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# The Right to Try: Expanded Access for the Terminally Ill in Clinical Trials

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## **The Right to Try: Expanded Access for the Terminally Ill in Clinical Trials**

Abigail Burroughs was nineteen years old when she was diagnosed with head and neck cancer.<sup>1</sup> Abigail underwent the conventional treatments for her disease, including chemotherapy and radiation therapy.<sup>2</sup> A year into her treatment, her doctors had exhausted all standard therapies but Abigail's condition had not improved. As a final attempt to save or prolong her life, Abigail's oncologist recommended that she attempt to enroll in a clinical trial for two unapproved drugs that he believed she might benefit from.<sup>3</sup> The drug targeted the same receptors as her cancer but it was only being studied in patients with colon cancer.<sup>4</sup> With her health deteriorating, Abigail was denied access to the trial because she did not meet the strict scientific criteria for inclusion.<sup>5</sup>

Several months later she was accepted into a trial for a third unapproved study, by the time she was granted access, Abigail was too ill to travel and passed away at the age of 21.<sup>6</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>7</sup>

Since 1987, the Food and Drug Administration ("FDA") has had rules in place that give terminally ill patients the opportunity to access drugs or biologics that are still in development

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<sup>1</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 469 F.3d 470 (2006).

<sup>2</sup> *Id.*

<sup>3</sup> *Id.*

<sup>4</sup> *Id.*

<sup>5</sup> *Id.*

<sup>6</sup> *Id.*

<sup>7</sup> *The Abigail Alliance Mission*, ABIGAIL ALLIANCE FOR BETTER ACCESS TO DEVELOPMENTAL DRUGS, (last visited October 15, 2010), <http://www.abigail-alliance.org>.

and pending approval to be used for treatment purposes.<sup>8</sup> Investigational or experimental drugs are new drugs that have not yet been approved by the FDA and are in the process of being tested for safety and effectiveness.<sup>9</sup> Patients may decide to seek access to investigational drugs for different reasons. Some patients, with serious or life-threatening illnesses, like Abigail, seek treatment with investigational drugs if FDA-approved therapies are not working or if their side effects are too severe.<sup>10</sup> Others may be encouraged to learn more if they heard of positive early study results for a specific investigational drug.<sup>11</sup>

Gaining access to these drugs is very difficult. In an attempt to ensure safety and adequacy of the research, the FDA enforces tight restrictions on who can participate in clinical trials. Patients and families dealing with terminal illness have attempted to assert a fundamental right in order to gain access to these unapproved therapies. For patients that have exhausted all other therapies, these investigational drugs can provide a final chance to fight for their lives. The issue of terminally ill patients' access to clinical trials and experimental drugs received increased public attention when it reached the U.S. Supreme Court in 2008. The court declined to review a federal appeals court decision that held that terminally ill patients do not have a constitutional right to obtain investigational drugs before the FDA has approved them.<sup>12</sup>

The issue also reached Congress in 2008 when Senator Sam Brownback (R-Kan.) introduced the “Access, Compassion, Care and Ethics for Seriously Ill Patients Act” (the “ACCESS Act”) that would serve to increase terminally ill patients' access to promising treatments in the

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<sup>8</sup> *FDA Expands Access to Investigational Drugs*, FDA (Aug. 12, 2009), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm176845.htm>

<sup>9</sup> *Id.*

<sup>10</sup> *Id.*

<sup>11</sup> *Id.*

<sup>12</sup> *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128 (3d Cir. N.J. 2008).

investigational phase of FDA approval.<sup>13</sup> The bill would allow patients to have access to promising new drugs and devices once Phase I clinical trials have been completed.<sup>14</sup> Under current law, patients with life-threatening diseases may only receive access to treatments that have completed Phase II clinical trials.

Subsequently, in 2009, to ensure “broad and equitable access to investigational drugs for treatment” the FDA amended these expanded access program rules.<sup>15</sup> An investigational drug may pose unknown risks to patients and it is uncertain if the drug will be effective, therefore, these drugs are available through two pathways specifically designed to protect patients.<sup>16</sup> Patients may be eligible to receive an investigational drug as a participant in a clinical trial or as part of an expanded access program; this is also known as compassionate use.<sup>17</sup>

Terminally ill patients, like Abigail, present a sympathetic claim for access to unapproved therapy when such access is the last hope for the patient. In the interest of patient autonomy and increased scientific knowledge, terminally ill patients should be granted expanded access to clinical trials. The current regulations that exist regarding patient access to unapproved drugs and the debate over a terminally ill patient’s constitutional right to access experimental drugs prior to FDA approval create obstacles for these patient’s that are fighting to save their lives.

## **I. Clinical Trials**

The Federal Food, Drug, and Cosmetic Act (“FDCA”) authorizes agency rulemaking, which gives the FDA the authority to set rules to implement and explain the provisions of the

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<sup>13</sup> Kurt Karst, *Access Act Reintroduced by Sen. Brownback; Previous Tiered Approval Nomenclature Scrapped and New Immunity Provision Add*, FDA LAW BLOG (June 4, 2008, 11:15 AM), [http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/2008/06/access-act-rein.html](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2008/06/access-act-rein.html).

<sup>14</sup> *Id.*

<sup>15</sup> *Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)*, FDA (Feb. 24, 2014), <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.html/>

<sup>16</sup> *Id.*

<sup>17</sup> *Id.*

FDCA. The FDA has the authority to regulate human drugs under the FDCA.<sup>18</sup> Regulation of human drugs includes manufacturing controls for quality purposes, labeling controls for consumer protection, and a premarket approval process for new drugs to determine safety and efficacy using a risk-benefit approach.<sup>19</sup>

The Center for Drug Evaluation and Research is responsible for the evaluation of safety and efficacy of brand name and generic prescription and over-the-counter drugs.<sup>20</sup> They are also responsible for the advertising of prescription drugs and post-market monitoring of drug products for risks and adverse events.<sup>21</sup> Through pre- and post-marketing phases, human drugs and medical devices are the most heavily regulated consumer products by the FDA.<sup>22</sup>

The development of new and investigational drugs follows three phases when testing in humans. Testing in animals, which always precedes human testing, is also a requirement for FDA drug approval and is referred to as Phase O or “Preclinical” testing.<sup>23</sup>

There are a number of Pre-Approval Phases involved in bringing a new drug to the market. The first phase is the preclinical investigation phase, consisting of laboratory and animal testing.<sup>24</sup> This does not require FDA prior notification. Following the successful completion of preclinical testing, an investigational new drug (“IND”) application must be filed prior to initiation of clinical trials, including a general investigative plan, clinical trial protocols,

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<sup>18</sup> Jordan Paradise et. al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 MED. & ETHICS J.L 598 (2009).

<sup>19</sup> *Id.*

<sup>20</sup> *How Drugs are Developed and Approved*, FDA (Feb. 13, 2014) <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/>

<sup>21</sup> *Id.*

<sup>22</sup> *Id.*

<sup>23</sup> Jordan Paradise et. al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 MED. & ETHICS J.L 598 (2009).

<sup>24</sup> *Id.* at 601.

information on proposed drug chemistry, pharmacology, toxicology, and manufacturing and controls, and a summary of previous human experience with the drug.<sup>25</sup>

There are three key phases to clinical trials. The first phase typically involves approximately 20-80 healthy participants using escalating doses of the drug in order to determine preliminary safety and tolerability data, metabolism, pharmacologic action and side effects.<sup>26</sup> In part, this is one reason why Phase I testing is usually done in healthy individuals as opposed to terminally ill patients. The objectives of Phase I trials are to gain an understanding of the side effects of new drugs, determine how the drug affects the targeted disease in patients and observe the patient response to the drug.<sup>27</sup> Phase I trials only enroll a small number of participants.<sup>28</sup> Trial participants are divided into small groups, known as cohorts; the first cohort receives a low dose of the new drug. Doctors may collect blood or urine samples to measure drug levels in the patients.<sup>29</sup> If the first cohort does not have any severe side effects, then a new cohort receives a higher dose of the same drug.<sup>30</sup> The dose increases until the trial investigators find the best dose for future testing. With each increasing dose, doctors test each patient to see if he or she is responding to the treatment.<sup>31</sup> If the doctors find that the treatment is safe, then it will advance to a Phase II of the clinical trial.

Phase II involves up to several hundred patients with the disease or condition under study and should obtain initial evidence of effectiveness against the targeted disease, explore further

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<sup>25</sup> *Id.*

<sup>26</sup> *Id.*

<sup>27</sup> *What are Phase I Clinical Trials?* MD ANDERSON CANCER CENTER (last visited Apr. 2014), [HTTP://WWW.MDANDERSON.ORG/PATIENT-AND-CANCER-INFORMATION/CARE-CENTERS-AND-CLINICS/CLINICS/CLINICAL-CENTER-FOR-TARGETED-THERAPY/WHAT-ARE-PHASE-1-CLINICAL-TRIALS/INDEX.HTML](http://www.mdanderson.org/patient-and-cancer-information/care-centers-and-clinics/clinics/clinical-center-for-targeted-therapy/what-are-phase-1-clinical-trials/index.html)

<sup>28</sup> *Id.*

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*

<sup>31</sup> *Id.*

risks and side effects, and confirm preliminary data on optimal doses.<sup>32</sup> Phase III involves thousands of people at many different locations and can be initiated after appropriate notification to FDA and gathering of preliminary efficacy data.<sup>33</sup>

The primary goal of a clinical trial is to collect data necessary to meet safety and efficacy standards required for FDA approval.<sup>34</sup> In addition to these three phases of the clinical trials, the FDA can require the sponsor to undertake post-approval Phase IV studies in order to secure further data.<sup>35</sup> Throughout the clinical trial phases, sponsors and investigators are obligated to obtain valid informed consent, elect appropriate investigators, adhere to protocols, maintain accurate and up-to-date records, engage in appropriate shipping and handling of products and report adverse events.<sup>36</sup>

Participating in a clinical study contributes to medical knowledge.<sup>37</sup> The results of these studies can make a difference in the care of future patients by providing information about the benefits and risks of therapeutic, preventative, or diagnostic products or interventions.<sup>38</sup>

Some trials may provide participants with the prospect of receiving direct medical benefits, while others do not.<sup>39</sup> Most trials involve some risk of harm or injury to the participant, although it may not be more than the risks related to routine medical care or disease progression.<sup>40</sup> Many trials require participants to undergo additional procedures, tests, and assessments based on the

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<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA (Apr. 25, 2014) <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>.

<sup>35</sup> *Id.*

<sup>36</sup> *Id.*

<sup>37</sup> U.S. Nat'l. Inst. of Health, *Learn About Clinical Studies*, CLINICALTRIALS.GOV (last reviewed Aug. 2012), <http://www.clinicaltrials.gov/ct2/about-studies/learn>.

<sup>38</sup> *Id.*

<sup>39</sup> *Id.*

<sup>40</sup> *Id.*

study protocol.<sup>41</sup> These are described to the patient in the informed consent document for a particular trial; a potential participant should also discuss these issues with members of the research team and with his or her usual health care provider.<sup>42</sup>

The length of a clinical study varies, depending on what is being studied. It can take 10 to 15 years or more to complete all three phases of clinical trials before the licensing stage.<sup>43</sup> This time span can vary greatly depending on certain factors, such as the type of disease, the type of treatment, the number of patients needed, the length of the treatment, the follow up period and any problems that arise with the new drug.<sup>44</sup>

Accelerating the development and availability of drugs that treat serious diseases is desirable, especially when the drugs are the first available treatment or can provide advantages over existing treatments.<sup>45</sup> Life-Saving treatments can be expedited through the accelerated approval (fast track) and treatment INDs. Treatment INDs enable the use of an investigational drug outside of clinical trials in order to treat patients with serious or immediately life-threatening diseases for which no comparable or alternative therapy is available.<sup>46</sup>

Surrogate endpoints are another mechanism in new drug approval. This approach is beneficial when the clinical trial would be dangerous to the patients or take an impractically long time to complete. It is based on an assumption about the adequacy of the endpoint to signal

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<sup>41</sup> *Id.*

<sup>42</sup> *Id.*

<sup>43</sup> *How long does it take for a new drug to go through clinical trials?*, CANCER RESEARCH UK (Oct. 9, 2013), <http://www.cancerresearchuk.org/cancer-help/about-cancer/cancer-questions/how-long-does-it-take-for-a-new-drug-to-go-through-clinical-trials#long%29>.

<sup>44</sup> *Id.*

<sup>45</sup> *Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review*, FDA (June 26, 2013), <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm>.

<sup>46</sup> *Id.*



safety and efficacy.<sup>47</sup>

The primary intent of expanded access is to provide treatment for a patient's disease or condition, rather than to collect data about the study drug. There are many benefits to allowing patient participation in expanded access programs. Expanded access can provide access to patients with serious or life-threatening disease who have no other alternatives and may be willing to accept greater risk. EAPs can provide patients a measure of autonomy over their own health care decisions.<sup>48</sup> The treatment IND can help bridge the gap between the latter stages of product development and approval by making a drug widely available during that period and expanded access use can help foster development of additional uses of a drug.<sup>49</sup> An example of this would be anecdotal evidence of benefit in a disease other than that being studied. Though the primary purpose would not be to necessarily to advance the research of the drug, allowing expanded access could have this effect while providing hope for patients with no other options.<sup>50</sup>

## II. Regulation of Access

The use of investigational drugs for treatment purposes is legal, but it is tightly restricted to patients who meet certain conditions. As previously discussed, the FDA regulations on access specify the criteria for patients to qualify for access to the clinical trials and expanded use programs.

The FDA must determine that the patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory

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<sup>47</sup> *Id.*

<sup>48</sup> RICHARD KLEIN, *Expanded Access Programs*, FDA (Mar. 1, 2012), <http://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/OPDNewsArchive/UCM294794.pdf>.

<sup>49</sup> *Id.*

<sup>50</sup> *Id.*

alternative therapy to diagnose, monitor, or treat the disease or condition.<sup>51</sup> The potential patient benefit must justify the potential risks of the treatment use and those potential risks must not be unreasonable in the context of the disease or condition to be treated.<sup>52</sup> Finally, providing the investigational drug for the requested use must not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.<sup>53</sup>

The FDA defines an “immediately life-threatening disease or condition” as a stage of disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.<sup>54</sup> “Serious disease or condition” is defined as a disease or condition associated with morbidity that has substantial impact on day-to-day functioning.<sup>55</sup> Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent.<sup>56</sup> 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.<sup>57</sup>

A company sponsoring a drug in the late stages of drug development, such as Phase III clinical trials, can offer expanded access programs for patients who are not able to enroll in a clinical trial.<sup>58</sup> The FDA generally approves these expanded access programs if the drug has

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<sup>51</sup> 21 C.F.R. §312.305 (2013).

<sup>52</sup> *Id.*

<sup>53</sup> *Id.*

<sup>54</sup> 21 C.F.R. §312.300 (2013).

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> *Id.*

<sup>58</sup> *Clinical Trials: What You Need to Know*, AMERICAN CANCER SOCIETY (last revised Sept. 21, 2012), <http://www.cancer.org/treatment/treatmentsandsideeffects/clinicaltrials/whatyouneedtoknowaboutclinicaltrials/index.htm?sitearea=eto>

shown that it works at least somewhat to treat cancer in the clinical trials that are being done.<sup>59</sup> This can allow a lot of people access to the unapproved drug, as long as they meet the requirements of the EAP.

Expanded access, sometimes called "compassionate use," is the use of an investigational drug *outside* of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options.<sup>60</sup>

FDA regulations allow access to investigational drugs outside of clinical trials for treatment purposes on a case-by-case basis for an individual patient, or for intermediate-size groups of patients with similar treatment needs who otherwise do not qualify to participate in a clinical trial.<sup>61</sup> Once more is known about the safety and potential effectiveness of a drug from ongoing or completed clinical trials, they also permit compassionate use for large groups of patients who do not have other treatment options available.<sup>62</sup> Just as in clinical trials, these investigational drugs have not yet been determined by the FDA to be safe and effective. It is uncertain whether the drug will be effective in the treatment of a condition or if the patient will experience unexpected serious side effects.<sup>63</sup>

Patients who don't qualify for either clinical trials or an expanded access program, may be able to get the unapproved new drug by applying for single patient access.<sup>64</sup> In order to gain single access, the patient's doctor must first ask the drug company if the drug can be used for the

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<sup>59</sup> *Id.*

<sup>60</sup> *Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)*, FDA (Feb. 24, 2014), <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.html/>

<sup>61</sup> *Id.*

<sup>62</sup> *Id.*

<sup>63</sup> *Id.*

<sup>64</sup> *Physician Request for an Individual Patient IND under Expanded Access for Non-emergency or Emergency Use*, FDA (Sept. 17, 2013), <http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm107434.htm>

patient and inquire as to whether the drug company will supply it. If the company agrees, the patient's doctor works with the drug company to ask the FDA for approval of the drug for use by this one patient.<sup>65</sup>

According to guidelines from the National Cancer Institute, most compassionate drug use is for patients who meet all of the following conditions: "have advanced disease, have used standard treatments that have not worked, are not eligible for any clinical trial that is in progress, have no other treatment options, have a type of cancer for which there's reason to expect the investigational drug will help and are likely to have benefits that outweigh the risks involved."<sup>66</sup> In a case like this, the doctor may consider trying to get a new, unapproved drug for a patient to see if it will help.<sup>67</sup>

The FDA requires the doctor to send information about the patient explaining why the request is being made, the proposed treatment plan, and signed informed consent from the patient.<sup>68</sup> The length of time it takes to get single patient access varies. But if it is an emergency, the FDA can complete the paperwork in 24 hours.<sup>69</sup>

Before a patient or group of patients can get an unapproved new or experimental drug outside of a clinical trial, two things must happen. The owner, typically a drug company, of the new, unapproved drug must agree to allow the use of their drug outside of a clinical trial and the FDA medical officer in charge of overseeing the new drug's development must approve the use of the drug for that person or group.<sup>70</sup>

The drug manufacturer and the patient's doctor must make special arrangements to obtain

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<sup>65</sup> *Id.*

<sup>66</sup> *Compassionate Drug Use*, AMERICAN CANCER SOCIETY (July 9, 2013), <http://www.cancer.org/treatment/treatmentsandsideeffects/clinicaltrials/compassionate-drug-use>

<sup>67</sup> *Id.*

<sup>68</sup> *Id.*

<sup>69</sup> *Id.*

<sup>70</sup> *Id.*

the drug for the patient and the FDA must authorize these arrangements.<sup>71</sup> These safeguards are in place to avoid exposing patients to unnecessary risks.<sup>72</sup> Manufacturers may not always be willing or able to provide access to a drug outside of their clinical trials.<sup>73</sup> Currently, the easiest way to get an unapproved drug is through a clinical trial. This is problematic because many people with life-threatening diseases are unable to find suitable clinical trials, live far from research centers, or are not eligible for any studies being done.<sup>74</sup>

Getting the drug through expanded access programs, or single-patient compassionate use is possible for some people though the process of satisfying each step necessary to be granted access can be long and frustrating for patients who do not have much time left. The drug companies policies and procedures can cause many obstacles along the way. For example, there may be very limited amounts of the drug; some companies establish lotteries to determine which patients will have treatment access, while others make the determination on a case-by-case basis.<sup>75</sup> Once the drug is FDA-approved, it may be marketed and made widely available.

Physicians may not always be able to seek expanded access for patients, depending on a patient's medical history and the risks associated with taking an investigational drug.<sup>76</sup> The physician must determine that the probable risk from the drug is not greater than the probable risk from the disease.<sup>77</sup> Not all physicians are willing to manage the use of an investigational

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<sup>71</sup> *Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)*, FDA (Feb. 24, 2014), <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.html/>

<sup>72</sup> *Id.*

<sup>73</sup> *Id.*

<sup>74</sup> *Compassionate Drug Use*, AMERICAN CANCER SOCIETY (July 9, 2013), <http://www.cancer.org/treatment/treatmentsandsideeffects/clinicaltrials/compassionate-drug-use>

<sup>75</sup> *Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)*, FDA (Feb. 24, 2014), <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.html/>

<sup>76</sup> *Id.*

<sup>77</sup> *Id.*

drug for patients in their care.

Participating in a Phase I study is always risky and never offers a realistic likelihood of direct medical benefit. For example, a review of the risks and benefits of a new anticancer agent undergoing Phase I testing revealed that 1 out of every 200 patients enrolled died as a direct result of taking the drug, the death rate was closer to 1 in every 100 patients during the early part of the study.<sup>78</sup> Only a very small percentage of patients (less than 4%) respond at all to these experimental drugs, and most of the responses are for very short period of time, sometimes a matter of weeks only and involve tumor shrinkage by only a small fraction.<sup>79</sup> The benefit would not outweigh the risk if a patient were to request access to drugs that have not yet completed Phase I of the clinical trial.<sup>80</sup>

Companies are not required to make their drug available through expanded access, or to make more of a drug for that purpose. Companies manufacture an investigational drug for the purpose of testing them in clinical trials, since that is the most effective and efficient way to determine whether the drugs work, and whether they are safe to use.<sup>81</sup> Producing extra medicine for patients that are not in clinical trials can be costly for the drug company; especially because there is an inherent risk that the drug may never be approved.<sup>82</sup>

Some companies provide the drug for free to patients, while other companies charge patients for costs associated with the manufacture of the drug.<sup>83</sup> Most insurance companies will not pay for access to an investigational drug. In addition, there may be extra costs associated with

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<sup>78</sup> Eric X. Chen and Ian F. Tannock, *Risks and Benefits of Phase I Clinical Trials Evaluating New Anticancer Agents*, 292 JAMA 2150 (2004).

<sup>79</sup> *Id.*

<sup>80</sup> *Id.*

<sup>81</sup> *Access to Investigational Drugs Outside of a Clinical Trial (Expanded Access)*, FDA (Feb. 24, 2014), <http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/AccessToInvestigationalDrugs/ucm176098.html/>

<sup>82</sup> *Id.*

<sup>83</sup> *Id.*

administration and monitoring of the investigational drug by healthcare professionals.<sup>84</sup>

In 2009, the FDA revised its 1987 charging rule in order to take into account unanticipated circumstances concerning charging for investigational charges, to set forth criteria for charging under all three categories of expanded access and to specify the types of costs that can be recovered.<sup>85</sup> One of the major goals the FDA had for the final rule was to extend its 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>86</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>87</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>88</sup> Second, the sponsor must provide the FDA with "reasonable assurance that charging will not interfere with developing the drug for marketing approval."<sup>89</sup> Third, the sponsor cannot charge patients who are not authorized to receive unapproved drugs through the expanded access program.<sup>90</sup>

Despite these difficulties, compassionate drug use does happen. Actual use is not well-documented, therefore there are limited numbers or statistics on how often it's done, who's doing

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<sup>84</sup> *Id.*

<sup>85</sup> Thomas Sullivan, *FDA Expanded Access to Investigational Drugs for Treatment Use: Draft Guidance*, POLICY AND MEDICINE (June 25, 2013, 5:09 AM), <http://www.policymed.com/2013/06/fda-expanded-access-to-investigational-drugs-for-treatment-use-draft-guidance.html>.

<sup>86</sup> See *Charging for Investigational Drugs*, 74 Fed. Reg. 40,872, 40,872 (Aug. 13, 2009) (to be codified at 21 C.F.R. §312).

<sup>87</sup> See *Id.* at 40,899.

<sup>88</sup> *Id.*

<sup>89</sup> *Id.*

<sup>90</sup> See *Id.*

it, or how well it's working for patients.<sup>91</sup> Compassionate use programs have the potential to positively impact terminally ill patients who are left with no other options after all treatments have been exhausted. As an initial step in expanding access, investigators, physicians and drug companies should provide better documentation of who is using the drug, how it is being used and the outcome of the use. By evaluating the types of uses and the types of patients using the drug, this information can be used to encourage patients to inquire about the drug and request access to participate in clinical trials.

Once Phase I has been completed, it can be determined whether the drug is safe to check for efficacy. Therefore, the risk of harmful side effects in providing the drug outside of the trial is reduced. In the interest of patient autonomy, a terminally ill patient that is left with no other alternative for treatment should be able to determine whether the benefit of potentially treating the illness and making a last attempt to save or prolong their life outweighs the risk of the possibly harmful or fatal side effects. The question then turns on whether the patient has a fundamental right to make this decision and access this treatment.

### **III. Right to Access**

The courts have addressed whether a fundamental right to access treatment exists. D.C. Circuit Judge Judith Rogers stated, "the prerogative asserted by the FDA, to prevent a terminally ill patient from using potentially life-saving medication to which those in Phase II clinical trials have access impinges upon an individual liberty deeply rooted in our Nation's history and tradition of self-preservation." <sup>92</sup>

The Due Process Clause of the Fifth Amendment provides that "no person shall be deprived

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<sup>91</sup> Zuzanna Fimirska, *Why Innovative Drug Access Can't Wait*, EYE FOR PHARMA (Apr. 24, 2014), <http://social.eyeforpharma.com/patients/why-innovative-drug-access-cant-wait>.

<sup>92</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 469 F.3d 129 (2006).



of life, liberty, or property, without due process of law.”<sup>93</sup> The United States Supreme Court has held that the protections of the Amendment guarantee more than fair process and has stated that the Clause provides heightened protection against government interference with certain fundamental rights and liberty interests, including the rights to marry, to have children, to direct the education and upbringing of one's children, to marital privacy, to use contraception, to bodily integrity, and to abortion.<sup>94</sup>

As substantive rights are not set forth in the language of the Constitution, the United States Supreme Court has cautioned against expanding the substantive rights protected by the Due Process Clause because “guideposts for responsible decision-making in this uncharted area are scarce and open-ended.”<sup>95</sup>

There is an additional and substantial concern that courts must also consider. By extending constitutional protection to an asserted right or liberty interest, the court, to a great extent, places the matter outside of the arena of public debate and legislative action.<sup>96</sup> Thus, the Supreme Court has directed courts to exercise the utmost care whenever they are asked to break new ground in this field, to avoid the risk of the liberty protected by the Due Process Clause being distorted into the policy preferences of the courts' members.

The United States Supreme Court has described its established method of substantive-due-process analysis as having two primary features.<sup>97</sup> First, the Court has regularly observed that the Due Process Clause specially protects those fundamental rights and liberties which are, objectively, deeply rooted in the nation's history and tradition and implicit in the concept of

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<sup>93</sup> *Id.*

<sup>94</sup> *Id.* at 137.

<sup>95</sup> *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007).

<sup>96</sup> *Id.* at 702; *see also Washington v. Glucksberg*, 521 U.S. 702, 720-21, 117 S. Ct. 2258, 117 S. Ct. 2302, 138 L. Ed. 2d 772 (1997).

<sup>97</sup> *Glucksberg*, 521 U.S. at 720.

ordered liberty, such that neither liberty nor justice would exist if they were sacrificed.<sup>98</sup> Second, the Court has required in substantive-due-process cases a careful description of the asserted fundamental liberty interest.<sup>99</sup>

“Creating constitutional rights to be free from regulation based solely upon a prior lack of regulation would undermine much of the modern administrative state, which, like drug regulation, has increased in scope as changing conditions have warranted.”<sup>100</sup>

The United States Supreme Court has held that for the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.<sup>101</sup> The Food and Drug Administration's policy of limiting access to investigational drugs is rationally related to the legitimate state interest of protecting patients, including the terminally ill, from potentially unsafe drugs with unknown therapeutic effects.<sup>102</sup> D.C. Circuit Judge Thomas Griffith stated, “I have serious doubt about how a court can know, as a matter of constitutional law, that the lesser of two evils will be achieved by providing all terminally ill patients access to all Phase I experimental drugs, given the risks these drugs present.”<sup>103</sup>

In 1979, the FDA had introduced specific rules allowing compassionate use of experimental therapies, terminally ill cancer patients and their spouses brought suit against the FDA to enjoin it from interfering in the marketing and distribution of a drug called Laetrile.<sup>104</sup> Laetrile was an extract of apricot pits and almonds, available outside of the U.S. and widely

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<sup>98</sup> *Id.*

<sup>99</sup> *Id.*

<sup>100</sup> *Abigail Alliance v. Von Eschenbach*, 495 F.3d at 707.

<sup>101</sup> *Id.* at 713.

<sup>102</sup> *Id.*

<sup>103</sup> *Abigail*, 445 F.3d at 492.

<sup>104</sup> *US v Rutherford*, 442 US 544 (1979).

believed to be effective in the treatment of cancer.<sup>105</sup> Parties to the suit believed Laetrile was their last and only option. The FDA had denied approval for marketing of the drug and was waiting for greater clinical research data on efficacy and safety.<sup>106</sup>

Recognizing the limited options that terminal cancer patients faced, the U.S. Supreme Court in *Rutherford* stood by the FDA actions and concluded that the right to access unproven therapies did not exist in this case.<sup>107</sup> Acknowledging that there is a clear protected right to refuse life-saving treatment, the Court distinguished this from a positive right to access a particular treatment or medication.<sup>108</sup> The Court argued that a drug is as unsafe for the terminally ill as for anyone else if its prospects of death and physical injury are not outweighed by its potential for benefit.<sup>109</sup> The FDA had not yet found evidence that Laetrile was safe and effective. Furthermore, the Court asserted, the government, specifically the FDA, has an interest in regulating unsafe drugs and protecting the public's health.<sup>110</sup>

Returning to the case of *Abigail Alliance v. Eschenbach*, in which the Court addressed whether the Constitution provides terminally ill patients a right of access to experimental drugs that have passed limited safety trials but have not been proven safe and effective. The Alliance argued that patients have a right to decide, for themselves, whether to take an investigational drug that the FDA has approved for clinical trials.<sup>111</sup> The FDA argued that the requested expanded access 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

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<sup>105</sup> *Id.* at 548.

<sup>106</sup> *Id.*

<sup>107</sup> *Id.*

<sup>108</sup> VALERIE BLAKE, J.D., M.A., *The Terminally Ill, Access to Investigational Drugs, and FDA Rules*, AM. MED. ASS'N. J. ETHICS (August, 2013), <http://virtualmentor.ama-assn.org/2013/08/pdf/hlaw1-1308.pdf>.

<sup>109</sup> *Id.*

<sup>110</sup> *Id.*

<sup>111</sup> *See Abigail*, 445 F.3d 495.

importance of marketing drugs with reasonable knowledge for patients and physicians of their likely clinical benefit and their toxicity.<sup>112</sup>

The district court held there is no such right. The FDA reserves the right, however, to deny any treatment IND request if the agency believes there is no “reasonable basis” to conclude that the drug is effective or if granting the request “would expose the patient to an unreasonable and significant additional risk of illness or injury.”<sup>113</sup> Sponsors may not profit from any approved treatment IND program and may only “recover costs of manufacture, research, development, and handling of the investigational drug.”<sup>114</sup>

The panel majority in *Abigail* ruled that “mentally competent, terminally ill adult patients with no government-approved treatment option have a constitutional right to access potentially life-saving investigational new drugs that the FDA has determined, after Phase I trials, are sufficiently safe for expanded human trials, post-Phase I investigational new drug.”<sup>115</sup> In their reasoning, the panel relied heavily on treatises and law review articles, the panel majority explained that “a right of control over one’s body has deep roots in the common law” and that “barring a terminally ill patient from the use of a potentially life-saving treatment impinges on the right of self-preservation.”<sup>116</sup>

Second, the panel majority observed that government regulation of drugs based on concerns over efficacy, as opposed to safety, is of recent origin, because Congress has regulated access to new drugs on efficacy grounds only since 1962.<sup>117</sup> Third, the panel majority argued, “the claimed right is implied by” the Supreme Court’s ruling which recognized that the Due

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<sup>112</sup> *Id.* at 487.

<sup>113</sup> *Id.* at 490.

<sup>114</sup> *Id.*

<sup>115</sup> *Id.* at 472.

<sup>116</sup> *Id.* at 480.

<sup>117</sup> *See Abigail*, 445 F.3d at 482.

Process Clause “protects a person’s right to refuse life-sustaining treatment.”<sup>118</sup> The panel majority observed that “if there is a protected liberty interest in self-determination that includes a right to refuse life-sustaining treatment, even though this will hasten death, then the same liberty interest must include the complementary right of access to potentially life-sustaining medication, in light of the explicit protection accorded ‘life.’”<sup>119</sup>

In 2007, the U.S. Court of Appeals for the District of Columbia reheard the case en banc. The Court issued an 8-2 decision against the Abigail Alliance, reversing the previous panel decision, thereby upholding the previous court decision that found there is no constitutional right to unapproved drugs by terminally ill patients.<sup>120</sup>

After determining that there is not a fundamental right to access, the court considered whether the common law doctrines of necessity, intentional interference, and self-defense supported a fundamental right of self-preservation.<sup>121</sup> The Court focused on whether an unapproved drug of uncertain safety and efficacy could be considered necessary for prolonging the life of a terminally ill patient.

Necessity provides an individual with a defense when “physical forces beyond the actor’s control rendered illegal conduct the lesser of two evils.”<sup>122</sup> There are two factors to consider when applying the necessity defense; 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.<sup>123</sup> A terminally ill patient who has exhausted all of the available treatments and therapies could have a good faith

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<sup>118</sup> *Id.* at 495; *see also Cruzan v. Dir., Mo. Dep’t of Health*, 497 U.S. 261 (U.S. 1990).

<sup>119</sup> *Id.* at 495.

<sup>120</sup> *See Abigail*, 495 F.3d 695.

<sup>121</sup> *Id.*

<sup>122</sup> *Id.* at 707; (quoting *United States v. Oakland Cannabis Buyers’ Cooperative*, 532 U.S. 483, 490 (2011)).

<sup>123</sup> *Id.* at 708.

belief that an unapproved drug is the only thing that could save her life and is therefore necessary for prolonging her life, despite evidence that the drug is unlikely to be effective.

Relying on *United States v. Oakland Cannabis Buyers' Cooperative*,<sup>124</sup> the majority dismissed the claim for necessity because Congress has already expressly eliminated a necessity defense in the context of access to unapproved drugs.<sup>125</sup> The Court stated "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."<sup>126</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>127</sup> In denying the necessity defense, the majority also relied on the fact that there is significant uncertainty regarding whether unapproved drugs can save patients' lives.

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>128</sup> Given the uncertainty surrounding the safety and efficacy of drugs in clinical trials, it was argued that terminally ill patients cannot assert in good faith that such drugs are necessary to save their lives.<sup>129</sup> There cannot be a viable claim to exercise the right to necessity without some degree of certainty that the treatment used will actually save the patient's life.

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<sup>124</sup> 532 U.S. 483 (2011),

<sup>125</sup> See *Abigail*, 495 F.3d at 707-08.

<sup>126</sup> *Id.*

<sup>127</sup> Seema Shah & Patricia Zettler, *From a Constitutional Right to a Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, YALE J. HEALTH POL'Y L & ETHICS (March 3, 2013), <http://digitalcommons.law.yale.edu/cgi/viewcontent.cgi>.

<sup>128</sup> *Id.* at 142.

<sup>129</sup> *Id.*

Congress has prohibited general access to experimental drugs, and has prescribed in detail how experimental drugs may be studied and used by the scientific and medical communities.<sup>130</sup> The United States Supreme Court has concluded that the common law defense of necessity remains controversial and cannot override a value judgment already determined by the legislature.<sup>131</sup>

Abigail Alliance also attempted to assert 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>132</sup> It was argued that the tort of intentional interference does provide a basis for an individual's interest in self-preservation by accessing unapproved drugs. This is because, in some cases, investigational treatments are the only means terminally ill patients have to prolong their lives.<sup>133</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>134</sup> For these reasons, the 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.

Self-defense and a right to self-preservation are 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>135</sup> According to Abigail Alliance, the correlation between medical self-defense and traditional self-defense is not effected by the fact that drugs pose risks of side

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<sup>130</sup> 21 U.S.C.S. § 355(a).

<sup>131</sup> *Id.*

<sup>132</sup> *Abigail*, 495 F.3d at 708; (citing Restatement (First) of Torts § 326).

<sup>133</sup> *Id.* at 709.

<sup>134</sup> *Id.*

<sup>135</sup> *Id.*

effects because an act of traditional self-defense may also pose risks.<sup>136</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>137</sup> Under this reasoning, terminally ill patients should be permitted to access unapproved drugs even if those drugs pose serious risks.

The Court did not agree with this reasoning stating "terminally ill patients cannot fairly be characterized as using reasonable force to defend themselves when they take unproven and possibly unsafe drugs."<sup>138</sup>

Following the decision in *Abigail*, the trial court in *Gunvalson v. PTC Therapeutics, Inc.*, issued an injunction which was later reversed, requiring a drug company, PTC Therapeutics, to provide an experimental drug to a patient outside of the context of a clinical trial.<sup>139</sup> Under the ruling, *Gunvalson*, would be able to start taking a drug intended to treat Duchenne muscular dystrophy, a rare and fatal disease that strikes boys and young men.<sup>140</sup> The developer, PTC Therapeutics contended that Jacob Gunvalson did not meet the criteria to be a part of the drug's clinical trial. The drug was still in phase II of clinical trials.<sup>141</sup>

The facts of the case set it apart and illustrate other ways in which the argument for expanded access may be denied. From the time Jacob was diagnosed with Duchenne Muscular Dystrophy, his mother worked to raise awareness as well as money for research, even appearing before Congress to lobby for government funding.<sup>142</sup> In the course of her efforts, she came in contact with the Vice President of PTC Therapeutics. Jacob and his mother were in close

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<sup>136</sup> *Id.*

<sup>137</sup> Seema Shah & Patricia Zettler, *From a Constitutional Right to a Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, YALE J. HEALTH POL'Y L & ETHICS (March 3, 2013), <http://digitalcommons.law.yale.edu/cgi>.

<sup>138</sup> *Abigail*, 495 F.3d at 710.

<sup>139</sup> *Gunvalson v. PTC Therapeutics, Inc.*, 303 Fed. Appx. 128 (3d Cir. N.J. 2008).

<sup>140</sup> *Id.*

<sup>141</sup> *Id.*

<sup>142</sup> *Id.*



communications with PTC Therapeutics' management and staff on a regular basis.<sup>143</sup> This does not occur in the usual clinical trial situation; typically the patient only has contact with the investigators and the site where the trial is being conducted, but not the drug company sponsor. As PTC Therapeutics was proceeding to the clinical trial stage of product development, his mother was helping the company obtain funding for the trials.<sup>144</sup> In early 2006, PTC Therapeutics began a Phase II trial that Jacob did not participate in because he was on another medication, which was still working for him.<sup>145</sup>

By 2008, Jacob's condition was deteriorating and his current medication was no longer working. PTC Therapeutics was conducting additional trials, but determined that Jacob was not eligible to participate in the study.<sup>146</sup> PTC announced that the company's investigational drug for the treatment of genetic disorders due to nonsense mutations was featured in a symposium at the Third Annual Congress of Myology 2008.<sup>147</sup> Dr. Thomas Voit, M.D., Medical and Scientific Director of the Myology Institute, stated that the drug "represents a promising new therapy for Duchenne muscular dystrophy and Becker muscular dystrophy as there are currently no available treatments that address the underlying cause of this disease."<sup>148</sup> He went on to say that "the Phase 2b PTC124 clinical trial sets a gold standard for future clinical trials in muscular dystrophies."<sup>149</sup>

The plaintiffs sought a preliminary injunction in the U.S. District Court requiring PTC Therapeutics to provide the drug. In its decision granting the injunction, the court held that in light of the plaintiff and his mother's unique relationship with senior management, the company,

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<sup>143</sup> *Id.*

<sup>144</sup> *Id.* at 132.

<sup>145</sup> *See Gunvalson*, 303 Fed. Appx. at 133.

<sup>146</sup> *Id.*

<sup>147</sup> *PTC124 Featured at Third Annual Congress of Myology*, MNT (June 2, 2008, 5:00 AM), <http://www.medicalnewstoday.com/releases/109526.php>

<sup>148</sup> *Id.*

<sup>149</sup> *Id.*

whether it intended to or not, had made an enforceable promise to provide the drug and could not deny its compassionate use.<sup>150</sup> The United States Court of Appeals for the Third Circuit, however, vacated the decision and remanded the case for further proceedings.<sup>151</sup>

The Appellate Court ruled that the plaintiffs had not shown that PTC Therapeutics had made a clear and definite promise, nor did they prove that the reason Jacob did not enroll in the 2006 trial was his reasonable reliance on the alleged promise.<sup>152</sup> With his health deteriorating, Jacob was ultimately denied access to the drug. Unlike the previous cases, the Gunvalson's did not attempt to assert a fundamental constitutional right to the experimental drug yet they were still unsuccessful in gaining access to the clinical trial. This further case illustrates the difficulty terminally ill patient's face in trying to gain access to an unapproved therapy and the Court's reluctance in granting access to investigational drugs despite evidence of positive clinical progress.

#### **IV. Recommendations**

The Abigail Alliance case and other claims for access involve terminally ill people who were unable to obtain access to expanded use programs and clinical trials. One solution might be to change the approach to clinical trials, perhaps by expanding the inclusion criteria for Phase II and Phase III trials. The purpose of current Phase II trials and Phase III trials would not change. What would change would be the number of participants allowed access to the experimental drug through Phase II trials.<sup>153</sup> Phase II studies could be more useful if they studied a larger sample size and had less restrictive inclusion and exclusion criteria to broaden the pool of patients

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<sup>150</sup> See *Gunvalson v. PTC*, 303 Fed. Appx. 128.

<sup>151</sup> *Id.*

<sup>152</sup> *Id.*

<sup>153</sup> 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, 456 (2008).

eligible to participate.

"In general, Phase II trials are smaller than they ought to be" for obtaining a precise estimated response rate.<sup>154</sup> The precision of the estimated response rate is important for designing Phase III of the clinical trial.<sup>155</sup> Phase III trials are comparative trials that focus on efficacy, while still monitoring for any adverse events. The FDA will not make a final safety and efficacy determination until these trials are completed.<sup>156</sup> Because the precision of the estimated response rate is largely attributed to the enrollment size of Phase II trials, it is common for investigational drugs that show promise after completing Phase II trials to fail Phase III trials.<sup>157</sup> Small Phase II trials produce drug responses that are not typically representative of the same drug responses in the larger Phase III trials.<sup>158</sup> Increasing the number of patients in a Phase II study would provide more accurate information as to the response rate and will show better indication if the drug will fail Phase III trials.

Making the inclusion criteria less restrictive for Phase II and III trials and increasing the number of patients enrolled in those phases might produce both valuable scientific knowledge and prevent expanded access programs from interfering with clinical investigation.<sup>159</sup> It would also ensure that individuals being exposed to unapproved drugs were provided the careful safety monitoring involved in clinical trials.

In addition, requiring sponsors to include more individuals in clinical trials might save sponsors money while providing much-needed data on an unapproved therapy. Better data collection through more inclusive Phase II clinical trials could be cost effective in that it would

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<sup>154</sup> *Id.*

<sup>155</sup> *Id.*

<sup>156</sup> *Id.*

<sup>157</sup> Melissa Fazzari et. al., *The Phase II/III Transition: Toward the Proof of Efficacy in Cancer Clinical Trials*, 21 CONTROLLED CLINICAL TRIALS 360, 367 (2000).

<sup>158</sup> *Id.*

<sup>159</sup> *Id.*

prevent companies from conducting expensive and unsuccessful Phase III trials.<sup>160</sup>

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>161</sup> The information that has been returned to the FDA has not been very useful. Unless expanded access programs can be better designed to produce data of some value, they cannot substitute for clinical trials on terminally ill patients. Clinical trials provide a systematic approach that serves to promote patient safety and adequate data collection.

Clinical trials with strict exclusion criteria make it difficult, if not 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>162</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>163</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>164</sup> More information about the effect of the drug on different subsections of the population prior to widely marketing that drug is clearly preferable for public health reasons.<sup>165</sup>

Sponsors may be reluctant to include terminally ill patients in clinical trials because this

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<sup>160</sup> See Fazzari et al., supra note 355, at 367.

<sup>161</sup> Seema Shah & Patricia Zettler, *From a Constitutional Right to a Policy of Exceptions: Abigail Alliance and the Future of Access to Experimental Therapy*, YALE J. HEALTH POL'Y L & ETHICS (March 3, 2013), <http://digitalcommons.law.yale.edu/cgi>.

<sup>162</sup> *Id.* at 191; see also Martin Fortin et al., *Randomized Controlled Trials: Do They Have External Validity for Patients with Multiple Comorbidities?*, 4 ANNALS OF FAM. MED., 104-05 (2006).

<sup>163</sup> *Id.*

<sup>164</sup> *Id.*

<sup>165</sup> *Id.*

could potentially increase the number of adverse events in the trial, making it more difficult to collect data and demonstrate the effect of the treatment.<sup>166</sup> The risk inherent in including people with terminal illness is the possibility that the disease, and not the drug, will cause them to experience morbidity or mortality. It may be more difficult to determine the cause of negative outcomes. The researchers would be tasked with determining whether the drug or the disease caused the adverse event.

To address these concerns the sponsors could create a subsection of the clinical trial that would include only those patient's that are terminally ill. One group would consist of those research subjects who would traditionally fit under the inclusion and exclusion criteria and the subsection of expanded access patient's would consist of those who would not traditionally fit into the strict criteria of the primary group.

The analysis of the data would focus on subjects who meet the traditional inclusion criteria, and the secondary analysis would be supplemental and include information from the subsection of terminally ill research subjects. Including patients that are in more advanced stages of the disease may make it more time-consuming and difficult to interpret the data. However, it has been found that the current inclusion and exclusion criteria is so strict that it is producing inadequate information for policymakers, physicians, and patients by excluding sicker patients or more representative members of the population.<sup>167</sup>

## **V. Conclusion**

An effective approach to expanded access is 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. For eligible patients that are

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<sup>166</sup> See, *Fortin*, supra note 365, at 107.

<sup>167</sup> See *Fortin*, supra note 365, at 108.

unable to participate in the clinical trial because they live too far away or for patient's who have been granted access through individual use, these patients could participate in the trial remotely. They could continue to see their usual health care providers while being enrolled in the clinical study for purposes of safety, monitoring and data collection. The approved health care provider should comply with the study protocol of the trial, monitor the patient's use and electronically report all records and findings to the researchers. By having the participant's current health care provider work with the research team, the participant will receive the benefit of the protections and close supervision of the clinical trial study protocol while continuing to receive the same health care that was provided prior to enrolling in the study. By using the patient's current health care provider the participant can also be sure that the study protocol does not conflict with other medications or treatments. Creating a system in which clinical trials and compassionate use programs work closely together under the same study protocol, would promote patient safety when using the drug outside of the clinical trial, produce valuable scientific knowledge through improved data collection and prevent expanded access programs from interfering with clinical investigation.