any product developed through such research will be made reasonably available to the inhabitants of the host community or country [where the research is conducted] at the completion of successful testing.”<sup>113</sup> A 2002 clarification extends this obligation to sponsors and investigators in situations where the research will be conducted in a population or community with limited resources and requires that the product “or knowledge generated” from the trial be made reasonably available after the study’s conclusion.<sup>114</sup> Yet this guidance offers little direction on important details. For example, much of the guidance concerns making the technology available to the community where the research was conducted.<sup>115</sup> Does this mean that residents in the community who did not participate in the

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112. See Michelle M. Mello & Steven Joffe, *Compact Versus Contract—Industry Sponsors’ Obligations to Their Research Subjects*, 356 *NEW ENG. J. MED.* 2737, 2740 (2007).

113. COUNCIL FOR INT’L ORG. OF MED. SCI. (CIOMS) & WORLD HEALTH ORG. (WHO), *INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS* 45 (1993).

114. See COUNCIL FOR INT’L ORG. OF MED. SCI. (CIOMS) & WORLD HEALTH ORG. (WHO), *INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS*, at Guideline 10 & cmt. (2002), available at [www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm).

115. See *id.*

research should have the same degree of post-trial access as the actual subjects? Is that fair to the subjects who actually participated and incurred direct risks? More importantly, it remains unclear under the CIOMS guidelines how much benefit an investigational technology must offer in order to trigger any post-trial access obligations.

### III. WHY REQUIRE POST-TRIAL ACCESS?

Is it even clear that subjects should enjoy special access post-trial to investigational technology? This section reviews primary arguments for and against expanded post-trial access. It aims to map out the key issues and provide a balanced, more nuanced framework for thinking about post-trial access disputes moving forward.

#### A. *Reasons for Expanded Post-Trial Access*

An initial reason to provide subjects with greater post-trial access is because this is what many subjects expect. Of course, not all expectations are reasonable and not all expectations lead to legally cognizable claims. But subjects' expectations of post-trial access, although often inaccurate, may be quite foreseeable and reasonable given the overall context. As noted, many consent forms fail to apprise subjects in sufficient detail of the likelihood of and reasons for study termination and subsequent denied access to the investigational technology, save for terse boilerplate statements that allow the subject to be withdrawn upon "termination or cancellation of the study by the sponsor."<sup>116</sup> Meanwhile, well-documented therapeutic misconception problems mean that many subjects already have difficulty distinguishing between experimentation and ordinary medical care.<sup>117</sup> Some subjects falsely believe that when they enroll in a trial, they will receive customary and proven treatment tailored to their individual condition. Conflation by subjects of reg-

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116. *Suthers v. Amgen, Inc. (Suthers II)*, 441 F. Supp. 2d 478, 484 (S.D.N.Y. 2006).

117. See Paul S. Appelbaum et al., *Therapeutic Misconception in Clinical Research: Frequency and Risk Factors*, IRB: ETHICS & HUM. RES., Mar.-Apr. 2004, at 1 (discussing the common misconceptions associated with clinical research); Sam Horng & Christine Grady, *Misunderstanding in Clinical Research: Distinguishing Therapeutic Misconception, Therapeutic Misestimation, & Therapeutic Optimism*, IRB: ETHICS & HUM. RES., Jan.-Feb. 2003, at 11, 12-13 (same).

ular clinical care and medical research continues to be a recurring problem.<sup>118</sup>

Accordingly, it can be expected that many subjects will not pay due attention to the salient aspects of a clinical trial that distinguish it from ordinary medical care, including, importantly, how the underlying relationship with the health care professional terminates and what happens afterward. Some subjects, influenced by therapeutic misconception, may think that a clinical relationship will continue so long as they benefit from participation in the study, similar to how an individual physician ordinarily continues to treat her patient through the whole episode of an illness. Subjects may not fully understand that they can be dropped from a study protocol or that the experiment itself can be terminated in an entirely different manner than a physician terminates a patient from his clinical practice. Similarly, many subjects are likely not aware of the complex web of medical research relationships and contracts that typically exist between the trial sponsors, the investigators, and the academic medical centers. Accordingly, they may not sufficiently appreciate the lesson of the *Amgen* cases: a promise by the investigator in a consent form to provide post-trial access to investigational technology may be unenforceable because the sponsor, who is not a party to the consent form, usually controls access.<sup>119</sup>

In short, many subjects may not anticipate how tenuous their post-trial access opportunities are when deciding to participate in a clinical trial. This raises significant concerns about the adequacy of the consent. It also suggests detrimental reliance by subjects that is foreseeable to investigators and sponsors, raising possible promissory estoppel concerns. When there is likely confusion about what happens at the end of the clinical trial, limiting post-trial access may manipulate and play upon subjects' desperate, uncritical access demands. It seems cruel and inappropriate to invite subjects to enroll in a trial and ask them to invest significant personal resources in participating without better addressing the possibility that their legitimate access concerns will be frustrated and disrupted when the trial concludes.

Apart from informed consent and promissory estoppel issues, legal obligations to provide post-trial access may also arise from the

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118. See Appelbaum et al., *supra* note 117, at 1. See generally Franklin G. Miller & Donald Rosenstein, *The Therapeutic Orientation to Clinical Trials*, 348 *NEW ENG. J. MED.* 1383 (2003) (reviewing various factors that contribute to conflation).

119. See Mello & Joffe, *supra* note 112, at 2741; see also *supra* Part I.B.1.

investigator-subject relationship. As previously noted, the legal parameters of this relationship and whether it imposes any special duties of care or loyalty upon investigators remain subject to continued debate.<sup>120</sup> To the extent that the relationship could be viewed under the partial entrustment model,<sup>121</sup> subjects may have stronger claims against investigators to ensure broader post-trial access. An investigator's limited responsibilities for the subject's health under the partial entrustment model could extend to ensuring post-trial access to beneficial technology for some reasonable duration. Alternatively, if the investigator-subject relationship is viewed as a fiduciary or even quasi-fiduciary relationship, then the law should police abuses of trust in the relationship as it does in other fiduciary contexts. One way to strengthen the fiduciary bonds, preserve trust, and protect subject welfare would be to impose some obligation on the investigator to ensure post-trial access.

Another related concern is whether denying subjects post-trial access is legally actionable abandonment. In ordinary medical care, once a physician enters into a treatment relationship with the patient, the physician has a legal duty not to abandon the patient.<sup>122</sup> This duty is breached when the physician unilaterally ends the treatment relationship without providing reasonable notice, and when medical necessity requires continued treatment of the patient.<sup>123</sup> The duty of nonabandonment may be thought of as a necessary corollary to and part of the general duty of care arising under the doctor-patient relationship or arising from the fiduciary aspects of the doctor-patient relationship.<sup>124</sup> Abandonment in regular clinical settings has typically been actionable as ordinary medical malpractice.<sup>125</sup>

Of course it remains debatable whether a legal duty of nonabandonment should apply with equal force, or at all, to the investigator-subject relationship as it does to the doctor-patient

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120. See *supra* notes 91-97 and accompanying text.

121. See *supra* notes 98-100 and accompanying text.

122. See *Church v. Perales*, 39 S.W.3d 149, 164 (Tenn. Ct. App. 2000) ("While the physician-patient relationship exists, the physician has a duty to continue providing care.").

123. See, e.g., *id.*; *King v. Fisher*, 918 S.W.2d 108, 112 (Tex. Ct. App. 1996). Many jurisdictions provide that the treatment relationship may be terminated after appropriate notice to the patient. See *Jackson v. Okla. Mem'l Hosp.*, 909 P.2d 765, 774 & n.38 (Okla. 1995). Far less clear is whether the physician, to fulfill the duty of nonabandonment, must also actively transition the patient to alternative care.

124. See *Rodwin*, *supra* note 91, at 247-48; see also *supra* text accompanying note 91.

125. See *King*, 918 S.W.2d at 111.

relationship. As noted, investigators conducting research do not necessarily assume the same robust duties of care and fiduciary obligations that arise for physicians treating individual patients. Similarly, investigators might not be held to the same nonabandonment obligations as physicians. But if the doctrinal justification for imposing strict nonabandonment duties on investigators is unclear, addressing abandonment hazards in the research context remains important, nonetheless, for compelling ethical and policy reasons. Blocking access to investigational technology after the trial concludes arguably treats subjects as mere experimental devices to be discarded after use. This violates general ethical principles that stress the need to treat subjects with dignity and respect as autonomous persons.<sup>126</sup> Put another way, “[a]bandoning participants at the end of a study, when their useful ‘life’ to the researchers and sponsor is over, is fiendish.”<sup>127</sup> Ethical (and possibly legal) duties to subjects, however vague and ill-defined, at least should include a commitment to protecting subject welfare,<sup>128</sup> and not abruptly jettisoning subjects or losing sight of their interests as soon as they are no longer needed to complete the research.<sup>129</sup> Flagrant abandonment conduct, if undeterred, also can create significant distrust by research subjects. The larger research enterprise depends on trust by subjects to function,<sup>130</sup> while endemic distrust seriously undermines the ability to recruit subjects for future studies.<sup>131</sup>

Ethical (if not legal) considerations of reciprocity and social contract also support expanding post-trial access opportunities for subjects. Subjects enroll in trials with generally unclear opportunities for therapeutic improvement because the benefits of investigational technology remain largely unknown pending further research.<sup>132</sup> Yet, investigators and sponsors could not complete their work and gather needed research data without the effort of subjects. Arguably, the investigators and sponsors owe something back—some form of reciprocal responsibilities or benefits—to the

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126. See LEVINE, *supra* note 94, at 15-16.

127. Editorial, *supra* note 109, at 1005 (discussing limited post-trial access of subjects in the context of research conducted in the developing world).

128. This minimal commitment can be found under the federal research regulations. See, e.g., 45 C.F.R. § 46.103(b)(1) (2008) (requiring institutions to file assurances detailing their commitment to “protecting the rights and welfare of human subjects”).

129. See Grady, *supra* note 15, at 430-31; Saver, *supra* note 90, at 1004.

130. See Mark A. Hall, *Law, Medicine, and Trust*, 55 STAN. L. REV. 463, 470-71 (2002); Gatter, *supra* note 14, at 356-57.

131. See Gatter, *supra* note 14, at 356.

132. See discussion *supra* Introduction.

subjects to acknowledge, honor, and reinforce these altruistic aspects of participating in medical research.<sup>133</sup> Similarly, society as a whole arguably owes something back to subjects for undertaking risks in order to advance medical progress for the good of the population.<sup>134</sup> Reciprocal obligations suggest that there should be greater concern about subjects' general status and ongoing health post-trial. These considerations likewise may support reform measures to ensure that subjects enjoy post-trial access to beneficial investigational technology.

#### B. *Problems with Expanded Post-Trial Access*

At the same time, a closer examination of the legal and ethical issues suggests that expanding post-trial access is not always necessary or warranted. Moreover, mandating some form of post-trial access rights for subjects introduces new concerns and may prove counterproductive for health policy. First, reciprocity arguments of owing subjects something back as justification for expanded post-trial access, while ethically appealing, may be overstated. If subjects deserve some form of post-trial access due to their research participation efforts, does that diminish legitimate access demands of other stakeholders? For example, it is not clear that participating subjects deserve preferential access when access opportunities may still be foreclosed to other patients.<sup>135</sup> Patients with the same type of illness as the research subjects could also benefit from access to the investigational technology once a clinical trial ends. But these similarly situated patients may have no opportunity to receive the technology because it is not commercially available until further clinical trials are concluded and they may not even be eligible for participation in the new studies.

More generally, a sponsor may only be able to accommodate a limited number of individuals seeking post-trial access while the technology undergoes further testing in subsequent studies. In such circumstances, an ethical presumption, translated into a regulatory directive, that trial participants should enjoy post-trial access could

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133. Cf. Brownsword, *supra* note 27, at 680 (discussing reciprocity obligations to provide subjects with ancillary care during the course of a clinical trial); Jennifer L. Gold & David M. Studdert, *Clinical Trial Registries: A Reform That is Past Due*, 33 J.L. MED. & ETHICS 811, 815 (2005) (discussing the research enterprise as a form of social contract).

134. See Grady, *supra* note 15, at 430.

135. See Maria Merritt & Christine Grady, *Reciprocity and Post-Trial Access for Participants in Antiretroviral Therapy Trials*, 20 AIDS 1791, 1792 (2006).

mean that the subjects in reality have preferred and exclusive access compared to other patients. Reciprocity concerns of owing something back to subjects do not necessarily support displacing other patients also in need and postponing their opportunities for therapeutic improvement. In trying to reward subjects with reciprocal benefits, it is important not to impose disproportionate burdens on other patients by further impeding or delaying their access.<sup>136</sup>

Second, as with reciprocity, concerns about abandonment do not necessarily support robustly expanding subjects' post-trial access. Because the investigator's duty of care to subjects may be more limited than the duty that arises in the ordinary physician-patient relationship, and the investigator does not undertake to provide individualized care,<sup>137</sup> nonabandonment restrictions seemingly should apply with less force in the research context than in ordinary clinical care. Arguably, the investigator's primary duties to the subject end when the protocol is carried out faithfully to its stopping point. Much of the conduct that defines the investigator-subject relationship has already ended upon the suspension of research activities at the protocol's conclusion. After that, there is little, if any, continuing research relationship to speak of. Hence, any accompanying duty of nonabandonment should also diminish because the essential research activities that were at the heart of the relationship are already coming to an end. While investigators may have an obligation to let subjects down easily and respectfully at the end of a trial, it is not clear that abandonment concerns require that a subject's access to investigational technology be continued when the investigator-subject relationship terminates.

Moreover, even in the ordinary doctor-patient relationship, nonabandonment obligations are not unlimited and abandonment concerns do not justify imposing a duty on physicians to continue all forms of personalized care that may be responsive to the patient's circumstances.<sup>138</sup> The traditional common law approach is quite flexible and supportive of physicians seeking to end a treatment relationship with a patient. So long as the physician gives proper notice to the patient that the treating relationship will end, generally the cessation of care is not actionable, even if the physi-

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136. *Id.*

137. See discussion *supra* Part II.A.3.

138. See, e.g., Edmund D. Pellegrino, *Nonabandonment: An Old Obligation Revisited*, 122 ANNALS INTERNAL MED. 377 (1995).



cian has no clear reason for the termination of care.<sup>139</sup> Accordingly, investigators might simply minimize any abandonment concerns by giving proper notice to subjects when all study-related activity will end. Also, some jurisdictions recognize abandonment claims only if the termination of care occurs when the patient is at a critical stage or in need of immediate medical attention.<sup>140</sup> Not all subjects at the end of a clinical trial will even be able to meet such criteria. Their continuing medical concerns may be quite personally important, but their clinical conditions are nonetheless not in a sufficiently acute stage.

Third, expanded post-trial access is not necessarily the appropriate remedy for the problems at hand. As noted, post-trial access disputes raise serious concerns, among other issues, of informed consent and therapeutic misconception problems.<sup>141</sup> Claims that subjects have been misled and even exploited underlie many of these disputes.<sup>142</sup> They may not fully appreciate how tenuous their post-trial access opportunities are, both because of their confusion about the differences between research and individualized care and their general desire to access investigational technology. But, if true, is the essential harm that needs remedying exploitation or deception? The distinction matters in terms of possible responses. If subject deception becomes the principle area of concern, then the usual regulatory response to deception is to require more accurate and complete disclosure going forward. Thus, to the extent that deception is the problem, requiring additional benefits post-trial (including the benefit of post-trial access) is not the obvious regulatory solution.<sup>143</sup>

Fourth, requiring increased post-trial access may simply exacerbate rather than appropriately address therapeutic misconception problems. Subjects in a clinical trial may be convinced that an investigational technology is ordinary clinical care precisely because it has been offered to them post-trial. Yet the particular trial that just concluded may have represented only a partial assessment of the technology, and the technology may require further evaluation

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139. Mark A. Hall, *A Theory of Economic Informed Consent*, 31 GA. L. REV. 511, 529 (1997).

140. See, e.g., *Miller v. Greater Se. Cmty. Hosp.*, 508 A.2d 927, 929 (D.C. 1986); *Surgical Consultants, P.C. v. Ball*, 447 N.W.2d 676, 682 (Iowa Ct. App. 1989).

141. See, e.g., *Abney v. Amgen*, 443 F.3d 540 (6th Cir. 2006); *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416 (S.D.N.Y. 2005).

142. See, e.g., *Abney*, 443 F.3d 540; *Suthers I*, 372 F. Supp. 2d 416.

143. See *Moral Standards for Research in Developing Countries*, *supra* note 15, at 19.

before firmer conclusions can be drawn about its appropriate use in regular clinical care.

Fifth, even if subjects deserve greater post-trial access, it is important to impose acceptable boundaries. Not all post-trial access claims will be equally valid, and the force of any right to post-trial access will likely vary depending on a number of context-specific factors. For example, even if the partial entrustment model or fiduciary law concepts are applied to the investigator-subject relationship, post-trial access claims under either approach would likely strengthen depending on a subject's increasing degree of vulnerability and dependency and the more significant information and resources that the subject entrusts to the researcher. In contrast, a subject's post-trial access claims should arguably weaken when it still remains uncertain post-study whether the investigational technology offers a clear benefit or significant improvement over existing alternatives. Indeed, the general ethical principle of beneficence<sup>144</sup> does not mean that subjects are owed the same degree of post-trial access for all clinical trials. The more ambiguous the efficacy data associated with investigational technology, the less clear the subject's welfare will be negatively affected by blocked access, and, accordingly, the weaker a subject's claim to post-trial technology necessarily becomes.<sup>145</sup> Denying subjects post-trial access in situations of unclear efficacy or unclear comparative advantages seems less an act of abandonment or failure to honor duties of care and loyalty and more the prudent and necessary allocation of limited resources. Some subjects' post-trial access demands may reflect sheer desperation. It does not help the research enterprise generally, or increase trust in medical research, if subjects can compel the continuation of access to investigational technology as they see fit, regardless of a more objective weighing of efficacy and safety issues and other larger interests at stake.

Related to the problem of imposing clear boundaries on *when* subjects can invoke a right to post-trial access is the need to develop

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144. The principle of beneficence in the research setting recognizes the importance of helping subjects while avoiding the imposition of harm. The beneficence principle requires that the risks associated with research be reasonable in light of the expected benefits, and that all possible benefits be maximized and the chance of harm minimized. See TOM BEAUCHAMP & JAMES CHILDRESS, *PRINCIPLES OF BIOMEDICAL ETHICS* 260 (4th ed. 1994).

145. See Henry S. Richardson, *Incidental Findings and Ancillary-Care Obligations*, 36 *J.L. MED. & ETHICS* 256, 268 (2008) (making a similar point for the related issue of when the research team should provide ancillary care during the trial).

a better understanding of *how much* access is appropriate.<sup>146</sup> Must investigators or sponsors provide the study technology *ad infinitum*? Does the length of post-trial access depend on whether the study was terminated for lack of efficacy or even for safety concerns? Should post-trial access be required only while the study technology awaits full regulatory approval and before it becomes commercially available? If the technology earns full regulatory approval but the subject still cannot afford the technology or obtain insurance coverage for it, must the investigator or sponsor pay for the subjects' continued access?

Expanded post-trial access also introduces new problems and may have negative implications for health policy. Requiring sponsors or investigators to ensure subjects' post-trial access will increase transaction costs for clinical trials, potentially over-detering beneficial research and limiting the number and kind of studies pursued. Insisting on post-trial access across the board runs the risk of paternalism and disrespect for subject autonomy by interfering with the decisions of individuals who might rationally choose to enroll in trials with limited or no post-trial access rather than forego important research opportunities altogether. The chilling effect of required post-trial access may prove particularly problematic in communities with limited availability to existing health care services. Researchers and sponsors will be especially wary of conducting research in such areas in order to avoid being encumbered by many post-trial access claims. The additional costs required to support greater post-trial access might also mean that limited research dollars are diverted away from new studies and toward ensuring post-trial access to investigational technology, even technology that seemingly offers only marginal benefit.

Also, sponsors and investigators have valid concerns that expanded post-trial access will expose them to greater risk of liability.<sup>147</sup> A clinical trial differs from ordinary clinical care in the degree of monitoring involved. When the clinical trial is underway, and its protocol followed, monitoring procedures are in place to collect data, identify safety issues, and evaluate subjects' progress in a systematic way, including the continuing review of ongoing studies performed by IRBs and, when applicable, data safety monitor-

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146. See *supra* Part II.B.

147. Cf. Talbott, *supra* note 20, at 318 (discussing related liability concerns for sponsors and investigators with increasing access to unapproved drugs outside of a formal study).

ing boards. But when the clinical trial ends, these formal monitoring procedures often end as well. Offering subjects continued access to investigational technology without more comprehensive monitoring in place runs the risk of the development of unanticipated hazards. In addition, investigators may be more vulnerable to post-trial claims that they failed to tailor medical treatment for each patient as needed. For example, a subject might argue that his clinical condition required changed dosage levels in the experimental medication or a different type of screening test. If this occurred while the trial was underway, the investigator could more easily defend against such negligence claims by arguing that the protocol in place required that the investigator follow standardized procedures for all subjects in order to develop generalizable research data for the study. Yet post-trial, such defenses may not succeed because there is no longer a clear need to follow the protocol.

Finally, and particularly pertinent to this Symposium's theme of the complicated connection between technology regulation and technology reimbursement, regulatory mandates to expand post-trial access could have negative and confounding reimbursement effects. Governmental and private payers look to the results of clinical trials as part of their assessment process to determine when to selectively reimburse new technologies. But if subjects are recognized as having more robust rights to post-trial access, this could lead to slippery slope problems and inevitable pressures, from both subjects and non-subjects, for payers to cover investigational technologies sooner and more broadly. For example, if subjects of a recently completed Phase III trial of an experimental cancer drug, now just approved by the FDA, can readily command continued post-trial access to the medication, other patients with the same condition will increasingly lobby (or even litigate for) their health plans to cover it. Payers may have a harder time restricting coverage for other patients on grounds that the technology is noncustomary or not reasonably necessary when a large group of subjects is receiving the technology. Much attention will likely be focused on anecdotal reports of success that subjects experience with the drug post-trial. But any such data, seized upon by stakeholders seeking greater coverage for all patients, will almost certainly have less statistical and predictive significance than data gathered while the subjects were on the protocol because of the lack of standardized procedures once the study has ended. Indeed, for legitimate reasons, payers might prefer to restrict reimbursement for the re-

cently approved technology until more significant studies assessing its cost-effectiveness can be performed. It is important for comprehensive technology assessments to be conducted before widespread coverage decisions are made; otherwise, expensive new technology will further strain limited health care resources.

Along the same lines, expanded post-trial access may complicate the ultimate conduct of the underlying study and skew the research findings. A regulatory approach that mandates expanded post-trial access invites strategic gamesmanship by certain subjects to terminate the trial early. Subjects in blinded, randomized studies usually do not know whether they are receiving the experimental intervention or the standard treatment to which it is being compared.<sup>148</sup> Subjects most concerned about access to investigational technology would realize that, while the trial was underway, they only have a possible but not guaranteed chance of receiving the investigational technology due to randomization procedures. But if all subjects enjoy a right to post-trial access, each subject's access chances actually increase when the study concludes. Accordingly, subjects might advocate for early study terminations—or even make continuation of the research difficult for investigators—to trigger a trial termination and actually increase their access chances. The possibility of additional early trial terminations is of considerable concern for health policy. It is important to carry clinical trials to statistically significant stopping points to ensure that the resulting data can better resolve clinical uncertainty and more effectively guide future health care treatment, reimbursement, and allocation decisions.<sup>149</sup>

#### IV. RECOMMENDATIONS

Providing detailed reform recommendations is beyond this Article's scope. Instead, the focus has been on critically reviewing the competing considerations at play in post-trial access disputes and identifying the important questions emerging for health law and policy. However, the status quo certainly needs improvement. Representative disputes, such as the *Amgen* cases,<sup>150</sup> indicate that investigators and, particularly, trial sponsors enjoy considerable discretion in rejecting often legitimate and foreseeable post-trial ac-

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148. See Menikoff, *supra* note 8, at 63.

149. See Stuart J. Pocock, *When to Stop a Clinical Trial*, 305 BRIT. MED. J. 235 (1992).

150. See *supra* Part I.B.1.

cess demands of subjects, which raises many problems.<sup>151</sup> The challenge is how to navigate an incremental reform approach that offers some improvement over the status quo yet minimizes the dangers of post-trial access completely unbound. In that spirit, this section recommends two preliminary strategies.

A. *More Focused Regulatory Review of Post-Trial Plans and a Presumption of Some Post-Trial Access*

Greater transparency about what will happen post-trial would certainly help address concerns that subjects are being misled or even exploited because of their post-trial access expectations. As noted, informed consent documents sometimes provide only brief statements about the possibility of study termination or early interruption and do not usually provide detailed information about post-trial access to the study technology. The federal research regulations should require that informed consent documents, in order to secure IRB approval, provide complete disclosures to subjects about when and why the study could be terminated. Also, informed consent documents should be required to have a distinct section that identifies what plans, if any, exist to provide the study technology to subjects after the trial, including, importantly, who will pay for this access. If there are no plans for continued access, the informed consent document should be required to explain that fact expressly and conspicuously, including statements that subjects will have no guarantee of post-trial access even if the technology improves their condition.

IRBs can only properly insist upon and monitor such disclosures in the informed consent documents if they do a better job of protocol review in the first place and ferret out what the plans are with respect to post-trial access.<sup>152</sup> As previously noted, the IRB review regulations at present do not provide sufficiently detailed instructions to IRBs as to what to look for in protocol applications regarding post-trial conduct.<sup>153</sup> Recent post-trial access disputes disturbingly suggest that IRBs have approved studies with minimal inquiry regarding post-trial plans. These cases also suggest that sponsors and investigators did not make sufficient transition plans

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151. See, e.g., *Abney v. Amgen, Inc.*, 443 F.3d 540, 553 (6th Cir. 2006); *Suthers v. Amgen, Inc. (Suthers II)*, 441 F. Supp. 2d 478 *passim* (S.D.N.Y. 2006); *Suthers v. Amgen, Inc. (Suthers I)*, 372 F. Supp. 2d 416, 429-30 (S.D.N.Y. 2005).

152. See, e.g., *Amgen*, 441 F. Supp. 2d at 484.

153. See *supra* note 79 and accompanying text.

or even budget for the likelihood that subjects would want post-trial access.<sup>154</sup>

To assist IRBs in monitoring these issues, the federal research regulations should require that protocol applications document in greater detail what will happen when the study ends, including the possibility that the study may be terminated early because of perceived lack of efficacy. This documentation should also make clear, for the IRB's consideration and approval, the decision-making process to be followed by the sponsor or investigator for determining whether the trial results show enough benefit to justify continuing post-trial access. The application could include descriptions of the criteria to be considered and statistical guidelines to be used.

Apart from transparency problems, the post-trial needs of subjects seemingly exert only a weak influence at best on sponsor and investigator decision making at the end of a study. This lack of consideration of subjects' access preferences has led to poor balancing of stakeholder interests and continual conflict. One approach to prod sponsors and investigators to consider subjects' access demands more consistently is through regulatory presumptions favoring some form of access. The federal research regulations might, for example, state that investigators and sponsors will be expected to provide subjects with some form of post-trial access when the trial is stopped for reasons other than safety. This default obligation could only be varied if the initial protocol contains a request to modify this obligation, along with justification from the sponsor or investigator that explains why no special access is warranted, and the IRB approves this variance. A related presumptive approach would make it a regulatory requirement that protocols, in order to receive IRB approval, include assistance programs that help subjects with maintaining post-trial access for a limited duration, such as one year after the study, similar to what some pharmaceutical companies already do on a limited basis in particular clinical trials.<sup>155</sup> This requirement could be waivable for good cause by the IRB.

A presumptive approach avoids making post-trial access an overly burdensome, open-ended obligation for sponsors and investigators. Instead, it is more likely to result in a finite commitment from the sponsor or investigator that would be time-limited and

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154. See *supra* notes 63-69 and accompanying text (discussing post-trial planning and supply problems in the Merck shingles vaccine study).

155. See Grady, *supra* note 15, at 429.

that could be anticipated and budgeted for in the planning process for developing the study. Also, a presumptive approach has sufficient flexibility and recognizes that in some clinical trials, such as where the technology offers limited efficacy, continuing post-trial access may not be warranted and can be waived for good cause by the IRB.

### B. *Benefits Other than Post-Trial Access*

Another promising strategy, presently underutilized, is to offer subjects other benefits as an alternative to post-trial access to the investigational technology. For example, instead of post-trial access, subjects could deem it a sufficient reciprocal benefit that their community experiences advantages from the research because health care professionals in the area receive special training as part of the clinical trial.<sup>156</sup> Or subjects might receive more personal alternative benefits, such as the opportunity to receive screening and primary health services not required under the protocol. All of these can be very real gains to subjects. Reciprocity and gratitude considerations suggest that subjects should receive something fair in exchange for what they have undertaken for society's benefit, not necessarily a specific claim to any particular benefit.<sup>157</sup>

Alternative benefits have the advantage of being less burdensome for sponsors and investigators, avoiding some of the chilling deterrent effects that might arise with required post-trial access. Alternative benefits can also avoid some of the implementation problems that arise with post-trial access, such as how much access is enough and whether it needs to be continued indefinitely. Alternative benefits may be more predictable, measured more consistently, and valued more highly than differing degrees of post-trial access. For example, Phase I drug trials evaluate primarily toxicity, not efficacy, of the experimental medicine. Mandating that subjects have post-trial access to the study medication after a Phase I trial can make things unduly complicated and difficult. A drug that has only cleared Phase I testing may still be produced in limited supplies because Phase I testing typically occurs with a smaller group of subjects than later testing phases.<sup>158</sup> More importantly, many basic efficacy questions about the drug remain, including what dosage

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156. See MORAL STANDARDS FOR RESEARCH IN DEVELOPING COUNTRIES, *supra* note 15, at 20.

157. See *id.* at 19-21.

158. See 21 C.F.R. § 312.21(a)(1), (b) (2008).



to use and on what schedule, because the medication has not been comprehensively tested yet for efficacy. In such situations, alternative benefits may be much easier to implement and the benefit to subjects more clearly understood.<sup>159</sup>

Greater use of alternative benefits also directly responds to the remedy gaps identified in litigation over post-trial access. Recall that in the *Amgen* cases allegedly misleading promises by the investigators about post-trial access were not binding on the trial sponsor—the party that controlled access to the experimental drug—because the sponsor was not a party to the informed consent documents.<sup>160</sup> This disconnect between what the investigator may promise and what actions may be brought against the sponsor to enforce access leaves subjects with incomplete remedies and without adequate recourse in response to potentially deceptive or misleading disclosures about post-trial access. Yet many alternative benefits, such as offering additional health services, are within the more direct control of the investigators. Subjects could more easily enforce promises of alternative benefits against investigators, and providing alternative benefits may be a more flexible way for investigators to discharge any obligations owed to subjects.

### CONCLUSION

Post-trial access disputes deserve greater regulatory and scholarly attention because of the challenging questions raised for health law and policy. Sponsors and investigators currently have considerable discretion to restrict post-trial access to investigational technology. Yet regularly blocking access undermines notions of protecting subject welfare, disrupts subjects' foreseeable and often legitimate expectations, and raises concerns of abandonment, among other problems. At the same time, closer examination of the legal and ethical justifications suggests that post-trial access is not always necessary or warranted. Subjects' access demands may be uncritical and clouded by therapeutic misconception; indeed, there are often valid reasons for restricting access. Further, the investigator's post-trial obligations to subjects are not necessarily equivalent to the continuing treatment duties that physicians owe to patients in ordinary clinical care. Thus, it is important to consider

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159. See *Moral Standards for Research in Developing Countries*, *supra* note 15, at 21.

160. See *supra* notes 37-44 and accompanying text.

incremental reform approaches that avoid the problems of unbounded post-trial access.

A critically needed next step is to develop regulatory standards that provide more transparency to subjects and more upfront disclosure to IRBs about post-trial access plans before protocols are approved and subjects are enrolled. Other possible reforms worth exploring include regulatory presumptions favoring some form of time-limited, post-trial access, waivable by an IRB for good cause. Complementary to these regulatory changes, greater consideration should be given to offering subjects alternative benefits to continued access. However, these are only preliminary strategies. Much important work remains to be done to delineate more clearly the obligations owed to subjects at the end of a clinical trial as well as to implement policies that can better avoid post-trial access conflicts from first developing.