

# **From a Constitutional Right to a Policy of Exceptions: *Abigail Alliance* and the Future of Access to Experimental Therapy**

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## INTRODUCTION

In 1999, nineteen-year-old Abigail Burroughs was diagnosed with head and neck cancer.<sup>1</sup> Abigail underwent the conventional treatments—chemotherapy and radiation therapy—with no success.<sup>2</sup> Her physician recommended that Abigail attempt to enroll in clinical trials for two unapproved drugs that her physician hoped might have an effect on her tumor.<sup>3</sup> Abigail, however, was unable to enroll in the trials because she did not meet the scientific criteria for inclusion.<sup>4</sup> In June 2001, shortly after enrolling in a clinical trial of a third unapproved drug, Abigail passed away.<sup>5</sup> Following her death, her father founded the Abigail Alliance for Better Access to Developmental Drugs (Abigail Alliance) to advocate for increased access to unapproved drugs for terminally ill patients.<sup>6</sup>

In January 2003, the Abigail Alliance submitted to the Food and Drug Administration (FDA) a proposal for new regulations to increase access to unapproved therapy. They proposed creating a tiered approval system that would allow terminally ill patients to purchase unapproved drugs that had completed Phase 1<sup>7</sup> clinical trials.<sup>8</sup> In April 2003, the FDA rejected this proposal because it

1. See Peter D. Jacobson & Wendy E. Parmet, *A New Era of Unapproved Drugs: The Case of Abigail Alliance v Von Eschenbach*, 297 JAMA 205, 205 (2007); Sue Kovach, *The Abigail Alliance: Motivated by Tragic Circumstances, Families Battle an Uncanny Bureaucracy*, LIFE EXTENSION MAG., Sept. 2007, [http://www.lef.org/magazine/mag2007/sep2007\\_report\\_abigail\\_01.htm](http://www.lef.org/magazine/mag2007/sep2007_report_abigail_01.htm).

2. See Jacobson & Parmet, *supra* note 1, at 205.

3. See *id.*; Kovach, *supra* note 1.

4. See Jacobson & Parmet, *supra* note 1, at 205. The cetuximab trial only enrolled patients with colon cancer, while the gefitinib trial was restricted to patients with lung cancer. See *id.*; Rabiya S. Tuma, *Expanded-Access Programs: Little-Heard Views from Industry*, ONCOLOGY TIMES, Aug. 10, 2008, at 19. The Abigail Alliance website also states that the drug companies that sponsored the trials “couldn’t provide [Abigail] with [the drug] for compassionate use.” See Kovach, *supra* note 1. Other sources suggest that the companies refused to seek FDA approval to supply Abigail the drug outside of clinical trials. See, e.g., Beryl Lieff Benderly, *Experimental Drugs on Trial*, SCI. AM., Oct. 2007, at 92, 96. The programs that provide patients access to unapproved drugs outside of clinical trials are discussed in more detail in Part III, *infra*.

5. See Jacobson & Parmet, *supra* note 1, at 205.

6. See *id.*; see also Abigail Alliance for Better Access to Developmental Drugs, <http://abigail-alliance.org> (last visited Nov. 20, 2009) [hereinafter Abigail Alliance Website].

7. Clinical trials are split up into four phases, each designed to answer a different research question. Phase 1 trials “test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.” See ClinicalTrials.gov, Frequently Asked Questions, <http://www.nlm.nih.gov/services/ctphases.html> (last visited Nov. 20, 2009). In Phase 2, trials involve larger numbers of subjects and collect further safety data, but this

“would upset the appropriate balance that [the FDA is] seeking to maintain, by giving almost total weight to the goal of early availability and giving little recognition to the importance of marketing drugs with reasonable knowledge for patients and physicians of their likely clinical benefit and their toxicity.”<sup>9</sup> The Abigail Alliance then filed a formal citizen petition with the FDA (a required step before one can file a lawsuit against the agency), again calling for a tiered approval system.<sup>10</sup> Before the FDA responded to the citizen petition, Abigail Alliance filed suit, alleging that FDA regulations that restrict terminally ill patients’ access to unapproved drugs violate a fundamental constitutional right protected by the Due Process Clause of the Fifth Amendment.<sup>11</sup>

A D.C. district court judge dismissed Abigail Alliance’s case, finding that a constitutional right to access unapproved drugs did not exist and that the government’s policy restricting access to unapproved drugs survived rational basis review.<sup>12</sup> The Alliance appealed to the D.C. Circuit.<sup>13</sup> In a decision that surprised many commentators,<sup>14</sup> Judges Rogers and Ginsburg reversed the

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phase also examines the efficacy of the investigational product. Phase 3 trials involve large groups of subjects in order to establish the efficacy and monitor side effects. Phase 4 trials are sometimes conducted after a drug goes onto the market to determine if the drug has side effects in particular subgroups and whether it has long-term complications. *Id.*

8. See *Abigail Alliance for Better Access to Developmental Drugs v. McClellan*, No. 03-1601, 2004 U.S. Dist. LEXIS 29594, at \*3-\*4 (D.D.C. Aug. 30, 2004); see also Citizen Petition of the Abigail Alliance & Wash. Legal Found. to the Food & Drug Admin., *In re Tier 1 Initial Approval Program To Expedite the Availability of Lifesaving Drugs* (June 11, 2003), available at [http://www.abigail-alliance.org/WLF\\_FDA.pdf](http://www.abigail-alliance.org/WLF_FDA.pdf). In addition to petitioning the FDA, the Abigail Alliance also lobbied Congress to advocate for their proposed legislation.

9. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 495 F.3d 695, 700 (D.C. Cir. 2007) (internal quotations and citation omitted). One of the more significant concerns that the Abigail Alliance raised is that in many clinical trials, research subjects are randomized to receive either the unapproved therapy or placebo. Many trials therefore offer patients only a fifty-fifty chance at getting the unapproved therapy. The Abigail Alliance was seeking to expand access outside of clinical trials for individuals who were not eligible or who did not want to risk receiving placebo instead of the unapproved therapy.

10. See *Abigail Alliance*, 2004 U.S. Dist. LEXIS 29594, at \*4.

11. See *id.* at \*4-\*5, \*25-\*26. The FDA officially responded to the citizen petition in December 2003, after Abigail Alliance filed suit against the agency. See U.S. Food and Drug Administration, Chronological List of Petitions and Advisory Opinions: From January 1, 2003 through December 30, 2003, <http://www.fda.gov/ohrms/dockets/CITPETS/03citpetlist.htm> (last visited Oct. 12, 2009).

12. See *Abigail Alliance*, 2004 U.S. Dist. LEXIS 29594, at \*2.

13. See *Abigail Alliance*, 495 F.3d at 700-01.

14. See, e.g., Susan Okie, *Access Before Approval — A Right To Take Experimental Drugs?*, 355 NEW ENG. J. MED. 437, 437 (2006) (discussing the “surprising court decision”).

district court's decision and held that terminally ill patients did, in fact, have a constitutional right to access unapproved drugs.<sup>15</sup> The FDA then filed a petition for rehearing en banc. That petition was granted, and the en banc court vacated the panel's decision.<sup>16</sup> Subsequently, the Supreme Court denied Abigail Alliance's petition for certiorari.<sup>17</sup> The D.C. Circuit is widely recognized as having special expertise on matters of administrative law, and the *Abigail Alliance* opinion is now considered an authoritative judgment on the topic of a constitutional right to access experimental therapies.<sup>18</sup>

The *Abigail Alliance* case demonstrates the highly sympathetic nature of claims for access to unapproved therapy outside of clinical trials when such access is the last hope of a terminally ill patient. In the wake of this case, legal claims for access have been made through contractual or quasi-contractual mechanisms.<sup>19</sup> These cases raise many complex policy questions, some of which may be difficult or inappropriate for courts to take into account.<sup>20</sup> In this Article, we argue that a constitutional right to access unapproved therapy should not be recognized by the courts. Further, claims for expanded access are too uncertain and costly to merit substantial regulatory changes. Rather than expanding access to unapproved therapy outside of clinical trials, we contend that more efforts should be made to expand access to the clinical trials themselves.

In Part I, we analyze the reasoning behind the *Abigail Alliance* decision, examine why the en banc D.C. Circuit did not grant a right of access to unapproved therapy, and consider objections that have been raised in favor of a right to medical self-defense. In Part II, we first consider the contractual and quasi-contractual litigation in this area and then demonstrate that courts lack the

15. *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*, 445 F.3d 470, 472 (D.C. Cir. 2006). Judge Griffith dissented. *See id.* at 486.

16. *Abigail Alliance*, 495 F.3d at 701.

17. *Abigail Alliance*, 495 F.3d at 695, *cert. denied*, 128 S. Ct. 1069 (2008).

18. The only subsequent opinion to cite *Abigail Alliance* on the question of a constitutional right to access unapproved treatment followed the majority's reasoning. *See CareToLive v. von Eschenbach*, 525 F. Supp. 2d 952 (S.D. Ohio 2007), *aff'd*, No. 07-4465, 2008 U.S. App. LEXIS 18780 (6th Cir. Aug. 28, 2008). In *CareToLive v. von Eschenbach*, a judge in the Southern District of Ohio relied on *Abigail Alliance* to reject prostate cancer patients' constitutional claim for access to Provenge, an unapproved "biological product intended to treat a particular type of metastatic prostate cancer." *See CareToLive*, 525 F. Supp. 2d at 958, 965-66.

19. *See, e.g., Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128, 129-30 (3d Cir. 2008) (discussing a claim for access based on a theory of promissory estoppel).

20. *Cf. O. Carter Snead, Unenumerated Rights and the Limits of Analogy: A Critique of the Right to Medical Self-Defense*, 121 HARV. L. REV. F. 1, 12 (2007) (arguing that the existence of a right to medical self-defense "must be resolved in the public square through the democratic process").

requisite institutional competence necessary to adjudicate these claims. We explain and evaluate existing FDA regulations in this area in Part III. In Part IV, we argue that, as a matter of policy, claims for access to unapproved therapy outside of clinical trials should rarely be granted. We conclude in Part V that the current approach to providing access to unapproved therapy outside of clinical trials runs the risk of creating a costly policy of exceptions. Instead, we propose reforming clinical trial requirements to involve more participants, including more terminally ill patients, in clinical trials, while providing access outside of clinical trials only in limited circumstances.

#### I. THE *ABIGAIL ALLIANCE* CASE: SHOULD WE GRANT ACCESS TO UNAPPROVED THERAPY OUTSIDE OF CLINICAL TRIALS?

In the *Abigail Alliance* case, the en banc D.C. Circuit faced the following question:

Whether the liberty protected by the Due Process Clause embraces the right of a terminally ill patient with no remaining approved treatment options to decide, in consultation with his or her own doctor, whether to seek access to investigational medications that the [FDA] concedes are safe and promising enough for substantial human testing.<sup>21</sup>

An eight-judge majority ruled that the constitutional right to liberty does not extend to a right to access unapproved drugs.<sup>22</sup> In reaching this conclusion, the majority relied on the two-part analysis for substantive due process cases that the Supreme Court articulated in *Washington v. Glucksberg*.<sup>23</sup> According to that analysis, a court first must consider whether the plaintiffs have provided “a careful description of the asserted fundamental liberty interest.”<sup>24</sup> The majority assumed, for the sake of argument, that *Abigail Alliance* had satisfied this first requirement.<sup>25</sup>

The dissent, written by Judge Rogers and joined by then-Chief Judge Ginsburg, disagreed with the majority’s description of the liberty interest at

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21. *Abigail Alliance v. von Eschenbach*, 495 F.3d 695, 701 (D.C. Cir. 2007).

22. See *Abigail Alliance*, 495 F.3d at 697, 701-02. Judge Griffith wrote the majority opinion for the en banc court. See *id.* at 697. Judges Ginsburg and Rogers, who formed the majority for the panel court’s decision, dissented from the en banc court’s decision. See *id.* at 714 (Rogers, J., dissenting).

23. *Washington v. Glucksberg*, 521 U.S. 702, 720-21 (1997).

24. *Abigail Alliance*, 495 F.3d at 701-02 (quoting *Glucksberg*, 521 U.S. at 720-21) (internal quotation marks omitted).

25. See *id.* at 702.

stake.<sup>26</sup> While the majority defined the interest asserted by Abigail Alliance as a right to take on “enormous risks” to obtain “*potentially* life-saving drugs,”<sup>27</sup> the dissent defined the asserted interest as a “specific right to act to save one’s own life.”<sup>28</sup> The dissent faulted the majority’s description as overly broad and inappropriately focused on personal autonomy, a concept that the Supreme Court has held cannot be the sole basis for a protected liberty interest.<sup>29</sup> The dissent argued that Abigail Alliance asserted a specific right grounded in self-preservation, not an abstract interest based in personal autonomy.<sup>30</sup> In order to make this argument, however, the dissent departed from how the Abigail Alliance itself had described the right at stake. Moreover, the majority rightly noted that redescribing the liberty interest as a broad right to save one’s life was not the kind of careful description required by *Glucksberg*.<sup>31</sup>

The second step under the *Glucksberg* analysis required the court to consider whether a liberty interest in access to unapproved drugs was “deeply rooted in this Nation’s history and tradition and implicit in the concept of ordered liberty, such that neither liberty nor justice would exist if they were sacrificed.”<sup>32</sup> Abigail Alliance argued that a protected liberty interest in access was deeply rooted in our nation’s history for two reasons: 1) there is a long history of the government not interfering with access to drugs; and 2) based on existing common law doctrines, prohibiting access to unapproved drugs was “inconsistent with the way that our legal tradition treats persons in all other life-threatening situations.”<sup>33</sup> Although the court ultimately ruled against Abigail Alliance, it focused a great deal of analysis on these issues. Examining the court’s analysis illuminates the complex policy issues involved in providing access to experimental therapy.

#### *A. The History and Tradition of Drug Regulation*

Abigail Alliance argued that a protected liberty interest in access was deeply rooted in our nation’s history because of a lack of governmental interference with access to drugs for much of our nation’s history. Government regulations did not address the efficacy of drugs before the 1962 Amendments to the Food, Drug,

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26. *See id.* at 714, 716 (Rogers, J. dissenting) (“[T]he description of the right is of crucial importance—too broad and a right becomes all-encompassing and impossible to evaluate; too narrow and a right appears trivial.”).

27. *Id.* at 710.

28. *Id.*

29. *Id.* at 716 (citing *Glucksberg*, 521 U.S. at 725).

30. *See id.*

31. *Id.* at 701 n.5.

32. *Id.* at 701-02 (quoting *Glucksberg*, 521 U.S. at 720-21) (internal quotations omitted).

33. *See id.* at 703, 707.

and Cosmetic Act (FDCA).<sup>34</sup> The majority opinion noted, however, that access to unapproved drugs of unproven safety has long been restricted.<sup>35</sup> States and colonies began regulating drugs for safety as early as 1736, when Virginia passed a law that regulated the sale of drugs in an attempt to prevent deceptive sales practices by pharmacies.<sup>36</sup> Federal drug safety regulation began in 1848, when the government banned the importation of adulterated drugs.<sup>37</sup>

The court further concluded that whether a historical right to access unapproved drugs existed did not depend on the fact that the first major efficacy regulation occurred in 1962. Focusing on the discretion granted to Congress and administrative agencies to regulate in light of new information, the court determined that “a lack of government interference throughout history might be some evidence that a right is deeply rooted. But standing alone, it cannot be enough.”<sup>38</sup> In sum, the court found evidence that the states and the federal government historically have regulated access to unapproved drugs, but it also concluded that a history of such regulation was not necessary to reject the argument that a constitutional right to access exists.

### *B. Common Law Doctrines Supporting a Right of Access*

After determining that the absence of efficacy regulation for much of our nation’s history was not enough to support a fundamental right of access, the court considered whether the common law doctrines of necessity, intentional interference, and self-defense supported a fundamental right of self-preservation. Much of this discussion focused on whether an unapproved drug of uncertain safety and efficacy could be considered necessary for prolonging the life of a terminally ill patient.

#### *1. The Doctrine of Necessity*

Necessity, or choice of evils, provides an individual with a defense when “physical forces beyond the actor’s control rendered illegal conduct the lesser of

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34. *See id.* at 703, 706.

35. *Id.* at 703.

36. *See id.* at 703-04. Specifically, the law sought to prevent “dangerous and intolerable” drug selling practices by prohibiting surgeons and apothecaries from selling patients greater quantities of drugs than the patients needed and from concealing the composition and treatment value of drugs. EDWARD KREMERS, GLENN SONNEDECKER & GEORGE URDANG, *KREMERS AND URDANG’S HISTORY OF PHARMACY* 158 (1986).

37. *See Abigail Alliance*, 495 F.3d at 704.

38. *Id.* at 706.

two evils.”<sup>39</sup> Relying on *United States v. Oakland Cannabis Buyers’ Cooperative*,<sup>40</sup> the majority dismissed the necessity argument because Congress had previously expressly eliminated a necessity defense in the context of access to unapproved drugs.<sup>41</sup> Through the FDCA, Congress explicitly restricted patients’ access to only those drugs that were approved as safe and effective, thereby eliminating a necessity defense for terminally ill patients.<sup>42</sup> Because Congress had clearly eliminated the necessity defense by passing the FDCA, the court did not reach the question of whether the necessity doctrine could ever provide support for a constitutional right.<sup>43</sup> In rejecting the necessity defense, the majority also relied on the fact that there is significant uncertainty regarding whether unapproved drugs can save patients’ lives.<sup>44</sup>

By contrast, the dissent argued that the necessity defense is evidence of a tradition of protection for the right to self-preservation. The dissent drew an analogy to *Cruzan v. Director, Missouri Department of Health*. In *Cruzan*, the Supreme Court acknowledged a fundamental right to refuse medical treatment grounded in the tort of battery.<sup>45</sup> Recognition of this right did not constitutionalize the tort of battery, nor did it take away Congressional power to override the common law protection of battery.<sup>46</sup> It simply took the existence of battery law protections as evidence of an underlying constitutional right to refuse medical treatment, just as, according to the dissent, the necessity defense is evidence of an underlying constitutional right to self-preservation.<sup>47</sup>

Although the majority relied on Congress’s elimination of the necessity defense and did not explicitly address these arguments by the dissent, there is reason to doubt that necessity could ground a constitutional right to medical self-defense. Professor Carter Snead has convincingly argued that necessity cannot

39. *Id.* at 707 (quoting *United States v. Oakland Cannabis Buyers’ Cooperative*, 532 U.S. 483, 490 (2001)).

40. 532 U.S. 483 (2001).

41. *See Abigail Alliance*, 495 F.3d at 707-08 (“Under any conception of legal necessity, one principle is clear: The defense cannot succeed when the legislature itself has made a determination of values . . . . Congress may limit or even eliminate a necessity defense that might otherwise be available. That is precisely what the FDCA has done.”).

42. *See id.*

43. *See id.*

44. *Abigail Alliance*, 495 F.3d at 709 n.15 (“[T]he safety and efficacy records of experimental drugs are not fully known. We thus cannot know until after the clinical testing process has been completed that these drugs are in fact necessary.”).

45. *Id.* at 718 (Rogers, J., dissenting) (citing *Cruzan v. Director, Mo. Dep’t of Health*, 497 U.S. 261 (1990)).

46. *See id.* at 718.

47. *See id.*

support the right to access unapproved drugs because of the uncertainty inherent in using such drugs.<sup>48</sup> One of the legal elements of the necessity defense is that “the individual must believe in good faith that the unlawful act will remedy the greater evil.”<sup>49</sup> Given the uncertainty surrounding the safety and efficacy of drugs in clinical trials, Snead argued that terminally ill patients cannot assert in good faith that such drugs are necessary to save their lives.<sup>50</sup> Without some degree of confidence that the means used will save the patient’s life, there cannot be a viable claim to exercise the right.

In the majority’s and dissent’s disagreement about the necessity defense, there are two factors at play. The first is the amount of certainty needed to trust that a particular means of self-defense will be useful, and the second factor is the desperation that may drive one to use a means of self-defense even if it is unlikely to be effective. A terminally ill patient who has no other treatment options could “believe in good faith” that an unapproved drug is the only thing that could possibly save her life and is therefore necessary for prolonging her life, despite evidence that the drug is unlikely to be effective.<sup>51</sup> Other contexts in which the necessity defense is used do not help resolve which of these factors should receive greater weight. It is not clear how to take into account uncertainties regarding whether an actor’s conduct will successfully protect him.<sup>52</sup> There is likely to be some degree of uncertainty about any extreme

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48. See Snead, *supra* note 20, at 10.

49. *Id.*

50. *Id.* (“It seems more accurate to say . . . terminally ill patients strongly hope (with some evidence derived from animal models) that the experimental unapproved therapy will yield some benefit.”).

51. Cf. *Abigail Alliance*, 495 F.3d at 715 (Rogers, J., dissenting) (“The court commits a logical error of dramatic consequence by concluding that the investigational drugs are somehow not ‘necessary.’ While the potential cures may not prove *sufficient* to save the life of a terminally ill patient, they are surely *necessary* if there is to be any possibility of preserving her life.”) (internal citation omitted); Geetaa Anand, *Saying No to Penelope*, WALL ST. J., May 1, 2007, at A1 (quoting the father of a terminally ill four-year-old girl as saying: “If anything has a prayer of saving her, how can you argue it’s not the right thing to do?”).

52. The legal literature does not discuss this question in depth, although cursory references to the interaction between the necessity doctrine and uncertainty can be found. See, e.g., Steven M. Bauer & Peter J. Eckerstrom, *The State Made Me Do It: The Applicability for the Necessity Defense to Civil Disobedience*, 39 STAN. L. REV. 1173, 1180 n.40 (1987) (discussing the fact that “[c]ausation is seldom an issue because necessity cases only reach trial after the defendant has performed an act averting some harm, so the court can look at the act retrospectively”); Shaun P. Martin, *The Radical Necessity Defense*, 75 U. CIN. L. REV. 1527, 1586 (2005) (observing that when assessing the efficacy of lawful and nonlawful alternatives, “[b]ecause there is inherent uncertainty regarding the consequences of any future act, any assessment of efficacy is both nonbinary and probabilistic”).

measure taken to protect one's life; an abortion may not succeed in saving the life of the mother and a handgun aimed at an intruder may not fire. It may be that the law only allows for the necessity defense when the likelihood that the measure will succeed is above some threshold of certainty, and medical procedures like abortions or weapons like handguns are assumed to function above this threshold of certainty. Alternatively, unapproved drugs may fall into a category of their own, because complicated scientific judgments are a prerequisite to establishing their safety and efficacy.

Resolving when drugs should be made available requires complex analysis of many factors, including the existing data about safety and efficacy, the severity of the diseases they would be used to treat, and the available alternatives. The policy solution to this problem has been to allow the FDA to regulate the testing and approval of drugs and to determine what evidence is needed before a particular drug can be made available for use. Therefore, the existence of a necessity defense does not directly pertain to the question of access to experimental therapy and cannot support a right of access to therapy before it has been approved.

## 2. *The Tort of Intentional Interference*

Abigail Alliance also argued that the tort of intentional interference provides support for a right to access unapproved drugs. This tort consists of a tortfeasor preventing an individual from providing aid that is *necessary* to another's bodily security.<sup>53</sup> However, the majority concluded that withholding unapproved drugs is not intentional interference because drugs that have not been proven safe and effective cannot be considered necessary to bodily security.<sup>54</sup> Thus, FDA regulations that restrict access to unapproved drugs do not prevent patients from receiving necessary aid, and intentional interference does not help establish a constitutional right to access.<sup>55</sup>

The dissent countered that the tort of intentional interference does provide grounding for the self-preservation interest in accessing unapproved drugs. In some cases, investigational treatments are the only means terminally ill patients have for prolonging their lives.<sup>56</sup> The majority “confuse[d] what is necessary with what is sufficient” when it concluded that unapproved drugs cannot be considered “reasonably necessary” because they have not been proven safe and

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53. *Abigail Alliance*, 495 F.3d at 708 (citing RESTATEMENT (FIRST) OF TORTS § 326).

54. *See id.* at 708-09.

55. *See id.*

56. *See id.* at 719 (Rogers, J., dissenting).

effective.<sup>57</sup>

Again, the crux of the disagreement between the majority and the dissent is how to evaluate the uncertain effects of untested drugs on terminally ill patients. At the time the patients want the drugs, neither doctors nor lawyers nor policymakers can know what effects, if any, those drugs may have. The dissent disregards this inherent uncertainty because of the lack of other options for saving the patient's life. The majority, on the other hand, relies on this uncertainty to dismiss the claim that unapproved drugs could ever be necessary, without acknowledging the lack of alternative treatments for patients. Balancing the many considerations involved is difficult when the choice before the court is binary—the court can either recognize a constitutional right of access or not. Agencies like the FDA may be able to make more nuanced judgments about access policy in general, and about particular drugs, based upon the available data. The FDA can create limited programs of access for individuals in great need when there are data to support that the drug will be safe and effective enough, weigh the risks and benefits to determine which particular conditions or patients should be eligible for these programs, or choose not to allow access in particular cases.

### *C. Right to Self-Defense*

Another argument asserted in favor of a constitutional right to access unapproved drugs was that both self-defense and abortion jurisprudence ground the right to self-preservation or medical self-defense.<sup>58</sup>

#### *1. Traditional Self-Defense as a Basis for the Right*

Self-defense and a right to self-preservation are clearly related concepts. A claim of self-defense can be made “when a victim is being attacked by an aggressor and uses reasonable force to overcome immediate danger.”<sup>59</sup> Abigail Alliance argued that the Supreme Court’s abortion jurisprudence has demonstrated that traditional self-defense applies to the medical context.<sup>60</sup> According to Abigail Alliance, the analogy between medical self-defense and traditional self-defense is not disturbed by the fact that drugs pose risks of side

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57. *Id.*

58. *See id.* at 717-22.

59. *Id.* at 709 (majority opinion).

60. *See id.* They argued that in addition to recognizing the right to privacy, *Roe v. Wade* “recognized another, entirely separate right to abortion: a woman's right to abort a fetus at any stage of a pregnancy if doing so is necessary to preserve her life or health.” *Id.*

effects because an act of traditional self-defense may also pose risks.<sup>61</sup> For example, a victim's attempt to defend herself may anger her attacker, leading her attacker to harm her more egregiously than he otherwise would have.<sup>62</sup> Under this reasoning, terminally ill patients should be permitted to access unapproved drugs even if those drugs pose serious risks.

The majority found the self-defense analogy inapt,<sup>63</sup> concluding that "terminally ill patients cannot fairly be characterized as using reasonable force to defend themselves when they take unproven and possibly unsafe drugs."<sup>64</sup> Abigail Alliance sought the right to assume "enormous risks in pursuit of *potentially* life-saving drugs," not the right to defend one's own life through the use of reasonable force.<sup>65</sup> Furthermore, the majority distinguished the interest in access to unapproved drugs from a woman's right to protect her health by terminating a pregnancy because terminating a pregnancy has known or estimable therapeutic value, while unapproved drugs do not.<sup>66</sup> Again, the court relied on the uncertain safety and efficacy of unapproved drugs to reject medical self-defense as a basis for a constitutional right.<sup>67</sup>

In opposition to the majority's reasoning, constitutional law scholar Eugene Volokh has argued forcefully for the right to medical self-defense. Volokh's first justification for a constitutional right to medical self-defense, its similarity to lethal self-defense, is based on the premise that a constitutional right to lethal self-defense exists.<sup>68</sup> Volokh argues that there are two important limitations on medical self-defense, both of which also apply to lethal self-defense.<sup>69</sup> These similarities between the limitations on lethal self-defense and medical self-defense appear to be the only basis Volokh provides to demonstrate that the two

61. *See id.*

62. *See id.*

63. *See id.* at 709-10.

64. *Id.* at 710.

65. *Id.* at 709-10.

66. *See id.* at 710.

67. *See id.*

68. For a full description of Volokh's arguments in favor of finding a constitutional right to lethal self-defense, see Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Treatments, and Payment for Organs*, 120 HARV. L. REV. 1813 (2007). Volokh's claim that lethal self-defense has constitutional roots has not been directly challenged by those who have responded to his assertion of a right to medical self-defense; however, there may be some debate about the constitutional roots of the lethal self-defense doctrine. *See, e.g.*, Kimberly Kessler Ferzan, *Self-Defense and State*, 5 OHIO ST. J. CRIM. L. 449, 473 (2008) ("First, it seems unimaginable that there is not a constitutional right to act in self-defense. Second, there does not seem to be any clear answer as to where one might find it.").

69. Volokh, *supra* note 68, at 1821.

rights are analogous.<sup>70</sup>

First, he argues that both rights are limited to situations in which the defense is both necessary to prevent death or “radically debilitating” harm and exercised against the source of the threatened harm.<sup>71</sup> For example, a victim may not injure a person who is not her attacker, and a terminally ill patient may not steal a drug from a drug company.<sup>72</sup> A terminally ill patient may, however, attack her disease with a “voluntarily provided” drug.<sup>73</sup>

The second limitation that Volokh elaborates is that both rights only exist in the face of an imminent threat.<sup>74</sup> A victim has a right to use lethal self-defense against an attacker only when a lethal response is necessary and the victim has no alternatives.<sup>75</sup> According to Volokh, a terminally ill patient similarly may use medical self-defense only when she is diagnosed with a “medical threat” and there is no “permitted satisfactory therapy.”<sup>76</sup> Volokh does not define what would constitute permitted satisfactory treatments, so it is difficult to determine when a patient could make a valid claim for access to unapproved therapy on his view.

Volokh’s relatively thin analogy between medical self-defense and traditional self-defense does not withstand critical examination.<sup>77</sup> Lethal self-defense “is conceived as a justification for the *use of force* to repel the application of *force* by another.”<sup>78</sup> Terminally ill patients seeking access to unapproved drugs cannot be understood to be using force against others.<sup>79</sup> Perhaps one could argue that terminally ill patients use force against their diseases when they seek medical treatment, and in that way they are like victims of crime who fight their attackers with lethal self-defense.<sup>80</sup> However, equating

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70. *See id.* at 1821.

71. *See* Volokh, *supra* note 68, at 1821-22. In Volokh’s view, radically debilitating or serious threats include the threat of dementia or paralysis but not the common cold or minor bruises.

72. *See id.*

73. *Id.* at 1822.

74. *See id.* at 1823-24.

75. *See id.* at 1823.

76. *Id.* at 1824.

77. *See* Richard M. Cooper, Response, 121 HARV. L. REV. F. 31, 32 (2007) (“In arguing by analogy for a ‘right of medical self-defense,’ Professor Volokh disregards the ways in which the proposed analogy does not hold.”); Snead, *supra* note 20, at 6 (“Granting for the sake of argument that there is a fundamental unenumerated right to lethal self-defense, it seems that this is materially different from the kind of entitlement Professor Volokh argues for in the medical domain.”).

78. Snead, *supra* note 20, at 7.

79. *See id.*; *see also* Abigail Alliance v. von Eschenbach, 495 F.3d 695, 710 (D.C. Cir. 2007) (“[T]erminally ill patients cannot fairly be characterized as using reasonable force to defend themselves when they take unproven and possibly unsafe drugs.”).

80. *See* Snead, *supra* note 20, at 7.

disease to human attackers is problematic.<sup>81</sup> Disease and death are fundamentally a part of human existence.<sup>82</sup> Life-threatening human attacks are relatively rare.<sup>83</sup> If self-defense is expanded to encompass disease threats, we will be left “in a state of perpetual emergency; permanently in the sphere of exceptions rather than rules. Taken to an extreme, this attitude might be corrosive of ethical safeguards crucial to the respect for persons in the realm of biomedical research.”<sup>84</sup> For example, if terminal illness is viewed as an emergency equivalent to a lethal attack perpetrated by another person, important protections, like informed consent, may be disregarded in favor of doing anything and everything possible to save a patient, regardless of the risks and that patient’s preferences.<sup>85</sup> Such an approach could also justify overriding individual patient rights in favor of important research that can address diseases that pose large risks for many others in society. For these reasons, Volokh’s analogy is unpersuasive.

## 2. Medical Self-Defense and Abortion

Volokh also argues that the Supreme Court’s abortion jurisprudence supports the right to medical self-defense by affirming a woman’s right to abort a postviability fetus to protect her own health.<sup>86</sup> The political controversy around abortion generally, and postviability abortion specifically, suggests that abortion jurisprudence may not be a promising basis for a right to medical self-defense.<sup>87</sup> Furthermore, within abortion jurisprudence itself, legislative deference is recommended in instances of scientific uncertainty.<sup>88</sup> *Gonzales v. Carhart*,<sup>89</sup>

81. *See id.* at 8-9.

82. *See id.* at 8.

83. *See* Melonie Heron et al., *Deaths: Final Data for 2006*, NAT’L VITAL STATISTICS REP., Apr. 17, 2009, at 1, 5 tbl.B, available at [http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\\_14.pdf](http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_14.pdf) (finding that assault was the fifteenth leading cause of death in the United States in 2006, accounting for only 0.8% of deaths).

84. Snead, *supra* note 20, at 8. Scholars have also offered other, less persuasive arguments that dispute the analogy between lethal and medical self-defense. For example, the law prescribes the relationships between persons, but not between persons and bacteria, viruses, genes, or other agents of disease. *See* Cooper, *supra* note 77, at 32-33. Also, a victim carries out lethal self-defense with whatever means are handy, while a terminally ill patient must engage in a transaction in interstate commerce to carry out medical self-defense. *See id.* at 33-34. These arguments may take an overly literal approach to the concept of self-defense.

85. *See* Snead, *supra* note 20, at 9.

86. *See* Volokh, *supra* note 68, at 1824 (“The Supreme Court has already recognized medical self-defense in one context: abortion needed to protect the woman’s life or health.”).

87. *See* Snead, *supra* note 20, at 3.

88. *Gonzales v. Carhart*, 550 U.S. 124, 166-67 (2007).

decided a month before Volokh published his article but likely after Volokh wrote the piece, suggests that courts should defer to “legislative judgment about the medical necessity of certain interventions” when there is ambiguity regarding the safety and efficacy of the intervention.<sup>90</sup> Issues about legislative deference are discussed later,<sup>91</sup> but it is important to note that a right to medical self-defense would require deference to an individual’s judgment (and not the legislature’s judgment) about medical necessity in the face of scientific uncertainty. If courts were to take this approach, they would come into conflict with the *Carhart* holding.<sup>92</sup>

#### *D. Judicial Reluctance to Recognize New Fundamental Rights*

Because the majority opinion in *Abigail Alliance* found no constitutional right to access unapproved drugs, the court determined that the FDA’s policy restricting access to unapproved drugs was subject to rational basis review.<sup>93</sup> The court then concluded that the FDA’s policy was rationally related to the legitimate government purpose of protecting patients from “unreasonable risks from investigational drugs that may be neither safe nor effective” and affirmed the district court’s decision.<sup>94</sup>

There are additional reasons that the court might have reached this verdict that were not explicitly addressed in the case. One other such reason is that extending substantive due process protection to previously unrecognized fundamental rights is an extraordinary exercise of power. The Supreme Court has

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89. 550 U.S. 124.

90. Snead, *supra* note 20, at 4; *see also* Cooper, *supra* note 77, at 37 (“In [*Gonzales v. Carhart*], the Supreme Court observed that it ‘has given state and federal legislatures wide discretion to pass legislation in areas where there is medical and scientific uncertainty.’”) (quoting *Gonzales v. Carhart*, 127 S. Ct. 1610, 1636 (2007)).

91. *See* Section II.B, *infra*.

92. *Carhart*, 550 U.S. 124.

93. *Abigail Alliance v. von Eschenbach*, 495 F.3d 695, 712 (D.C. Cir. 2007); *see also* *Washington v. Glucksberg*, 521 U.S. 702, 721, 728 (1997) (holding that if the interest at issue is not a protected liberty interest, the government may burden that interest as long as the infringing policy is “rationally related to legitimate government interests”).

94. *Abigail Alliance*, 495 F.3d at 712-14. By contrast, the dissent considered whether the liberty interest to save one’s life was deeply rooted in our traditions and implicit in the concept of ordered liberty. The dissent concluded that this interest was entrenched in our nation’s history, dating back to Samuel Adams’s 1772 reference to “the duty of self-preservation.” *Id.* at 717 (Rogers, J., dissenting). Having determined that a protected liberty interest existed, the dissent would have remanded the case to the district court to determine whether “there exist[ed] a compelling governmental interest, narrowly tailored, to overcome the Alliance’s interest.” *Id.* at 728.

explained that:

[W]e “have always been reluctant to expand the concept of substantive due process because guideposts for responsible decisionmaking in this unchartered area are scarce and open-ended.” By extending constitutional protection to an asserted right or liberty interest, we, to a great extent, place the matter outside the arena of public debate and legislative action. We must therefore “exercise the utmost care whenever we are asked to break new ground in this field,” lest the liberty protected by the Due Process Clause be subtly transformed into the policy preferences of the Members of this Court.<sup>95</sup>

Moreover, as argued below,<sup>96</sup> this area is one in which “there is no defect in the system of democratic deliberation and . . . reasonable people might decide the underlying questions of value and fact either way.”<sup>97</sup> Thus, courts may rightly be more reluctant to intervene here.

Furthermore, the consequences of recognizing a right to medical self-defense may be dangerous. A right to medical self-defense might create “an exemption for a large class of transactions from a central provision of the drug regulatory system that has been instrumental in creating the conditions in which medical products, including drugs to treat life-threatening and otherwise serious medical conditions, are developed.”<sup>98</sup> Such an exemption might necessitate radical changes to FDA policies and the Controlled Substances Act.<sup>99</sup> Courts might be reluctant to recognize a right to medical defense that is destructive of trusted and important regulatory programs. For these reasons, and for the reasons examined above, it is easy to understand the decision reached in *Abigail Alliance*. Recognizing a fundamental right to access unapproved drugs is a tenuous proposition that is unlikely to be revisited by the courts.

95. *Glucksberg*, 521 U.S. at 720 (quoting *Collins v. Harker Heights*, 503 U.S. 115, 125 (1992)) (citations omitted).

96. Section II.B, *infra*.

97. Cass R. Sunstein, *The Right to Die*, 106 YALE L.J. 1123, 1162 (1997).

98. Cooper, *supra* note 77, at 35.

99. *See id.* A decision that was destructive of these regulatory schemes might be viewed as analogous to *Lochner v. New York*, 198 U.S. 45 (1905). *See* Cooper, *supra* note 77, at 39. *Lochner* was an early twentieth century decision in which the Supreme Court invalidated a law that aimed to protect the health of bakers by limiting the number of hours they could work, on the ground that it violated a constitutional right to freely contract. *See* 198 U.S. at 53. *Lochner* ushered in an era in which the Court overturned more laws and regulations than it historically had invalidated, and it has been widely criticized as an example of judicial overreaching by defining constitutional rights too broadly. *See, e.g.,* Keith E. Whittington, *Congress Before the Lochner Court*, 85 B.U. L. REV. 821, 821 (2005).

## II. CONTRACTUAL AND QUASI-CONTRACTUAL CLAIMS TO OBTAIN ACCESS TO EXPERIMENTAL THERAPY THROUGH LITIGATION

Abigail Alliance's attempt to establish a constitutional right of access to experimental therapy may have been unsuccessful, but others have brought cases with the aim of expanding access to experimental therapies under contractual and quasi-contractual legal theories. However, these claims are unlikely to be successful, in part because courts properly recognize that the judicial system is not the appropriate forum for review of this issue.

### *A. Efforts to Obtain Access Through Litigation*

Although there has been a great deal of discussion about litigation as an effective tool to compel access to experimental therapy,<sup>100</sup> patients' hopes and commentators' concerns seem largely unfounded. The majority of individual claims seeking access to unapproved drugs have involved allegations that a research sponsor had a contractual duty to provide access to the experimental therapy.<sup>101</sup> Whether the amount of litigation increases may turn on whether courts determine that by providing informed consent documents to research participants, research sponsors incur contractual obligations. If courts find contractual claims can flow from consent documents, a variety of novel legal theories may be applied against research sponsors, which could lead to a flurry of litigation. In this section, we examine whether contractual claims for access are legally

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100. John D. Winter, *Is it Time to Abandon FDA's No Release from Liability Regulation for Clinical Studies?*, 63 FOOD & DRUG L.J. 525, 526 (2008) ("At the same time that manufacturers are being required to accept the additional risks associated with pediatric and geriatric patients in clinical studies, there has been a growing number of theories of clinical trial liability and a trend of patients advocating for early or continued access to investigational medicines when a sponsor did not wish to proceed with a study, principally because of an uncertain risk/benefit ratio. To the extent courts or FDA prospectively require greater access to investigational medicines because of patient demand, sponsor liability risks are increased."). See generally Michelle M. Mello, David M. Studdert & Troyen A. Brennan, *The Rise of Litigation in Human Subjects Research*, 139 ANNALS INTERNAL MED. 40, 40 (2003) (arguing that the rise in litigation will lead to a "more legalistic, mechanistic approach to ethical review that does not further the interests of human subjects or scientific progress").

101. See *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128 (3d Cir. 2008) (discussing a claim for access based on a theory of promissory estoppel); *Vinion v. Amgen Inc.*, 272 Fed. Appx. 582 (9th Cir. 2008); *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006); *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993); *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006). In addition to these cases, there has been at least one claim alleging a right of access based on unfair business practices. See Bernadette Tansey, *The Dilemma of a Dying Man*, S.F. CHRON., Feb. 16, 2003, at 11.

viable.<sup>102</sup>

Courts have split on the question of whether informed consent documents for clinical trials constitute contracts.<sup>103</sup> One court has found that informed consent documents are unilateral contracts.<sup>104</sup> Other courts have distinguished informed consent documents from contracts either because of the absence of consideration and a meeting of the minds or because researchers have discretionary power to end the study at any time.<sup>105</sup> A subset of the courts that have distinguished informed consent documents from contracts have found that while the documents are not themselves contracts, elements of the consent documents or consent processes may support contractual claims.<sup>106</sup> As a result of these diverse decisions, the legal effect of informed consent documents remains unclear.<sup>107</sup>

102. We do not attempt to predict the very complicated issue of what consequences might flow from increased litigation. It is possible that if courts are more inclined to recognize consent forms as contracts, research sponsors will simply include disclaimers of any obligation to provide access to experimental therapy. Courts may respond, however, by finding some clauses unconscionable. Furthermore, consent forms are subject to review by institutional review boards that may not permit sponsors to make such broad disclaimers. Therefore, it is hard to know what the effects of increased litigation might be.

103. See *Vinion v. Amgen Inc.*, 272 Fed. Appx. 582 (9th Cir. 2008); *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006); *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993); *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006). Courts have also split on the question of whether informed consent documents for medical treatment constitute contracts. See, e.g., 61 AM. JUR. 2D *Physicians, Surgeons, and Other Healers* § 164 (2008).

104. *Dahl*, 7 F.3d at 1404-05.

105. See *Abney*, 443 F.3d at 547; *Suthers*, 441 F. Supp. 2d at 482-84.

106. See *Vinion*, 272 Fed. Appx. 582; *Abney*, 443 F.3d at 547; *Suthers*, 441 F. Supp. 2d at 482-84.

107. Compare Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 972 (2006) (“Notwithstanding the fact that most subjects sign written consent documents to enroll in a study, courts have displayed reluctance to find binding contractual obligations in the research setting.”), and E. Haavi Morreim, *Medical Research Litigation and Malpractice Tort Doctrines: Courts on a Learning Curve*, 4 HOUS. J. HEALTH L. & POL’Y 1, 33 (2003) (arguing that there is no discernible trend suggesting that consent documents constitute contracts), with Michelle M. Mello & Steven Joffe, *Compact Versus Contract – Industry Sponsors’ Obligations to Their Research Subjects*, 356 NEW ENG. J. MED. 2737, 2738 (2007) (“Only a few courts have ruled on whether a research consent form can constitute a legal contract that binds the investigators and institution, but their answer has nearly always been yes.”).

*1. Decisions Holding that Informed Consent Documents Constitute Contracts*

Plaintiffs have succeeded in only one case regarding access to unapproved therapy; there, the court provided access by holding that the informed consent document constituted a contract.<sup>108</sup> In *Dahl v. HEM Pharmaceuticals Corp.*, the Ninth Circuit found that an informed consent document constituted a unilateral contract.<sup>109</sup> A unilateral contract exists when an offer does not invite a return promise and the offer is accepted through performance, such as when a reward is offered for a lost pet.<sup>110</sup> The petitioners in *Dahl* participated in a double-blind, placebo-controlled clinical trial<sup>111</sup> of Ampligen, an unapproved drug.<sup>112</sup> They had signed consent forms in which HEM Pharmaceuticals promised to offer them Ampligen for twelve months through an open-label study<sup>113</sup> at the conclusion of the placebo-controlled trial, provided that Ampligen proved more effective than the placebo.<sup>114</sup> At the conclusion of the trial, HEM refused to provide the participants with Ampligen, and the petitioners sought a preliminary injunction that would compel HEM to provide them Ampligen.<sup>115</sup>

The court held that a binding unilateral contract was formed once the participants completed the double-blind, placebo-controlled trial.<sup>116</sup> In *Dahl*,

108. *Dahl*, 7 F.3d 1399. In *Grimes v. Kennedy Krieger Institute, Inc.*, the Maryland Supreme Court found that an informed consent document for research constituted a bilateral contract. 782 A.2d 807, 843, 858 (Md. 2001). However, *Grimes* is outside the scope of this Article because it did not concern claims for access to unapproved therapy.

109. *Dahl*, 7 F.3d at 1404; see also Mello & Joffe, *supra* note 107, at 2740 (noting that *Dahl* “supports the general proposition that a consent form can create a binding obligation on an industry sponsor to provide the investigational medication after the trial is over”); Saver, *supra* note 107, at 973 n.135 (noting that the *Dahl* court held that the informed consent form and other study documents constituted a unilateral contract).

110. See RESTATEMENT (SECOND) OF CONTRACTS § 50 (1981); see also *Dahl*, 7 F.3d at 1404-05 (explaining unilateral contracts).

111. In a double-blind, placebo-controlled trial, some participants receive the experimental drug and some receive the placebo; neither the participants nor the researchers know who is receiving the experimental drug or the placebo. See *Dahl*, 7 F.3d at 1401.

112. See *id.*

113. In an open-label study both the researchers and the participants know that the participants are receiving the experimental drug and not a placebo or control drug. See *id.* at 1402.

114. See *id.* at 1401-02.

115. See *id.* at 1401. FDA rejected HEM’s application for a treatment Investigational New Drug (IND) for Ampligen due to safety concerns about liver toxicity, severe abdominal pain, and irregular heartbeat. But FDA did permit HEM to continue with clinical trials of Ampligen. See *id.* at 1402.

116. See *id.* at 1405.

“[t]he deal was, ‘if you submit to our experiment, we will give you a year’s supply of Ampligen at no charge.’”<sup>117</sup> The Ninth Circuit concluded that a unilateral contract was formed because the participants “performed by submitting to the double-blind tests. They incurred the detriment of being tested upon for HEM’s studies in exchange for the promise of a year’s treatment of Ampligen.”<sup>118</sup> While this holding was a success for the terminally ill plaintiffs, the situation in *Dahl* is unlikely to recur. Pharmaceutical companies and sponsors have likely learned from this case that explicit promises to provide future access should not be made in consent forms.

## 2. Decisions that Distinguish Informed Consent Documents from Contracts

In two very similar cases brought by research participants against Amgen, courts concluded that consent documents may provide evidence for some contractual obligations but did not hold that the consent documents themselves constituted contracts.<sup>119</sup> Both *Abney v. Amgen* and *Suthers v. Amgen* involved Parkinson’s patients who had participated in Phase 2 clinical trials of a synthetic protein delivered to the brain.<sup>120</sup> In *Abney*, the protocol and the informed consent document stated that participants could elect to continue the protein treatment for twenty-four months following the end of the trial, but they also stated that Amgen could choose to discontinue the trial for various reasons, including safety concerns.<sup>121</sup> In *Suthers*, subjects were told they might be invited to participate in a study after the initial trial was over in which they would be guaranteed to receive the protein, but the informed consent document did not indicate the length of time that they would receive treatment nor did it guarantee they would

117. *Dahl*, 7 F.3d at 1405.

118. *Id.*

119. See *Abney v. Amgen, Inc.*, 443 F.3d 540, 547 n.5 (6th Cir. 2006); *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478, 483 (S.D.N.Y. 2006). But see Mello & Joffe, *supra* note 107, at 2738 (arguing that the *Abney* court held that the informed consent document created a contract between the university and the participants).

120. See *Abney*, 443 F.3d at 543-44; *Suthers*, 441 F. Supp. 2d at 481; Mello & Joffe, *supra* note 107, at 2737. Parkinson’s disease is a progressive neurodegenerative disorder that involves the loss of nerve cells in the brain that produce the neurotransmitter dopamine. Symptoms include motor problems (e.g., tremors) as well as cognitive deficits. The protein at issue in *Abney* and *Suthers*, glial cell line-derived neurotrophic factor (GDNF), was considered a promising treatment for Parkinson’s disease for various reasons, including its positive effect on dopaminergic neuron survival in vitro. See Erika Check, *Second Chance*, 13 NATURE MED. 770, 770 (2007); Carrie B. Hurelbrink & Roger A. Barker, *The Potential of GDNF as a Treatment for Parkinson’s Disease*, 185 EXPERIMENTAL NEUROLOGY 1, 1 (2004).

121. See *Abney*, 443 F.3d at 544; *Suthers*, 441 F. Supp. 2d at 481.

be chosen for the follow-up study.<sup>122</sup> Nevertheless, the plaintiffs in *Suthers* claimed that they were promised they would “receive [the protein] indefinitely.”<sup>123</sup>

After new findings raised safety and efficacy concerns about the protein used in these two trials, Amgen exercised its discretion to halt the trials and all use of the protein.<sup>124</sup> Following Amgen’s decision to stop the trial, the research participants filed suit against Amgen and moved for a preliminary injunction to compel the company to provide them with the treatment.<sup>125</sup> The participants based part of their motion on breach of contract.<sup>126</sup> The plaintiffs in both *Abney* and *Suthers* alleged that the informed consent document created a binding contract through which Amgen was obligated to supply them with the protein.<sup>127</sup>

The *Abney* and *Suthers* decisions addressed the participants’ contract claims differently. In *Abney*, the Sixth Circuit held that even if the informed consent documents constituted contracts, they did not bind the sponsor, Amgen.<sup>128</sup> The documents memorialized an agreement between the participants and the researchers, and the researchers were independent contractors hired by the sponsor.<sup>129</sup> The court found that, under Kentucky law, independent contractors could not be considered Amgen’s agents or employees.<sup>130</sup> Therefore, any agreement between the researchers and subjects could not bind Amgen.<sup>131</sup> Because the court concluded that any agreement memorialized in the consent document did not bind Amgen, it did not reach the question of whether the

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122. *Suthers*, 441 F. Supp. 2d at 483-84.

123. *Id.* at 484.

124. *See Abney*, 443 F.3d at 544-45. The new findings were: 1) several of the participants had developed neutralizing antibodies that Amgen worried would clear the synthetic GDNF from the patients’ systems or attack naturally-occurring GDNF, which would result in permanent damage to vital organs; 2) results from a long-term study of GDNF in primates indicated that some of the primates had developed cerebral toxicity; and 3) results of the clinical trial indicated that GDNF was not significantly more effective than placebo. Amgen consulted the FDA before ending the clinical trial. The FDA allowed but did not compel Amgen to supply GDNF to these patients for compassionate use. After consulting three bioethicists and five Parkinson’s disease experts, Amgen concluded it should halt use of GDNF. *See Abney*, 443 F.3d at 545.

125. *See id.* at 545; *Suthers*, 441 F. Supp. 2d at 482.

126. *See Abney*, 443 F.3d at 546; *Suthers*, 441 F. Supp. 2d at 480.

127. *See Abney*, 443 F.3d at 545, 547; *Suthers*, 441 F. Supp. 2d at 482.

128. *Abney*, 443 F.3d at 548.

129. *Id.*

130. *See Abney*, 443 F.3d at 547; *Abney v. Amgen, Inc.*, 2005 U.S. Dist. LEXIS 14258, at \*17 (E.D. Ky. July 8, 2005).

131. *Abney*, 443 F.3d at 549.

consent document constituted a contract.<sup>132</sup>

In *Suthers*, the court concluded that the participants may be able to prove a set of facts to support the claim that the informed consent document imposed some contractual obligations on Amgen.<sup>133</sup> However, the court only referred to the possibility that consent forms could provide evidence for certain contractual obligations and never referred to the consent forms as contracts.<sup>134</sup> Moreover, the court concluded that Amgen did not have the specific contractual obligation asserted by the participants—the obligation to supply the treatment to participants indefinitely—because the consent document informed participants that Amgen could halt the clinical trial at any time.<sup>135</sup> By deciding the issues on these grounds, the court did not reach the question of whether the researchers were Amgen’s agents.<sup>136</sup> The *Suthers* decision therefore suggests that a consent form may provide evidence for some contractual obligations, but it also indirectly distinguishes consent documents from contracts.<sup>137</sup>

In a third case brought against Amgen, the Ninth Circuit addressed an oral rather than a written contract claim and concluded that the informed consent document did not support the plaintiffs’ claim that Amgen breached an oral contract.<sup>138</sup> The plaintiffs in *Vinion v. Amgen* were two individuals suffering from asbestosis, an incurable lung condition,<sup>139</sup> who entered a clinical trial of Amgen’s drug Enbrel.<sup>140</sup> The plaintiffs alleged that during the initial consent process for

132. See *Abney*, 443 F.3d at 547.

133. See *Suthers*, 441 F. Supp. 2d at 486. The *Suthers* court did not reach the question of whether the investigators were Amgen’s agents because it determined that no “clear and unambiguous” promise of access to GDNF was made. See *id.*

134. See *id.* at 482-84.

135. See *id.* at 484.

136. See *id.* at 486.

137. See *Suthers*, 441 F. Supp. 2d at 483 (“That the Informed Consent contains language consistent with the existence of *some* contractual obligation on the part of Amgen does not answer the question of whether the contractual promise that plaintiffs seek to impose can be fairly read into the Informed Consent.”).

138. See *Vinion v. Amgen*, 52 Fed. Appx. 582 (9th Cir. 2008).

139. Asbestosis is caused by the inhalation of asbestosis fibers. Asbestosis patients suffer from scarred lung tissue and progressively decreasing breathing capacity. Asbestosis can cause death or other serious diseases, including lung cancer. See Thomas A. Sporn & Victor L. Roggli, *Asbestosis*, in *PATHOLOGY OF ASBESTOS-ASSOCIATED DISEASES* 71 (Victor L. Roggli, Tim D. Oury & Thomas A. Sporn, eds., 2004); MayoClinic.com, *Asbestosis*, <http://www.mayoclinic.com/health/asbestosis/DS00482> (last visited Nov. 18, 2009).

140. Appellants’ Opening Brief at 7-9, *Vinion v. Amgen*, 252 Fed. Appx. 582 (9th Cir. 2008) (No. 05-36121). Enbrel was approved for the treatment of arthritis but was not approved for the treatment of asbestosis. See *id.* at 9.

the trial, the investigator (who was also their personal physician) made an oral promise that Amgen would provide them with Enbrel free of charge at the conclusion of the trial.<sup>141</sup> According to the plaintiffs, this oral promise constituted a contract that Amgen breached when it did not provide them with Enbrel after the trial concluded.<sup>142</sup>

Both the Montana district court and the Ninth Circuit rejected the plaintiffs' oral contract claim.<sup>143</sup> The courts examined the consent document, as well as the contract between Amgen and the principal investigator, to assess the oral contract claim, concluding that "the written agreements did not contain a promise that the Companies would provide the study drug for free indefinitely once the study ended."<sup>144</sup> Neither court directly addressed the question of whether an informed consent document constitutes a contract. However, the courts' decisions to look to the consent documents for evidence of an oral contract suggest a willingness to use consent documents as evidence of some contractual obligations<sup>145</sup> but not necessarily as contracts in themselves.

As in *Abney*, the *Vinion* court found that the investigators were not acting as Amgen's agents and therefore could not make oral promises to bind the company.<sup>146</sup> In her dissent, Judge Betty Fletcher suggested that this finding did not take adequate account of Montana state law, which allows for agency to be established in a variety of ways.<sup>147</sup> More specifically, under Montana law, the mere silence of the principal can create ostensible agency in another party.<sup>148</sup> She

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141. *See id.* at 8.

142. *See id.* at 22-29. The plaintiffs could have obtained Enbrel legally through an off-label prescription; however, the plaintiffs' insurance would not pay for Enbrel, and the plaintiffs could not afford to purchase Enbrel themselves. *See id.* at 8.

143. *See Vinion*, 52 Fed. Appx. at 584; *Vinion v. Amgen*, CV 03-202-M-DWM, slip op. at 2 (D. Mont. Nov. 9, 2005), available at <http://www.websupp.org/data/DMT/9:03-cv-00202-166-DMT.pdf>. In the Ninth Circuit appeal, Judge Betty Fletcher dissented; however, she agreed with the majority that the plaintiffs' contract claims were properly dismissed by the district court. *See Vinion*, 52 Fed. Appx. at 585 (Fletcher, J., dissenting).

144. *Vinion*, 272 Fed. Appx. 582; *see also Vinion*, CV 03-202-M-DWM, slip op. at 8 ("Neither the original Consent Form nor the amended form contained any indication that study subjects would be entitled to receive Enbrel after the study was terminated or after they were withdrawn from the study, even if they had shown a positive response to the drug.").

145. *See Vinion*, 272 Fed. Appx. 582; *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478, 483 (S.D.N.Y. 2006); *Vinion*, CV 03-202-M-DWM, slip op. at 8.

146. *Vinion*, 272 Fed. Appx. at 584 (affirming that the investigator was not the "Companies' actual or apparent agent" because "there was no action or inaction by the Companies that would have led the Appellants to a reasonable belief that [the investigator] was the Companies' agent").

147. *Id.* at 585 (Fletcher, J., dissenting).

148. *Id.* (citing *C.A.R. Transp. Brokerage Co., Inc. v. Darden Rests., Inc.*, 213 F.3d 474 (9th

argued that the informed consent document failed to indicate that the investigator was not Amgen's agent and that provisions of the document could be read to imply that the investigator was, in fact, Amgen's agent.<sup>149</sup> Judge Fletcher contended that, "In the present context, while it is true that the nature of clinical studies requires pharmaceutical companies to let the doctors deal with patients, it is incumbent upon the companies to make its role and the physician's role clear at the outset."<sup>150</sup>

The question of whether investigators may be acting as agents of the research sponsor when obtaining informed consent may vary by state and also by how the informed consent document describes the relationship between investigator and sponsor. This agency issue is important because to the extent that research sponsors employ independent contractors to conduct the research, informed consent discussions and documents are less likely to support a contractual claim against the sponsor. Judge Fletcher's opinion suggests that there may be some legal interpretations that would hold sponsors liable for the statements made by independent contractors they hire, but only in certain cases. Of course, the more lucrative contractual claims are those made against research sponsors, so the increasing use of independent contractors or organizations to conduct research may decrease incentives to bring suit.

### 3. Recovery Under Promissory Estoppel

A recent case tested the viability of using a promissory estoppel theory in claims for access to experimental therapy. In *Gunvalson v. PTC Therapeutics, Inc.*, a teenager seeking access to an unapproved drug for muscular dystrophy succeeded in obtaining a preliminary injunction under the theory of promissory estoppel (or quasi-contract).<sup>151</sup> The district court found that the company was obligated to provide access and issued the injunction.<sup>152</sup> However, the defendants filed for interlocutory appeal, and the Third Circuit overturned the decision, concluding that the district court had abused its discretion because Gunvalson's promissory estoppel claim was not reasonably likely to succeed on the merits.<sup>153</sup>

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Cir. 2000)).

149. *Id.* at 586.

150. *Id.* at 585.

151. *Gunvalson v. PTC Therapeutics, Inc.*, Civ. No. 08-cv-3559, 2008 U.S. Dist. LEXIS 64012, at \*4 (D.N.J. Aug. 21, 2008). The plaintiff also moved for the preliminary injunction on fraudulent misrepresentation and negligent misrepresentation grounds; however, because the court granted the injunction on the promissory estoppel ground, the discussion focuses on that theory. *See id.*

152. *See id.* at \*7.

153. *See Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128, 129 (3d Cir. 2008).

This result is in line with the general trend of courts looking unfavorably on claims for access to experimental therapy. What is interesting about the *Gunvalson* case, however, is that the fact pattern and analysis in the case illuminate how strong the barriers are to obtaining access to experimental therapy through litigation.

First, even when plaintiffs craft creative arguments that lower the evidentiary burdens, it may still be difficult to obtain access to unapproved treatments. The plaintiff in *Gunvalson* was Jacob Gunvalson, a sixteen-year-old boy diagnosed with Duchenne Muscular Dystrophy (DMD).<sup>154</sup> Jacob's mother became an advocate of DMD research, and through her advocacy work, she developed a relationship with officers and employees of PTC Therapeutics (PTC). In 2006, PTC began a Phase 2a clinical trial of PTC124, an unapproved drug being studied for the treatment of DMD,<sup>155</sup> in which participants were selected to receive PTC124 after eligibility was determined using a muscle biopsy.<sup>156</sup> At the time, Jacob was enrolled in a different clinical trial, and the Gunvalsons claimed that PTC's vice president, a friend of the family, advised them to keep Jacob in that trial, assuring them Jacob could receive PTC124 at a later date.<sup>157</sup> This alleged promise became the basis for the Jacob's promissory estoppel claim.<sup>158</sup> Promissory estoppel claims require less documentary and testimonial evidence than written or even oral contract claims. In order to obtain a preliminary injunction, Jacob merely had to demonstrate that his claim had a reasonable likelihood of success.<sup>159</sup> However, even with this relatively low evidentiary burden, Jacob's claim ultimately did not succeed.

Second, although some courts may be swayed by the very sympathetic

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154. See *Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*2; Malorye Allison, *Gunvalson Decision Sends Shockwaves Through Industry*, 11 NATURE BIOTECH. 1201, 1201 (2008).

155. See *Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*11; see also Reed Abelson, *Advocating a Treatment, but Denied Access to It*, N.Y. TIMES, July 17, 2008, at C3; PTC Therapeutics, About Us, [http://www.ptcbio.com/1.0\\_about\\_us.aspx](http://www.ptcbio.com/1.0_about_us.aspx) (last visited Nov. 18, 2009).

156. *Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*2. PTC conducted the phase 2a trial for four weeks using thirty-eight participants. See Defendant PTC Therapeutics, Inc.'s Memorandum of Law in Opposition to Plaintiff's Motion for a Preliminary Injunction at 6, *Gunvalson v. PTC Therapeutics, Inc.*, Civ. No. 08-cv-3559, 2008 U.S. Dist. LEXIS 64012 (D.N.J. Aug. 21, 2008) [hereinafter Defendant PTC Therapeutics' Memorandum].

157. See *Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*3; Brief of Plaintiffs Jacob, John and Cheri Gunvalson in Support of Their Motion for a Preliminary Injunction, *Gunvalson v. PTC Therapeutics, Inc.*, Civ. No. 08-cv-3559, 2008 U.S. Dist. LEXIS 64012 (D.N.J. Aug. 21, 2008).

158. See *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. at 129-30; *Gunvalson*, 2008 U.S. Dist. LEXIS 64012 at \*3-\*4.

159. See *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. at 129-30; *Gunvalson*, 2008 U.S. Dist. LEXIS 64012 at \*4.

nature of claims for access, as the district court may have been in this case,<sup>160</sup> many others will not, as the Third Circuit demonstrated.<sup>161</sup> DMD, the disease with which Jacob was diagnosed, is a genetic disease without any approved treatments that causes degenerative deterioration of skeletal and cardiac muscle tissue, usually leading to death by age twenty-five.<sup>162</sup> The grave nature of Jacob's condition and his youth may have made his promissory estoppel claim particularly sympathetic.<sup>163</sup> Indeed, the district court concluded that the Gunvalsons were reasonably likely to be able to show that PTC had a legal obligation to provide Jacob PTC124 based on their promissory estoppel claim, despite the fact that there was a serious question about whether Jacob could show that he detrimentally relied on the vice president's alleged promise.<sup>164</sup> However, the Third Circuit overturned the district court's holding based on their conclusion that Jacob could not demonstrate he had detrimentally relied on the statements that he need not enroll in the earlier trial in order to be eligible for later trials.<sup>165</sup> The court noted in particular that Mrs. Gunvalson had sent emails expressing her disappointment that Jacob had been found ineligible for the trial, indicating that Jacob's reason for not enrolling in the initial trial was his ineligibility, not any statement that the vice president might have made.<sup>166</sup> The highly sympathetic

160. *See Gunvalson*, 2008 U.S. Dist. LEXIS 64012.

161. While the judges of the Third Circuit were not swayed by their sympathies, the opinion indicates the court was sensitive to the family's circumstances. *Gunvalson*, 303 Fed. Appx. at 130 (“[W]e are sympathetic to the plight of Jacob and his family. . . . Nevertheless, we are constrained by the law . . .”).

162. *See Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*2; Lisa Phillips, *Contract Law and Ethical Issues Underscore the Latest Lawsuit About Access to Experimental Drugs for Duchenne Muscular Dystrophy*, NEUROLOGY TODAY, Sept. 2008, at 20, 20.

163. *See Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*14-\*16 (noting that the harm to Jacob without access to the medication is much greater than the harm to PTC in distributing the medication and describing the Gunvalson's unique relationship with PTC's vice president); *see also Gunvalson*, 303 Fed. Appx. at 130 (noting the court's sympathy for the Gunvalson family).

164. *See Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*7. Specifically, there was some question about whether Jacob had the correct diagnosis to be eligible for PTC's Phase 2a trial. PTC Therapeutics argued that when it was enrolling participants in the Phase 2a trial, Jacob was diagnosed with Becker Muscular Dystrophy (BMD), not DMD. Only patients diagnosed with DMD were eligible to participate in clinical trials of PTC124. Thus, according to PTC, Jacob did not enroll in the trial because he was ineligible, not because he relied on a promise made by the vice president. But the district court found that “the evidence suggests that Jacob actually does have DMD, not BMD.” *See Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*13.

165. *See Gunvalson*, 303 Fed. Appx. at 130.

166. *See id.* at 130 n.6 (“It is apparent from the record [that Jacob's ineligibility] is the real reason [Ms. Gunvalson] did not attempt to enroll Jacob in the Phase 2a trial, as Mrs. Gunvalson e-mailed a number of parties reporting her disappointment upon hearing of his ineligibility.”).

nature of Jacob's claim did not sway the Third Circuit to interpret the evidence in his favor.

Third, the major bottleneck in claims for access may be neither the FDA nor the courts, but rather the drug companies themselves, who are wary of granting access in a way that may interfere with obtaining final approval for the drug in question.<sup>167</sup> Prior to initiating litigation, Jacob asked PTC to provide him the drug through "an FDA-regulated 'compassionate use' exception."<sup>168</sup> PTC refused Jacob's request because it feared that allowing individual access to PTC124 outside of the clinical trials would hinder its ability to enroll participants in the Phase 2b clinical trial and delay the approval of PTC124.<sup>169</sup> Thus, this case illustrates that because drug companies may have many reasons not to allow access, the most effective approach may be to address companies' incentives.

In sum, although informed consent documents have been interpreted to give rise to contractual obligations in some cases, this change may not forecast a rise in successful claims. Courts have generally looked unfavorably on contractual claims seeking access to experimental therapy.<sup>170</sup> Even when plaintiffs have sympathetic claims that are carefully crafted to lower their evidentiary burdens, courts are still wary of granting litigants access to unapproved drugs, as the Third Circuit decision in *Gunvalson* demonstrated. Nevertheless, there are a few exceptions to this trend, including *Dahl* and the district court's decision in *Gunvalson*.<sup>171</sup> Thus, pharmaceutical companies and research sponsors may still rightly fear litigation costs, novel legal claims, and the uncertainty of litigation. In the next section, we examine the reasons for judicial reluctance to grant access and conclude that they are warranted.

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167. See, e.g., George J. Annas, *Cancer and the Constitution – Choice at Life's End*, 357 NEW ENG. J. MED. 408, 411 (2007) ("[T]he major bottleneck in the compassionate-use program has never been the FDA. The manufacturers have no incentives to make their investigational products available outside clinical trials.").

168. See *Gunvalson*, 2008 U.S. Dist. LEXIS 64012, at \*4.

169. See *id.* (noting that PTC denied Jacob's request for compassionate use); Defendant PTC Therapeutics' Memorandum, *supra* note 156, at 8 (arguing that allowing access outside of the clinical trials will hinder PTC's ability to enroll participants in its trials and gain FDA approval); PTC Therapeutics, PTC News, Appeals Court Rules for PTC, [http://www.ptcbio.com/PTCStatement.1\\_news.htm](http://www.ptcbio.com/PTCStatement.1_news.htm) (last visited Nov. 18, 2009) ("The sooner we can complete the required clinical trials and get this drug approved, the sooner all who suffer from the type of Duchenne Muscular Dystrophy (DMD) addressed by PTC124 may benefit.").

170. See *Vinion v. Amgen Inc.*, 272 Fed. Appx. 582 (9th Cir. 2008); *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006); *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006).

171. See *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993); *Gunvalson*, 2008 U.S. Dist. LEXIS 64012. *But see* *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128, 129 (3d Cir. 2008) (vacating the lower court's decision to grant a preliminary injunction).

*B. Why Courts Should Not Consider Contractual Claims Brought by Former or Potential Research Subjects*

Courts may not be well-placed to assess whether claims for access to unapproved therapy should be granted. In fact, judges appear to be reluctant to recognize the right to medical self-defense because doing so would require the judicial branch to decide complex issues related to science and medicine.<sup>172</sup> The Supreme Court has held that the judiciary has limited institutional competence when “making distinctions in a murky constitutional context, or where line-drawing is inherently complex.”<sup>173</sup> Instead, Congress and administrative agencies are deemed the appropriate governmental bodies to make controversial policy decisions in the context of scientific uncertainty.<sup>174</sup>

Courts and scholars have offered various reasons why legislatures, rather than courts, generally should make complicated policy decisions. The legislature can consider the broad and long-term effects of a particular choice.<sup>175</sup> Conversely, “[the] basic function of courts is . . . the function of settling disputes” based on past facts and present law.<sup>176</sup> Legislatures may also consider a wider range of facts and evidence than courts may consider,<sup>177</sup> or they may

172. Cooper, *supra* note 77, at 40. For example, a court may be asked to determine whether a terminally ill patient truly has no treatment options other than an unapproved drug.

173. Ayotte v. Planned Parenthood of N. New Eng., 546 U.S. 320, 330 (2006); *see also* Marshall v. United States, 414 U.S. 417, 427 (1974) (“When Congress undertakes to act in areas fraught with medical and scientific uncertainties, legislative options must be especially broad and courts should be cautious not to rewrite legislation, even assuming, *arguendo*, that judges with more direct exposure to the problem might make wiser choices.”).

174. *See* Snead, *supra* note 20, at 12 (“[A]s with other contested matters in a morally pluralistic society, this issue must be resolved in the public square through the democratic process.”).

175. *Pers. Adm’r of Mass. v. Feeney*, 442 U.S. 256, 272 (1979) (holding that Congress should consider “the manner in which a particular law reverberates in a society”); *Prentis v. Atlantic Coast Line Co.*, 211 U.S. 210, 226 (1908) (“A judicial inquiry investigates, declares and enforces liabilities as they stand on present or past facts and under laws supposed already to exist. That is its purpose and end. Legislation on the other hand looks to the future and changes existing conditions by making a new rule to be applied thereafter to all or some part of those subject to its power.”).

176. Robert F. Blomquist, *The Good American Legislature: Some Legal Process Perspectives and Possibilities*, 38 AKRON L. REV. 895, 921 (2005) (quoting HENRY M. HART, JR. & ALBERT M. SACKS, *THE LEGAL PROCESS: BASIC PROBLEMS IN THE MAKING AND APPLICATIONS OF LAW* 343 (William N. Eskridge, Jr. & Philip P. Frickey eds., 1994)) (internal quotation marks omitted); *see also* *Sinclair Refining Co. v. Atkinson*, 370 U.S. 195, 215 (1962) (holding that a court’s “task is the more limited one of interpreting the law as it now stands”).

177. *See* Robert A. Schapiro, *Judicial Deference and Interpretive Coordinacy in State and Federal Constitutional Law*, 85 CORNELL L. REV. 656, 701 (2000).

develop the necessary evidence by holding hearings or commissioning studies.<sup>178</sup>

Congress and administrative agencies also possess the freedom to experiment with policy solutions that can later be changed; courts do not have the same degree of flexibility.<sup>179</sup> For example, if the FDA's regulations pertaining to access to unapproved drugs are inadequate, the regulations can be modified through new regulations or a change to the FDCA.<sup>180</sup> This freedom to experiment with various policy solutions may be especially useful for scientific questions, which involve continuously evolving technology. Conversely, if circumstances warrant a change in the interpretation of the law, a court must wait for an appropriate controversy to present itself before making the necessary change. Once a court has made a change, it cannot make any necessary adjustments or overturn its previous decision until a new controversy arises.

In addition, the legislature, unlike the judiciary, is directly subject to political pressure and public opinion.<sup>181</sup> Through the democratic process, the public can express its disapproval of a particular policy or policies by voting legislators out of office.<sup>182</sup> Legislative decisions, therefore, are more likely to take into account majoritarian values and contain inherent democratic legitimacy.<sup>183</sup> Such legitimacy may be important in situations that require the government to balance conflicting goals, such as early availability for promising new drugs and obtaining sufficient information about the safety and efficacy of pharmaceuticals.

It may be appropriate for courts to decide policy issues when the political

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178. *See id.*; cf. Cooper, *supra* note 77, at 40 (noting that the FDA has unique access to the results of clinical trials, and personnel with the scientific expertise needed to evaluate the data). Additionally, these arguments may be construed as arguments in favor of judicial deference to legislative bodies. However, authors like Cooper discuss the broader policy implications of allowing courts to decide scientific and policy issues, and not the narrower legal question of whether *Chevron* deference is warranted in the face of agency expertise, and we have followed suit. *See Chevron, U.S.A., Inc. v. Natural Res. Defense Council*, 467 U.S. 837 (1984) (establishing the legal test for determining when courts should defer to administrative agencies' statutory interpretations).

179. *Ferguson v. Skrupa*, 372 U.S. 726, 730 (1963) ("Legislative bodies have broad scope to experiment with economic problems, and this Court does not sit to 'subject the State to an intolerable supervision hostile to the basic principles of our government and wholly beyond the protection which the general clause of the Fourteenth Amendment was intended to secure.'" (quoting *Sproles v. Binford*, 286 U.S. 374, 388 (1932))).

180. *See Cooper, supra* note 77, at 40.

181. *See Edward O. Correia, A Legislative Conception of Legislative Supremacy*, 42 CASE W. RES. L. REV. 1129, 1134 (1992).

182. *See id.*

183. *See id.*

process has failed.<sup>184</sup> However, in the context of medical self-defense, there is little evidence that this has occurred.<sup>185</sup> Instead, the evidence suggests that the political process has functioned appropriately to address the issue of access to unapproved drugs.<sup>186</sup> After Abigail Alliance filed suit against the FDA, a bill was introduced into the Senate that would have expanded access to unapproved drugs, and the FDA proposed new regulations that clarified and expanded its access programs, which will be discussed below.<sup>187</sup>

Courts also may not be the appropriate venue for consideration of claims to access experimental therapy because they wield powerful equitable tools, including preliminary injunctions.<sup>188</sup> At the preliminary injunction stage, courts simply have to assess whether a claim is reasonably likely to succeed, and they may rule as the district court did in *Gunvalson*.<sup>189</sup> From the perspective of a patient seeking access to experimental therapy, a preliminary injunction requiring a company to provide the experimental therapy is exactly the relief desired.<sup>190</sup> This approach would be likely to result in a piecemeal approach to granting access to experimental therapy. Moreover, courts may not be well-placed to sift through data from preclinical and Phase 1 and 2 studies to determine whether receiving experimental therapy poses any risks to the litigant. The sympathetic nature of claims to access experimental therapy may lead courts to make compassionate decisions that would not work at a policy level.<sup>191</sup> In *Gunvalson*,

184. See Cooper, *supra* note 77, at 41. Some might argue that the Court's intervention in *Brown v. Board of Education*, 347 U.S. 483 (1954) to move the racial integration of schools forward was an example of a judicial response to a failure of the political processes.

185. See Cooper, *supra* note 77, at 42.

186. See *id.*

187. See *id.*; see also Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R. § 312) (providing the text of the proposed changes to FDA's access regulations); Charging for Investigational Drugs, 71 Fed. Reg. 75,168, 75,172-73 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R. § 312) (providing the text of the proposed changes to FDA's regulations concerning prices for unapproved drugs). See Sections III.A-E, *infra*, for a discussion of the proposed regulations.

188. See, e.g., *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128, 128 n.3 (3d Cir. 2008).

189. See *id.*

190. Cf. Michael M. Grynbaum, *Judge Orders Drug Maker To Provide Experimental Treatment to Terminally Ill Teenager*, N.Y. TIMES, Aug. 20, 2008, at C3 (quoting *Gunvalson*'s attorney saying, "[t]his was the relief that we sought," after the district court granted the preliminary injunction).

191. See *Gunvalson*, 303 Fed. Appx. at 130 ("As we explained in open court following oral argument, we are sympathetic to the plight of Jacob and his family. . . . Nevertheless, we are constrained by the law to conclude that the *Gunvalsons* cannot demonstrate either a clear and

the Third Circuit appeared to have recognized the danger of these tools when it overturned the district court ruling.<sup>192</sup>

Finally, courts should be wary of opening the floodgates of litigation. Contract law offers a variety of claims that plaintiffs can bring. Courts have now litigated claims in contract law that alleged bilateral contracts, unilateral contracts, oral contracts, and promissory estoppel.<sup>193</sup> The fact that these types of claims have been for the most part unsuccessful may not fully stem the tide of litigation on claims for access to experimental therapy.<sup>194</sup> The possible claims for plaintiffs are varied enough that courts should be wary of encouraging further litigation in this area. For all of these reasons, courts are appropriately reluctant to provide litigants access to unapproved drugs.

### III. EXISTING LAWS AND REGULATIONS PROVIDING EXPANDED ACCESS TO UNAPPROVED DRUGS

Given that the courts may not have the institutional competence to address claims for access to unapproved therapy, a more appropriate way to handle these claims may be through regulation. After the D.C. Circuit panel decision in *Abigail Alliance*, the FDA issued a proposed rule to modify its expanded access regulations.<sup>195</sup> The FDA intended that the new rule would broaden the availability of investigational drugs through increasing awareness of expanded access programs and procedures and by “eas[ing] the administrative burdens on individual physicians seeking investigational drugs for their patients, as well as the burdens on sponsors who make investigational drugs available for treatment use.”<sup>196</sup>

In August 2009, the FDA published a final version of the rule that establishes three programs through which terminally and seriously ill patients may access unapproved drugs.<sup>197</sup> The three programs are based on the size of the

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definite promise or detrimental reliance, requirements for a promissory estoppel claim.”).

192. *See id.*

193. *See id.*; *Vinion v. Amgen Inc.*, 272 Fed. Appx. 582 (9th Cir. 2008); *Abney v. Amgen, Inc.*, 443 F.3d 540 (6th Cir. 2006); *Dahl v. HEM Pharmaceuticals Corp.*, 7 F.3d 1399 (9th Cir. 1993); *Suthers v. Amgen, Inc.*, 441 F. Supp. 2d 478 (S.D.N.Y. 2006).

194. *Cf. Mello*, *supra* note 100, at 43 (arguing that research-related litigation is likely to increase).

195. *See Expanded Access to Investigational Drugs for Treatment Use*, 71 Fed. Reg. 75,147 (proposed Dec. 14, 2006) (to be codified at 21 C.F.R. § 312); Jerry Menikoff, *Beyond Abigail Alliance: The Reality Behind the Right To Get Experimental Drugs*, 56 KAN. L. REV. 1045, 1058 (2008).

196. *Id.*

197. *See Expanded Access to Investigational Drugs for Treatment Use*, 74 Fed. Reg. 40,900

patient population seeking access: 1) treatment use (for “widespread” use), 2) intermediate-size patient population use, and 3) individual use.<sup>198</sup> The rule establishes different criteria and risk-benefit ratios for the different patient population sizes,<sup>199</sup> although it is not clear why different standards are justified.<sup>200</sup> In addition to the three expanded access programs, the rule clarifies the FDA’s policy regarding what sponsors are permitted to charge expanded access patients.<sup>201</sup>

*A. General Requirements and Safeguards for Access*

For a patient to legally receive an unapproved drug outside of clinical trials under the three expanded access programs, two conditions must be met. Not only must the FDA approve an expanded access application for treatment use or individual use, but the drug sponsor must agree to provide expanded access to an unapproved drug.<sup>202</sup> As mentioned above, many sponsors may believe it is not in their best interest to apply for and provide expanded access, and the FDA has no authority to mandate the provision of an unapproved drug by an unwilling sponsor.<sup>203</sup>

The final rule also outlines some requirements and safeguards that are applicable to all three programs,<sup>204</sup> which are provided in Tables 1 and 2 below.

(Aug. 13, 2009) (to be codified at 21 C.F.R. § 312). Prior to the publication of the final rule, there were only two programs—treatment use and individual use—relevant to the discussion of terminally ill patients’ attempts to gain access to unapproved drugs. *See* 21 U.S.C. § 360bbb(a), (c) (2006); 21 C.F.R. § 312.36 (2008).

198. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,900.

199. *See id.* at 40,944-45.

200. The individual use program establishes more lenient eligibility criteria than do the programs intended to provide access to larger groups of patients. However, it may be unfair to create more lenient eligibility criteria for individual patients, who, as the earliest to seek access, are likely to be relatively affluent and connected. Expanded access programs are likely not very accessible for the poor, uninformed, and unconnected. *But see* Judy Vale, *Expanding Expanded Access: How the Food and Drug Administration Can Achieve Better Access to Experimental Drugs for Seriously Ill Patients*, 96 GEO. L.J. 2143, 2161-62 (2008) (arguing that more lenient criteria for individual patients is appropriate).

201. *See* Charging for Investigational Drugs, 74 Fed. Reg. 40,872 (Aug. 13, 2009) (to be codified at 21 C.F.R. 312).

202. *See* 21 C.F.R. §§ 312.34, 312.36 (2008) (not mentioning any authority to force drug companies to provide expanded access).

203. *See id.*

204. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,943-44.

Table 1: Requirements <sup>205</sup>
1) Patients have a “serious <sup>206</sup> or immediately life-threatening disease” <sup>207</sup> and no alternative treatment.
2) The potential benefits justify the potential risks.
3) Expanded access does not interfere with clinical trials to support marketing approval.

Table 2: Safeguards <sup>208</sup>
1) A physician who treats expanded access patients is considered an investigator, and “must comply with the responsibilities for investigators.” <sup>209</sup>
2) A drug company or physician who applied for expanded access on behalf of patients is a sponsor (or sponsor-investigator), and “must comply with the responsibilities for sponsors.” <sup>210</sup>

### B. Treatment Use

Treatment use is directed at groups of patients, rather than individuals, and is intended to allow “widespread” access.<sup>211</sup> Under the final rule, the treatment use program does not differ significantly from the treatment use program under the former regulations.<sup>212</sup> The final rule suggests that drugs should not be made

205. *Id.* at 40,943.

206. A serious disease is defined as “a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.” Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,943.

207. An immediately life-threatening disease is “a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.” *Id.*

208. *Id.* at 40,943-44.

209. Investigator responsibilities include reporting adverse events to the sponsor and ensuring that informed consent requirements are met. *See id.* at 40,943.

210. Sponsor responsibilities include submitting safety reports to the FDA and ensuring physician-investigators are qualified to administer the unapproved drug. *See id.* at 40,943-44.

211. *See* Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,945.

212. *Compare* Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at

available earlier than Phase 2 clinical trials, but it does not mandate that timeline.<sup>213</sup> In addition to the general requirements, three criteria must be satisfied in order for a drug to be provided under the treatment access program: 1) the drug must be in clinical trials or clinical trials must have been completed; 2) the sponsor must be pursuing approval with due diligence; and 3) there must be sufficient scientific or clinical evidence of the safety and effectiveness of the drug to support the expanded access use. The final rule also requires sponsors to ensure that investigators comply with the research protocol and applicable regulations.<sup>214</sup>

### *C. Intermediate-Size Patient Population Use*

The intermediate-size patient population expanded access program represents the final rule's most significant change to the former regulations.<sup>215</sup> Intermediate-size patient population use is intended to provide expanded access to "a patient population smaller than that typical of a treatment [Investigational New Drug (IND)] or treatment protocol," a group of a size not mentioned in the previous regulations.<sup>216</sup>

The final rule establishes two safeguards for intermediate use: 1) each year,

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40,945 (allowing the FDA to permit widespread treatment use of experimental drugs if the patients have a life-threatening illness, the drug is being investigated in clinical trials, and the sponsor is actively pursuing marketing approval), *with* 21 U.S.C. § 360bbb(c) (2006) (allowing the granting of expanded access of an investigational new drug if there is no alternative therapy available, the drug is being investigated under clinical trials, and the sponsor of the drug is pursuing marketing approval), *and* 21 C.F.R. § 312.34 (2008) (allowing the FDA to permit treatment use of an investigational drug if there is no alternative treatment, the drug is being investigated in clinical trials, and the sponsor is pursuing marketing approval).

213. *See* Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,945.

214. *See id.*

215. *Compare* Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,944-45 (allowing the FDA to permit investigational drugs to be used for intermediate-size patient populations under certain circumstances), *with* 21 U.S.C. § 360bbb (2006) (allowing access to investigational drugs only for individual patients and widespread use), *and* 21 C.F.R. §§ 312.34, 312.36 (2008) (describing how an investigational drug may be made available to patients with life-threatening diseases in accordance with a treatment protocol or treatment IND); *see also* Alice K. Marcee, *Expanded Access to Phase II Clinical Trials in Oncology: A Step Toward Increasing Scientific Validity and Compassion*, 63 FOOD & DRUG L.J. 439, 447 (2008) (noting that the "mid-size group access is a new category").

216. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,926; Marcee, *supra* note 215, at 447.

the FDA will reassess whether expanded access is appropriate,<sup>217</sup> and 2) sponsors must ensure that researchers comply with protocol requirements and relevant regulations. Table 3 outlines the three criteria for intermediate-size population use.<sup>218</sup>

Table 3: Intermediate-Size Population Use Criteria <sup>219</sup>
1) "There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use to justify a clinical trial" in a population similar in size to the proposed expanded access population.
2) There must be "preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option."
3) Sponsors must explain in their applications why patients cannot be enrolled in clinical trials, and if drug is not being developed for marketing, why this is the case.

One of the most significant changes in the final rule for intermediate-size use is that it allows "off-label" expanded access (access for patients with a disease other than the one the drug is intended to treat). Sponsors typically study an unapproved drug's safety and efficacy for one indication, even if there is reason to believe that the drug would be safe and effective for other conditions.<sup>220</sup> Some patients like Abigail Burroughs<sup>221</sup> have diseases that are not being studied in clinical trials, and may have great difficulty obtaining access to unapproved medications. For patients like these, allowing off-label expanded access may be critically important in that it offers access to individuals who cannot obtain access through clinical trials.

In addition, the intermediate-size program allows access to drugs not being developed for marketing because they are intended to treat a particularly rare

217. In its reassessment, the FDA will consider "whether it is possible to conduct a clinical study of the expanded access use," "whether providing the investigational drug for expanded access use is interfering with the clinical development of the drug," and whether the number of patients seeking access has increased such that FDA should ask the sponsor to submit an application for a treatment use program. *See Expanded Access to Investigational Drugs for Treatment Use*, 74 Fed. Reg. at 40,945.

218. *See id.* at 40,945-46.

219. *See id.*

220. *Cf.* Steven R. Salbu, *Off-Label Use, Prescription, and Marketing of FDA-Approved Drugs: An Assessment of Legislative and Regulatory Policy*, 51 FLA. L. REV. 181, 186-87 (1999) (explaining that FDA approves drugs for particular conditions).

221. *See, e.g.,* Jacobson & Parmet, *supra* note 1, at 205.

condition.<sup>222</sup> This change is significant because patients with rare conditions may be unfairly barred from expanded access programs if a sponsor halts clinical trials of an unapproved drug because the market for the drug is too small to be profitable.<sup>223</sup> The final rule also provides for access to approved drugs that have been taken off the market or have the same active ingredient as approved drugs.<sup>224</sup>

#### *D. Individual Use*

The final rule's individual use program establishes eligibility criteria similar to the previous individual use program.<sup>225</sup> The final rule requires that, in addition to the general requirements, two criteria must be met for a patient to gain access to an unapproved drug through the individual use program: 1) a "physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease," and 2) the patient must not be able to obtain the drug through clinical trials or another expanded access program.<sup>226</sup>

The most significant new criterion in the final rule is the second one—that a patient on the individual use program must not also be eligible to receive the unapproved drug through a clinical trial or other type of expanded access program. Although the prior regulations mandated that the FDA allow individual use only when it would not interfere with clinical trials,<sup>227</sup> the final rule's more specific requirement that individuals be allowed expanded access only if they cannot receive the unapproved drug as a participant in a clinical trial is a stronger protection. If strictly enforced, it may help to ensure that expanded access programs will not interfere with or impede the completion of clinical trials. This addition should provide reassurance to sponsors that allowing expanded access will not delay the approval process. Protecting the integrity of clinical trials in this fashion is also important to ensure that wider access to approved drugs is not delayed or prevented by the interests of those seeking expanded access to unapproved drugs.

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222. See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,944.

223. Cf. 21 C.F.R. § 312.34(b) (2008) (permitting expanded access only if the sponsor is pursuing full marketing approval with due diligence).

224. See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,944.

225. See 21 U.S.C. § 360bbb(b) (2006); Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,943-44.

226. Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,944.

227. See 21 U.S.C. § 360bbb(b) (2006).

The final rule also creates four additional safeguards for patients.<sup>228</sup> First, treatment is limited to “a single course of therapy for a specified duration unless the FDA expressly authorizes multiple courses or chronic therapy.”<sup>229</sup> Second, the FDA may require a sponsor to monitor the patient receiving individual access if the treatment lasts for an extended length of time.<sup>230</sup> Third, if more than a few patients request individual use, the FDA may require a sponsor to submit a treatment use application.<sup>231</sup> Finally, at the conclusion of the individual use, the sponsor or investigator must provide the FDA “a written summary of the results of the expanded access use, including any adverse effects.”<sup>232</sup>

These additional safeguards may help to ensure the safety of the individual use patients and to encourage the collection of data provided by individual use patients. However, these safeguards are still less protective than those that have been designed for clinical trials. Clinical trials are typically subject to safety monitoring by external committees such as Institutional Review Boards<sup>233</sup> and Data and Safety Monitoring Committees.<sup>234</sup> Usually, trials must be halted if significant safety concerns arise.<sup>235</sup> These protections are not completely replicated by the FDA’s regulations for expanded access programs and may not be possible to replicate in the context of expanded access. When a few individuals obtain access at varied locations across the country without being connected to a particular trial site, the potential for rigorous safety monitoring is greatly reduced.

### *E. Costs that a Drug Sponsor May Recover*

One of the major goals the FDA had for the final rule was to extend its

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228. See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. at 40,944.

229. *Id.*

230. *Id.*

231. *Id.*

232. *Id.*

233. 45 C.F.R. § 46.109 (2008) (requiring Institutional Review Board review of research).

234. FOOD & DRUG ADMIN., GUIDANCE FOR CLINICAL TRIAL SPONSORS: ESTABLISHMENT AND OPERATION OF CLINICAL TRIAL DATA MONITORING COMMITTEES 3-4 (2006), *available at* <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf>

(recommending Data and Safety Monitoring Boards for “large, randomized multisite studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome,” and for any controlled trial of any size that will compare rates of mortality or major morbidity).

235. Michael A. Morse et al., *Monitoring and Ensuring Safety During Clinical Research*, 285 JAMA 1201, 1201 (2001) (explaining the oversight function of institutional review boards and data monitoring committees or data and safety monitoring boards).

previous charging regulations to cover all types of expanded access programs and to describe more specifically the types of costs that sponsors may recover.<sup>236</sup> Sponsors typically are allowed to charge expanded access patients for the unapproved drug for one year from the time of FDA authorization, unless the FDA approves a different time period.<sup>237</sup> Sponsors must meet three criteria for charging patients. First, they must justify the amount they plan to charge and obtain prior written approval from the FDA.<sup>238</sup> Second, the sponsor must provide the FDA with “reasonable assurance that charging will not interfere with developing the drug for marketing approval.”<sup>239</sup> Third, the sponsor cannot charge patients who are not authorized to receive unapproved drugs through the expanded access program.<sup>240</sup>

For all three types of expanded access programs, sponsors may recover “the direct costs of making [the] investigational drug available.”<sup>241</sup> For treatment use and intermediate-size patient population use programs sponsors may recover some additional costs, which are described in the following table.<sup>242</sup>

<b>Table 4: Costs that the Sponsor May Recover for Treatment Use and Intermediate-size Patient Populations<sup>243</sup></b>
1) The cost of “monitoring the expanded access protocol” and other administrative costs directly associated with the expanded access.
2) The cost of complying with reporting requirements.
3) “[O]ther administrative costs directly associated with the expanded access.”

The final rule’s charging regulation offers two benefits when compared with

236. See Charging for Investigational Drugs, 74 Fed. Reg. 40,872, 40,872 (Aug. 13, 2009) (to be codified at 21 C.F.R. § 312).

237. See *id.* at 40,899.

238. See *id.*

239. For treatment use, the assurance must include at least three items: 1) “[e]vidence of sufficient enrollment in any ongoing clinical trial(s) . . . to reasonably assure FDA that the trial(s) will be successfully completed as planned”; 2) “[e]vidence of adequate progress in the development of the drug for marketing approval”; and 3) “[i]nformation submitted under the general investigational plan specifying the drug development milestones the sponsor plans to meet in the next year.” *Id.* This provision appears to safeguard against creating a novel business model in which a company only develops drugs until the expanded access phase and never seeks full approval.

240. See *id.*

241. *Id.*

242. See *id.* at 40,899-900.

243. See *id.*

the previous regulation. First, the final rule explicitly applies to all types of expanded access regulations,<sup>244</sup> while the current regulations do not explicitly address permissible charging practices for individual use.<sup>245</sup> Second, the final rule provides more explicit guidance for sponsors regarding what are permissible charges. For example, the proposed regulation provides specific examples of direct costs that a sponsor may recover, including “raw materials, labor, and nonreusable supplies and equipment used to manufacture the quantity of drug” and “costs to acquire the drug from another manufacturing source, and direct costs to ship and handle (e.g., store) the drug.”<sup>246</sup> The extent to which these clarifications in the final rule are truly beneficial is difficult to anticipate, but as we discuss below,<sup>247</sup> it is not clear that an ability to recover costs is the major bottleneck impeding access to unapproved therapy.

#### F. Alternative Proposals to FDA Regulations

Some commentators have argued that the existing FDA regulations overly restrict which patients are eligible for expanded access.<sup>248</sup> Scholars have offered two proposals that would deregulate expanded access to varying degrees. One proposal would allow completely open, deregulated access to unapproved drugs, while the second proposal would amend the FDCA to lessen FDA control of expanded access.<sup>249</sup> Both deregulation proposals emphasize the importance of patient autonomy.<sup>250</sup> Incidentally, proponents of both proposals also have argued that a constitutional right to access exists and that *Abigail Alliance* was wrongly decided.<sup>251</sup>

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244. *See id.*

245. *See* 21 U.S.C. § 360bbb (2006); 21 C.F.R. § 312 (2008).

246. Charging for Investigational Drugs, 74 Fed. Reg. at 40,899. The final rule also provides examples of indirect costs that sponsors may not recover, including “costs for facilities and equipment used to manufacture the supply of investigational drug, but that are primarily intended to produce large quantities of drug for eventual commercial sale[] and . . . other costs that would be incurred even if the . . . treatment use for which charging is authorized did not occur.” *Id.*

247. *See* discussion *infra* Section IV.B.

248. *See* Meghan K. Talbott, *The Implications of Expanding Access to Unapproved Drugs*, 35 J.L. MED. & ETHICS 316, 318 (2007); Vale, *supra* note 200, at 2160.

249. *See, e.g.*, Richard A. Epstein, *The Erosion of Individual Autonomy in Medical Decisionmaking: Of the FDA and IRBs*, 96 GEO. L.J. 559, 577-80 (2008) (describing open access and the amendments to the FDCA); Steven R. Salbu, *Regulation of Drug Treatments for HIV and AIDS: A Contractarian Model of Access*, 11 YALE J. REG. 401, 420-22 (1994) (describing open access, existing regulations, and a contractarian model).

250. *See* Epstein, *supra* note 249; Salbu, *supra* note 249.

251. *See, e.g.*, Epstein, *supra* note 249, at 577; Robert M. Harper, *A Matter of Life and Death: Affording Terminally Ill Patients Access to Post-Phase I Investigational New Drugs*, 12 MICH. ST.

### 1. Open Access

A few scholars have argued for open access, in which patients may elect to take any unapproved drug that a company will provide and the FDA does not regulate expanded access at all.<sup>252</sup> Open access supporters have acknowledged that most unapproved drugs are eventually proven ineffective or unsafe.<sup>253</sup> However, they argue that an open access model does not threaten the state's interest in promoting public health because the state's interest is limited when "the individual is terminally ill."<sup>254</sup> Moreover, proponents of open access contend that the clinical trials process fails to achieve the public health goal of producing a market of safe and efficacious drugs.<sup>255</sup> Consequently, they argue that the emphasis of the expanded access debate should not be on the state's public health interests but on the importance of patient autonomy.<sup>256</sup> Open access supporters claim that patients are the best parties to decide whether an unapproved drug is an appropriate treatment and in their best interests.<sup>257</sup>

U. J. MED. & L. 265, 286-87 (2008).

252. See Epstein, *supra* note 249, at 574-80; Salbu, *supra* note 249, at 420-22. Salbu actually supports a "contractarian" model of access, which he distinguishes from open access on the assumption that open access would require drug companies to provide unapproved drugs to patients who want them. See Salbu, *supra* note 249, at 429-30. However, other scholars do not advocate an open access model that would require companies to provide unapproved drugs. Instead, they characterize open access the way Salbu characterizes the contractarian model—as a model allowing parties to contract for the sale or purchase of unapproved drugs without government interference or regulation. See Epstein, *supra* note 249, at 574-80. Thus, we do not distinguish between open access and contractarian models.

253. See Epstein, *supra* note 249, at 578.

254. Salbu, *supra* note 249, at 430. Salbu appears to limit this argument to cases in which the terminally ill patient also has no FDA-approved treatments; it is not clear that Epstein would similarly limit the argument.

255. See Epstein, *supra* note 249, at 578 ("It is easy to point to particular cases in which a fuller trial has indicated the imprudence of resorting to certain kinds of therapies. But a fuller analysis would also have to include those cases in which the gold-standard approach *confirmed* the informal field judgment but nonetheless delayed the delivery of the treatment to the market."); Salbu, *supra* note 249, at 421 ("Open-access arguments are further strengthened by the claim that the stringent drug review processes of the 1962 Amendments fail to achieve the ultimate goal of the paternalistic model: the pursuit of public health and safety."). According to open access supporters, open access to unapproved drugs may even help to enhance clinical trials by providing information about use of drugs in a larger number of patients. See Salbu, *supra* note 249, at 432.

256. Epstein, *supra* note 249, at 579.

257. See *id.*; see also Salbu, *supra* note 249, at 420 ("[T]he open-access model is built on a vision of unconstrained patient autonomy and self-determination.").

## 2. *The ACCESS Act*

Several commentators have argued that enacting the Access, Compassion, Care, and Ethics for Seriously Ill Patients Act (ACCESS Act) would best provide terminally ill patients' access to unapproved drugs.<sup>258</sup> The ACCESS Act, first introduced in the Senate in 2005, would amend the FDCA to create a tiered approval process for drugs.<sup>259</sup> The ACCESS Act was intended to offer a compromise position between complete patient autonomy and some FDA control of the expanded access process.<sup>260</sup>

Under the ACCESS Act, if Phase I clinical trials provided preliminary evidence of effectiveness and safety of a drug, and if the drug company was actively pursuing drug approval, the FDA could approve the drug for limited marketing.<sup>261</sup> The FDA could also permit the company to sell the drug for a profit.<sup>262</sup> Patients seeking access to drugs prior to full marketing approval would be required to waive their right to file suit against a drug company.<sup>263</sup>

Supporters, including Abigail Alliance, claim that adopting the ACCESS Act would appropriately balance individual autonomy and the public health need for safe and effective drugs and would also address some of the practical problems associated with expanded access programs.<sup>264</sup> According to its proponents, the ACCESS Act would not interfere with enrollment in clinical trials because, in order to be eligible for early access, patients have to exhaust all available treatment and clinical trial options.<sup>265</sup> ACCESS Act supporters argue

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258. See Harper, *supra* note 251, at 286-87; see also Amy Heverly, *Abigail Alliance is Not the End: A Legislative Solution to a Human Problem*, 12 LEWIS & CLARK L. REV. 825, 842-47 (2008) (advocating legislation consistent with the ACCESS Act with some modifications); Linda Katherine Leibfarth, Note, *Giving the Terminally Ill Their Due (Process): A Case for Expanded Access to Experimental Drugs through the Political Process*, 61 VAND. L. REV. 1281, 1283 (2008) (endorsing the ACCESS Act with some modifications).

259. Access, Compassion, Care, and Ethics for Seriously Ill Patients Act, S. 1956, 109th Cong. (2005); see Harper, *supra* note 251, at 287.

260. See Epstein, *supra* note 249, at 577-78 ("It is clear that the structure of this bill is meant to compromise between the demands for individual access and the demands for public protection.").

261. See Harper, *supra* note 251, at 287 (noting that this option is available for sponsors seeking full marketing approval); see also Access, Compassion, Care, and Ethics for Seriously Ill Patients Act, H.R. 6270, 110th Cong. (2008).

262. See H.R. 6270.

263. See *id.*

264. See Harper, *supra* note 251, at 290.

265. See Harper, *supra* note 258, at 289-90; see also Heverly, *supra* note 258, at 844 (arguing that the ACCESS Act will not interfere with clinical trial enrollment if it is modified such that only

that it will increase drug companies' incentives to provide expanded access by allowing them to profit from expanded access sales.<sup>266</sup> The ACCESS Act is also intended to decrease drug companies' disincentives to provide access by requiring patients to waive liability against drug companies and physicians administering the drugs.<sup>267</sup>

The ACCESS Act is the only proposal that directly addresses physician liability.<sup>268</sup> Under the FDA's final rule, physicians who treat patients with unapproved drugs through expanded access protocols would be responsible for meeting various regulatory requirements, such as reporting adverse events.<sup>269</sup> Ordinarily, physicians may be sued under any of the theories common to research-related litigation or under theories of malpractice for treating patients with unapproved drugs.<sup>270</sup> In contrast to the FDA's regulations, the ACCESS Act would require patients to waive their right to hold physicians liable for adverse events that occur during treatment through an expanded access program.<sup>271</sup> It is not clear whether the ACCESS Act would also waive physicians' liability for failing to meet regulatory reporting requirements.<sup>272</sup>

These proposals for greatly expanding access to unapproved therapy would have a number of negative downstream consequences that their proponents do not fully acknowledge. In light of these consequences, we argue in the next section that these proposals are not in society's interest and that access to

the sickest patients are eligible and personal physicians cannot make clinical trial eligibility determinations); Leibfarth, *supra* note 258, at 1313-14 (arguing that the ACCESS act will not interfere with clinical trial enrollment if FDA promulgates additional regulations prohibiting patients currently enrolled in a clinical trial from leaving the trial to receive expanded access to a drug).

266. See Heverly, *supra* note 258, at 846; Abigail Alliance Website, *supra* note 6.

267. See Harper, *supra* note 251, at 289; see also Heverly, *supra* note 258, at 846 (arguing for allowing drug companies to profit from early access sales, but against a complete waiver of sponsor liability); Leibfarth, *supra* note 258, at 1311-13 (supporting the profit and waiver provisions, but arguing for some marketing restrictions additional to those in the ACCESS Act).

268. See H.R. 6270.

269. See *id.*

270. See Talbott, *supra* note 248, at 317.

271. See H.R. 6270.

272. See *id.* ("No claim or cause of action against a . . . physician who . . . supplies, distributes or prescribes a product subject to an approved Compassionate Investigational Access application shall exist in any Federal or State court for claims of property, personal injury, or death caused by, arising out of, or relating to the design, development, clinical testing and investigation, manufacture, labeling, distribution, sale, purchase, donation, dispensing, prescribing, administration, efficacy, or use of a drug, biological product, or device subject to an approved Compassionate Investigational Access application.").

unapproved drugs should be offered only under very limited circumstances.

#### IV. AVOIDING A POLICY OF EXCEPTIONS: THE ARGUMENT FOR VERY LIMITED ACCESS TO EXPERIMENTAL THERAPY

There are two reasons why access to experimental therapies should be granted only in very limited situations, if at all. First, because there are significant safety and efficacy concerns about unapproved drugs, patients should not receive access to those drugs at early stages outside the context of clinical trials. Second, the solutions proposed attempt to further the interests of a few individuals at significant cost to society. Rather than drafting policy around these exceptional cases, it would be better to reform the general approval process for drugs. Our focus should be on testing interventions efficiently but carefully and making them available to the market as soon as that can be safely achieved.

##### *A. Highly Uncertain Safety and Efficacy*

Access to unapproved therapy should be limited because of the considerable uncertainty about the safety and efficacy of unapproved drugs. It is difficult to overstate the importance of data in determining whether and when medical interventions should be made available to the public. There are several examples of drugs or procedures that were disseminated without being tested sufficiently and resulted in large costs to our health care system, resulting in many patients being subjected to great risk for no clear benefit.<sup>273</sup> The most prominent example is a treatment for breast cancer—high dose chemotherapy and autologous bone marrow transplant—that was effectively adopted as the standard of care before it could be validated in clinical trials.<sup>274</sup> Clinicians and patients were so convinced of its effectiveness that clinical trials were delayed for many years. Yet, when clinical trials were finally conducted, it became clear that the risky procedure offered no benefit over standard, less-risky chemotherapeutic regimens and had

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273. See generally David Atkins et al., *Making Policy When the Evidence is in Dispute*, 24 HEALTH AFF. 102 (2005) (discussing the controversies surrounding screening for prostate cancer, high-dose chemotherapy and bone marrow transplant for breast cancer, antibiotic use, and newborn hearing screening).

274. See generally Cynthia M. Farquhar et al., *High Dose Chemotherapy for Poor Prognosis Breast Cancer: Systematic Review and Meta-Analysis*, 33 CANCER TREATMENT REVS. 325 (2007); Michelle M. Mello & Troyen A. Brennan, *The Controversy Over High-Dose Chemotherapy with Autologous Bone Marrow Transplant For Breast Cancer*, 20 HEALTH AFF. 101 (2001); H.G. Welch & J. Mogielnicki, *Presumed Benefit: Lessons from the American Experience with Marrow Transplantation for Breast Cancer*, 324 BRIT. MED. J. 1088 (2002).

even caused harm.<sup>275</sup> Another example is found in knee surgery—after many years of use, arthroscopic lavage or debridement for osteoarthritis of the knee was found to be no more effective than placebo surgery.<sup>276</sup>

Of all of the drugs that are tested in humans, the vast majority of potential therapeutic agents never make it through the approval process.<sup>277</sup> In Europe and the United States, for every nine compounds that undergo drug testing, only one will ultimately receive regulatory approval.<sup>278</sup> A given therapy may fail for a number of reasons, but the main reason that drugs fail is that they simply do not work.<sup>279</sup> In 2000, the majority of drug failures were due to lack of efficacy, with safety concerns a close second.<sup>280</sup> The drug approval process typically involves three phases of testing,<sup>281</sup> and the Abigail Alliance sought access to unapproved drugs after the first phase. Significantly, however, over 60% of treatments fail after Phase 2,<sup>282</sup> and as many as 45% fail even after entering the final phase of testing.<sup>283</sup>

Much of the litigation around expanded access involves patients suffering from cancer. However, cancer presents unique therapeutic challenges, and approval rates for oncology drugs are even lower than the average; only 5% of oncology drugs ultimately receive approval.<sup>284</sup> Oncology drugs are also unique

275. See, e.g., Farquhar et al., *supra* note 274, at 332 (reporting that there were sixty-five deaths attributed to treatment toxicity among women who received the high dose chemotherapy treatment and only four such deaths among the women in control groups).

276. Shira Bender, Lauren Flicker & Rosamond Rhodes, *Access for the Terminally Ill to Experimental Medical Innovations: A Three-Pronged Test*, 7 AM. J. BIOETHICS 3, 4 (2007).

277. Robert Kinders et al., *Phase 0 Clinical Trials in Cancer Drug Development: From FDA Guidance to Clinical Practice*, 7 MOLECULAR INTERVENTIONS 325, 326 (2007) (“[L]ess than ten percent of Investigational New Drug (IND) applications for novel molecules [move] beyond the earliest stage of development.”).

278. Ismail Kola & John Landis, *Can the Pharmaceutical Industry Reduce Attrition Rates?*, 3 NATURE REVS. DRUG DISCOVERY 711, 711 (2004).

279. Kinders et al., *supra* note 277, at 263.

280. Kola & Landis, *supra* note 278, at 712 (noting that together, efficacy and safety problems accounted for approximately 60% of all failures).

281. *Id.* at 712-13.

282. *Id.* at 712.

283. *Id.*

284. Kinders et al., *supra* note 277, at 326 (“[C]urrent approval rates for new oncology drugs are estimated to be no more than 5% . . . .”); Kola & Landis, *supra* note 278, at 712; see also Eric K. Rowinsky, *Curtailing the High Rate of Late-Stage Attrition of Investigational Therapeutics Against Unprecedented Targets in Patients with Lung and Other Malignancies*, 10 CLINICAL CANCER RES. 4220s, 4221s (2004) (“Even with more than 500 oncology therapeutics in active development, only a small fraction are achieving regulatory approval each year . . . .”).

because they are more likely than other classes of drugs to fail late in the testing process.<sup>285</sup> Of all oncology drugs that seem promising after completing Phase 1 trials, only about one third eventually obtain approval.<sup>286</sup> Thus, Abigail Alliance's proposal to allow access after Phase 1 trials would be especially problematic with regard to oncology drugs.

Even before controversy arose over allowing access to unapproved therapy, there was a longstanding debate in the literature about the ethics of including patients in Phase 1 trials. Many have argued that given the low prospects for benefit, most patients' expectations are unreasonable and it may not be ethical to allow them to enroll in research.<sup>287</sup> Several studies have shown that patients in Phase 1 oncology trials are very unlikely to benefit from the study treatment—less than 6% show some response to the study treatment.<sup>288</sup> One comprehensive study involving 460 Phase 1 oncology trials conducted over a period of nine years found that only 11% of research participants had a complete or partial response to experimental treatment, and most participants had no response to experimental treatment.<sup>289</sup> Although clinical trials offer some chance of benefit, most people have no measurable response from receiving experimental therapy even within trials.

In addition to providing only uncertain benefits, clinical trials also carry significant risks. Approximately 38% of oncological research subjects experience

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285. See, e.g., Bruce Booth, Robert Glassman & Philip Ma, *Oncology's Trials*, 2 NATURE REVS. DRUG DISCOVERY 609, 609 (2003) (noting that oncology drugs "have higher average success rates than other therapeutic areas in early-stage trials (that is, Phase I and Phase II), [but] . . . a lower average success rate than other therapeutic areas at Phase III"). Oncology drugs that survive Phase 1 testing go on to fail at Phase 2 in very high rates—70% of all oncology treatments that enter Phase 2 fail at this stage. Of the oncology treatments that go on to Phase 3 trials, 59% fail at the final stage of testing. Kola & Landis, *supra* note 278, at 712.

286. Benjamin J. Falit & Cary P. Gross, *Access to Experimental Drugs for Terminally Ill Patients*, 300 JAMA 2793, 2793 (2008) (citing Joseph A. DiMasi & Henry G. Grabowski, *Economics of New Oncology Drug Development*, 25 J. CLINICAL ONCOLOGY 209 (2007)).

287. See A. Italiano et al., *Treatment Outcome and Survival in Participants of Phase I Oncology Trials Carried Out from 2003 to 2006 at Institut Gustave Roussy*, 19 ANNALS ONCOLOGY 787, 787 (2007) (noting that "many authors have expressed ethical concerns about phase 1 cancer research").

288. See *id.*

289. Elizabeth Horstmann et al., *Risks and Benefits of Phase 1 Oncology Trials, 1991 Through 2002*, 352 NEW ENG. J. MED. 895, 898-99 (2005). A partial response is defined as "an overall 50 percent reduction in the tumor, measured as the sum of the products of the two longest diameters . . . or as an overall 30 percent reduction in tumor size, measured as the sum of the longest diameters." *Id.* at 897.

toxic events,<sup>290</sup> and about 14% experience the most serious category of toxic events.<sup>291</sup> Approximately one out of every two hundred research subjects in oncology trials dies from treatment-related side effects.<sup>292</sup> Risks such as these are not rendered trivial for patients seeking access to experimental therapy because they have few options left. People who are terminally ill may suffer more or even die sooner if they are exposed to drugs with significant and uncertain risks,<sup>293</sup> and these are important reasons to limit access to experimental therapy.

*B. Wider Access Proposals Will Not Solve Existing Problems and Are Too Costly for Society To Adopt*

The existing proposals for increasing access to experimental therapy are likely to cause more problems than they solve. When powerful groups are formed to represent sympathetic interests, there is always the potential that the response will be out of proportion to the size of the problem and the risk that the new policy will devolve into a policy of exceptions.<sup>294</sup> Existing proposals for expanded access are problematic for several reasons: 1) the great difficulty in limiting the scope of expanded access programs; 2) the failure of existing proposals to adequately address drug companies' incentives; 3) the fact that addressing sponsors' concerns about liability comes at too great a cost to patients; 4) the danger of slowing the approval process; 5) the risks of creating of potentially dangerous markets in unapproved therapies; and 6) the negative consequences of finding ways to fund expanded access programs.

First, there is a danger that a policy of providing access cannot be effectively limited simply by referring to "terminally ill patients" or patients with "serious" diseases. Although a common legal definition of a terminally ill patient is someone who has six months to live, this is very difficult to predict.<sup>295</sup> It may

290. Italiano et al., *supra* note 287, at 791.

291. Horstmann et al., *supra* note 289, at 899.

292. Horstmann et al., *supra* note 289, at 899 (finding a treatment-related mortality rate of 0.49%); Italiano et al., *supra* note 287, at 787 (finding a potentially treatment-related mortality rate of approximately 0.5%); Thomas G. Roberts et al., *Trends in the Risks and Benefits to Patients with Cancer Participating in Phase I Clinical Trials*, 292 JAMA 2130, 2136 (2004) (finding a treatment-related mortality rate of 0.54%).

293. See Arthur Caplan, *Is It Sound Public Policy To Let the Terminally Ill Access Experimental Medical Innovations?*, AM. J. BIOETHICS, June 2007, at 1, 2.

294. See, e.g., Mello & Brennan, *supra* note 274, at 106 (observing that "[a] powerful breast cancer lobby succeeded in persuading or, in some states, forcing insurers to provide coverage for HDC-ABMT at a time when research into the treatment's effectiveness was still in its early stages").

295. See Caplan, *supra* note 293, at 2 (citing federal statute governing access to Social

also be difficult to justify distinguishing patients suffering from very debilitating but chronic diseases from those with terminal illnesses.<sup>296</sup>

Second, drug companies, not the FDA, are often the bottleneck for access to unapproved drugs,<sup>297</sup> and addressing drug companies' incentives and interests adequately is far too costly. The FDA does not have the authority to require that drug companies provide expanded access.<sup>298</sup> Drug companies may be reluctant to provide expanded access for a variety of reasons, including concerns that expanded access will place the company at increased risk for litigation from patients taking unapproved drugs, delay or prevent drug approval because of adverse events, and fail to offer enough financial incentive to merit the investment.<sup>299</sup> A drug company can always choose to spend more on marketing approved drugs and is more likely to be able to obtain profits from these efforts, rather than just recovering costs. Of course, there may be public relations benefits from running an expanded access program, but these benefits would have to be significant to offset the costs of providing access to unapproved therapy.

Third, proposals to address sponsors' concerns about liability may endanger patients. The problem for sponsors is that even if most patients' lawsuits are not ultimately successful, they still cause drug companies to incur the financial costs of legal representation and, possibly, to endure negative publicity.<sup>300</sup>

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Security benefits for children, hospice care reimbursement by Medicare, and the right to use assisted suicide in the state of Oregon under the Death with Dignity Act).

296. *See id.*

297. *See, e.g.,* Annas, *supra* note 167, at 411 (“[T]he major bottleneck in the compassionate-use program has never been the FDA. The manufacturers have no incentives to make their investigational products available outside clinical trials.”); Menikoff, *supra* note 195, at 1060 (“[T]he FDA appears to almost uniformly approve requests for compassionate-use access to a drug . . .”). *See also* Part II, *supra*, in which we discuss several cases where drug companies have declined to provide access to patients who would otherwise qualify under FDA regulations.

298. *See* 21 U.S.C. § 360bbb (2006) (providing no authority for FDA to require sponsors to provide expanded access); 21 C.F.R. § 312.34 (2008) (allowing but not requiring that sponsors provide expanded access to eligible patients); *see also* Marcee, *supra* note 215, at 453 (noting that Congress and FDA allow sponsors to choose whether to provide expanded access).

299. *See* Peter M. Currie, *Restricting Access to Unapproved Drugs: A Compelling Government Interest?*, 20 J.L. & HEALTH 309, 319 (2006) (acknowledging validity of these concerns but questioning whether “these fears justify government action to restrict access to Phase I experimental drugs”); Richard A. Epstein, *supra* note 249, at 577-80; Marcee, *supra* note 215, at 450-55; Menikoff, *supra* note 195, at 1060-64; Talbott, *supra* note 248, at 318; Vale, *supra* note 200, at 2157-74.

300. *See* Joanna R. Cerino, Comment, *The Statutory Limits of Compassion: Can Treatment INDs Provide Meaningful Access to Investigational Drugs for the Terminally Ill?*, 27 TEMP. J. SCI. TECH. & ENVTL. L. 79, 94 (2008).

Consequently, one commentator has recommended that FDA regulations contain a waiver provision that prohibits expanded access patients from “later suing for adverse and even deadly effects.”<sup>301</sup> If sponsors were certain that patients who received unapproved drugs would not hold them liable for negative outcomes, sponsors might be more willing to provide wider expanded access.<sup>302</sup> Some advocates for FDA’s final rule also have explicitly recommended waiving liability against physicians.<sup>303</sup>

Although a blanket waiver of liability for injuries related to expanded access would eliminate the uncertainty regarding liability resulting from providing access, it raises significant concerns. Pharmaceutical companies should not be able to obtain waivers for grossly negligent or intentional actions for several reasons.<sup>304</sup> If patients are unable to hold drug companies liable for their products, drug companies may not use sufficient caution when deciding whether to provide patients risky products.<sup>305</sup> Also, because sponsors conduct a great deal of preliminary research (including research that is never published), they may be in the best position to evaluate the limited data that is available about drugs at this stage and therefore in the best position to decide when to conduct clinical trials that will expose people to those risks.<sup>306</sup> Those in charge of research and manufacturing should be held responsible if they test experimental therapies without sufficient data or in excessively risky circumstances. Finally, in an environment in which many individuals do not have health insurance,<sup>307</sup> providing sponsors with immunity from lawsuits arising from expanded access injuries may leave uninsured individuals who are injured with no access to the

301. *See id.*

302. *See id.*

303. Talbott, *supra* note 248, at 317-18 (identifying physician liability as a problem, but not recommending liability waivers).

304. *See* Heverly, *supra* note 258, at 847 (proposing that any waivers of liability for early access to pharmaceuticals should allow patients to retain their right to hold sponsors liable for grossly negligent or malicious acts). Patient waivers of liability would not preclude FDA from holding sponsors liable for failing to meet regulatory requirements, such as sponsors’ obligation to report adverse events to FDA.

305. *See* Bender et al., *supra* note 276, at 5.

306. *See* *In re Zyprexa Prods. Liab. Litig.*, 253 F.R.D. 69, 107 (E.D.N.Y. 2008) (“Because drug manufacturers often delay or suppress negative results from clinical trials they or their affiliated research institutions conduct, doctors, formulary committees, and policy makers [may base] their decisions on an unrepresentative fraction of the available scientific evidence.”) (internal quotation marks omitted).

307. *See* U.S. Census Bureau, Health Insurance Coverage: 2008, <http://www.census.gov/hhes/www/hlthins/hlthin08/hlth08asc.html> (last visited Nov. 18, 2009) (reporting that approximately 15% of the U.S. population does not have health insurance).

health care they need.<sup>308</sup> Thus, waiving sponsor or physician liability in any significant way may put some patients in a very difficult position.

Fourth, expanded access has the potential to slow the approval process. Expanded access may reduce clinical trial enrollment, which in turn will slow the completion of the clinical trials needed for approval.<sup>309</sup> If potential subjects had the choice to either enroll in a clinical trial with a placebo control and a 50% chance of obtaining treatment or enter an expanded access program knowing that they would receive access to the unapproved therapy, few would choose to enroll in clinical trials. Patients may have an incentive to try to manipulate the system and render themselves ineligible for clinical trials in order to obtain treatment through an expanded access program.<sup>310</sup> In addition, sponsors also have legitimate concerns that expanded access programs will result in more adverse events, which could in turn delay or even prevent approval.<sup>311</sup> Finally, expanded programs will result in a larger amount of data for the FDA to review, potentially slowing the approval process.<sup>312</sup> Delays to the approval process for drugs eventually found to be safe and effective not only affect sponsors' bottom lines, but, more importantly, will negatively affect the public health.<sup>313</sup>

According to commentators, sponsors' fears about delays to the approval process are exacerbated by the lack of clarity in the regulations.<sup>314</sup> One commentator has recommended that the FDA promulgate specific regulations as to the extent a patient receiving therapy through an expanded access program will affect "the FDA's determination of the drug's safety and effectiveness in the decision to grant or deny marketing approval."<sup>315</sup> In its 2009 final rule, the FDA did not provide specific regulations regarding the analysis of data from the expanded access patients.<sup>316</sup> However, the FDA made clear that it anticipates

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308. Cf. John D. Winter, *Is It Time To Abandon FDA's No Release from Liability Regulation for Clinical Studies?*, 63 FOOD & DRUG L.J. 525, 530 (2008) (describing compensation funds, such as the vaccine injury compensation fund, that require injured individuals to waive liability in order to be compensated for their injuries). Of course, if U.S. citizens were universally covered for their health care, an injury compensation fund would not be needed to justly institute waivers of liability.

309. See Cerino, *supra* note 300, at 94, Menikoff, *supra* note 195, at 1062-64.

310. Tuma, *supra* note 4, at 22.

311. See *id.* at 23.

312. See *id.* (noting that expanded access programs will create more data regarding adverse events for FDA to review).

313. Cf. Bender et al., *supra* note 276, at 4 (noting that large expanded access programs may delay clinical trial results that ultimately show the drug is ineffective).

314. See Cerino, *supra* note 300, at 94.

315. *Id.*

316. See Expanded Access to Investigational Drugs for Treatment Use, 74 Fed. Reg. 40,900, 40,905 (Aug. 13, 2009) (to be codified at 21 C.F.R. §§ 312, 316).

expanded access data will be more useful for safety assessments than for efficacy assessments because without a control group, it is difficult to derive efficacy information from expanded access data.<sup>317</sup> Moreover, the FDA stated that it was unaware of any case in which adverse event data from expanded access programs caused a drug to be denied approval,<sup>318</sup> suggesting that sponsors' fears that expanded access data will prevent approval of their drugs may not be justified. Although the FDA has offered limited clarification regarding how it will evaluate expanded access data,<sup>319</sup> it is hard to imagine a new process for reviewing additional data that would not cause significant delays relative to current approval times.

Fifth, creating financial incentives for manufacturers to make unapproved therapies widely available could lead to markets in selling unapproved therapies. The costs of drug development and clinical trials are significant, and many drugs do not make it to final approval.<sup>320</sup> Were the FDA to allow much wider access to unapproved drugs, and if pharmaceutical companies could make profits at earlier stages in the development process, companies would face perverse market incentives. Pharmaceutical companies could devise alternative and potentially lucrative business models selling unapproved drugs to terminally ill patients with few, if any, alternatives.<sup>321</sup> The prospect of a market with such a high potential for exploitation of the sickest and most vulnerable patients is troubling.

Finally, and perhaps most significantly, proposals to incentivize drug companies to provide expanded access in various ways are very problematic. Scholars have argued that drug companies' unwillingness to provide expanded access is partially caused by the costs associated with providing expanded access.<sup>322</sup> One commentator has advocated that sponsors be required to provide

317. *See id.*

318. *See id.*

319. *See id.*

320. *See* Joseph A. DiMasi, Ronald W. Hansen & Henry G. Grabowski, *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003) (finding that the total cost of pre-approval research and development of a new drug was \$802 million in 2000 dollars); Joseph A. DiMasi, *Risks in New Drug Development: Approval Success Rates for Investigational Drugs*, 69 CLINICAL PHARMACOLOGY & THERAPEUTICS 297, 303 fig.7 (2001) (finding that only 24% of drugs that enter Phase 1 trials are eventually approved).

321. *See, e.g.*, Judith Randal, *Investigational Drug Access Taken to Task in Lawsuit Against FDA*, 95 J. NAT'L CANCER INST. 1818, 1820 (2003) ("You only have to look to the world of unproven nutritional products and dietary supplements . . . to realize that Tier 1 approvals would give pharmaceutical firms less incentive to invest in research and a lot of incentive to engage in misleading advertising and promotion." (quoting Bob Erwin, President, Marti Nelson Cancer Found.) (internal quotation marks omitted)).

322. *See* Cerino, *supra* note 300, at 94-95; Marcee, *supra* note 215, at 452-53; Tuma, *supra*

expanded access as part of the drug approval process, so that sponsors cannot choose to restrict expanded access because of cost.<sup>323</sup> However, this solution raises concerns about government intrusion on corporate autonomy.<sup>324</sup> There may be cases in which it is highly inefficient for sponsors to provide access at an early stage or where a sponsor feels that safety concerns suggest that early access would be particularly risky. A blanket requirement that all sponsors provide expanded access as a condition of obtaining drug approval seems ill-considered.

Other scholars have proposed various mechanisms to fund expanded access programs as a means of incentivizing sponsors. However, successfully decreasing sponsors' expanded access costs while also appropriately using limited health care resources is a particularly difficult problem for the expanded access system. Proposed solutions include: 1) providing incentives to sponsors in the form of delayed profits that are only released upon FDA approval,<sup>325</sup> 2) offering drug companies extended market exclusivity for a drug that is eventually approved by the FDA,<sup>326</sup> 3) creating a private foundation to subsidize the costs of unapproved drugs,<sup>327</sup> or 4) requiring health insurance companies to pay for unapproved drugs obtained through expanded access.<sup>328</sup> The most complex proposal is to allow sponsors to charge expanded access patients full market price, as long as they place the proceeds in excess of direct costs in an interest-bearing escrow account until the drug is approved.<sup>329</sup> If a drug is ultimately approved, the sponsor would gain access to the profits in the account.<sup>330</sup> If a drug

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note 4, at 19, 22; Vale, *supra* note 200, at 2165. *But see* Menikoff, *supra* note 195, at 1060-62 (arguing that fears about interference with clinical trials and FDA approval, not cost concerns, motivate drug companies' reluctance to provide expanded access).

323. *See* Marcee, *supra* note 215, at 452-53; *cf.* Nicole E. Lombard, Note, *Paternalism vs. Autonomy: Steps Toward Resolving the Conflict Over Experimental Drug Access Between the Food and Drug Administration and the Terminally Ill*, 3 J. HEALTH & BIOMED. L. 163, 185 (2007) (advocating "active involvement" of the FDA in pressuring drug companies to provide expanded access, but not explicitly advocating that the FDA require companies to provide expanded access).

324. *Cf.* Salbu, *supra* note 249, at 429-30 (discussing the potential negative effects of government mandated expanded access to HIV drugs).

325. *See* Falit & Gross, *supra* note 286, at 2794-95; Vale, *supra* note 200, at 2165-71.

326. *See* Vale, *supra* note 200, at 2165-71.

327. Cerino, *supra* note 300, at 94-95 (citing Frank Burroughs, co-founder of Abigail Alliance).

328. *Cf.* Sharona Hoffman, *A Proposal for Federal Legislation To Address Health Insurance Coverage for Experimental and Investigational Treatments*, 78 OR. L. REV. 203, 206-07 (1999) (proposing that insurance companies be required to pay for treatments provided through Phase III trials).

329. *See* Falit & Gross, *supra* note 286, at 2794.

330. *See id.*

is ultimately not approved, the profits from sales of that drug would be transferred to the federal government for health-related use.<sup>331</sup>

However, many of these proposals to decrease sponsor's expanded access costs may not be adequate to incentivize sponsors to provide access. Even if sponsors sell unapproved drugs at a profit, they would likely not gain a net profit large enough to make providing expanded access attractive.<sup>332</sup> It is not clear that there are a large number of patients who would be financially able to purchase unapproved drugs.<sup>333</sup> And even if a relatively large expanded access market did exist, drug companies might not be able to meet demand.<sup>334</sup> Early in the drug development process, sponsors have limited production capacity because sponsors are reluctant to scale up production of a drug until Phase 3 trials, when the drug is more likely to be approved.<sup>335</sup> In addition, drug companies would likely not charge "full price" for expanded access drugs because of fears that the public would react negatively to high prices for unapproved drugs with uncertain risks and benefits, especially in the case of terminally ill patients in highly sympathetic situations.<sup>336</sup> Finally, since the likelihood of any given drug being approved is low, the escrow account and market exclusivity proposals may not provide drug companies with a significant incentive to provide expanded access early in clinical trials.<sup>337</sup>

In addition to concerns about sponsors' costs, commentators have raised concerns about patients' ability to pay for expanded access.<sup>338</sup> Even if drug companies only recover the direct costs of expanded access drugs, drugs may still be too costly for some patients. Furthermore, limiting access to those who can afford to pay for it raises serious concerns about equity. Consequently, some

331. *See id.*

332. *See* Currie, *supra* note 299, at 321-23; Okie, *supra* note 14, at 440.

333. *See* Cerino, *supra* note 300, at 92, 94-95; Menikoff, *supra* note 195, at 1065-66; Okie, *supra* note 14, at 440.

334. *See* Currie, *supra* note 299, at 322; Okie, *supra* note 14, at 440.

335. *See* Currie, *supra* note 299, at 322; *see also* Kola & Landis, *supra* note 278, at 711-12 (finding that approximately 11% of drugs that enter Phase 1 trials, 38% of drugs that enter Phase 2 trials, and 55% of drugs that enter Phase 3 trials are eventually approved).

336. Okie, *supra* note 14, at 440 (quoting a representative of Pharmaceutical Research and Manufacturers of America as saying that drug companies "certainly couldn't charge full price" for post-Phase 1 drugs); *cf.* KAISER FAMILY FOUND., KAISER PUBLIC OPINION SPOTLIGHT, VIEWS ON PRESCRIPTION DRUGS AND THE PHARMACEUTICAL INDUSTRY 8 (2008), [http://www.kff.org/spotlight/rxdrugs/upload/rx\\_drugs.pdf](http://www.kff.org/spotlight/rxdrugs/upload/rx_drugs.pdf) (finding that 74% of the U.S. public believes that the pharmaceutical industry makes "too much profit").

337. *See* DiMasi, *supra* note 320 (reporting that 20% of drugs that enter Phase 1 clinical trials are eventually approved); Kola & Landis, *supra* note 278, at 711.

338. *See* Cerino, *supra* note 300, at 94-95; Hoffman, *supra* note 328, at 206-07.

commentators have argued that health insurance should pay for expanded access when a patient has no other treatment option.<sup>339</sup>

This proposed solution would generate quite a few problems. In a context of limited health care resources, paying for potentially unsafe and ineffective drugs may not be the most appropriate use of the resources.<sup>340</sup> For example, in Britain, the National Health Service does not cover some drugs that are approved, but also are expensive and provide relatively short extensions of lifespan, because purchasing such drugs is not the most effective use Britain's limited health care resources.<sup>341</sup> Creating a private foundation to subsidize patients' purchase of unapproved drugs similarly raises questions about how to wisely use finite resources, and, moreover, seems unlikely to occur.<sup>342</sup> Awarding market exclusivity extensions to sponsors who provide expanded access would exacerbate concerns about health care costs and resource allocation. Although drug companies would provide unapproved drugs to expanded access patients free of charge under the market exclusivity proposal, sponsors might be able to pass on the costs of expanded access programs to future patients in the form of higher drug prices.<sup>343</sup>

Devising a system that could increase health care costs for uncertain benefit seems unwise. The price of drugs already contributes significantly to increases in health care costs.<sup>344</sup> The United States has the most expensive health care system in the world and spends more per person on health care than any other country.<sup>345</sup> Spending on health care has increased above the rate of inflation for a number of years.<sup>346</sup> High costs have led to decreased access to health care for many,<sup>347</sup> and studies have shown that lack of insurance may result in as many as 18,000

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339. See Hoffman, *supra* note 328, at 206-207.

340. See Falit & Gross, *supra* note 286, at 2795.

341. See Gardiner Harris, *British Balance Benefit vs. Cost of Latest Drugs*, N.Y. TIMES, Dec. 2, 2008, at A1.

342. *But see* Cerino, *supra* note 300, at 94-95 (arguing that a private foundation should be created).

343. See Vale, *supra* note 200, at 2165-71.

344. See, e.g., Thomas Bodenheimer, *High and Rising Health Care Costs. Part 2: Technological Innovation*, 142 ANNALS INTERNAL MED. 932, 932 (2005) (noting that technological innovations, including pharmaceutical innovation, contribute to rising health care costs); Zijun Wang, *The Convergence of Health Care Expenditure in the US States*, 18 HEALTH ECON. 55, 69 (2008) (finding that the cost of prescription drugs was one of the most significant factors in explaining divergence in health care costs in state programs).

345. See Bodenheimer, *supra* note 344, at 932.

346. *Id.*

347. Ezekiel Emanuel, *The Cost-Coverage Tradeoff: "It's Health Care Costs, Stupid,"* 299 JAMA 947, 947 (2008).

increased deaths a year.<sup>348</sup> Rising health care expenditures also have significant economic consequences more generally, because they make it difficult for American firms to remain competitive in a global marketplace.<sup>349</sup> These problems have led to significant, if unpredictable, movement in the direction of health care reform.<sup>350</sup> If health care reform efforts are to succeed, there is little, if any, room for adding to our enormous health care expenditures.<sup>351</sup> The drive for reform may therefore have created an inhospitable climate for expanding access to unproven therapy in a way that increases health care costs.

## V. PROPOSAL FOR REFORM: CHANGING CLINICAL TRIALS

The *Abigail Alliance* case and other claims for access involve terminally ill people who were unable to obtain access to clinical trials. One solution might be to change the approach to clinical trials more dramatically, perhaps by expanding the inclusion criteria for later phase (Phase 2b and 3) trials.<sup>352</sup> Scientists have argued that Phase 2 studies would be more useful if they studied a larger sample size<sup>353</sup> and had less restrictive inclusion and exclusion criteria to broaden the pool of patients eligible to participate.<sup>354</sup> Making the inclusion criteria less restrictive for Phase 2 and 3 trials and increasing the number of patients enrolled in those phases might both produce valuable scientific knowledge and prevent expanded access programs from interfering with clinical investigation.<sup>355</sup> It would also ensure that individuals being exposed to unapproved drugs were provided the careful safety monitoring involved in clinical trials. Moreover, increasing the size

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348. INST. OF MED., *INSURING AMERICA'S HEALTH – PRINCIPLES AND RECOMMENDATIONS* 8 (2004).

349. Ron Wyden & Bob Bennett, *Finally, Fixing Health Care: What's Different Now?*, 27 HEALTH AFF. 689, 690 (2008).

350. Sheryl Gay Stolberg, *Missing in Health Bills: Solutions for Rising Costs*, N.Y. TIMES, Nov. 10, 2009, at A1 (describing Congressional health care reform legislation).

351. *Id.* (noting that “[t]here are a variety of ideas for attacking costs more aggressively,” and Senators and administrative officials are focusing on containing costs, but there are important barriers to cost-cutting); see also *Transcript: Obama's Health Care Address*, WASH. POST, Sept. 9, 2009, <http://specials.washingtonpost.com/annotations/obama-health-care-address> (last visited Nov. 17, 2009) (“[O]ur health care system is placing an unsustainable burden on taxpayers. . . . Put simply, our health care problem is our deficit problem.”).

352. See Marcee, *supra* note 215, at 456 (recommending increasing the size of Phase 2 trials).

353. LAWRENCE FRIEDMAN ET AL., *FUNDAMENTALS OF CLINICAL TRIALS* 5 (1996); see Melissa Fazzari et al., *The Phase II/III Transition: Toward the Proof of Efficacy in Cancer Clinical Trials*, 21 CONTROLLED CLINICAL TRIALS 360, 361 (2000).

354. See Fazzari et al., *supra* note 353, at 363.

355. See Marcee, *supra* note 215, at 455-57.

of Phase 2 trials might not increase drug companies' overall costs because better data earlier in the process might prevent companies from conducting some costly, but ultimately unsuccessful, Phase 3 trials.<sup>356</sup> Our analysis has demonstrated that it is the research sponsors, not the FDA or the courts, who are the real bottleneck preventing individuals from receiving access to unapproved therapy. Yet, it is difficult, if not impossible, to create sound incentives for sponsors to provide access to unapproved therapy without raising concerns about the exploitation of desperate individuals who have limited treatment options. Requiring sponsors to include more individuals in clinical trials might save sponsors money while providing much-needed data on unapproved therapy, and thus may be much more effective than the proposals that have been made to date.

Of course, enrolling more subjects in clinical trials may not adequately address the concerns of individuals suffering from rare conditions or for whom off-label indications are the last resort.<sup>357</sup> There may also be other important exceptions, including trials for which there are important scientific reasons not to enroll patients with complex conditions. Therefore, we do not propose that the FDA's regulations for expanded access to unapproved therapy be abandoned, but that the provisions in these regulations be interpreted in a careful and restrictive fashion.

Many clinical trials do not have sufficient numbers of subjects enrolled,<sup>358</sup> and so it seems unwise to further decrease the incentives for patients to participate in clinical trials. Additionally, although tens of thousands of patients have been enrolled in expanded access programs, the data collected from these programs have been incomplete, with information about less than half of the patients involved being sent back to the FDA.<sup>359</sup> The information that has been returned to the FDA has not been very useful.<sup>360</sup> Unless expanded access programs can be better designed to produce data of some value (which is a proposal we would also support), they cannot substitute for clinical trials on people with complex conditions.

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356. See Fazzari et al., *supra* note 353, at 367.

357. See Section III.C, *supra*; see also 21 U.S.C. § 360bbb (2006); 21 C.F.R. §§ 312.34, 312.36 (2008); Expanded Access to Investigational Drugs for Treatment Use, 71 Fed. Reg. 75,147, 75,167 (proposed Dec. 14, 2006) (to be codified at 21 CFR § 312). Significantly, individuals seeking to enroll in trials for the off-label use of a drug may have fewer options than if the sponsor was seeking to approve the drug for use in their disease.

358. Gina Kolata, *Lack of Study Volunteers Is Said To Hobble Fight Against Cancer*, N.Y. TIMES, Aug. 3, 2009, at A1.

359. Ann T. Farrell, Food & Drug Admin., Address at Accelerating Anticancer Agent Development Workshop: FDA: Center for Drug Evaluation and Research Oncology Expanded Access (June 18, 2009).

360. *Id.*

Significantly, the idea of transforming clinical trials in this manner is not without precedent. Some have argued that “[t]he current clinical research enterprise in the United States is not consistently producing an adequate supply of information to meet the needs of clinical and health policy decision makers.”<sup>361</sup> In 1993, Sir Richard Peto and colleagues advocated for “large, simple trials,” involving less complex protocols, enrollment of large numbers of research subjects, limited exclusion criteria, and only a few measures on which data would be collected, for this very reason.<sup>362</sup>

In particular, clinical trials with strict exclusion criteria make it impossible to obtain systematic data on subpopulations of patients with complex conditions before a drug is released for use by the population at large.<sup>363</sup> Researchers have advocated for clinical trials that “include a more diverse study population . . . to enroll patients in the trial with characteristics that reflect the range and distribution of patients observed in clinical practice.”<sup>364</sup> Unlike smaller studies with relatively homogenous groups of people, larger, more diverse clinical trials can provide enough information to examine the effects of interventions on subgroups based on race, age, gender, and stage of disease.<sup>365</sup> More information about a drug prior to widely marketing that drug is clearly preferable for public health reasons.<sup>366</sup>

Sponsors may be concerned that moving in the direction of large, simple trials may produce more information about the risks of a drug before the approval process is completed.<sup>367</sup> Including sicker patients in clinical trials may increase

361. Sean R. Tunis et al., *Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy*, 290 JAMA 1624, 1625 (2003).

362. Richard Peto et al., *Large-Scale Randomized Evidence: Large, Simple Trials and Overviews of Trials*, 703 ANNALS OF N.Y. ACAD. SCI. 314 (1993); accord John S. March et al., *The Case for Practical Trials in Psychiatry*, 162 AM. J. PSYCHIATRY 836, 842 (2005); Tunis, *supra* note 361, at 1630.

363. Martin Fortin et al., *Randomized Controlled Trials: Do They Have External Validity for Patients with Multiple Comorbidities?*, 4 ANNALS OF FAMILY MED. 104, 104-05 (2006) (“To ensure the internal validity of their findings, many [Randomized Controlled Trials (RCTs)] exclude patients with multiple comorbid conditions. In other cases, comorbidities of patients actually enrolled in the RCTs are not reported. These trials, however, provide the data that inform the justification for use of new treatments and interventions for all patients. Excluding a subset of the population from such trials or from the final reports means important information about the proper use of a treatment or intervention for that subset is not available.”).

364. Tunis, *supra* note 361, at 1626.

365. March, *supra* note 362, at 838.

366. See Vale, *supra* note 200, at 2172.

367. Cf. Jerome Groopman, *The Right to a Trial: Should Dying Patients Have Access to Experimental Drugs?*, NEW YORKER, Dec. 18, 2006, at 40 (quoting the director of the Office of

the number of adverse events in the trial, making it more difficult to demonstrate a treatment effect.<sup>368</sup> In other words, if people are so sick that the disease causes them to experience morbidity or mortality, it may be more difficult to separate which negative outcomes should be attributed to their disease and which should be attributed to the unapproved drug. One way to address these concerns is to stratify the sample into two groups: those research subjects who would traditionally fit under rigid inclusion/exclusion criteria and those who would not. The primary analysis of the data would focus on subjects who would meet traditional inclusion criteria, and secondary analyses could include information from sicker or more fragile research subjects. It is true that including sicker patients may still make it more time-consuming and difficult to interpret the data. However, as we have discussed, the current approach has been forcefully criticized for offering inadequate information for policymakers, physicians, and patients by excluding sicker patients or more representative members of the population.<sup>369</sup>

While these expansions probably would slow down the approval process, it is not clear that sponsors' concerns about delays to or denials of approval represent the most important concerns. Many commentators have argued that the FDA approval process is too lenient.<sup>370</sup> The post-approval revelation that Vioxx<sup>371</sup> increased patients' risk of heart attacks by a factor of five provides a prominent example of an instance in which the FDA approval process was not adequately stringent.<sup>372</sup> If the FDA approval process is slowed in order to obtain

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Oncology Drug Products as saying that many companies fear "the FDA will find some toxicity in the expanded-access program . . . and the drug will be killed").

368. See, e.g., Fortin, *supra* note 363, at 107 (noting that "depression in patients with hypertension can result in a difficult clinical course because depression may adversely affect the patients' adherence to medication and self-care regimens"); Yves Lacourcière, *A Multicenter, Randomized, Double-Blind Study of the Antihypertensive Efficacy and Tolerability of Irbesartan in Patients Aged ≥ 65 Years with Mild to Moderate Hypertension*, 22 CLINICAL THERAPEUTICS 1213, 1213 (2000) (examining the effectiveness of a drug to lower blood pressure excluding conditions that may lead to adverse outcomes such as high blood pressure, previous cardiac disease, and stroke, "as well as other preexisting or present severe medical or psychologic conditions").

369. See Fortin, *supra* note 363, at 108 ("Research devoted to generating knowledge to be applied in medical practice should take into consideration the complex reality of the situation."); March, *supra* note 362, at 838; Peto, *supra* note 362, at 378; Tunis, *supra* note 361, at 1625.

370. See, e.g., INST. OF MED., THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 37 (2007).

371. Vioxx was a painkiller that was intended to provide pain relief without causing the stomach problems associated with other common painkillers such as aspirin. See, e.g., Marc Kaufman, *Merck Found Liable in Vioxx Case*, WASH. POST, Aug. 20, 2005, at A1.

372. See, e.g., Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing*

much-needed data, this is an important cost to factor into our decisionmaking, but some reasonable amount of delay may be a wise cost for the public to incur.

Finally, it is also important to note that these same arguments could have been raised against including children in research<sup>373</sup> and are currently being made regarding the inclusion of pregnant women.<sup>374</sup> The Pediatric Rule and the Best Pharmaceuticals for Children Act were passed in recognition of the fact that many drugs had not been tested in children at all before they were put into use.<sup>375</sup> Many have rightly realized that when vulnerable populations are protected through exclusion from research, or when data is protected by excluding vulnerable populations, the result is ad-hoc experimentation on patients by their doctors.<sup>376</sup> In this case, these protections also result in a denial of access to

(Phase IV) Study Requirements: Exception to the Rule?, 61 FOOD & DRUG L.J. 295, 365 (2006).

373. See, e.g., Kathleen C. Glass & Ariella Binik, *Rethinking Risk in Pediatric Research*, 36 J.L. MED. & ETHICS 567, 567-68 (2008) (discussing the history of pediatric research regulations); L.L. Mathis & S. Iyasu, *Safety Monitoring of Drugs Granted Exclusivity Under the Best Pharmaceuticals for Children Act: What the FDA Has Learned*, 82 CLINICAL PHARMACOLOGY & THERAPEUTICS 133, 133 (2007) (“Because of features unique to the pediatric population and medication usage in this population, it may be difficult to identify adverse drug-related safety events in children.”).

374. Janice K. Bush, *The Industry Perspective on the Inclusion of Women in Clinical Trials*, 69 ACAD. MED. 708, 710 (1994) (explaining that birth defects occur naturally, and spontaneous abortion occurs in 20-30% of pregnancies, so the “dilemma is how to separate which defects might be due to drugs versus those that are just occurring naturally”); R. Alta Charo, *Protecting Us to Death: Women, Pregnancy, and Clinical Research Trials*, 38 ST. LOUIS L.J. 135, 141, 144 (1993) (noting that some have argued that “[i]nclusion of women equals ‘noise’ in the data,” and have raised concerns about liability as a result of harm to fetuses).

375. Best Pharmaceuticals for Children Act, 42 U.S.C. § 284m (2006); Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66,631 (Dec. 2, 1998) (to be codified at 21 C.F.R. pts. 201, 312, 314, 601) (noting that the absence of pediatric testing and labeling may put pediatric patients at risk of adverse events or expose pediatric patients to ineffective treatments).

376. Glass & Binik, *supra* note 373, at 574 (“We strongly support an increase in pediatric research to provide the pediatric population with effective medical care, and finally to eradicate the ‘therapeutic orphan.’”); Am. Acad. of Pediatrics Comm. on Drugs, *Guidelines for the Ethical Conduct of Studies To Evaluate Drugs in Pediatric Populations*, 95 PEDIATRICS 286, 294 (1995) (“The AAP believes it is unethical to deny children appropriate access to existing and new therapeutic agents.”) (guidelines were reaffirmed in September 2005); Nat’l Insts. of Health, NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects, Mar. 6, 1998, <http://grants.nih.gov/grants/guide/notice-files/not98-024.html> (“After reviewing reports, background papers, and a study of a sample of NIH-sponsored clinical research abstracts that suggested that 10-20% inappropriately excluded children, the conveners concluded that there is a need to enhance the inclusion of children in clinical research. This conclusion is

clinical trials that could be a valuable option for people with one last hope for treatment.

One of the difficulties that our proposal cannot address adequately is that enrolling more individuals in clinical trials means that these individuals may receive placebo instead of the unapproved treatment. Our proposal does not give individuals a guarantee of receiving access to unapproved therapy. Still, the chance of a placebo is an improvement compared to any proposal which does not adequately address the most important barrier to access: the lack of incentives for drug companies to provide treatment. We have attempted to address this problem directly. Additionally, in many cases, there are significant risks posed by unapproved therapy. Because experimental therapies by definition have not been proven to be effective, placebo-controlled trials are both scientifically important and morally acceptable.<sup>377</sup>

It is true that the terminally ill who are seeking a chance at a cure or an extension of life have very sympathetic claims that we cannot ignore. However, there are other situations in which the law privileges societal needs over the sympathetic claims of individuals in difficult situations.<sup>378</sup> For instance, witnesses may have good reason to fear that if they provide testimony in certain criminal cases, the defendants they testify against may threaten their lives or the lives of their family.<sup>379</sup> However, fear for one's life is not a valid defense for contempt of court.<sup>380</sup> The witness protection program was created to protect witnesses who place themselves in danger by testifying, but the witness protection program involves considerable sacrifices and does not offer a guarantee that a witness and her family will be kept safe. Justice Frankfurter justified this approach by explaining that "[e]very citizen of course owes to his society the duty of giving testimony to aid in the enforcement of the law."<sup>381</sup> In the case of *People v. Carradine*, the Supreme Court of Illinois explained why it

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based upon scientific information, demonstrated human need, and considerations of justice for children in receiving adequately evaluated treatments.”).

377. See, e.g., COUNCIL FOR INT’L ORGS. OF MED. SCIS., INTERNATIONAL ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS, Guideline 11 (2002), available at [http://www.cioms.ch/frame\\_guidelines\\_nov\\_2002.htm](http://www.cioms.ch/frame_guidelines_nov_2002.htm) (“Placebo may be used: when there is no established effective intervention . . . .”); WORLD MED. ASS’N, DECLARATION OF HELSINKI: ETHICAL PRINCIPLES FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (2008), available at <http://www.wma.net/en/30publications/10policies/b3/index.html> (“The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists . . . .”).

378. ALAN WERTHEIMER, COERCION 158 (1987).

379. *Id.*

380. *Id.*; John Lawrence Hill, *A Utilitarian Theory of Duress*, 84 IOWA L. REV. 275, 327 (1999).

381. *Piemonte v. United States*, 367 U.S. 556, 559 n.2 (1961).

upheld a contempt of court conviction of a woman too fearful to testify as follows:

[O]ne of the problems that the Court has is that unless we receive the cooperation of the citizens who see certain alleged events take place these events are not going to be rooted out, nor are perpetrators of these acts going to be brought before the bar of justice unless citizens stand up to be counted, and I think this [fear] is not a valid reason for not testifying. If it's a valid reason then we might as well close the doors.<sup>382</sup>

The court made it clear that creating an exception for witnesses to testify out of fear for their lives would come at too high a price for the legal system to bear. Proposals to permit access to unapproved drugs outside clinical trials come at a similarly high price, in this case risking the integrity of our system for evaluating the safety and efficacy of drugs.

Finally, we are in no way proposing to eliminate expanded access programs. There are likely to be circumstances in which expanded access programs are necessary. For instance, there may be cases where the Phase 1 data raises few safety concerns for a particular drug, and individuals are seeking off-label use, requesting treatment for a rare condition, or have some other need that clinical trials simply cannot meet. Although it is still important to develop ways to collect some limited data on the safety and efficacy of treatments in compassionate use programs, the FDA may appropriately decide that there is an important role for expanded access programs in these and similar instances.

#### CONCLUSION

The highly sympathetic nature of the claims for access to experimental therapy by terminally or seriously ill patients makes it difficult to confront the hard policy questions at the heart of this debate. Courts lack the institutional competence and policymaking expertise to address these questions, questions which are better confronted through the legislative branch. Moreover, a careful examination of the possible solutions to the problem of sponsors' incentives to provide access reveals that the proposed solutions are costly and unsound, especially given the current climate of health care reform. Instead of short-sighted proposals to modify the current health care and research system, a better approach would be to allow very limited access to unapproved drugs outside of clinical trials while expanding eligibility for clinical trials in order to ensure that more people receive access in a controlled and systematic fashion. Although our proposal may not satisfy those desperately seeking their last hope for a cure, it is

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382. *People v. Carradine*, 52 Ill. 2d 231, 234 (1972) (quoting the trial court's reasoning).

time to recognize that the cost of providing broad access to unapproved therapy is far too high to bear.