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Ethical Considerations in Access to Experimental Drugs for Treatment Use

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ETHICAL CONSIDERATIONS IN ACCESS TO EXPERIMENTAL DRUGS FOR TREATMENT USE. Sonja K. Rakowski (Sponsored by Thomas P. Duffy and Robert A. Burt). Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT.

Do dying patients have a moral claim to access experimental drugs when all else has failed? This question has been the focus of an active and evolving debate concerning the rights of terminally ill patients, the nature of the drug development process, and the scope of federal regulation, with supporters arguing that seriously ill patients should be able to decide for themselves whether and when to attempt experimental therapies and opponents arguing that the resulting state of affairs would be disastrous for patient safety and for the integrity of the drug development process. This thesis concerns the ethical considerations surrounding the provision of experimental drugs for treatment—often termed "compassionate use" or "expanded access"—and argues that compelling ethical merits on both sides of the debate complicate the formation of satisfactory public policy. Although patient autonomy is often invoked to support liberal access to experimental drugs, the paucity of known information about investigational compounds as well as the unique vulnerability of the terminally ill patient call into question the wisdom of the unfettered exercise of autonomy in this context. Although equitable distribution of experimental drugs is often felt to be a concern, the meaning of equity in this context has not been clearly defined, and in fact several working concepts of equitable access may not be achievable or desirable. Although the financial burden on drug manufacturers is frequently recognized as a barrier to expanded access, the potential for expanded access programs to constitute a marketing strategy should be recognized, and the mixing of profit motives with altruistic ones brought to light. Parsing these and other ethical nuances points to certain ways in which policies governing expanded access can be refined to allow for access while maximizing patient protection and ensuring the generation of scientific knowledge. Physicians, as frequent mediators of requests for experimental drugs, should be knowledgeable of the ethical issues inherent and should help to ensure the judicious use of experimental therapies. Finally, general misconceptions about the benefits of experimental therapy, pervasive in our culture, heighten the contentiousness of this debate. A workable legislative solution should be accompanied by a thoughtful and deliberate effort to educate patients, their advocates, and broader society about the realistic pace of drug development and the limits of modern medicine. This thesis recognizes that individuals who seek expanded access often have valid moral claims to do so, but advocates a cautious attitude toward the dissemination of experimental drugs for treatment and maintains the importance of government and physician participation in adjudicating access.

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Introduction

The ability of medical science to devise cures for diseases that were once devastating and intractable is a triumph of modern society. Tremendous advances in medical interventions over the last half-century have given rise to a social credo that medical research, given enough time and resources, promises a cure for even the most advanced and perplexing diseases. Yet the development of new drugs for biologically complex diseases is fraught with challenges on many fronts—scientific, economic, and ethical.

We live in an era in which supposed medical breakthroughs are declared at an astounding rate, in which it often seems as though major new cures are just barely out of reach. There is considerable pressure to speed the process by which new therapies are developed, evaluated, and brought to market. Yet, despite monumental advances in medical technology over the last half-century with transformative results in many domains, there are still many diseases—including many cancers—for which treatment and prognosis are frustratingly stagnant.

We also live in an era in which patient autonomy is prized, in which patient values and preferences figure centrally in medical decision-making. The confluence of rapid medical progress with high credence in the rights of patients to self-determine has given rise to numerous ethical debates about the extent to which patients should dictate their own course of treatment, questions that take on additional gravity when they concern decisions made at the end of life.

One such question is whether dying patients who have exhausted standard therapy should be permitted to attempt treatment with experimental drugs outside of conventional clinical trials. This practice is often known as "compassionate use," but more recently has been termed "expanded access." In most cases, expanded access is granted when a drug has completed or nearly completed clinical testing and is pending FDA approval; its status is still investigational, but its safety and efficacy have been well-characterized. In recent years, however, patients with life-threatening illness have clamored for access to experimental drugs and devices at earlier and earlier stages of development, often before safety and efficacy testing are complete, arguing that

the risks associated with such drugs are trivial next to the certainty of disease progression, that the drug testing process is blind to the needs of patients who suffer in the present, and that decisions about the appropriateness of experimental therapy should be made by patient and doctor, free of government interference.

The question of access to experimental drugs is a particularly complex one because it encompasses legal and economic, as well as medical, concerns: efforts to reach a satisfactory solution on behalf of individual patients carry implications for regulatory policy and drug development more broadly. This thesis seeks to illuminate the ethical issues that underlie the debate on expanded access and to demonstrate that compelling moral claims on both sides complicate efforts to formulate satisfactory public policy. This thesis contends that individual patients and society stand to benefit from the availability of expanded access programs, but overall encourages a cautious attitude toward experimental drugs and devices as a mode of therapy and suggests that a culturally-entrenched inability to accept death plays into the contentious nature of this controversy.

Statement of Purpose

The central aim of this thesis is to identify the ethical problems that would result from overly strict regulation of experimental therapies and also from overly liberal access to them. More specifically, it aims to identify the pitfalls of invoking patient autonomy to justify liberal access policies, to question whether equity in access to experimental drugs can and should be achieved, and to explore whether programs through which patients receive early access to experimental drugs carry conflicts of interest. This thesis also seeks to advance recommendations for public policy in light of the ethical concerns identified, and also to explore what role there might be for physicians, who are traditionally side-lined in this conflict, to help mediate a solution, both with individual patients and on a broader societal level.

Methods

This thesis centers on the ethical considerations inherent in the provision of experimental drugs with therapeutic intent. The historical, political, and legal context for such considerations was provided by reviewing the history of FDA regulation of investigational compounds, the evolution of ethical codes governing human subjects protection in research, the challenges to the drug development process that were presented by the onset of HIV/AIDS, recent trends in oncology drug development, and a recent court case that highlights the rights-based arguments concerning the use of experimental drugs for treatment. The existing literature on expanded access was reviewed through Medline and Lexis Nexis searches in order to encompass medical, legal, and lay literature. Ethical considerations that were either unexplored in the literature or that merited consideration from a different angle were identified. These included the question of whether patient autonomy is unjustifiably compromised by restrictions on access to experimental drugs, the question of how to define equity in access to experimental drugs and whether equity should be a priority, and the question of conflicts of interest in the administration of programs through which patients obtain experimental drugs. These domains were explored through both normative and consequentialist reasoning. Additionally, a Medline search of published results of expanded access programs was conducted using the search terms “compassionate use trial/program/study,” “expanded access trial/program/study,” and “parallel track.” This literature was reviewed to determine the size of the programs, their enrollment criteria, and the quality of the data that are collected during their administration. These results were not analyzed systematically, but rather incorporated where they were informative of the ethical arguments.

Background

In May of 2009, the *New York Times* reported in depth the heartrending story of 34-year old Joshua Thompson, who was suffering from amyotrophic lateral sclerosis (ALS), a progressive and fatal neurodegenerative disease (1). Thompson's disease had advanced relentlessly despite treatment with the only FDA-approved therapy for ALS. Confronted with a bleak prognosis, Thompson's mother turned her attention toward procuring any other therapy that might possibly benefit her son. Scouring the Internet, she discovered Iplex, a growth factor analogue that had been developed for a pediatric growth deficiency and that was being pulled from the market due to concerns over a patent infringement. Although Iplex had never been systematically tested in patients with ALS and FDA expressed concerns about its safety in that population, Thompson's mother came across self-reports from patients who had obtained the compound off-label and had reported improvements in their ALS symptoms with its use. She then embarked on a vigorous attempt to persuade FDA to release Iplex to her son and to other ALS patients on a "compassionate use" basis. Underscoring Thompson's persistence in her crusade to obtain access to Iplex, the *Times* noted that, in such tragic cases, "the hope of prevailing can sometimes eclipse the hope held out for the drug itself" (1).

What are the ethical issues inherent in the provision of an investigational drug for therapeutic use, especially to a patient who is terminally ill? What restrictions, if any, should there be on the rights of patients who have exhausted all standard therapies to procure drugs of their choosing? Who should determine whether and when a patient can access new drugs before they are approved? What is the nature of the physician's responsibility in adjudicating patients' requests for expanded access?

These questions, which form the basis for this thesis, must be considered with reference to the historical and political events that have shaped policies governing access to experimental therapies. First, a brief history of pharmaceutical regulation by FDA is provided, with a focus on how FDA gained the authority to oversee the distribution of investigational compounds both for

research and treatment purposes. Second, given that expanded access concerns products that are by definition experimental, the ethical codes governing human subjects protection in clinical research, as well as some of the historical cases that led to their promulgation, are briefly reviewed. Third, the establishment of expanded access policies during the late 1980s and early 1990s in response to the crisis posed by HIV/AIDS is reviewed. The contemporary process by which patients obtain access to investigational drugs for treatment use is also discussed. Selected data on trends in the testing and approval of new oncologic drugs are provided as empirical context for the subsequent ethical analysis. Lastly, the question of whether our Constitution guarantees the right to access experimental drugs is explored through a discussion of a controversial legal case, resolved in 2007, in which a patient advocacy group brought suit against FDA.

Historical Landmarks In Federal Drug Regulation

The perennial challenge facing FDA in the regulation of drug development is to achieve the proper balance between ensuring the safety of new drugs and devices and encouraging their efficient development. The appropriate degree of federal oversight of product testing is a matter of ongoing controversy (2). However, throughout most of the previous century, the trajectory of federal drug regulation in the United States has been one of increasing protections forced by public safety concerns.

Federal involvement in product regulation began in 1906 with the introduction of the Pure Food and Drug Act. In the early twentieth century, an explosion of investigative reporting in the lay press brought to light the widespread prevalence of toxic and adulterated medicinals, the unsanitary practices throughout the meat-processing industry, and the ease with which products promising “miracle cures” could be marketed without substantiation of those claims (2). In response to public uproar, Congress passed the Pure Food and Drug Act, which mandated the accurate labeling of food and drug contents, placing safety in the hands of the well-informed

consumer (2). While the Act represented a major expansion of government's role in regulating commerce, it restricted that role to the policing of labels and the removal of dangerous products from the market (2).

Public pressure for expanded federal oversight of product safety mounted throughout the 1920s and 1930s, but tougher regulation was vigorously opposed by industry (3). Eventually, however, reform was forced by a major public health crisis. In 1937, more than 100 people, including many children, died after ingesting a novel liquid preparation of the antibiotic sulfanilamide that used diethylene glycol, the toxic ingredient in antifreeze, as the diluent. The manufacturer had sold a tablet formulation of the drug for years without incident and, seeking to expand its use in children, introduced the liquid preparation without any safety testing, as none was mandated at the time (4). The sulfanilamide scandal became the major impetus for passage of the Federal Food, Drug and Cosmetic Act (FDCA) in 1938, which mandated that new products undergo safety testing, and vested in FDA the authority to proactively evaluate products before they entered the market (4). Manufacturers were required to submit to FDA a new drug application (NDA) detailing evidence of the compound's safety for human consumption. NDAs gained approval automatically after 60 days unless blocked by an FDA reviewer. Importantly, FDCA did not mandate any standardized procedure for evaluating drug efficacy (2). Neither did it require FDA oversight of the clinical testing necessary for NDA approval; new drugs could be developed and tested without any FDA knowledge or assent (2).

In 1962, the scope of FDA's authority was broadened considerably, again in response to a crisis over public safety. A key impetus for reform was the distribution of thalidomide to several hundred pregnant women in the U.S. in the setting of investigational studies (2). Thalidomide, used to treat morning sickness in pregnancy, had caused an epidemic of severe birth defects throughout Europe in the 1950s. While a diligent FDA officer, Frances Kelsey, repeatedly blocked the drug from approval for commercial use, FDA had no authority to regulate its dissemination for research purposes (2). The recognition of this loophole, plus widespread fears

that thalidomide, or a drug like it, could slip into the commercial market, fueled strong public support for regulatory expansion.

This expansion came in the form of the 1962 Kefauver-Harris Drug Amendments, sweeping legislation enacted by both houses of Congress, which codified the modern framework for drug testing and approval and cemented FDA's authority to regulate the distribution of experimental compounds (2). The Kefauver amendments required for the first time that new drugs be proven effective, as well as safe, through controlled clinical trials. Furthermore, given the lesson of thalidomide, the commencement and conduction of clinical trials now required FDA oversight. Prior to initiating clinical testing, manufacturers were required to submit to FDA an investigational new drug application (IND), which required affirmative approval before testing could begin (5). The amendments therefore generated major changes not only to consumer protection in the commercial domain, but also to human subjects protection in the research domain. They also caused a dramatic shift of authority out of from the hands of seasoned physicians and onto the shoulders of FDA. Writes Philip Hilts, "The old standard allowed 'experienced' doctors to declare what was safe and what worked. The new law was a direct threat to that authority, and the AMA's house of delegates unsuccessfully demanded outright repeal of the new law, at least as far as it suggested that a drug's effectiveness could be determined by scientific tests. For the first time, experts were in second place and investigations themselves were central" (2).

The Kefauver amendments introduced the stepwise framework for drug testing that exists today, in which clinical trials are conducted in three phases. After pre-clinical testing (e.g. animal studies) and FDA approval of the IND, a sponsor may initiate the first phase of testing in human volunteers. Phase I trials are designed to characterize drug pharmacology and projected side effects and are conducted in very small numbers (usually less than 100) of healthy human

subjects (6).[1] Participants are exposed to increasing doses of the experimental agent until a maximum tolerable dose is determined. If an acceptable safety profile is observed, the drug may advance to phase II, in which the primary aim is to determine efficacy. Phase II testing is conducted in larger numbers of subjects, often up to several hundred, who are affected by the disease or condition of interest (6). Phase III marks the final stage of pre-approval testing and is extremely time-intensive and costly. The hallmark of phase III testing is the randomized, controlled trial (RCT), which evaluates the efficacy of the new agent against standard therapy and more fully characterizes its side effects. Phase III takes many years to complete and may involve several thousand patients. At present, the average cost of phase III testing for a single drug exceeds $85 million dollars (8). Upon successful completion of clinical trials, a sponsor may then submit to FDA a formal proposal for approval (the NDA).

Although the Kefauver amendments and the other political landmarks discussed here describe a trajectory of increasing regulatory oversight, this general trend has been punctuated repeatedly by efforts to de-regulate what is arguably an overly laborious and bureaucratic drug testing and approval process (2). A particularly decisive critique of FDA protectionism was leveled during the early years of HIV/AIDS, and will be explored subsequently. However, even before the first case of HIV was described, the Reagan administration undertook a sweeping effort to weaken federal agencies including FDA, with the intention of emancipating business from a perceived regulatory stranglehold (2). At the inception of Reagan's presidency, FDA's budget was slashed, officials with strong industry ties were appointed to head FDA and the Occupational Safety and Health Administration, and an executive order giving the president total control over federal regulatory policies was enacted (2). Thus, while some critiques of federal

[1] Healthy subjects traditionally are favored for phase I investigations because they are assumed to be less vulnerable to potential toxicities relative to sick patients, to have superior organ function allowing for better characterization of pharmacology, and to not require other medications that could interact with the investigational compound (7). Importantly, phase I testing of cancer drugs is conducted in patients who are affected by the disease of interest, and difficult ethical questions arise when patients expect to benefit from trials that are not designed with therapeutic intent and that may realistically induce more harm than good (6).

drug regulation have originated from patient activists asserting individual rights and compassion, others have emanated from industry leaders and elected officials favoring a pro-business, free-market paradigm.

Research Ethics and Human Subjects Protection

The question of whether patients should be able to access experimental drugs for treatment is informed by the ethical standards governing human subjects protection in the domain of clinical research. Robert Levine writes that the field of research ethics "began as a search for secure defenses against a repetition of the most egregious assaults on the rights and welfare of human beings ever committed in the name of science" (7). Levine refers to the promulgation of the Nuremburg Code in 1947 in response to the heinous experiments conducted on political prisoners by Nazi physicians. Given that research ethics evolved as a response to the exploitation of patient-subjects, it is understandable that its major ethical codes have been dominated by an ethos of protectionism.

Through the greater part of the twentieth century, major scandals in medical experimentation, in addition to Nuremberg, fueled legitimate mistrust in the research enterprise. The most notorious of these was the Tuskegee syphilis experiment. Conducted by the U.S. Public Health Service from 1932 to 1972, Tuskegee was a longitudinal study of the natural history of untreated syphilis in African-American males, in which curative antibiotics were intentionally withheld from participants (9). Dispelling the possibility that such exploitation was occurring at the margins of the field or being conducted by a few miscreants, a landmark paper in 1966 by Harvard clinical investigator Henry Beecher documented 22 cases of clinical research endeavors conducted at highly venerable institutions in which patients were subjected to dangerous and invasive investigations without disclosure or consent (10). Beecher's distressing conclusions were that such abuses were far more widespread than commonly believed, and that self-regulation by the medical profession was an inadequate guard against the exploitation of patient-subjects.

Clinical investigations thus became conceived of as harmful—or, at a minimum, burdensome—to subjects, and the objective of ethical codes governing research was to minimize those harms.

The seminal document on research ethics to emerge from the U.S. was the 1979 Belmont Report, which articulated three core principles requisite to the protection of human subjects during the conduction of clinical research: respect for persons, beneficence, and justice (11). The principle of respect for persons encompassed two ethical norms: first, that individuals who are capable of self-determination must be treated in a manner that recognizes and respects their choices, and, second, that individuals with limited capacity for self-determination must be accorded special protections (11). Respect for persons therefore points to the requirement of obtaining informed consent either from the research participant or, in case of diminished capacity, from a third party acting in the participant's best interest. Beneficence is the duty to promote well-being and to minimize harm, and requires that any risk associated with research participation be reasonably tempered by potential benefits. The norm of justice dictates the fair distribution of burdens and benefits. Its major application to the conduction of clinical research is in the judicious selection of subjects, such that potential harms and benefits are allocated fairly. The justice principle mandates the exclusion, where possible, of subjects who already are at heightened vulnerability, such as the disabled, institutionalized, or incarcerated (11).

As medical progress gained speed in the 1970s, public acceptance of clinical research strengthened with the recognition that research participation conferred access to promising new therapies (7). However, the foremost challenge to the protectionist paradigm of the Belmont Report came with the onset of the AIDS crisis. Both the enormity of the public health crisis posed by AIDS, as well as the tremendous organizational capacity and political intelligence of the leaders of the AIDS patient advocacy movement, forced major policy changes at FDA designed to hasten drugs to market and allow early access to promising new therapeutics. The AIDS activists reconceived clinical research as a portal to treatment, and leveled a formidable attack on the prevailing ethics and assumptions of clinical experimentation.

HIV and Patient Activism

The first case of HIV/AIDS was reported to the CDC in 1981, and by 1985 there were over 15,000 reported cases, over 8,000 deaths, and no FDA-approved therapies (12). The populations chiefly affected by HIV/AIDS in the early years of the epidemic were politically marginalized minorities—gay men and intravenous drug users. This epidemiology undoubtedly fed resistance on the part of government officials to acknowledge the scale of the crisis and to initiate research efforts in a timely fashion (13). The first antiretroviral, zidovudine, did not enter clinical trials until 1985, and was not approved until 1987 (14).

The desperation of patients affected by AIDS, coupled with their sense that they had been betrayed by a government indifferent to their plight, fueled a vociferous patient advocacy movement that arose in the early years of the epidemic. This movement, embodied by groups such as the Gay Men's Health Crisis and the AIDS Coalition to Unleash Power (ACT UP), had myriad objectives, one of which was intense lobbying of Congress and FDA to ramp up research efforts and ensure quick access to the new therapies (13).

The leaders of this patient advocacy movement, such as Martin Delaney of the San Francisco-based Project Inform, questioned the very ethics of the clinical trials enterprise. First, they charged, measures focusing on the protection of research subjects were paternalistic and irrelevant to dying patients who faced the choice between untested therapies and certain death. Whatever the dangers of ingesting untested compounds, they seemed trivial compared to the consequences of doing nothing. Before a 1988 meeting of the Infectious Disease Society, Delaney, arguing for liberalized access to experimental HIV drugs, quoted the perspective of an HIV-positive patient:

> It is as if I am in a disabled airplane, speeding downward out of control. I see a parachute hanging on the cabin wall, one small moment of hope. I try to strap it on, when a government employee reaches out and tears it off my back, admonishing, 'You can't use that! It doesn't have a Federal Aviation Administration inspection sticker on it. We don't know if it will work' (15).

Second, the use of placebo controls in clinical trials struck many activists as unethical given the complete absence of standard therapy. Assuming the drug under testing was almost certainly more efficacious than placebo, randomization of subjects to the control arm of a trial violated the justice requirement of fair distribution of burdens and benefits. Furthermore, randomization was a condition that no one lacking therapeutic recourse would *voluntarily* accept, and thus patients enrolling in clinical trials were effectively coerced into research participation (15, 16).[2]

Additionally, early HIV trials relied on endpoints that necessitated an extensive duration of testing and significant morbidity in the placebo arm, such as the relative incidence of mortality and opportunistic infections between the two arms. The activists argued that drug efficacy could be just as plausibly inferred from measurable effects on CD4 counts and viral load, the biologic markers of the severity and rate or progression of HIV. Drugs found to successfully lower these markers on lab testing should in theory confer an eventual survival benefit. This led to efforts to approve drugs based on such "surrogate markers" of efficacy (17). In an illuminating case study, medical anthropologist Steven Epstein documented the way in which AIDS activists injected value judgments into FDA's deliberations on the efficacy of a specific HIV regimen, altering the way in which the scientific data were judged and incorporated into practice (18). He writes, "clinical trials do not occur in a vacuum—and when the environment in which trials are conducted and interpreted is so contentious, then these experiments, rather than settling controversies, may instead reflect and propel them" (18).

The leaders of the movement to fight AIDS breached the wall between patients and regulatory authorities, inserting themselves and their priorities into the decision-making process at every level, including shaping the research agenda, challenging the design of clinical trials, and criticizing the criteria by which drug efficacy was evaluated (17-19). Importantly, they also

[2] Prior to 1988 there was no centralized, publicly-accessible registry of clinical trials, so even patients desperately seeking to enroll had no reliable means of finding new trials, other than referral by their physicians or word of mouth. A grassroots effort by the Boston chapter of ACT UP eventually led to the founding of the AIDS Treatment Registry to publicly disseminate information on trials (17). Today, FDA maintains a comprehensive, national online registry of clinical trials.

advanced the attitude that the use investigational drugs represented a viable mode of therapy—an ACT UP slogan famously stated "A Drug Trial is Health Care Too" (19).

Although AIDS activism was at the forefront of these changes, there were other contributing forces. The mid-1980s saw a rise in activism on the part of women's health advocates, drawing attention to the widespread exclusion of women from clinical trials and the lack of research initiatives targeting women's health (19). These efforts led to the 1993 repeal of an FDA rule barring "women of childbearing potential" from participating in early-phase clinical trials and new guidelines directing expanded enrollment of women and minorities in research studies (19). Similarly, advocates and physicians charged that the exclusion of children as research participants had slowed progress on treating pediatric diseases, and in 1998 FDA and NIH issued new regulations and guidelines mandating greater inclusion of children as study participants (19). Thus, the 1980s and 1990s saw a shift in public attitudes toward a concept of clinical research as a social good—not just for the generation of knowledge, but also for its potential benefits to participants.

Notably, this shift has not been without backlash. Several well-publicized cases in which serious harm befell participants in clinical research have kept the pendulum of attitudes toward experimental therapies in swing. One such scandal involved a 1999 trial at the University of Pennsylvania in which Jesse Gelsinger, an adolescent with a rare genetic disorder, died suddenly after receiving experimental gene therapy (20). Investigations following Gelsigner's death revealed a failure on the part of investigators to disclose adverse events that had befallen other participants in the study. It was also revealed that the lead investigator, as well as the University, had significant financial stake in the success of the technology under development (20). The University was disparaged in the lay press for perceived negligence, and reactions to the case demonstrate that the research enterprise on the whole still evokes significant public suspicion and apprehension (21).

The Birth of Expanded Access

In the late 1980s and early 1990s, multiple reforms were enacted by FDA in response to criticisms leveled in the wake of AIDS. These policies aimed primarily to redress the lengthy gestation and slow evaluation of new drugs, but they also authorized means by which patients with serious and pressing medical needs could access experimental drugs and devices prior to regulatory approval.

Prior to 1987 the only recognized means for patients to access investigational drugs prior to commercial release was through participation in clinical trials. However, therapeutic use of investigational drugs through "treatment protocols" did occur before there were policies authorizing it (5). In the 1970s, several thousand patients received the beta-blocker metoprolol prior to commercial availability through a treatment protocol; similar procedures were employed throughout the 1980s to provide access to other major cardiac medications including amiodarone, nifedipine, and verapamil and to promising cancer drugs (14). However, the crisis generated by HIV triggered the formal codification and expansion of these practices.

Starting in 1987, several key revisions to the FDA regulations on investigational drugs were introduced (22). First, the IND regulations were amended to include "treatment INDs," protocols through which investigational drugs could be distributed for therapeutic use prior to approval. The requirements for opening a treatment IND are discussed in more detail in the following section. The following year, an amendment known as "Subpart E," was added to improve the flow of information between drug sponsors and FDA so that the testing necessary for approval would be clarified early in the drug development process. A mechanism for "accelerated approval" was introduced in 1992, expediting drug review by allowing for determination of efficacy based on surrogate markers of disease reduction, rather than on clinical outcomes such as mortality or progression-free survival. Use of accelerated approval requires that the drug demonstrate the proposed clinical outcome in post-marketing trials. Additionally, the 1992 Prescription Drug User Fee Act created two tracks for drug review – standard review and priority

review, the latter for therapies targeting an unmet clinical need and with a goal review time of six months (5). Also in 1992, a "parallel track" mechanism was issued, which was akin to a treatment IND, but reserved for antiretroviral drugs. According to FDA, this track was utilized for only one HIV drug (Stavudine), and sponsors have since favored the treatment IND pathway (22).

The primary objective of these reforms was to expedite the development and review of drugs to treat serious illness, not to broaden off-trial access. Nevertheless, "expanded access programs" (EAPs) became a widely utilized means of administering HIV treatment to patients throughout the 1980s and 1990s (22). Large EAPs were conducted during the development of many antiretrovirals, and several of these served thousand HIV patients (Table 1). As large-scale treatment protocols with mandated data collection, the EAPs sometimes yielded clinically important information that did not surface in the controlled trials. For instance, the stavudine EAP demonstrated that drug-associated peripheral neuropathy was dose-dependent, and the didanoside EAP revealed predictive factors for developing the drug's most worrisome side effects (23, 24).

Table 1. Dates of Enrollment and Number of Patients Treated in HIV-Specific Expanded Access Programs. (Adapted from www.fda.gov (22).)

Drug	Dates	Number Enrolled
AZT	1986-87	4,804
trimetrexate	1988-94	753
pentamidine	1989	728
ddI	1989-91	>21,000
ddC	1990-92	6,705
atovaquone	1991-93	1,054
rifabutin	1992-93	2,506
D4T	1992-94	12,551
3TC	1993-95	29,430
saquinavir	1995	2,200
indinavir	1995	1,500

However, the EAPs were also criticized for exposing large numbers of vulnerable patients to unknown and serious risks (in fact, the National Gay and Lesbian Task Force initially opposed FDA's treatment IND provisions (2)), for failing to follow patients closely enough to generate clinically useful data, and for enrolling relatively healthy patients for whom use of a new agent may have been more risky and more likely to produce viral resistance than continuation on established therapy (23). However, even acknowledging certain deficiencies in the conduction of the EAPs, there is now near-unanimous consensus that the FDA reforms of the 1980s represented a major advancement in the domain of patient rights (2).

Contemporary Modes of Expanded Access

The modern regulatory framework contains multiple avenues through which patients may obtain experimental drugs outside of controlled clinical trials, which are reviewed prior to considering whether such access should be broadened. Of note, revisions to the FDA regulations on treatment INDs were issued as recently as 2009, and these revisions are discussed subsequently.

A working definition of "expanded access" is important to this discussion. Here, the term will be defined as the provision of investigational drugs to patients for therapeutic use prior to FDA approval and outside of controlled clinical trials. The term "compassionate use" is frequently used to describe this practice, both in the lay press and in medical publications. While the term does appear in the FDA regulations, it is not clearly defined and seems to connote a variety of practices (5). Therefore, the term "expanded access" is preferred for this discussion.

The FDA regulations contain multiple provisions for expanded access to investigational drugs, of which the most widely-used is the treatment IND (5). Treatment INDs can be filed on behalf of a single patient or a cohort of patients, and permit the distribution for "treatment use" of

investigational drugs that are well into clinical trials but not yet approved. The regulations stipulate:

> (1) "the patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;"
> (2) "the potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated;" and
> (3) "providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval" (25).

Importantly, FDA has no authority to require that manufacturers provide expanded access. The treatment IND must either be filed by the manufacturer or by a physician overseeing the protocol with explicit permission and support from the manufacturer. The protocol must be approved prospectively by an institutional review board (IRB), and informed consent is required of all patients enrolled (26).

Current regulations include several other provisions for obtaining investigational drugs. An Emergency Use IND allows the release of investigational drugs in an imminently life-threatening situation where there is no time to file a treatment IND or obtain IRB approval. The Parallel Track mechanism, as discussed above, is akin to a treatment IND for HIV-related therapies. A "Group C" Treatment IND allows for the treatment use of promising cancer drugs that are close to approval. "Group C" programs are conducted by the National Cancer Institute (NCI), which distributes the drugs to qualified physicians who supervise their therapeutic use in patients and report relevant data to NCI (5). The cost of the medication typically is covered by NCI; patients enroll free of charge (5). Lastly, Open Protocol INDs refer to uncontrolled trials or extensions of previously controlled trials, through which patients who had been receiving the drug on-trial can continue to do so while approval is sought (26).

While the authority to arbitrate applications for expanded access rests with FDA, expanded access legislation has also emerged from Congress. In 1997, Congress passed the Food

and Drug Administration Modernization Act (FDAMA), with the primary aim of accelerating the development and review of new drugs intended to treat serious illnesses and unmet clinical needs. Responding to allegations that the FDA regulations were vague and confusing on the subject of expanded access, FDAMA also explicitly defined conditions under which expanded access to investigational drugs could be granted to individuals or groups of patients. The legislation either mirrored the treatment IND regulations from 1987 or mandated what had effectively been FDA practice for many years (5). For example, FDA had for decades granted individual patients access to investigational drugs for treatment use, but (prior to 2009) this was not stated explicitly in its regulations. To correct this discrepancy, a section of FDAMA explicitly allowed individual patients to seek permission from FDA to obtain expanded access (5).

While there are additional policies beyond those described that authorize the treatment use of investigational drugs, their details are complex and immaterial to a discussion of the ethical considerations surrounding this practice. However, even a cursory review of the various means of expanded access reveals one interesting observation: the diversity of the various mechanisms for access, and the redundancy and overlap between them, evidences a reactive regulatory process, a continual recasting of the rules in the face of new and changing circumstances that do not easily lend themselves to clear-cut rules.

A Constitutional Right?: Abigail Alliance v. von Eschenbach

Quite recently, the debate over expanded access moved into the courts, culminating in a 2007 decision of the District of Columbia Court of Appeals, *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach* (27). This involvement of the courts is of particular interest because it reframed the debate as a question of constitutional rights.

The Abigail Alliance, a patient advocacy group, was founded in response to the failed attempts of its namesake, Abigail Burroughs, to obtain off-trial access to an investigational cancer drug. Burroughs was diagnosed at age 19 with squamous cell carcinoma of the head and neck.

When her tumor failed to respond to conventional therapy, her father together with her oncologist sought access via existing compassionate use avenues to the oncologics Ertibux and Iressa, which at the time were in clinical trials for which Burroughs did not meet inclusion criteria. Their efforts proved unsuccessful, and, following Burroughs' death in 2001, her father formed the Alliance with the aim of securing early access to investigational drugs for terminally ill patients who have exhausted other options (5, 28).

Initially the Alliance, together with the Washington Legal Foundation, a conservative public interest firm, petitioned FDA to allow patients who were ineligible for clinical trials to purchase drugs that have passed phase I testing directly from manufacturers, with the condition that higher-phase testing be conducted concurrently (5). When FDA failed to respond, the Alliance filed suit against then-commissioner Andrew von Eschenbach, holding that the restrictions on access to phase I drugs constitute deprivation of life without due process of law and violate the Fifth Amendment.

The case was initially heard in 2004 before the District Court for the District of Columbia, where it was dismissed. The plaintiffs appealed the ruling, and in May 2006, a three-judge panel of the D.C. Court of Appeals court ruled in their favor, finding a constitutional right for dying patients to access drugs that have passed only phase I testing. This decision provoked substantial controversy in the medical community concerning the projected consequences on patient safety and the integrity of the drug development process (29-32). FDA appealed the ruling, with explicit support from the American Society of Clinical Oncology, and the case was reheard before the full Court of Appeals (*en banc*) in March 2007. In an 8-to-2 ruling, the court reversed its original decision, finding no constitutional basis for the proposed right. In 2008, the U.S. Supreme Court declined to hear an appeal (5).[3]

[3] Concurrent with the ongoing court case, the Alliance in 2005 sought to advance congressional legislation with similar aims. Sponsored by Senators Tom Inhofe and Sam Brownback, the ACCESS (Access, Compassion, Care and Ethics for Seriously Ill Patients) Act would have created a tiered system for drug approval, permitting patients to purchase investigational drugs from manufacturers while clinical testing

The grounds on which appellate court failed to find a constitutional right to access phase I drugs are relevant to the ethics surrounding this debate. Two main justifications were offered in the majority opinion. First, the proposed right is not "deeply rooted in our Nation's history and traditions"—rather, U.S. history reflects continual efforts, dating to colonial times, to contain the distribution of drugs whose safety and efficacy were in doubt. Second, the proposed right does not withstand "rational basis" scrutiny, which would require that the existing FDA regulations "bear no relationship to a legitimate state interest." Rather, according to the majority, FDA efforts to restrict access to drugs that are potentially unsafe and have "no proven therapeutic benefit" is consistent with a compelling state interest to protect patients, including the terminally ill, from undue harm (27).

The *Abigail Alliance* case remains central to the ongoing debate on expanded access because of the provocative question it posed. Importantly, the issue at the heart of the case was not whether or not patients should be allowed to take phase I drugs for treatment purposes—indeed existing policy supported access at phase I if certain conditions were met. Rather, the more weighty and provocative question put forth by the case whether or not such access ought to be enshrined as a right.

2009: New Revisions to FDA Policy

On the heels of the *Alliance* case, FDA issued revisions to the IND regulations, which were released for comment in December 2006 and as final rules in August 2009. The first of these new rules aims to clarify the various processes by which patients access investigational drugs, streamline these processes in order to promote the participation of patients and sponsors, and "increase awareness and knowledge" of expanded access programs (25). The rule includes a new "Subpart I," which defines three settings for expanded access—individual patients, intermediate-

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was ongoing. Newer versions of the bill were filed in the House and Senate in 2008, but neither came up for a vote (33).

sized populations, and larger patient populations—and aims to shift expanded access utilization away from single-patient INDs and toward treatment protocols encompassing larger numbers of patients (25).

Consistent with prior policy, the new regulations uphold the requirements that patients enrolling in expanded access be ineligible for ongoing clinical trials, that expanded access programs not interfere with the conduction of those trials in any other way, and that sponsors providing expanded access pursue marketing approval of those agents "with due diligence" (25).

A notable feature of the new rule is that it specifies different evidentiary requirements of safety and efficacy for the different expanded access settings. A relatively low safety and efficacy threshold—typically the successful completion of phase I along with "preliminary evidence suggesting possible effectiveness"—may be sufficient for the approval of expanded access for individual patients, especially in the case of an immediately life-threatening condition (25). A higher threshold—typically completion of phase II or phase III testing—is required for larger treatment protocols or for granting access in the face of serious but not imminently life-threatening illness. This is notable because it codifies the theoretical concept that the threshold of acceptable risk (or acceptable uncertainty of risk) should correlate with severity of illness and imminence of harm.

The second new rule issued in 2009 concerns charging for investigational drugs under INDs and clarifies the specific costs that can be recovered by the drug sponsor during expanded access programs (34). The rule aims to incentivize participation by manufacturers in larger-scale treatment protocols by slightly broadening the types of costs that are recoverable, while demanding assurance that recovery of such costs will not interfere with clinical trials or efforts to seek marketing approval. For drugs being made available in treatment protocols, the new rule authorizes the manufacturer to recover the "direct costs" of providing the drug for treatment use (e.g. manufacturing and distribution costs), as well as the costs of administering the program. It prohibits the recovery of any cost not directly associated with making the drug available for

expanded access. While the stated purpose of this rule is to encourage expanded access participation by manufacturers through better reimbursement, some have argued that this rule, as with previous policy, offers limited financial incentives and will little impact participation in such programs (5). However, whether or not financial incentives should be offered to encourage expanded access is yet debatable.

Recent Trends in Oncologic Drug Development

As the expanded access debate frequently concerns patients with cancer who have exhausted established therapy, it is worthwhile to review briefly the present landscape of cancer drug development, emphasizing several key observations. First, a striking minority of cancer drugs that enter the pipeline ultimately win FDA approval. Second, the development of novel oncologics appears to have slowed in recent years, fueling patient advocates' claims that industry and FDA are failing to meet their obligations to patients. Third, the risks and morbidity associated with participation in phase I oncology clinical trials seems to have diminished somewhat in recent decades, hinting that experimental therapies might actually be safer than they once were.

The approval rates of oncologic drugs are staggeringly low. Current estimates are that only five per cent of cancer drugs that enter clinical testing (29) and only half of cancer drugs that enter phase III (35) will ultimately win FDA approval. Among oncology drugs that successfully pass the phase I safety threshold, only 30 to 60 per cent successfully transition from phase II to phase III (29, 35). Additionally, a 2009 study found that only 26 per cent of oncologic drugs that gained accelerated approved based on optimistic phase II findings proved effective in confirmatory trials (36).

Regarding the pace of oncology drug development, a troubling trend has emerged in recent years. Initially, the reforms of the 1980s and 1990s, which introduced accelerated approval and incentivized the development of drugs for unmet clinical needs, seemed to have their intended effect. The middle to late 1990s saw an impressive increase in the number of drugs

approved for life-threatening diseases (notably cancer and HIV) and a concomitant decrease in approval times (37). However, in the early 2000s, that trend reversed: a declining number of applications for these classes of drugs are being submitted and approval times are lengthening (37). On average, the development time for novel anti-cancer compounds is seven to eight years, with no significant difference between cancer drugs receiving accelerated versus regular approval (36). The approval process itself lasts, on average, upwards of one year. Among all oncology drugs approved between 1993 and 2002, the average approval time was 1.3 years, despite widespread usage of accelerated approval (35). The remarkably lengthy gestation of new oncologic agents, as well as the apparent failure of the mechanisms put in place to expedite the process, has given powerful legitimacy to those parties who claim that industry and FDA are deaf to the urgency of their needs.

Another trend in clinical cancer research that bears on the expanded access debate is that participation in phase I trials (and by extension the use of cancer therapies about which little is known) appears to be safer for patients than it was in the past. A 2004 meta-analysis of 6474 cancer patients participating in phase I oncology trials between 1991 and 2002 demonstrated several indicators of improved safety over that period (38). There was a significant decline in the toxic death rate between the first and final four-year periods, a decline in the rate of serious (nonfatal) adverse events over the latter six years, and a decrease over time in the frequency with which trials were halted due to toxicity (38). The authors attribute these trends to the rise of targeted therapies that have narrower side effect profiles than conventional cytotoxic agents, better supportive care, the advent of hematologic growth factors that ameliorate side effects, increasingly stringent IRB oversight, and increasingly selective enrollment criteria (38). While some aspects of this study may not generalize well to patients using experimental drugs outside of clinical trials, the findings nevertheless hint that experimental cancer agents may be safer than they were in the past. It remains to be seen whether these trends sustain themselves, but should

the rise of targeted therapies indeed make clinical trials safer for participants, expanded access proponents would have additional fodder for their ethical claims.

Ethical Considerations in the Use of Experimental Drugs for Treatment

Although the judicious administration of expanded access to experimental drugs relies on sound public policy, those policies should be informed by a nuanced understanding of the ethical concerns inherent in providing experimental drugs for therapeutic purposes. To explore those concerns, we will first review the major arguments on either side of the debate.

Arguments in Favor of Expanded Access

Arguments in favor of liberal access policies center on the concept that it is the right of the individual to choose for herself whether or not to use investigational compounds, and that restricting access infringes on her autonomy and her civil liberties (15, 16). Proponents of early-phase expanded access argue that the patient is her own best judge of what constitutes an acceptable threshold of risk (and furthermore an acceptable body of information on which to base risk-assessment) and should not be prohibited from assuming such risks, especially to the end of promoting her own survival.

Proponents of phase I access also level pragmatic arguments that could be extended from the principles of justice. They argue that patients with advanced-stage disease are typically poor candidates for clinical trials and are often excluded based on disease severity, prior therapy, and comorbid conditions. Therefore, those most in need of novel therapies are disproportionately denied them (39). Furthermore, participation in clinical trials is financially and emotionally burdensome, requiring patients to submit to invasive testing and spend long periods of time away from home under close medical supervision. For dying patients, these burdens justify avenues of access that require less effort and sacrifice (39). Importantly, these claims assume that

experimental therapy is medically beneficial. This assumption also underlies the term "compassionate use," which connotes that providing experimental drugs is an act of beneficence.

In response to the concern that expanded access threatens the integrity of the clinical trials process, proponents of early access counter that broader access would in fact produce the opposite effect. By providing experimental drugs to a less-selected group of patients than is typically represented in clinical trials, more realistic and generalizable information about the effect of those drugs can be obtained. Broadened access is therefore in the interest not only of participating patients, but also of future patients and of society at large (39).

Lastly, advocates for expanded access argue that, even if patients with end-stage disease derive no medical benefit from trying experimental drugs, there are significant psychological gains. First, patients who are disempowered by terminal prognoses will feel strengthened by having continued choice at the end of life. Indeed the transition to palliative care still carries connotations of defeat—both for physicians and patients (40, 41)—and some patients might prefer to die during the active pursuit of therapy than to shift focus in the direction of comfort care. Working closely with a physician to obtain access to treatment protocols may reinforce the therapeutic bond between patient and doctor and guard against abandonment or the perception thereof. On a broader level, expanded access practices may bolster patients' trust in the medical establishment and counter perceptions that it is deaf to their needs.

Arguments Opposing Expanded Access

The opposing viewpoint is that liberalized access to drugs that are minimally tested or not yet approved is misguided and potentially harmful for all parties involved, including participating patients, future patients, and society as a whole.

Concerning consequences for the individual patient, opponents argue that the use of partially-tested compounds in fact confers a substantial risk of physical harm. Safety concerns account for approximately 30 per cent of attrition during clinical testing of new pharmaceuticals

(42). Phase I testing, in particular, offers only limited evidence of safety, and the potential for serious toxicity is real. In a chilling example, Jerome Groopman writes of the initial optimism surrounding the use of interferon gamma in AIDS patients, and the unexpected outcome of the phase I trials:

> In 1984…I helped run a trial of gamma interferon for AIDS patients who had Kaposi's sarcoma…Gamma interferon appeared to be the ideal treatment for these patients. It had been shown to have powerful anti-viral effects in test-tube studies and to reduce the size of tumors in rodents. I enthusiastically told my AIDS patients about the trial, including George…George was in reasonably good health; he had not developed any serious infections, and his Kaposi's-sarcoma lesions were mostly on his chest and arms. The goal of the trial was to test the effects of different doses of gamma interferon, and George belonged to the group that received the largest dose. Like many participants, he experienced unpleasant side effects—fevers, muscle pain, and headaches…After six weeks, however, new lesions appeared on his skin and in his mouth, and a chest X-ray suggested that the cancer had spread to his lungs. George was not the only patient who grew sicker on gamma interferon. None of the patients improved, and in at least four cases we believed that the therapy had hastened the tumor's growth. Ultimately, the trial was judged a failure (43).

Opponents caution that a terminal diagnosis should not be equated with having "nothing to lose," that increased suffering and diminished quality of life are outcomes potentially worse than death alone. They also caution that there may be psychological harm in pursuing last-ditch therapies that are unlikely to substantially alter the course of disease, that such behavior impairs the ability to candidly and openly confront one's prognosis and to initiate appropriate end-of-life planning. The desperation accompanying terminal illness may serve as its own coercive pressure, or patients may feel compelled to "try everything" so as not to disappoint loved ones. Broadening access to experimental drugs might also distract physicians from the more appropriate task of initiating palliative care and, more broadly, may perpetuate an already-entrenched cultural resistance to thinking and talking about death.

In terms of consequences for the broader community of patients, a potent argument against liberalizing access is that such policies would jeopardize the welfare of future patients who depend on a rigorous clinical trials process to verify the safety and efficacy of new drugs.

The logic is that expanded access will cause patients to flock to treatment protocols, thinning the pool in which clinically meaningful research can be conducted. Although FDA's treatment IND regulations state ineligibility for clinical trials as a condition for entry into treatment protocols, there is historical precedent for fearing that liberalized access could jeopardize the timely acquisition of important data. The most well-studied example is the use in the 1990s of high dose chemotherapy plus autologous bone marrow transplantation for the treatment of metastatic breast cancer. Initially, clinical trials involving small numbers of patients suggested that this treatment dramatically reduced tumor burden, and the therapy—though still experimental—rapidly gained acceptance as a standard of care (28). Lawsuits in several states and overwhelming public pressure forced insurance companies to reimburse for the costly procedure (19). More than 40,000 women received the procedure outside of clinical trials and, sapped of participants, randomized trials were not completed for several years (30). When results finally became available, the novel treatment conferred no survival benefit over conventional chemotherapy and in fact was associated with significantly higher morbidity (44). Thus, uncontrolled and optimistic data from off-trial use can cause premature allegiance to therapies that ultimately prove no better (and possibly worse) than prior standards of care.

On related grounds, a chief concern on the part of drug sponsors is that the use of experimental compounds in patients too sick for clinical trials will produce confounded data on drug side effects. If a patient with end-stage disease develops a particular complication while taking the drug, it can be difficult to discern whether such was the result of drug toxicity or disease progression (43). (Of note, FDA attests that no drug has ever failed to win approval based on toxicities discovered during expanded access (25).) There is also concern that if industry were allowed to profit from expanded access by charging for investigational drugs, the incentive and funding to conduct expensive clinical trials would erode (43).

Those opposing expanded access also point to the potential for less clear-cut, but nonetheless worrisome, implications for society at large. They argue that expanded access will

intensify the hype surrounding "breakthrough" drugs, generating false hope and exacerbating impatience with the legitimately slow pace of developing new drugs (30). A focus on expanded access diverts attention from other efforts that would bring more substantial improvements to the care of patients with serious illness, such as early detection, the provision of existing therapies to underserved populations (19), or broadened access to high-quality palliative care. They charge that a focus on expanded access perpetuates the misconception that there are "miracle cures that the government is concealing from the public" (29), or that modern medicine promises a cure for every disease, no matter how advanced.

Lastly, some argue that expanded access exacerbates existing inequities in health care, that information about such policies and programs is more readily available to wealthy, well-connected, and medically-savvy patients, and that lifting existing restrictions on access could result in a system in which the rich would purchase promising new therapies at their discretion, further widening the gulf in treatment options and outcomes between those with and without access to the most advanced care (25).

Three of these arguments have been under-explored to date and merit closer consideration. First is the question of whether restrictions on access unjustifiably infringe on autonomy. Second is the question of whether concerns about equity should enter into the debate on expanded access, and if so, how policies could be designed to support equity and justice. Third is whether expanded access programs constitute early marketing of investigational compounds, thereby incurring conflicts of interest.

Expanded Access and Patient Autonomy

The central ethical claim of those favoring liberalized access to experimental drugs is that the principle of autonomy encompasses the right to decide whether or not to assume the risks associated with taking investigational drugs. Two questions extend from this claim that merit closer exploration: Can the choice by a terminally ill patient to take investigational drugs be

authentically autonomous? Even if so, is there cause for concern with the untempered exercise of autonomy in this context?

At a minimum, an autonomous choice to take investigational drugs would need to be adequately informed and voluntary. Yet there may be problems with the degree to which such a choice *can* be informed and voluntary (19). An informed decision—one that accounts for relative risks and benefits—to use an experimental drug is complicated by inherent unknowns. At early stages of drug development, it can be impossible for anyone to estimate the odds of efficacy or even to predict what risks there might be. Such absence of guiding data upsets the conventional method of decision-making, and calls for alternative constructs of an "informed" choice. One approach might be to rigorously emphasize the uncertainty of success and the uncertainty of risk, so that the patient is maximally *aware* of the uncertainty. The patient might then weigh the extent of uncertainty against the degree of medical urgency, accepting greater uncertainty with increasing urgency.

Yet there is good reason to think that even an approach that emphasizes uncertainty will yield misunderstanding. Studies of patients enrolling in clinical trials have shown that participants often believe the trial is designed to aid them personally and overestimate their likelihood of benefit, even when a vigorous effort is made to reinforce its data-gathering objectives (45-47), the so-called "therapeutic misconception."[4] Studies of physicians have demonstrated that doctors too confuse the purpose of clinical trials and overstate their therapeutic potential (48) and even falsify entry criteria to ensure their own patients are enrolled (49). When programmed toward hopefulness, it seems legitimately difficult to keep uncertainty closely in mind. This is not to say that hope ought to be shunned; indeed it can temper the awful impotence that accompanies

[4] It could be argued that the therapeutic misconception does not apply to experimental drugs in treatment INDs because the explicit intention is to treat the patient and so there can be no confounding with research objectives. However, the uncertainty that justifies the research enterprise ("clinical equipoise") should be present in equal measure when using those same drugs for treatment. Furthermore, as expanded access moves toward larger-scale treatment protocols in which data are collected, it begins to take on a form somewhere between research and treatment.

terminal illness (50). Yet there is a difference between maintaining hope in the face of known and remote odds (e.g. a treatment that carries a 10 per cent likelihood of success), and allowing hope to reign in the face of completely unknown odds. There is a deception inherent in prescribing an experimental drug with strictly therapeutic intent if there is no evidence to support therapeutic efficacy. This deception is lessened in the context of a clinical trial, where there is an ulterior, knowledge-generating objective.

Returning to the question of whether autonomy can be realized in this setting, one could argue that the desperation surrounding terminal illness and the incomprehensibility of death encumber one's ability to act voluntarily. For a patient who so desperately wants to live, the process of weighing near-certain death against possibly prolonged life results in a false choice. How can a patient so situated reject even a long-shot chance of survival of his own volition and on rational grounds? Also, it seems as though physicians may easily mistake resoluteness for fearlessness (28), and fail to recognize that the patients with the greatest apparent resolve to "keep fighting" actually harbor the greatest fear and the greatest need for counsel. This is not to suggest that we impose more stringent criteria for decision-making capacity for terminally ill patients than for other patients, or that experimental therapy is never appropriate for terminally ill patients, but rather to argue that physicians have an increasing obligation to provide guidance at the end of life, an obligation that derives from the vulnerability of the dying patient.

Even granting that the decision to pursue experimental therapy could be adequately informed and voluntary, it is worth considering whether complete deference to autonomy in this setting ultimately will serve patients well. This is a much larger question that bears on many aspects of patient care, but it is worth touching on briefly here.

There is a dark side to the construct of autonomy as the patient unilaterally asserting himself against domineering outsiders. The readily apparent harm that can from this is the potential for the patient to make self-injurious decisions. This is a risk that we might accept for the sake of promoting self-determination. However, there are other subtle harms that might

extend from this construct that we might not tolerate. One is that a patient so bent on exercising his autonomy may alienate the people who are best positioned to support him in making choices authentic to his values—his doctors and his loved ones. With those parties absented, the patient is left to navigate the field of decisions solitarily. While the idea of unilateral decision-making seems unobjectionable or even desirable in many domains, when one considers the extreme vulnerability of patients at the end of life, the idea of solitary decision-making begins to resemble abandonment (28).

There are other potential harms associated with yielding completely to autonomy. Efforts to protect the agency of the patient will back-fire if the right to make a certain decision is valued above the reasons for making it. If restrictions on unproven therapies were lifted, patients might clamor for them more because it is their right to do so, than because it best accords with their needs and goals. More importantly, redefining autonomy to include a right to demand treatment saps physicians of their rightful agency in decisions of care, transforms them into technicians, and erodes the hallowed trust at the core of the relationship between doctor and patient.[5] In shunning the authority of the government to help regulate this process, the already tenuous faith that society vests in government to shield its citizens from injury and manipulation unravels even further. These harms associated with over-deference to autonomy should caution against the implementation of policies that allow patients to choose experimental therapies without regulation or interference. Some restrictions on access constitute a justifiable infringement on autonomy.

[5] Although this trust remains the essential foundation of the doctor-patient relationship, social confidence in the medical profession has drastically eroded over the previous century. Public opinion polling from 1966 revealed a 73 percent rate of "great confidence" in the profession. This figure fell to 44 percent in 1973 and then to 22 percent in 1993. In 1993, trust in doctors even fell below that of lawyers and politicians (51).

Problems of Equity

One issue that recurs frequently in discussions of expanded access is how to guarantee equity of access, that is, how to ensure that experimental therapies are available to those for whom they are most indicated, rather than to those who can most readily learn about and pay for them. However, less attention is paid to what the actual impact of expanded access programs on health outcomes might be, whether promoting equity in access to unproven therapies should be a concern at all, and, if so, what equitable policies might look like.

Some are concerned that expanded access programs will widen existing health care and health outcome disparities by giving preferential access to the wealthy and well-informed (25). Others counter that expanded access programs have the potential to close existing gaps in health care outcomes, but that reimbursement by third-party payers including Medicare is necessary to ensure equity in access (52). Some have suggested that FDA implement specific outreach initiatives to inform minority patients of expanded access programs, given existing disparities in cancer survival rates (25). These opinions are remarkable not only for the degree of faith they express that expanded access will yield measurable results, but also for the consequentialist argument they advance, i.e. that *outcomes* will justify expanded access policies, and therefore equitable implementation must be a primary concern.

Yet, the assertion that better access policies will substantially improve outcomes is unconvincing. One approximate way to evaluate this claim is to examine the major setting in which patients receive early exposure to experimental therapies: the clinical trial. Although the notion that trial enrollment represents the best-possible cancer care persists in the oncology community (53), there is little high-quality evidence to support the idea that patients who enroll in clinical trials have better outcomes than those who do not. In a 2004 study in The Lancet, Peppercorn et al analyzed twenty-six studies that compared outcomes between cancer patients treated within and outside of clinical trials and failed to find convincing evidence for an

"inclusion benefit" (53).[6] These data should encourage a cautious attitude toward the claim that expanded access programs will measurably improve the care of seriously ill patients. Moreover, overstating the potential public health impact of expanded access policies obscures their fundamental justification: that, while they may meaningfully benefit very few patients, those patients nevertheless have a compelling moral claim to obtain the newest therapies when all else has failed, a claim that cannot be validated or invalidated by the outcome of their attempt.

Even if measurable effects on health outcomes are not a prime concern, there might still be reason to be concerned about equity in expanded access. One could argue that, irrespective of outcomes, all patients in similar straits should have the same opportunity to attempt all available therapy. Yet this would be difficult to achieve given inherent clinical concerns in this domain. For instance, we might argue that access should not be limited to patients who receive care in large academic centers. Yet, it might only be safe and practical to administer experimental therapies in that setting due to requirements for skilled nursing or advanced monitoring technology. We might propose that all patients who desire the experimental drug but do not meet trial entry criteria be allowed admission to the treatment protocol, yet safety concerns preclude discounting disease severity. Treatment protocols for cancer drugs often have less stringent entry criteria than the corresponding randomized controlled trials, yet most still exclude patients with poor functional status (54-56).

The most worrisome concern in the domain of equity is that socioeconomic factors might dictate who receives access among patients with equal need and equal suitability for treatment, that out-of-pocket costs would prohibit the use of experimental drugs by poor patients, or, worst, that wealthy patients might buy their way into treatment protocols, relegating underserved patients to clinical trials. It is important to note that current FDA regulations forbid the entry of any patient who qualifies for an ongoing trial to enter a treatment protocol. It also seems that

[6] A search of the literature revealed no study comparing outcomes for patients treated within and outside of the HIV EAPs, although such would be a worthwhile empirical inquiry.

many third-parties already subsidize the cost of experimental drugs for patients in treatment protocols (e.g. "Group C" cancer treatments are paid for by NCI). As treatment protocols become more commonplace, there will likely be mounting pressure on insurance companies to reimburse for patient participation. Therefore, the more pertinent concern in this domain might not be individual exclusion on socioeconomic grounds, but rather mounting costs to society and to an already-burdened health care system resulting from generous coverage of experimental treatments. Or, if the cost is absorbed by manufacturers as part of research and development expenditures, this may drive up already exorbitant prices for the latest drugs once they do reach the market. Thus, a more significant concern is that the costs of ensuring equity in access to drugs pre-approval will sap resources on a systemic level, and that this will weaken our ability to provide equitable care in other domains or equitable access to the same drugs once they are commercially available.

In a society that does not guarantee a basic standard of health care to its members, it is difficult to argue that equality in access to unvalidated therapies ought to be guaranteed. While it may be defensible to spend large sums on *proven* interventions that benefit only a few patients, the case for devoting public resources to unvalidated therapies is much less persuasive—unless perhaps we learn something valuable by doing so (i.e. if genuinely useful data are collected within EAPs). Expanded access is a poor target for redressing general inequities in health care, particularly in the domain of cancer, where disparities in screening, early diagnosis, access to first-line care, and modifiable risk factors are the major culprits (57, 58).

Conflicts of Interest

One area of this debate that is infrequently discussed is the potential for expanded access policies to result in conflicts of interest when financial considerations, rather than altruistic ones, drive decisions about when drugs are made available to patients. While the cost of expanded access programs is often prohibitive for fledgling drug companies or devices with astronomical

production costs, in other cases, manufacturers might stand to profit from expanded access programs through early access to the market.

FDA regulations expressly prohibit sponsors from commercializing drugs released in expanded access programs, allowing only the recovery of costs directly associated with making the drugs available (34). Yet expanded access provide early contact with target patients and prescribers, and those parties may develop confidence in and loyalty to the new therapies before they are fully evaluated or approved. Large treatment INDs in particular may serve as a means for the company to "seed" its product among future prescribers before it enters the market.[7]

Examining the high stakes surrounding the introduction of new therapies into crowded markets hints at the mixed motives underlying expanded access programs. One illustrative example is lapatinib, one of several new targeted therapies for breast cancer, which was released pre-approval in 2006 through a global expanded access program.

Worldwide, breast cancer is the most common cause of cancer mortality among women, and over one million new cases are diagnosed annually (60). Approximately 17 to 30 percent of breast tumors over-express the growth factor receptor known as HER2, and such tumors are associated with a poorer prognosis overall (54). Efforts to treat HER2-positive cancers have focused on targeted inhibition of that receptor, and trastuzumab (Herceptin), approved in 1998, was the major breakthrough in that effort (60). Since tumors eventually develop resistance to Herceptin, there is high demand for multi-targeted therapies that will delay or prevent resistance and that can be used in patients refractory to Herceptin (54).

The pharmaceutical GlaxoSmithKline answered this demand with the dual-receptor-targeted, small molecule lapatinib (Tykerb), which offers theoretical advantages over trastuzumab in being multi-targeted (hitting HER2, a related molecule HER1, and the epidermal growth factor

[7] "Seeding" trials, described infrequently in the literature, are marketing initiatives disguised as research studies. See Hill et al (59) for an exposé of one such trial. One common feature of seeding trials is that they are funded and conducted by the marketing division of a pharmaceutical company. No research has yet examined the funding and conduction of the cancer EAPs.

receptor), being a small molecule with the possibility to cross the blood-brain barrier, and being orally bioavailable, rather than administered by injection (54, 60). Approved in 2007 for metastatic breast cancer resistant to first-line chemotherapy, and currently in clinical trials for numerous indications including other forms of cancer, lapatinib is poised to become a major competitor to Herceptin (60). Yet, the success of lapatinib is jeopardized not only by established therapies, but also by multiple other competitors currently in the drug pipeline. As of 2007, Roche, Pfizer, and AstraZeneca were all conducting clinical trials for targeted therapies in breast cancer (60). Given that head-to-head comparisons across all agents for any given indication are non-existent at the time of approval, the initial success of individual drugs hinges to a great extent on marketing prowess (60). Said one analyst, "You have to have strength to market a targeted therapy…[GSK's] biggest obstacle is how much money they're willing to invest in it" (60).

Might the global expanded access program for lapatinib have constituted one such investment? The lapatinib expanded access program (LEAP) was opened after the RCT was terminated due to favorable interim analysis. LEAP subsequently enrolled over 4200 patients in 45 countries, with a stated treatment objective (54). (The intent-to-treat population in the RCT included just 324 patients (61).) Enrollment in LEAP was closed to patients in the U.S. and Europe following regulatory approval in 2007 and 2008, respectively. As of October 2009, LEAP was still enrolling patients in countries where decisions on approval are pending, including China, Thailand, Mexico, Peru, Canada, and Israel (62).

That EAPs might be profitable for manufacturers does not necessarily mean they are bad for patients. However, as a profession we should be wary that economic considerations above clinical utility may dictate when drugs are released for treatment use. We also should bear in mind that just because a new drug is made available through expanded access does not necessarily imply it will be a clinical breakthrough. Otherwise, the existence of an expanded access program might itself exacerbate the hype surrounding therapies about which little is still known. It is also worth noting that many patient advocacy groups who champion expanded access

receive significant funding from the pharmaceutical industry, so their claims and actions are neither free of conflict of interest (63, 64).

An Unsolvable Problem?

Assuming that there is an ethical imperative to make promising drugs available as early as possible (if not a constitutional right for patients to access them), there is still the fundamental problem of what boundaries ought to define who should get access and when. As with any difficult ethical question, efforts to preserve certain values run up against competing ones. Although both positions (pro-access and pro-regulatory) seem untenable when carried to their logical extremes, it nevertheless difficult to determine where lines should be drawn; there is no obvious stopping point on either side. Considering first the claim advanced by the Abigail Alliance, we discover that a full expression of the asserted right would likely breach even the boundaries that the Alliance identified.

First, it is unclear why the asserted right to access an experimental drug should hinge on the completion of phase I testing. Setting a phase I boundary seems arbitrary in two ways. First, such a threshold relies on an administrative benchmark that is subject to change (25). Undoubtedly, the Alliance and their supporters would object if FDA were to increase the evidentiary requirements of phase I testing—requiring for example that phase I trials be conducted in hundreds of patients to fully characterize toxicity. Second, the Alliance asserts the right to assume "enormous risk" (25) in exchange for any chance of benefit. If a substantial risk of harm is accepted as a given, then why should patients be stopped from accessing any therapy that, in their best estimation, might benefit them? (Interestingly, the language of the Alliance's claim alternates between suggesting that post-phase I drugs are essentially safe and suggesting that they expose patients to substantial, but justifiable, risks.) While there may have been tactical reasons for identifying a phase I threshold for the court case, there doesn't seem to be a clear logical one. The most ardent supporters of expanded access would argue, therefore, that a

competent, terminally ill patient should be able to access any investigational drug of their choosing.

Another problematic question is whether "terminal illness" is an identifiable condition deserving of special rights. The Alliance and others have argued that terminal illness is a distinctive state that upsets the usual risk-benefit calculus because, without intervention, the patient is certain to die. The terminally ill, therefore, are uniquely vulnerable and, because of this, are deserving of special privileges, including the privilege of attempting treatments that might be considered too risky for patients in better health. However, the question of whether terminal illness is a special condition is debatable. For one thing, it is difficult to arrive at a coherent definition of "terminally ill." Prognostication (and even diagnosis) is a notoriously imprecise science, with well-known potentials for error. But even acknowledging that there are illnesses or conditions in which fatality is certain, it is difficult to identify appropriate criteria for defining when "terminal" status has been reached (e.g. estimated survival time, absence of effective treatment, rapidity of disease progression). And even if a coherent definition is achieved, there is the problem of who should be the judge of whether the conditions for terminal illness have been met (65).

The more fundamental problem, however, is whether patients who are terminally ill have special moral claims that don't extend to other patients with pressing medical needs. On the one hand, it would seem that, if our central concern is the supreme value of life and the avoidance of conditions that threaten life, then terminally ill patients may have claims that other sick patients do not. However, it is difficult to draw a moral distinction between patients whose life is endangered and patients whose fundamental well-being is endangered by disabling, but non-fatal disease:

> Those facing loss of cognitive capacity from Alzheimer's, who have had a massive stroke which may leave them severely disabled if not soon dead, those with rapidly progressing Parkinsonism, multiple sclerosis or cystic fibrosis or, even those facing certain blindness or the loss of one or more limbs may all reasonably claim that, while death is the ultimate harm, it is not so clear that

> other terribly disabling or even moderately disabling conditions should not command moral force in garnering access to what is new and innovative especially when time is of the essence (65).

If the proposed right were extended to encompass all patients with legitimate and urgent medical needs, there would be an enormous population of patients with compelling claims to access.

A third questionable boundary enclosing the right in question pertains to who should be involved in the decision to attempt new and untested therapies. The Abigail Alliance often invokes the idea that the decision to use new and risky therapies should rest privately with the patient and his doctor. There is a sacred quality to the image of patient and doctor consciously and jointly choosing the course of treatment that best accords with the patient's individual needs and psychology. And it seems indisputable that one's personal doctor must understand those needs in a way that a third-party—especially a faceless bureaucrat—never could. However, the language of patient rights employed by the Abigail Alliance does not in fact preserve the participation of physicians—or anyone save the patient—in these important decisions. In targeting FDA as the roadblock, the Alliance assumes that doctors are willing participants in the efforts of patients to secure experimental drugs. But they likely would not accept that the patient's right to experimental treatment be limited by their doctor's willingness to recommend it. The concept of inviolable autonomy removes the inducement for outside parties to participate in decision-making.

The logical extreme of the case for expanded access would be a system in which any patient with a compelling medical need, however he defines it, could purchase any drug prior to approval, and that neither FDA nor medical providers could obstruct that process. Such a scenario seems on the surface to be alarming for a number of reasons: it would allow the unscrupulous marketing of quack therapies, allow patients to deplete their financial resources and time in pursuit of unproven therapies, expose sick individuals to unknown physical danger, and destroy the acquisition of scientific knowledge for the greater good. And in addition to these concrete

consequences, there are those more abstract harms that result from the exercise of unfettered autonomy, as previously discussed.

However, while the logical extreme of the access position seems untenable, the same can be said for the opposing position, that expanded access has no place in the drug development process. One could argue that, while the fruits of research—the therapies we know to be effective—should be available universally, there is no ethical imperative to provide access to unvalidated therapies. Redirecting the energy, time, and cost invested in expanded access toward larger clinical trials and toward quicker incorporation of approved therapies would yield greater benefits. However, there are several grounds on which we should reject the pro-regulatory extreme.

First, identifying regulatory approval as a strict threshold for access suffers from the problem of arbitrariness and reliance on administrative standards. Both the criteria for approval of a new drug and the process of measuring the raw data against those criteria entail subjectivity. Deliberations on the approval of new cancer drugs are highly contentious; the same evidence is interpreted and valued differently by different observers, and the quantity and quality of evidence required to make such decisions is often disputed.[8] Thus, even regulatory approval does not represent a unanimous consensus on the utility of a new drug. Furthermore, there is no logical limit to the extent of federal regulation. One could imagine a scenario in which FDA drastically ramped up the evidentiary requirements for NDAs or eliminated approval based on surrogate markers. At some point, ever-increasing stringency in the name of patient protection or scientific rigor would become intolerable, as it would violate our commitment to those patients with urgent needs in the present. Even though there might be plausible moral reasons for strict adherence to federal guidelines, such as maintaining social order or maximally protecting consumers from

[8] One prominent and controversial case involved a 2007 decision by FDA not to approve the prostate cancer vaccine Provenge until more robust efficacy data were available (66). This was against the recommendation of FDA's key advisory committee, evidencing the subjective nature of such judgments. Patient advocacy groups reacted in outrage to the decision, even targeting two experts involved in the decision with death threats (67, 68).

harm, eventually they would run up against the competing moral mandate of valuing and aiding the person facing imminent harm.[9]

Of course, dismantling expanded access policies would not eliminate patient access to unapproved drugs; it would only contain it within clinical trials. This would limit pre-approval access to patients who happen to meet the eligibility criteria for clinical trials, which are based not on medical need, but on suitability for study under the specified conditions. We generally accept that no patient has a *right* to enter a clinical trial, and that individuals routinely are excluded from opportunities which they strongly desire or need, including medical ones. However, when these facts are played out in the real world, and we see that Abigail Burroughs could not access a drug that her peers eligible for a trial could, we are confronted with a sense of injustice, which stems from knowing that the trial is blind to the needs of its participants – a classic problem in research ethics. There is no accounting for the fact that both Abigail and her peers were equally in need and perhaps equally likely to benefit, and Abigail only had "the right cells in the wrong place" (31). While we know that clinical trials are not designed with any

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[9] This recalls the ethical norm in the parable of the Good Samaritan, namely a moral obligation not to turn a blind eye to someone who is suffering in order to avoid hypothetical injury to oneself. This was the dilemma confronting a committee convened by the Institute of Medicine in 1996 to evaluate the ethical issues surrounding xenograft transplantation, the grafting of animal organs into humans (69). The most significant ethical concern confronting the committee was the hypothetical risk that xenografts might introduce animal-borne pathogens into the human population, with effects of unpredictable scale and severity, and whether this was grounds to abandon the technology despite the pressing human need for organs:

> "[W]e as a society are obliged to choose between two risks of harm: to those who will suffer from illnesses potentially treatable by xenografts versus those who might suffer from infectious diseases potentially let loose in the general population by xenotransplantation…[S]ome committee members were guided by what they regarded as the moral imperative that our own humanity is diminished if, in order to protect ourselves, we turn away from others whose suffering is both clearly visible to us and more clearly devastating in its impact on them. This viewpoint, then, further holds that we are morally obligated not only as individuals, but as a community, to accept some risk to ourselves to save our fellow human beings from more certain harm."

The development of xenotransplantation ultimately was abandoned in light of evidence, which only came available after the IOM report was released, that using organs from animal donors carried a substantial risk of infectious disease transmission. Nevertheless the ethical tension described serves as an interesting parallel in considering whether our obligation to safeguard public welfare should trump the claims of desperate individuals in the present.

therapeutic intent, the fact is that they sometimes result in meaningful treatment (6). That being so, the justice principle should motivate us to create policies that rectify the unequal distribution of those benefits.

We should also reject the pro-regulatory extreme because it would fail to recognize that desperate conditions call for exceptional measures. While "terminal illness" itself may not be a condition deserving of special rights and privileges, our policies should acknowledge that serious, disabling illness does demand greater attention than does minor illness, and warrants special efforts and policies aimed at alleviating it. If we strive to uphold the dignity of all patients, including those with devastating illness, our response to their need should mirror the gravity and urgency of the problem at hand. Whereas we might not tolerate expanded access for a new acne treatment, we might demand it in the case of AIDS.

Lastly, just as the unilateral assertion of patient rights incurs worrisome consequences, there is also reason to be concerned about policies that over-emphasize the authority of regulations or the sanctity of the protocol. While there is a clear need for treatment guidelines based on solid evidence, patients in the real world do not always behave in predictable ways. There is no guarantee that a therapy effective in an RCT is going to have reproducible effects in an individual patient with unique pathology and psychology. Some allowance for the use of unvalidated therapies (which is regularly done through off-label use, alternative medicine, and trial-and-error approaches to treatment) upholds the singularity of an individual patient's needs. However, with increasing demands for evidence-based practice and comparative effectiveness research, we may be facing a future of much stricter adherence to guidelines, not only in the name of cost control, but also for the sake of informed, rational practice. This changing climate will undoubtedly continue to play host to an active debate over how much we should bend rules in the name of addressing individual needs.

Navigating the Impasse: Recommendations

Confronted with a problem in which both sides of the debate are so compelling and yet both extremes so intolerable, the way forward would seem to be to carve out a middle ground, a compromise between extremes. Indeed, this has been the unwieldy task of FDA for many years, and its continual refining of the rules over time points to the imperfection of each attempt. How, then, do we begin to draw lines? Are we destined to dance back and forth between competing extremes, to rely on vague guidelines because specific ones are too fraught? Maybe so, but maybe this approach is a sign of commitment to certain absolutes in our societal values.

In a seminal essay, *Tragic Choices*, Guido Calabresi documents the methods by which society allocates what he terms "tragically scarce resources." He explores various approaches to allocation, including markets, political processes, lotteries, and adherence to custom, concluding that all are destined to fail because they compromise values held as fundamental by that society (70). This leads societies to devise mixed-methods approaches and to continually revise those approaches as their shortcomings become evident. Thus ensues a process of cyclical reform, in which the method of dispensing the scare resource is repeatedly adjusted. The moral advantage of this cycling is its "admission that society is attempting to preserve essential yet conflicting values" (70). The very fact that our policies concerning tragic choices are in flux demonstrates that on some level, we comprehend our ambivalence.

The contemporary approach to determining who should receive experimental drugs and through what avenues reflects such a conflict of values. We feel obligated in equal measure to protect the vulnerable from injury, to uphold self-determination by competent individuals, and to ensure validated medical therapies for society at large. And we have in effect arrived at a mixed-methods approach to expanded access, resting largely on political regulations, but incorporating

market forces and lotteries.[10] Yet Calabresi's insights are observational rather than prescriptive. We cannot draw from his theory any conclusions about which mixture will best balance our competing values, or whether certain values should speak louder than others in guiding our policies.

Recognizing that we might never arrive at a flawless method for adjudicating this tragic choice, we should nevertheless attempt to refine what we have at present. Historically, this debate has been worked out politically, rather than normatively, with adjustments in policy made in response to public demands. Indeed, sound regulatory policies lie at the heart of a workable solution, however the shortcoming of a political solution is that it will likely favor parties who speak the loudest on these issues (e.g. patient advocacy groups, drug manufacturers), sidelining those who have a stake in the outcome but have less pressing claims (e.g. health care providers, tax-payers, and "future patients"). It is therefore worthwhile to consider how other parties, including physicians, can remain involved in carving out the elusive middle ground.

Recommendations for Physicians

With greater availability of experimental drugs for treatment, physicians may be confronted in increasing numbers by patients wishing to pursue this avenue. Physicians—particularly those in disciplines in which experimental therapy is a mainstay, such as oncology—therefore are positioned to help make judicious recommendations about when experimental therapies are an appropriate course of action. A physician who sees a patient through this process confronts many challenges. The most apparent of these is that he must navigate this terrain without validated evidence, the traditional beacon of medical decision-making. But perhaps even more formidable than this is the challenge of recognizing his own biases: that he himself may be

[10] For example, when Iplex was released for compassionate use in ALS, there was an insufficient supply to satisfy the number of requests for single-patient treatment INDs, so some patients were granted treatment access, and some were enrolled in a randomized trial (71).

blinded by hope, or feel discomfort confronting death, or view transitions to comfort care as a personal failure. With all of these challenges, what principles should serve as a guide?

A primary duty of the physician should be to identify the patient's goals for treatment with an experimental drug so that decisions about whether or not to proceed are made with explicit knowledge of those goals. That is, the decision should be patient-centered without being strictly patient-determined. Patient-centeredness does not mandate that the physician defer to the patient's every wish, but rather that she guide him in making decisions that best accord with his fundamental values and preferences. Neither should physicians bow out of their professional duty to advise the patient in light of all existing evidence, and to advise against experimental therapy if there is no evidence to support its use.

Another crucial task for the physician is to aid her patient in recognition of the inherent uncertainty surrounding pursuit of experimental treatments. When little information about the desired drug is known, the physician must rigorously emphasize the paucity of evidence and the uncertainty of benefit, recognizing that the ability of both doctor and patient to grasp uncertainty may be complicated by the fact of using the experimental drug with therapeutic intent.

One way in which uncertainty of success can be implemented in practice is to adopt a dual-objective counseling technique, sometimes referred to as "hope for the best, prepare for the worst" (72). In such an approach, parallel plans are constructed, one involving the pursuit of further treatment, and one involving arrangements for palliative care, with both revisited frequently and revised as preferences change. A dual approach to end-of-life care emphasizes the uncertainty of prognosis and of treatment success, while also guarding against perceptions of physician abandonment. Initiating planning for palliative care in parallel with pursuing experimental drugs might provide a good way forward for those terminally ill patients who have valid reasons for attempting experimental treatment, yet face a poor prognosis. Although admission to hospice usually requires patients to forego life-sustaining therapy, other aspects of palliative care can still be employed. Acknowledging the practical barriers to a dual approach,

David Casarett et al have argued for alternatives to hospice that balance many patients' wishes to continue treatment while also receiving care from providers experienced in palliation and end-of-life planning (73).

On a broader level, physicians can utilize their stature to improve public awareness of the pace of medical innovation and the unknowns of experimental therapy. Physicians can collaborate with media to interpret the real-world implications of new medical technology and can help temper the hype and misconception that so often distorts reports of new therapies. They can help to reinforce the scientific purpose of clinical trials, and the need for comprehensive evaluation of new therapies.

Recommendations for Policy Makers

Sound public policy concerning access to experimental drugs must reconcile various and competing goals: protecting patients from undue harm, ensuring thoroughness in drug testing, and preventing the premature commercialization of investigational agents. Both a more nuanced understanding of the ethics, as well as better empirical data about outcomes within expanded access programs, can help refine those policies.

One over-arching principle that should guide public policy is that access be predicated on evidence of efficacy. That a product is safe cannot alone justify access. Because expanded access is a good-faith attempt at *treatment*, we would deceive our patients and ourselves if we pursued that treatment without any reason to think it would work. Therefore, drugs that have passed phase I but have not demonstrated efficacy should almost always be restricted from treatment use. Recognizing that with the growing development of targeted therapies there will undoubtedly be circumstances where evidence for efficacy is revealed at phase I, phase benchmarks are non-ideal thresholds for access. This leads to the more complicated question of how much evidence for efficacy should be required. Is a case report sufficient? If surrogate markers are used, how large an effect is necessary? These questions must to some degree be addressed on a case-by-case

basis, however FDA's general rule that more substantial evidence of efficacy is required as greater numbers of patients receive access (25), is an appropriate general guideline.

Regarding larger expanded access programs such as those being offered for new oncologics (54-56), several principles should apply. First, given the investigational status of the compound or device, admission to a treatment protocol should entail a rigorous informed consent process that clarifies the stage of development of the treatment in question, the therapeutic purpose of the protocol, and what steps are yet required for regulatory approval. Second, in order to ensure that clinical trial enrollment does not suffer as a result of expanded access, admission to a treatment protocol should be restricted to patients ineligible for ongoing clinical trials, as is currently required by FDA. This will have the added effect of ensuring that the treatment protocol has more generous enrollment criteria than the corresponding clinical trial, allowing access to patients with medical need but poor suitability for controlled trials.

Notwithstanding the explicit treatment objective of expanded access programs, it is both permissible and preferable for such programs to be a hybrid of research and treatment. The privilege of receiving an investigational drug should carry the obligation to undergo a certain amount of testing so that broadly applicable knowledge about the drug or device can be derived from its pre-approval use. At a minimum, patients in treatment protocols should be monitored closely for toxicity. Optimally, data on efficacy also should be obtained. EAPs should be advertised through the clinical trials registry to promote transparency, and to ensure that they are made known to all patients who might stand to benefit from them.

Expanded access programs, by virtue of disseminating therapies widely before they are approved, carry the potential to constitute advanced marketing of unapproved therapies. The current FDA rules appropriately restrict cost recovery to prevent the generation of profits from expanded access programs. Some authors have suggested that manufacturers be allowed to generate profits from pre-approval use, but not collect those profits until the drug is approved (74). This may well increase incentive to participate, but might lend excessive legitimacy to

unapproved drugs. Sponsoring companies should finance EAPs through their research and development divisions, not through their marketing divisions, so as to reduce any appearance of pre-approval commercialization or conflict of interest.

If the issue at the heart of the expanded access debate is how to deliver promising new therapies in a timely manner to the patients who need them most, then expanded access policies will fall short if they are not accompanied by sound reforms in the clinical trials process. As we have seen, the current mechanisms in place, such as accelerated approval, seem to have fallen short of their objectives. Better policies are needed to encourage efficiency and improve the success of drug development. In 2004, FDA announced the Critical Path Initiative (CPI), a commitment to optimizing the funding and conduction of translational clinical research (5). An "Opportunities List" of top priorities was released in 2006 (75) specifying the areas most in need of investigation, such as identifying patterns that predict drug failure so that sponsors can avoid past missteps; re-designing trials to focus on sub-populations most likely to demonstrate a response; and developing valid biomarkers (and the capacity to measure them) that accurately correlate with clinical outcomes (75). It remains to be seen what results emerge from this research and how they impact the pace and success of drug development in the decades ahead.

Conclusions

The heated tenor of today's debate over expanded access stems in part from a belief by those who advocate most forcefully for access that government bureaucrats are callously withholding life-saving therapies, that, if only drugs were released sooner or clinical trials redesigned, scores of lives would be saved. A 2008 opinion piece in the Wall Street Journal supporting the ACCESS Act and entitled, "How the Senate Can Help Ted Kennedy" vividly illustrates this sentiment. The authors, key advisors to the Abigail Alliance, write:

> There are many promising new cancer treatments in the pipeline, but under current [FDA] regulations, almost no one gains access to them, no matter how dire the need or how compelling the evidence that the drugs work. Most people

> receiving a terminal cancer diagnosis die before the most promising treatments in the pipeline reach them. Why? Because those tragic events occur on the wrong side of the magical moment when someone at the FDA puts an approval letter on a fax machine declaring the drug they needed – and never got – is "safe and effective" (76).

The claims made in this piece, if accurate, would indeed be cause for outrage and for massive policy overhaul. Yet the idea that FDA is guarding miracle drugs behind a regulatory wall has little credence. Why, then, is FDA the focus of advocates' disdain?

There is a need to find fault in the face of tragic circumstances and FDA is a convenient target for blame. Someone or something must be responsible for the tragedy that, in this era of medical miracles, there are diseases we cannot cure, patients we cannot save. It is easier to point the finger at FDA, the heartless intermediary, than to confront the more disturbing possibility that for patients with devastating illness, there actually might be nothing worth clamoring for behind FDA's door. By convincing ourselves that the answers are there, only concealed, we can deny a more fearsome truth: that even if FDA were dismantled altogether, we might still be at a loss to help a patient like Abigail Burroughs.

We are also living in times in which government participation in "private" medical decisions is viewed as an ugly intrusion into private affairs and an assault on individual rights. Despite the fact that expanded access programs today seem to depend more on manufacturers' willingness to offer them than on FDA's willingness to allow them, there is nevertheless the urge to identify FDA as the roadblock. Perhaps this is because, in today's political climate, it is easy to rally support around the idea that government officials should not be calling the shots where individual patients are concerned. It may be politically expedient to paint FDA as having greater responsibility for the current state of affairs than in reality it does.

The controversy over expanded access also points to a general unwillingness, pervasive in American society, to accept death and dying—except, perhaps, on our own terms. Maybe the allure of expanded access is that it places a semblance of control back into the hands of the dying patient, allowing him at least to define the *terms* of his death, if not to change the outcome.

Although we will never achieve mastery over death, either literally or psychologically, one lesson we might learn from expanded access is the imperative to help patients continue to articulate their own terms at the end of life—perhaps in ways other than through the pursuit of last-ditch therapies.

Finally, a broadly acceptable solution to this problem will require something beyond sound public policy. To change the tenor of this debate, we must initiate an honest discussion on a societal level about the limits of experimental therapies. Health care professionals, whose voice on this issue is vital, must lead this discussion in concert with patient advocacy groups and media. We must candidly address the daunting challenges we face in finding effective drugs for many types of cancer, the little we know about drugs at phase I, and the extent to which economic factors dictate research priorities. It is natural to think that leaders who take a cautious stance toward experimental therapies would be criticized as pessimistic and hostile to progress. Yet their efforts might prove effective if they come with the sincere assurance—backed up by action—that when major medical breakthroughs do occur, the regulatory system will bend to promote rapid approval and to allow early access.

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