Research on the Terminally Ill: A Balancing Act Between Facilitating Access to Innovative Therapies and Protecting Vulnerable Subjects in Search of One Last Hope for Survival

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Research on the Terminally Ill: A Balancing Act Between Facilitating Access to Innovative Therapies and Protecting Vulnerable Subjects in Search of One Last Hope for Survival

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Abstract

This paper presents the application of the current federal regulatory system governing clinical research in the United States to research involving terminally ill subjects, with a special emphasis on those patients battling terminal cancer. To begin, I describe the current regulatory system governing the approval process for new drugs, the guidelines established by the federal regulations for the conduct of clinical research involving human subjects, and the federal initiatives that have been developed to increase and expedite access to experimental therapies for terminally ill patients. In addition to tracing the roots of the informed consent paradigm in research with human subjects, I also consider the sufficiency and efficacy of this model as applied to clinical research involving the terminally ill. Addressing in particular the continuing war against cancer, I present some of the most notorious controversies and case law that have emerged in the last century with respect to new experimental cancer therapies, as well as the role of Congress in the ongoing debate concerning access to investigational treatments by terminal patients. Finally, I consider the specific vulnerabilities and experiences of desperately ill individuals fighting to survive, characteristics that make them particularly susceptible to coercion and exploitation, and, therefore, potentially in need of additional safeguards to adequately protect them in the research endeavor.

I. Introduction

During a congressional hearing held last year addressing the current state of cancer prevention and research in the United States, Tommy Thompson, Secretary of the Department of Health and Human Services, offered sobering statistics from the war against cancer: in 2002, 1.2 million new cases of cancer were expected in the United States, and approximately 550,000 Americans are expected to die of cancer annually, translating into roughly 1,500 deaths per day, and a quarter of all deaths annually, caused by various forms of the destructive disease.[1] In addition, Senator Tom Harkin aptly noted in his opening statement, "[a]ll of us in this room today have had our lives touched by this killer," revealing that he had lost his only two sisters and two of his three brothers to cancer.[2]

Dismal as the numbers are, the hearing did not focus on the devastating statistics with which we are all undoubtedly aware, but rather was devoted to addressing the effectiveness and progress of the administration's "three-pronged offensive – research, treatment and prevention."[3] Of particular relevance to this paper, several witnesses at the hearing stressed the importance of clinical trials in cancer research. Secretary Thompson, for example, posed the crucial question of how to get new and promising cancer drugs to the market as quickly as possible, and noted a positive trend toward increased access to such therapies, stating that one-half of the cancer drugs in the last three years have made it to the market within six months.[4]

While effective clinical research has significantly contributed to the advances made thus far in the fight

[1] *See Cancer Prevention and Research: Hearing Before the Subcomm. on Labor, Health and Human Services, and Education of the Senate Comm. on Appropriations*, 107th Cong. (June 4, 2002) (statement of Sec. Tommy Thompson, Department of Health and Human Services).

[2] *See id.* (statement of Sen. Tom Harkin, Chairman, Senate Subcomm. on Labor, Health and Human Services, and Education).

[3] *Id.*

[4] *See id.* (statement of Tommy Thompson).

against cancer, and will unquestionably continue to do so in the future, several aspects of the current clinical research mechanisms in place have prompted interested parties to enlist in the war against cancer, as well as other life-threatening diseases, and to voice their concerns on a number of issues, including claims that there are insufficient resources to make clinical trials function as effectively as possible and complaints that investigators are overly burdened with complex regulatory procedures. In addition, and more germane to this paper, there is a concern that strikes at the heart of the ethics of clinical trial research: the protection of human subjects. As one witness testifying at the above hearing asserted, while clinical trials involving patients with cancer are "the requisite path for our advances" in cancer research, "unfortunately, there are infrequent – but, in some cases, serious – lapses in protection of human subjects."[5]

In the pages that follow I will focus on one group of human subjects in particular, a group of individuals for whom conventional therapies are either unavailable or ineffective and for whom experimental therapies and drugs may offer their only hope of survival. Perhaps more so than any other class of research subjects, the plight of terminally ill patients exemplifies the balancing act engaged in by the Food and Drug Administration (FDA), which has struggled at times to emphasize the value of promoting access to experimental and unapproved treatments, while at the same time, recognizing the importance and value of protecting vulnerable research subjects.[6] Specifically, this paper presents the application of the current regulatory framework for clinical research to trials and research involving terminally ill subjects, with a special emphasis on those patients battling terminal cancer. Questions posed and considered include whether the informed consent model adequately protects terminally ill subjects who choose to participate in research; whether the vulnerabilities of this class of subjects warrants their inclusion in the federal regulations that explicitly provide additional safeguards to certain "vulnerable" populations, such as pregnant women, children, and prisoners;

[5] *Id.* (statement of Dr. Ronald Herberman, Director, University of Pittsburgh Cancer Institute).

[6] *See* Baruch A. Brody, *Research on the Vulnerable Sick*, *in* Beyond Consent 45 (Jeffrey P. Kahn et al. eds., Oxford University Press, 1998).

and whether the FDA and related regulatory powers have struck an appropriate balance between providing expanded and expedited access to potentially life-saving, albeit experimental, therapies and sufficiently protecting those subjects who may be willing to try anything in the hope that they will win the war that has likely already ravaged them both physically as well as psychologically.

With those issues in mind, this paper first sets out the federal regulatory system governing the approval process for new drugs in the United States, the guidelines established by the federal regulations for the conduct of research involving human subjects, and the federal initiatives that have been developed in order to increase and expedite access to experimental therapies for terminally ill patients. In addition, it traces the roots of the informed consent paradigm that has become central to clinical research with human subjects, and considers the efficacy and sufficiency of this model as applied to clinical research involving the terminally ill. Delving more specifically into the war on cancer, this paper briefly describes some of the most notorious controversies and case law that have emerged in the last century concerning new experimental cancer therapies and the experiences of desperate patients fighting to gain access to them. Likewise, the role of Congress and the efforts of concerned members to increase access to investigational treatments, as well as attempts by other interested parties to ensure the safety and protection of research subjects, will be highlighted. Finally, this paper will consider the specific vulnerabilities of individuals battling terminal illnesses, characteristics that make them particularly susceptible to coercion, undue influence and exploitation in the research endeavor. After considering such issues, the reader is encouraged to draw his or her own conclusion concerning the appropriate balance to be struck between expanding access to experimental therapies for the terminally ill and providing adequate safeguards to guarantee the protection of desperately ill subjects who may view investigational and unapproved treatments as their last chance for survival.

II. An Overview of the Drug Approval Process

In order to get governmental approval for new drugs, applicants must meet the safety and effectiveness standards established under the federal Food, Drug and Cosmetic Act of 1938 (FDCA), which requires "substantial evidence" of safety and efficacy prior to approval.[7] Spurred by a national scandal in which nearly one hundred people died after ingesting a drug marketed as "Elixir Sulfanilamide," the liquid base of which was poisonous, the FDCA imposed a new and strengthened drug approval process requiring, among other things, drug sponsors to provide evidence of safety before marketing a drug.[8] However, it did not require evidence that the drug was in fact beneficial for its intended uses.[9] It was not until another drug-related tragedy in the early 1960s that FDA control over the approval and distribution of new drugs was tightened. The thalidomide tragedy and the tremendous public reaction to its horrific side-effects, including severely deformed and disabled babies, prompted Congress to amend the FDCA in 1962 to provide a more aggressive system of pre-market review and mandatory approval before bringing new drugs into the market.[10] In addition to adding the safety and effectiveness "substantial evidence" standard, the amendments granted the FDA discretionary power over determining necessary clinical testing of proposed drugs and allowed the FDA to revoke authorization for clinical trials if there was any evidence that the drug was unsafe.[11]

A. Investigational New Drugs (INDs) and Preclinical Hurdles

[7] 21 U.S.C. § 355(d); *see* Michael E. Horwin, *"War on Cancer": Why Does the FDA Deny Access to Alternative Cancer Treatments?*, 38 Cal. W.L. Rev. 189, 197 (2001).

[8] *See* Richard J. Nelson, Note & Comment, *Regulation of Investigational New Drugs: "Giant Step for the Sick and Dying"?*, 77 Geo. L.J. 463, 469 (1988).

[9] *See id.*

[10] *See id.*; *see also FDA Proposals to Ease Restrictions on the Use and Sale of Experimental Drugs, 1987: Hearing Before a Subcomm. of the Comm. on Government Operations*, 100th Cong., 1st Sess. 15 (1987) (testimony of Richard Cooper, former Chief Counsel of FDA) (asserting that the thalidomide disaster was the "actual triggering point" for the 1962 amendments); *Views of Senators Kefauver, Carroll, Dodd, Hart, and Long*, 1962 U.S. Code Cong. & Admin. News 2898, 2905-07 (citing history of thalidomide as reason for strengthening drug approval process, and noting that "[u]nder [the present system] it is the American people who unknowingly serve as guinea pigs for experiments by the drug companies"); 108 Cong. Rec. 17,378 (1962) (statement of Sen. Hruska) (citing history of thalidomide "to illustrate the necessity of additional provisions in the law").

[11] Drug Amendments of 1962, Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified in scattered sections of 21 U.S.C. §§ 301-81); *see* 21 U.S.C. §§ 321, 355.

The preclinical hurdles that must be passed in order to gain FDA approval begin with an initial phase of preclinical investigations and animal studies to determine whether the drug is reasonably safe for clinical trials and has potential for treating a specific disease.[12] If such a determination is made, the drug's sponsor or manufacturer may submit an application for an investigational new drug (IND) exemption in order to facilitate further drug research and development.[13] Included in the IND application must be such items as a description of both the drug composition and manufacturing and quality controls methods, all information derived from preclinical testing, statements about the drug's history, an outline of the proposed phases of further testing, a statement identifying an institutional review board with reviewing authority over the investigation, and an agreement by the applicant to report any significant hazards and side effects.[14] At this stage in the approval process, and thirty days after the FDA receives the IND application,[15] the drug's sponsor may begin the three required phases of human trials, which must satisfy certain human subject protections and be approved by an Investigational Review Board ("IRB"), which is appointed to oversee the trials and ensure that they are ethical and the rights of study participants are protected.

B. The Role of IRBs in Clinical Research

Peer review by IRBs characterizes clinical research with human subjects in the United States. An IRB is an independent committee of physicians, statisticians, community advocates, and others that must initially approve and periodically review every clinical trial in the U.S. to ensure that the risks are as low as possible

[12] *See* John Patrick Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 Vand. L. Rev. 925, 928 (1991).

[13] FDCA § 505(i); *see* 21 C.F.R. § 312.40 (2003); *see also* Patricia C. Kuszler, *Financing Clinical Research and Experimental Therapies: Payment Due, But From Whom?*, 3 DePaul J. Health Care L. 441, 447 (2000); *see also* Horwin, *supra* note 7, at 199.

[14] *See* Dillman, *supra* note 12, at 928.

[15] *See* 21 C.F.R. § 312.40(c).

and are justified by the potential benefits of the research.[16] Consisting of at least five individuals with varying backgrounds and diverse training, IRB membership is intended to promote objectivity in the review process and to counter any institutional or professional bias that might interfere with the IRB's critical objective of protecting research subjects.[17] Moreover, membership requirements are designed to ensure the professional competence and expertise of an IRB as well as to foster "sensitivity to such issues as community attitudes" and respect for certain "vulnerable categor[ies] of subjects."[18] Its primary role is to make sure that each research institution is ethically and scientifically sound, as well as to ensure that the human subjects are selected in an equitable manner and have given their informed, voluntary consent before participating in any studies.[19] In order to protect the rights and welfare of human research subjects, IRBs review the informed consent documents and procedures involved in research projects and require research investigators to address several ethical issues before submitting their protocols for review.[20] This early pressure imposed by IRBs has led many investigators and IRB members to agree that the main effect of an IRB is felt before they even review a protocol.[21]

In evaluating a research protocol, IRB members consider several features outlined in the federal regulations under which IRBs operate.[22] These regulations require, for example, that the risks to subjects are minimized and are reasonable in relation to the anticipated benefits and the importance of the knowledge to be gained by the research.[23] Additionally, an IRB must find that the selection of subjects is equitable; that material facts will be disclosed; that research investigators and sponsors have obtained and documented informed consent

[16] *See ClinicalTrials.gov: An Introduction to Clinical Trials*, A Service of the National Institutes of Health, *at* http://www.clinicaltrials.gov/ct/gui/info (last visited Mar. 31, 2003).

[17] *See* 21 C.F.R. § 56.107(a).

[18] *Id.*

[19] *See* 21 C.F.R. § 56.111 (2003); *see also* D. Christian Addicott, *Regulating Research on the Terminally Ill: A Proposal for Heightened Safeguards*, 15 J. Contemp. Health L. & Pol'y 479, 482 (1999).

[20] *See* Charles R. McCarthy, *The Institutional Review Board: Its Origins, Purpose, Function, and Future*, *in* Research on Human Subjects: Ethics, Law and Social Policy 316 (David N. Weisstub ed., 1998).

[21] *See id.*

[22] 21 C.F.R. § 56.111; *see* Dale L. Moore, *An IRB Member's Perspective on Access to Innovative Therapy*, 57 Alb. L. Rev. 559, 562 (1994).

[23] 21 C.F.R. § 56.111(a)(1)-(2).

from each prospective subject or authorized representative; and that additional safeguards are established for "vulnerable" subjects.[24] After completing its evaluation, an IRB may approve a research protocol, approve a protocol contingent on certain modifications, or disapprove and reject a protocol. Perhaps it is because of their broad authority and responsibility for scrutinizing all research protocols that IRBs are considered by some to be the "backbone of the federal regulatory system."[25]

C. The Phases of Clinical Trial Research

Clinical trials on human subjects generally include three phases. Phase I trials, which typically include a small group of healthy human subjects, focus on determining the safety, relative toxicity, and side effects of a drug at various doses.[26] In addition to its primary goal of determining a drug's safety profile, investigators in Phase I trials also work to determine how, and at what rate, the drug is absorbed, metabolized, and eliminated from the body.[27] In Phase II testing, investigators first administer the drug to symptomatic patients who actually suffer from the condition or disease being targeted by the drug.[28] At this stage investigators evaluate the drug's safety in a larger population than Phase I and attempt to establish the optimal dosage, as well as statistical end points that represent the targeted favorable outcome of the study, and to preliminarily assess the drug's efficacy.[29]

Phase III trials offer the next opportunity for investigators to further refine their research and again to gauge the safety and effectiveness of their drug. At this stage the investigators' objective is to determine the effec-

[24] *Id.* § 56.111(3)-(5).
[25] Addicott, *supra* note 19, at 482.
[26] *See* Dillman, *supra* note 12, at 928; *see also ClinicalTrials.gov: An Introduction to Clinical Trials*, *supra* note 16, *at* http://www.clinicaltrials.gov/ct/gui/info.
[27] *See* Dillman, *supra* note 12, at 928-29.
[28] *See id.* at 929.
[29] *See id.*

tiveness of the drug or treatment in the affected population, based on the statistical end points established in Phase II. By conducting at least two studies within a larger subject population, the investigators strive to confirm the drug's effectiveness, monitor side effects and adverse reactions resulting from long-term use, compare the study drug to more common treatments, and collect and record information that will facilitate the safe use of the drug or treatment by patients.[30]

Although the FDA's assessment of safety and effectiveness, as well as its determination whether to approve or reject a drug's entry into the market, occurs after Phase III, an additional phase resembling post-marketing surveillance, rather than testing, is sometimes added.[31] Phase IV includes the company's ongoing evaluation of the drug's safety during routine use, and allows the FDA to similarly reevaluate its approval and, in certain circumstances, to demand either a recall or relabeling of the drug.[32] Additionally, if the drug is being successfully administered for off-label indications, the company will often begin further clinical testing for those uses in an effort to expand the potential market for the drug.

Upon successful completion of Phase III trials, and where the data indicates that the drug is safe and effective for its intended purpose, the drug's sponsor may file a New Drug Application (NDA) with the FDA.[33] Frequently spanning thousands of pages of accumulated data and analyses, the NDA supplies FDA reviewers with information about test results, chemical compositions, proposed labeling, manufacturing methods, and data surrounding safety and effectiveness.[34] If the application is deemed complete, the FDA must respond within 180 days with an action letter that either (1) approves the application and grants permission to market the drug, (2) determines that the application is basically approvable, but deficient in some respect, (3) rejects the application for cause, indicating the need for substantial amendment to the application, or

[30] *See id.*; *see also ClinicalTrials.gov: An Introduction to Clinical Trials, supra* note 16, *at* http://www.clinicaltrials.gov/ct/gui/info.
[31] *See* Dillman, *supra* note 12, at 929.
[32] *See id.*
[33] *See id.* at 930.
[34] *See id.*

(4) requests supplemental information from the drug's sponsor.[35]

At this stage in the drug approval process, an applicant that has been rejected by the FDA can either amend the application or request a notice of opportunity to be heard (NOOH). Depending on whether the FDA considers the amendment to be a "major amendment," the FDA has certain time limits within which to review the revision and/or to issue a NOOH, and additionally exercises further discretionary power in granting, postponing, or denying the hearing.[36]

III. Loosening the Regulations for Desperately Ill Patients

A. Compassionate Use INDs and Other Access Mechanisms

While federal regulations offer a protective framework to ensure the safety and effectiveness of drugs that enter the market, critics of the regulatory regime have urged a relaxation of its more stringent requirements, attacking, for instance, the long delays associated with compiling sufficient information to satisfy the "substantial evidence" standard for new drugs and the barriers it imposes to innovative drugs and therapies.[37] Perhaps, in part, as a response to these calls for a less rigid regime, in 1977 the FDA introduced the "compassionate use IND" exemption to the regulation's prohibition against the use of unapproved drugs to treat severe forms of illness.[38] Often conceived as the forerunner to the new "Treatment IND," compassionate use INDs represented one of the FDA's informal attempts to respond to and satisfy the demands of the

[35] *See id.* at 930-31.
[36] *Id.* at 931.
[37] *See* Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U.J. Legis. & Pub. Pol'y 295, 315 (1999/2000) (noting that the "downside to the system is the substantial barrier that it imposes to new and innovative forms of treatment").
[38] *See* 4 [Drugs-Cosmetics] Food Drug Cosm. L. Rep. (CCH) P71,112 (Oct. 5, 1987); *see also* Nelson, *supra* note 8, at 471; Greenberg, *supra* note 37, at 315-16.

desperately ill to gain access to experimental treatments.[39] In particular, such exemptions were granted on a case-by-case basis pursuant to the request of the primary care physician of a critically ill patient to prescribe an experimental drug not yet approved by the FDA patient in certain circumstances "even though the primary purpose [was] not investigation but treatment."[40]

Although compassionate use INDs offered another potential avenue for severely ill patients to pursue, and "were oriented to the end of treatment rather than the end of clinical research,"[41] critics noted the inadequacies of such exemptions, pointing out that they were not formalized in the federal regulations and their use was largely ad hoc and very poorly publicized.[42] Specifically, critics argued that access to new drugs via the compassionate use exemption became a function of individual doctors' willingness and capacity to petition the FDA for its approval, a process typically involving significant paperwork, delay, and bureaucracy.[43] Moreover, such exemptions depended considerably on the willingness of drug companies to supply their experimental new drugs, without charge, based on the prospect of future profit from commercialization.[44] Limited or uncertain incentives for these companies, in addition to the ad hoc and potentially very burdensome FDA approval process for individual, patient-by-patient applications, as well as escalating pressure on the FDA to adopt new reforms in the drug approval process in the face of the increasingly formidable AIDS epidemic, prompted the FDA to adopt new regulations designed to increase access to, and accelerate the approval process for, new and experimental drugs and therapies for seriously or terminally ill patients.[45]

Similar to the compassionate use procedure, another early informal access mechanism designed to make ex-

[39] *See* Lois K. Perrin, Note, *The Catch-22 for Persons with AIDS: To Have or Not to Have Easy Access to Experimental Therapies and Early Approval for New Drugs,* 69 S. Cal. L. Rev. 105, 119 (1995).
[40] *See* 4 [Drugs-Cosmetics] Food Drug Cosm. L. Rep. (CCH) P71,112; *see also* Nelson, *supra* note 8, at 471.
[41] Greenberg, *supra* note 37, at 316.
[42] *See* Nelson, *supra* note 8, at 471.
[43] *See* Greenberg, *supra* note 37, at 316; *see also* Peter S. Arno & Karyn L. Feiden, *Against the Odds: The Story of AIDS Drug Development, Politics and Profits* 34-35 (1992) (noting that, reportedly, the informality of the compassionate use procedure favored well-connected patients over those less fortunate).
[44] *See* Greenberg, *supra* note 37, at 316.
[45] *See id.*

perimental treatments more accessible to desperate patients was the personal use import exemption, which permitted individual patients to import limited quantities of unapproved drugs for their own personal medical use.[46] As with the compassionate use procedure, the personal use exemption was never formally enacted into federal regulation and suffered from its own set of criticisms.[47] For example, the personal use exemption provided fertile ground for the growth of buying clubs to facilitate the importation of experimental drugs from Europe and South America, and posed potentially significant and damaging risks to the effectiveness and success of American clinical trials, either by leading research subjects to secretly supplement their treatment protocols, perhaps to avoid receiving a placebo, or by decreasing the number of voluntary research participants.[48] Likewise, it was criticized as an additional threat to effective drug development due to the potential financial disincentives to domestic drug development, likely motivating patients to take advantage of cheaper drugs made available for importation from overseas, even though such drugs may also have been approved in the United States, albeit marketed at a higher price.[49] Lastly, by allowing those patients "desperately in need of treatment" to opt out of the regulatory regime, the personal use exemption was criticized as skewing consumer choice and leading to the commercial exploitation of such individuals, who would likely lack the information required to evaluate the utility of many experimental therapies.[50]

B. Treatment INDs and Expanded Access Initiatives

[46] *See id.*; *see also* Eric Lindemann, Note, *Importing AIDS Drugs: Food and Drug Administration Policy and its Limitations*, 28 Geo. Wash. J. Int'l L. & Econ. 133, 134 n.8 (1994).

[47] *See* Greenberg, *supra* note 37, at 316n.125; *see also* Lindemann, *supra* note 46, at 134n.8.

[48] *See* Greenberg, *supra* note 37, at 317; *see also* Arno & Feiden, *supra* note 43, at 60-70.

[49] *See* Greenberg, *supra* note 37, at 317; *see also* Lindemann, *supra* note 46, at 154-56.

[50] *See* Greenberg, *supra* note 37, at 317 (offering as an example of this scenario the situation that occurred in the late 1980s with a widely imported, unapproved anti-AIDS drug, dextran sulfate, that was later shown to be ineffective as treatment); *see also* Arno & Feiden, *supra* note 43, at 71-82 (noting that one AIDS activist took the position that it was irrelevant whether the drug worked, and that AIDS patients should be allowed import access regardless).

In response to calls for more expansive and formalized reforms in the drug approval process, including measures that would surpass the informal and frequently inconsistent efforts already attempted, the FDA instituted significant reforms in the late 1980s, loosening its long-standing policy of requiring extensive testing of new drugs.[51] The first such reform came in 1987, when the FDA changed its approach and policy regarding investigational new drugs by enacting provisions that specifically authorized the "treatment use" of such agents,[52] allowing patients with "serious or immediately life-threatening" diseases[53] to gain access to some experimental drugs for medical treatment, rather than for the traditional purpose of research, where "no comparable or satisfactory alternative drug or other therapy is available."[54] Accordingly, a drug manufacturer may apply for permission to distribute a "Treatment IND" before final approval by the FDA, with the primary objective being "to facilitate the availability of promising new drugs to desperately ill patients as early in the drug development as possible, before general marketing begins, and to obtain additional data on the drug's safety and effectiveness."[55] One observer noted that such an effort to expand access to experimental therapies signaled a shift in the way the FDA, Congress, the pharmaceutical industry, health professionals, and health activists view the role of drug development and regulation in the U.S., as it highlighted the use of an investigational agent not primarily to gain information about its safety and effectiveness, as in controlled clinical studies, but to treat certain seriously ill patients.[56]

In order to promote the goal of speeding the "journey from laboratory to bedside of important new drugs

[51] *See* Nelson, *supra* note 8, at 463.

[52] The "treatment use" of a drug includes the use of a drug for diagnostic purposes. If a protocol for an investigational drug meets the criteria of the applicable regulations, the protocol is to be submitted as a treatment protocol under the same provisions. *See* 21 C.F.R. § 312.34(a) (2003).

[53] The regulations define an "immediately life-threatening disease" as "a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment." 21 C.F.R. § 312.34(b)(3)(ii) (2003). Although the regulations do not define "serious" disease, the preamble to the regulations offer several illustrations "normally [to] be considered serious diseases or stages of diseases," including Alzheimer's disease, advanced multiple sclerosis, and advanced Parkinson's disease. 52 Fed. Reg. 19,466, 19,467 (May 22, 1987) (codified at 21 C.F.R. § 312). By contrast, diseases that are "normally [to] be considered to be immediately life-threatening" include advanced cases of AIDS, advanced congestive heart failure, and most advanced metastatic refractory cancers. *Id.*

[54] 21 C.F.R. § 312.34(a) (2003). *See* Nelson, *supra* note 8, at 463; *see also* Perrin, *supra* note 39, at 127.

[55] 21 C.F.R. § 312.34(a); *see* Perrin, *supra* note 39, at 127.

[56] *See* Ken Flieger, *FDA Finds New Ways to Speed Treatments to Patients*, FDA Consumer Special Report (Jan. 1995), *at* http://www.fda.gov/fdac/special/newdrug/speeding.html.

for devastating illness," while simultaneously safeguarding the public from unsafe or ineffective products and ensuring the validity and integrity of controlled clinical trials, the Treatment IND regulations set forth certain criteria to be met by any IND treatment or treatment protocol, including: (i) the drug is intended to treat a serious or immediately life-threatening disease; (ii) there is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population; (iii) the drug is under investigation in a controlled clinical trial, under an IND in effect for the trial, or all clinical trials have been completed; and (iv) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.[57] Furthermore, treatment protocols and INDs are conditional upon compliance with safeguards in place for the IND process, including the regulations governing informed consent of human subjects, institutional review boards, distribution of the drug through qualified experts, adequate production facilities, and submission of IND safety reports.[58]

For a drug intended to treat a "serious disease," the FDA Commissioner may deny a request for Treatment IND status if there is insufficient evidence of the drug's safety and effectiveness to support such use.[59] If the Commissioner grants such request, however, a drug may be made available for treatment use during of after Phase III clinical trials, or, in appropriate circumstances, as early as Phase II trials.[60] For an "immediately life-threatening disease," the Commissioner may similarly deny a drug's Treatment IND status if the available evidence "fails to provide a reasonable basis for concluding that the drug: (A) May be effective for its intended use in its intended patient population; or (B) Would not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury."[61] However, approval of Treatment IND status for drugs targeting such immediately terminal diseases may be available

[57] 21 C.F.R. § 312.34(b)(1).
[58] *Id.* § 312.34(c).
[59] *Id.* § 312.34(b)(2).
[60] *Id.* § 312.34(a).
[61] *Id.* § 312.34(b)(3).

"earlier than Phase III, but ordinarily not earlier than Phase II."[62] By allowing early access to new and innovative drugs and therapies, Treatment INDs offer some relief from the long delays often associated with the normal drug approval process, relief that is obviously welcomed by terminally ill patients with little hope left of finding effective alternative therapies.

C. Expedited Development and Accelerated Approval Reforms

In addition to Treatment INDs, expanding access to experimental drugs and therapies was a motivating force behind the FDA's expedited review provisions, which focus on accelerating or short-cutting the ordinary clinical trial process in order to obtain full FDA approval in a shorter period of time.[63] In August of 1988, Vice President George Bush, Chairman of the Presidential Task Force of Regulatory Relief, asked the FDA to design procedures to speed the "marketing of new therapies intended to treat AIDS and other life-threatening illness," urging the FDA to more efficiently facilitate the approval process and to "transfer ... the fruits of biomedical research to the marketplace."[64] Quickly responding to the clear sense of urgency, the FDA issued a "fast-track" regulation in October of 1988, which was to include procedures "designed to speed the availability of new therapies to desperately ill patients, while preserving appropriate guarantees for safety and effectiveness."[65]

The expedited development regulations, known as "Subpart E" regulations, initially proposed in 1988, were codified in 1992 in order to expedite the review of new drugs by introducing several reform measures and new aspects of FDA review for the approval of new drugs and biologicals that treat "life-threatening and severely-

[62] *Id.* § 312.34(a).
[63] *See* Greenberg, *supra* note 37, at 321.
[64] *See* Perrin, *supra* note 39, at 129 (citations omitted).
[65] 53 Fed. Reg. 41,516, 41,516 (Oct. 21, 1988); *see* Nelson, *supra* note 8, at 473.

debilitating illnesses," including: early consultation between the FDA and pharmaceutical developers; FDA monitoring of the clinical trial process; abbreviation of clinical trials required in NDA submissions; and FDA authority to require Phase IV post-marketing research as a condition for NDA approval.[66]

An additional step in reforming the traditional FDA review process came in 1993 when the FDA's "accelerated approval" regulations were codified and included as an essential element a provision adopting "surrogate endpoints" to be used as standards for gauging treatment outcomes and the empirical basis for FDA approval of a new drug.[67] Rather than defining positive outcome in terms of extended patient survival, as was typical in earlier clinical research practice, the accelerated approval procedure allows "surrogate endpoints" to serve as predictive measures of clinical and therapeutic benefit, despite the fact that they may not be direct measures of how a patient feels, functions or survives.[68] Moreover, the regulations suggest that surrogate endpoints may be used in clinical trials even "where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome," provided that additional post-marketing studies are diligently carried out in order to verify the ultimate clinical benefit of the new drug.[69] Bypassing more conservative empirical methods, such as strict reliance on "survival or irreversible morbidity" data, and by permitting the use of surrogate endpoints, the FDA demonstrates its commitment to making new drug products more widely and rapidly available to patients who otherwise have little hope to gain access to alternative and innovative drugs and therapies.

[66] *See* 21 C.F.R. §§ 312.80-321.88; *see also* Greenberg, *supra* note 37, at 321-22 (adding that, at a policy level, the Subpart E regulations stressed the importance of flexibility in the FDA's application of the FDCA's safety and effectiveness standards, especially in recognition f the increased risk-tolerance of seriously ill patients for whom no effective treatment alternatives existed).

[67] *See* 21 C.F.R. § 314.510; *see also* Greenberg, *supra* note 37, at 322 (asserting that the accelerated approval and Subpart E regulations, together, "reflected a substantial shift in FDA policy to accommodate the reality of the AIDS epidemic and its attendant political pressures").

[68] *See id.*; *see also* Flieger, *supra* note 56, at 4; Greenberg, *supra* note 37, at 323 (using as an example research on AIDS drugs where clinical trial outcome might be measured in terms of CD4 cell counts, an index of human immune function that marks the physiological progression of AIDS).

[69] 21 C.F.R. § 314.510.

While expanded access to new drugs may offer desperate patients some comfort when standard treatments have been exhausted and proven futile, some have argued that efforts such as the FDA's policy for expedited approval of new drugs lack specific prerequisites for follow-up studies and fail to enumerate FDA enforcement power.[70] Moreover, skeptics claim that the accelerated approval process exposes an even larger number of people to uncertainty than expanded access protocols, and emphasize the inherent uncertainty in relying upon surrogate endpoint data, as well as the possibility that the clinical benefit may never even emerge.[71] Although other federal initiatives have been introduced to streamline the drug approval process and make new drugs more quickly available to certain desperate populations, such as terminal AIDS and cancer patients, the FDA procedures designed to expand access and accelerate approval have dominated its efforts at regulatory reform of drug development and the guidelines concerning research with human subjects.[72]

Despite the above reforms initiated during the late 1980s and early 1990s, concerned consumers, legislators and drug manufacturers continued to criticize the rising costs and delays of FDA review.[73] In particular, critics stressed the inefficiencies in the coordination between the FDA and pharmaceutical manufacturers in the design of clinical trial research, as well as the burdensome delays caused by "confusing [FDA] communications" and "inadequate [FDA] guidance."[74] In response to these and other concerns, the Food and Drug Administration Modernization Act (FDAMA), signed into law in 1997, contained several provisions

[70] *See* Perrin, *supra* note 39, at 136.

[71] *See id.* at 136, 144.

[72] For example, the "parallel track" program, for example, was designed exclusively to target AIDS and HIV-related conditions, and, although very similar to the treatment IND regulations, it took an additional step by providing that "expanding availability protocols might be approved for promising investigational drugs when the evidence for effectiveness is less than that generally required for a treatment IND." Expanded Availability of Investigational New Drugs Through a Parallel Track Mechanism for People with AIDS and other HIV-Related Disease, 57 Fed. Reg. 13,250, 13,256 (1992); *see* Greenberg, *supra* note 37, at 324-25. The parallel track initiative developed in part based on an earlier joint protocol sponsored by the FDA and National Cancer Institute, referred to as "Group C" procedures, which permitted oncologists treatment access to experimental cancer drugs outside of controlled clinical trials. *See* Expanded Availability, 57 Fed. Reg. at 13,256; *see also* Greenberg, *supra* note 37, at 325 (asserting that the parallel track policy purposely excluded diseases other than AIDS from its reach and was intended as a pilot program to assess the incremental benefits and risks of expanded access beyond that provided by other FDA initiatives).

[73] *See* Greenberg, *supra* note 37, at 343 (noting that by 1993, the average drug development time for FDA approval was approximately 12 years, at an average cost of 350 million dollars per new drug).

[74] *See id.*; *Drugs and Biologics: Hearings Before the Subcomm. on Oversight and Investigations of the House Comm. on Commerce*, 104th Cong. 13-15 (1995) (statement of Christian W. Nolet, National Director, Life Sciences Industry Group).

that addressed the new drug approval process. One commentator succinctly enumerated these elements of the FDAMA,[75] which included, among other provisions, the following: (1) Congress adopted into law a set of expanded access provisions intended to supplement the FDA's regulatory reforms and to stress the access of experimental drugs to patients with serious and life-threatening diseases;[76] (2) Congress amended the FDCA to formalize the "fast track" status for expedited approval of new drugs, including corresponding federal review procedures based on surrogate endpoint data, as well as allowed the FDA to begin its review before the completion of an NDA;[77] and (3) Congress set out for the FDA an explicit mission statement, which holds the agency to protecting the public health through product regulation and to providing prompt review of clinical trials and drug research.[78] The balancing act in which the FDA seems to be constantly engaged is reflected in these more recent efforts to reform the new drug approval process, as the agency attempts to effectively maneuver itself and its resources between the two primary objectives of expanding access to potentially life-saving drugs for the seriously and terminally ill and protecting those individuals from the risks inherent in clinical trial research. At the core of the debate concerning early access to experimental therapies and clinical research for the terminally ill seems to be the issue of the meaningfulness of the patients' informed consent, particularly where information available to desperately ill subjects is less than perfect and the potential risks are often not easily quantifiable. Because of the centrality of informed consent to any discussion of clinical research involving human subjects, it is that topic to which I will now turn.

IV. The Informed Consent Paradigm in Human Subject Research

[75] *See* Greenberg, *supra* note 37, at 344-45. Greenberg also noted other provisions in the FDAMA that bear on the drug approval process, such as the renewal of the Prescription Drug User Fee Act of 1992, which permits the FDA to collect user fees from drug companies filing new drug applications, as well as provisions calling for increased FDA accountability. *See* S. Rep. No. 105-43, at 2, 4-5.

[76] *See* Pub. L. No. 105-115 561, 111 Stat. 2296 (1997); *see also* S. Rep. No. 105-43, at 76 (explaining the preconditions to expanded access under statute).

[77] *See* Pub. L. No. 105-115 112, 111 Stat. 2296; *see also* S. Rep. No. 105-43, at 88.

[78] *See* Pub. L. No. 105-115 406, 111 Stat. 2296; *see also* S. Rep. No. 105-43, at 2.

The National Institutes of Health (NIH) define "informed consent" as "the process of learning the key facts about a clinical trial before deciding whether or not to participate," as well as "a continuing process throughout the study to provide information for participants."[79] In order to gain approval from an IRB to conduct clinical trials, researchers must give subjects "sufficient opportunity to consider whether or not to participate [and] minimize the possibility of coercion or undue influence."[80] As set forth explicitly in the regulations, the "basic elements of informed consent" include such items as a statement that the study involves research; a description of the purposes of the research and the procedures to be followed; an explanation of any reasonably foreseeable risks and discomforts to the subject, as well as any expected benefits; and a disclosure of any alternative courses of treatment that might be beneficial.[81]

While some evidence suggests that the informed consent framework was recognized in regulations for clinical research and experimentation as early as the nineteenth century, in general the Nuremberg Code of 1947 ("Code") is recognized as the first document to set out ethical principles in human subject research based on informed consent.[82] Promulgated at the end of the 1946-47 trial of Nazi physician-experimenters, the Nuremberg Code was created by U.S. judges in response to the horrific non-therapeutic and nonconsensual Nazi experiments involving the murder and torture of concentration camp prisoners.[83] Although it was

[79] *ClinicalTrials.gov: An Introduction to Clinical Trials*, *supra* note 16, *at* http://www.clinicaltrials.gov/ct/gui/info.

[80] 21 C.F.R. § 50.20.

[81] *Id.* § 50.25(a) ("Basic elements of informed consent"). In addition to the "basic elements of informed consent," the regulations set forth several additional elements of informed consent that are required in special circumstances. *See id.* §§ 50.25(a)(5)-(8), 50.25(b)-(d), 50.27 ("Documentation of informed consent").

[82] *See* Debra Johnson & Kathleen E. Squires, *Women and Clinical Trials*, *at* http://www.natap.org, at 3 (last visited Mar. 31, 2003; *see also* David N. Weisstub et al., *Establishing the Boundaries of Ethically Permissible Research with Vulnerable Populations*, *in* Research on Human Subjects: Ethics, Law and Social Policy, *supra* note 20, at 355 (asserting that the Nuremberg Code "initiated a process of inquiry on an international scale that has led to the evolution of various general ethical principles intending to guide participants in the research endeavor").

[83] *See* George J. Annas, *Questing for Grails: Duplicity, Betrayal and Self-Deception in Postmodern Medical Research*, 12 J. Contemp. Health L. & Pol'y 297, 301 (1996).

formulated in reaction to such deplorable experiments, it was intended to be, and, indeed, has become, a universal and authoritative legal and ethical document regulating human research standards internationally.[84] Declaring that "[t]he voluntary consent of the human subject is absolutely essential," and setting out nine other required elements in any research involving human subjects, the Code paved the way for today's informed consent guidelines and regulation of clinical research.[85]

Despite the promotion of the Code as an international ethical guide for researchers, its stringent and demanding standards led to the formulation of other codes of ethics and research, regulations, and laws that provided a more balanced approach to research involving human subjects. One such creation, the Helsinki Declaration of 1964 ("Declaration"), which seemed ostensibly to reaffirm the Code's dedication to ensuring that research with human subjects "conform[s] to the ethics of the medical profession generally" and that "certain basic principles [are] observed in order to satisfy moral, ethical and legal concepts,"[86] offers more flexible guidelines and a broader framework within which physicians and researchers can ethically conduct their trials.[87] In addition to presenting "basic principles" applicable to all research involving human subjects, the Declaration further divides research into therapeutic ("Medical Research Combined with Professional Care," or "Clinical Research") and non-therapeutic (or "Non-Clinical Research").[88] As a result, Professor

[84] *See id.* (adding that it remains "one of the premier human rights documents in world history").

[85] *Nuremberg Code*, *excerpted from*: *"Permissible Medical Experiments*," Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10: Nuremberg (Oct. 1946-Apr. 1949), vol. 2, at 181-81 (setting out 10 principles to aid physicians and researchers in human subject research, including providing proper preparations and adequate facilities to protect subjects against injury, disability or death, and permitting subjects to terminate the experiment if desired), *reprinted in* Ethics of Research with Human Subjects: Selected Policies and Resources 12-13 (Jeremy Sugarman et al. eds., 1998).

[86] Introduction to the *Nuremberg Code*, *Trial of War Criminal Before the Nuremberg Military Tribunals Under Control Council Law No. 10* (Oct. 1946-Apr. 1949).

[87] *See* Annas, *supra* note 83, at 303 (adding that the goal of the Declaration of Helsinki was "to replace the human rights-based agenda of the Nuremberg Code with a more lenient medical ethics model that permits paternalism"); *see also* Richard W. Garnett, *Why Informed Consent? Human Experimentation and the Ethics of Autonomy*, 36 Cath. Law. 455, 472-73 (1996) (noting that the new approaches, such as the Helsinki Declaration, "strike a compromise between the Code's idealism and the perceived need for more flexible, permissive, and perhaps realistic guidelines for research"); Jay Katz, *The Consent Principles of the Nuremberg Code: Its Significance Then and Now*, *in* The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation 227, 238 (suggesting that modern research regulations are less rigid and demanding than the Code).

[88] *World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research In-*

George Annas suggests that the line between treatment and research is blurred, and the distinction between researcher and physician, as well as between subject and patient, is effectively eliminated.[89] Asserting that "research becomes treatment, the researcher becomes the healer, and the subject becomes the patient," Annas adds that in this way the current trend in clinical research goes further than the Declaration's principles, as "language is used to obscure the truth and justify the unjustifiable," not only in the more primitive cold war radiation experiments conducted in the U.S. in the 1940s through the 1960s, but in today's clinical trials and research performed on terminally ill cancer and AIDS patients as well.[90]

In an effort to further broaden the reach and increase the ease of applicability of ethical principles to guide research involving human subjects, in 1979 the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research ("Commission") published the *Belmont Report*, described by the Commission as a statement of three "basic ethical principles" and guidelines that should provide an analytical framework to guide the resolution of ethical problems arising from research involving human subjects.[91] Stating that the codes and rules developed in the latter half of the twentieth century "often are inadequate to cover complex situations," and "at times they come into conflict, and they are frequently difficult to interpret or apply," the *Belmont Report* suggests that "[b]roader ethical principles will provide a basis on which specific rules may be formulated, criticized and interpreted."[92] With that principle in mind,

volving Human Subjects, adopted by the 18th World Medical Assembly in Helsinki in 1964, as amended by the 29th World Medical Assembly (1975), 35th World Medical Assembly (1983), 41st World Medical Assembly (1989), *reprinted in* Ethics of Research with Human Subjects, *supra* note 85, at 14-18. Garnett noted that a major difference between the two codes is the Declaration's recognition and regulation of therapeutic research. While the Declaration recognized that the same ethical principles should govern when conducting research with healthy volunteers as with those in need of care, the Code only addressed non-therapeutic experimentation. *See* Garnett, *supra* note 87, at 473n.83 (citations omitted).

[89] *See* Annas, *supra* note 83, at 303.

[90] *See id.* at 304.

[91] The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, 79 Fed. Reg. 12,065 (Apr. 18, 1979), *reprinted in* Ethics of Research with Human Subjects, *supra* note 85, at 19-30.

[92] *Id.* at 19.

the *Belmont Report* sets out three "basic ethical principles" to form the basis for the protection of human subjects: respect for persons, beneficence, and justice.[93] Moreover, it provides a set of requirements based on those three comprehensive principles, focusing on (1) informed consent, (2) risk/benefit assessment, and (3) the selection of subjects of research.[94] Likewise, the federal regulations governing research with human subjects, known as the federal "Common Rule," requires the establishment of IRBs to review and approve research, and sets out the conditions of such approval, including extensive informed consent requirements, a mandate that risks to subjects be minimized and reasonable in relation to expected benefits, that subjects be selected equitably, and that appropriate protections exist for special populations of subjects.[95] Before considering these regulations as they are applied, and perhaps should be applied, to one such "special population," namely, terminally ill cancer patients, it may be helpful to first consider the unique experiences and characteristics of the patients themselves and their battle against not only the disease, but at times the regulatory powers that deny them access to experimental treatments which, at least in their minds, offer one last hope for a cure.

V. Cancer Research: Lessons from the Past and Implications for the Future

A. An Introduction to Cancer Research

Approaching clinical cancer research as a model for clinical trials overall, it has been argued that the "char-

[93] *See id.* at 20-24.

[94] *See id.* at 24-30; *see also* Nancy M. P. King et al., *Relationships in Research: A New Paradigm*, *in* Beyond Regulations: Ethics in Human Subjects Research 8-10 (Nancy M. P. King et al. eds., 1999) (noting that the current system of federal regulation of research with human subjects reflects, and is both grounded in and justified by, the "principlist paradigm in the *Belmont Report*").

[95] *The Common Rule*, 56 Fed. Reg. 28012 (June 18, 1991); *see* King et al., *supra* note 94, at 10. Promulgated in 1991, the Common Rule applies to all research involving human subjects conducted, supported or otherwise subject to regulation by any federal department or agency. In addition, IRBs are required under the Common Rule by 16 federal departments and agencies, as well as for research involving drugs, medical devices and biologics, regulated by the FDA. *See* McCarthy, *supra* note 20, at 316.

acteristics that make clinical trials ethically important, and problematic, exist in cancer trials in exaggerated form."[96] In particular, and from an ethical point of view, "cancer research has been the paradigm of trials entailing not simply uncertainty but very serious risks on the part of subject participants."[97] Moreover, a phenomenon well known in cancer research is equally applicable to all areas of clinical research: the misconception on the part of patients participating in a study that they will be receiving effective treatments not otherwise available.[98]

As an illustration, in the 1980s and 1990s, researchers searching for more effective breast cancer treatments began administering higher doses of chemotherapy followed by procedures to curb the severe adverse and toxic side effects by re-infusing harvested bone marrow to rescue the patient from the chemotherapy's ravishing effects.[99] Despite the treatment's life-threatening side effects, including bleeding disorders, infections, organ dysfunction, severe nausea and gastrointestinal problems, to name just a few, desperate cancer patients willing to try anything viewed it as their final chance for a cure.[100] Although there had been little research showing the safety and efficacy of the treatment, and despite the high mortality rate involved, many women, approximately 12,000 to 30,000 in the United States, embraced it as their last chance for survival in a devastating struggle in which no other therapies had proven effective.[101]

Given the often lethal side effects experienced by cancer patients who through their pain and suffering "choose" to go still further in their search for a cure by participating in experimental drug trials, researchers have begun to question what these increasingly invasive and severe approaches translate into for the quality of life of the patients involved.[102] As a result, quality of life research and evaluation have become an integral

[96] Benjamin Freedman, *The Ethical Analysis of Clinical Trials: New Lessons for and from Cancer Research*, *in* The Ethics of Research Involving Human Subjects: Facing the 21st Century 320 (Harold Y. Vanderpool ed., 1996).
[97] *Id.* at 321.
[98] *See id.*
[99] *See* Kuszler, *supra* note 13, at 457.
[100] *See id.* at 458.
[101] *See id.* at 459.
[102] *See* Freedman, *supra* note 96, at 323.

part of the efforts to refine the ethics of cancer clinical trials.[103] Below is a brief overview of some of the most widely publicized and influential "battles" in the war on cancer, including those that ended in the courtroom, as well as in the halls of Congress, before arbiters positioned ultimately to decide the fate of patients ravaged both physically and psychologically by the disease.

B. Cancer "Quackery": The Laetrile Experience

Throughout the twentieth century desperately ill cancer patients have been promised a variety of "cures" or effective therapies for cancer by anxious researchers and often well-meaning physicians hoping to conquer the deadly disease once and for all. Harry Hoxsey presented his cancer "cure" before World War II, but was ultimately found guilty of fraud only after many patients had become victims of his scam.[104] Another unproven remedy, Krebiozen, gained popularity in the 1950s after being endorsed by a distinguished investigator, although ultimately it, too, had vanished by the beginning of the 1970s.[105] Not to be outdone by these more primitive therapies, Laetrile entered the scene with little noise in the 1960s and early 1970s, and soon garnered much support and positive publicity as the new miracle "cure" for cancer.[106]

The Laetrile experience was perhaps the most notorious controversy involving the public policy questions and concerns surrounding the access to experimental and highly unconventional treatments by desperately

[103] *See id.*

[104] *See* Stuart L. Nightingale, *Second Binational Symposium: United States—Israel – Papers on the Role of Epidemiology and Regulatory Programs*, Public Health Rep. 1984; 99: 333-338 (1984).

[105] *See id.*; *see also United States v. Rutherford*, 442 U.S. 544, 558 (1979) (citing other examples of the "wide variety of purportedly simple and painless cures for cancer, including liniments of turpentine, mustard, oil, eggs, and ammonia; peat moss; arrangements of colored floodlamps; pastes made from glycerin and limburger cheese; mineral tablets; and "Fountain of Youth" mixtures of spices, oil, and suet").

[106] *See* Nightingale, *supra* note 104, at 334.

ill patients.[107] Touted by advocates to be an effective therapy for cancer, the uncertainties surrounding the "remedy" were profound. Besides agreement that Laetrile is obtained from apricot kernels, there was much confusion over what the substance exactly was and how it should be promoted to the public.[108] Similarly, confusion also marked the actual proven value in treating patients, as supporters praised its effectiveness in curing, mitigating, and even preventing cancer, as an analgesic, as well as in treating such conditions as sickle cell anemia, hypertension, and parasitic diseases.[109] Despite their clamorous words of support, the fact remained that there was no controlled trial data upon which to hang their cause, and FDA approval, therefore, remained out of reach.[110] The result was disheartening, as desperate patients were lured into the hands of suspicious black-market practitioners, who successfully peddled the scientifically mysterious and unapproved substance.[111] At the same time, the FDA's rejection of Laetrile did not stop several states from passing pro-Laetrile legislation in the years prior to the release of clinical study results that finally put an end to the lingering uncertainty of the drug's efficacy.[112]

In order to understand the promotional success of Laetrile, one need only consider the desperate position in which cancer patients find themselves, particularly in the terminal stages of the disease. The psychological distress of these patients would certainly lead them to embrace therapies, no matter how unconventional, that offer some hope for a "cure," or at least alleviation of some of their pain and suffering. In addition, some claim that the popularized "success" of Laetrile was due in part to the messages relayed to the public by its supporters, who claimed that organized medicine, colluding with the drug industry, the American

[107] *See* Greenberg, *supra* note 37, at 306-07.

[108] *See* Nightingale, *supra* note 104, at 334 (noting that supporters claimed that Laetrile is 1-mendelonitrile beta glucuronide, confiscated samples revealed amygdalin, and it was additionally advertised as vitamin B-17, a drug, and a food).

[109] *See id.*

[110] *See id.*; *see also* Greenberg, *supra* note 37, at 307.

[111] *See* Dale H. Gieringer, *Compassion Vs. Control: FDA Investigational-Drug Regulation*, Cato Policy Analysis No. 72 (May 20, 1986), at 9-10 (suggesting that, "[g]iven that Laetrile was relatively non-toxic, especially in comparison with other cancer treatments at the time, a rational medical case could have been made for its use, especially in conjunction with other treatment, and it might at least have been beneficial as a placebo"); *but see* Victor Herbert, *Laetrile: The Cult of Cyanide Promoting Poison for Profit*, American Journal of Clinical Nutrition 32 (May 1979), at 1121-58 (noting that a couple of accidental poisonings from Laetrile overdoses were reported).

[112] In 1978, studies conducted by the National Cancer Institute finally began to conclusively dispel the lingering scientific uncertainty over Laetrile's efficacy. *See* Geiringer, *supra* note 111, at 10.

Cancer Society, and the government, was taking part in a conspiracy to prevent Laetrile from entering the market.[113] By participating in the campaign supporting Laetrile, cancer patients were fighting not only to gain access to the treatment, but were also taking part in an effort to defy the establishment, a prospect that was likely attractive to those patients with little trust in government regulations and critical of any motives colored by paternalism.[114]

Psychological anxieties aside, many cancer patients and Laetrile advocates pushed to the forefront of the debate "freedom of choice" arguments, asserting that Laetrile should be accessible to them regardless of whether the FDA had approved it or the scientific community stood behind it.[115] In other words, patients and advocates argued that when no other therapies had proven effective and nothing else was left to try, they, as informed and consenting adults, should be free to use Laetrile without government interference. In time, the "freedom of choice" line of argument developed into a more sophisticated claim for a comprehensive "right of access" to experimental therapies such as Laetrile.[116] One critical issue posed by such an expansive right is whether FDA regulations, in accordance with the FDCA, should apply without modification to the terminally or seriously ill seeking to gain access to investigational or unapproved treatments.[117] In 1979, the United States Supreme Court first spoke on this issue, and it is its unanimous opinion in *United States v. Rutherford* to which I will now turn.

C. When Courts Intervene: *Rutherford* and Related Case Law

In *Rutherford*, the Supreme Court addressed the issue of whether the government has the right to prevent

[113] *See* Nightingale, *supra* note 104, at 334.
[114] *See id.*
[115] *See id.*
[116] *See* Perrin, *supra* note 39, at 123.
[117] *See id.*

terminally ill patients from choosing a drug treatment that is unapproved by the FDA.[118] Terminally ill cancer patients brought suit against the U.S. Government to enjoin the interference with the shipment and sale of Laetrile.[119] The Tenth Circuit had remanded the case to the FDA to determine whether Laetrile was a "new drug" under § 201(p)(1) of the Act and, therefore, was subject to the "safety" and "effectiveness" standards of the FDCA. The FDA concluded that Laetrile was a "new drug" as defined in § 201(p)(1) and fell within neither of the FDCA's grandfather provisions. After reviewing the FDA's decision, the district court found that Laetrile was exempt from premarketing approval under the Act's 1962 grandfather clause, and, alternatively, that the Commissioner of the FDA had infringed constitutionally protected privacy interests by denying cancer patients access to Laetrile. Upholding the district court's injunction, which allowed plaintiffs to receive the drug, the Tenth Circuit asserted that "as a matter of law . . . the 'safety' and 'effectiveness' terms used in the statute have no reasonable application to terminally ill cancer patients."[120] In order to address concerns that Laetrile was toxic when orally administered, the court limited relief to intravenous injections for patients under a doctor's supervision and directed the FDA to promulgate regulations "as if" the drug had been found "safe" and "effective" for terminally ill cancer patients.[121]

In a unanimous opinion written by Justice Marshall, the Supreme Court reversed, holding that the FDA had the authority to require safety and effectiveness for all drugs, including those intended to treat terminally ill patients.[122] The Court reasoned that "[n]othing in the history of the 1938 Food, Drug, and Cosmetic Act, which first established procedures for review of drug safety, or of the 1962 Amendments, which added the current safety and effectiveness standards in § 201(p)(1), suggests that Congress intended protection

[118] 442 U.S. 544 (1979).
[119] *Id.* at 548.
[120] 582 F.2d 1234, 1236 (1978).
[121] *Id.* at 1237.
[122] 442 U.S. at 552.

only for persons suffering from curable diseases."[123] In fact, the Court pointed to concerns expressed in congressional deliberations surrounding the 1938 Act and 1962 Amendments that even "individuals with fatal illnesses, such as cancer, should be shielded from fraudulent cures," as well as to Committee Reports noting the "FDA's policy of considering effectiveness when passing on the safety of drugs prescribed for 'life-threatening disease.'"[124]

Deferring to the FDA's determination not to allow the distribution of Laetrile, the Court cautioned that to accept the Court of Appeals' ruling that the FDCA's safety and efficacy standards have no relevance for terminally ill patients "is to deny the Commissioner's authority over all drugs, however toxic or ineffectual, for such individuals."[125] Furthermore, the Court offered a justification for the uniform application of the FDCA's efficacy standard, stating, "if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible."[126] Expressing concern over the inherent imprecision in labeling patients as "terminally ill," which it asserted is "often impossible . . . except in retrospect," the Court warned that exempting experimental drugs with no proven effectiveness in the treatment of cancer "would lead to needless deaths and suffering among . . . patients characterized as 'terminal' who could actually be helped by legitimate therapy."[127]

Subsequent cases have applied the reasoning presented by the Court in *Rutherford*, affirming its conclusion

[123] *Id.* at 552.

[124] *Id.* at 552-53; *see, e.g.*, 79 Cong. Rec. 5023 (1935) (remarks of Sen. Copeland, sponsor of the 1938 Act); 83 Cong. Rec. 7786-7787, 7789 (1938) (remarks of Reps. Phillips and Lea); 108 Cong. Rec. 17399 (1962) (remarks of Sen. Kefauver).

[125] 442 U.S. at 557-58; *see* Horwin, *supra* note 7, at 200 (asserting that the Court in *Rutherford* was "sensitive to the authority of the FDA" and its position that only FDA approval can ensure that terminal cancer patients are ensured a "therapeutic gain").

[126] 442 U.S. at 556.

[127] *Id.* at 556-57 (noting also that "[e]ven critically ill individuals may have unexpected remissions and may respond to conventional treatment") (citations omitted).

that the FDCA contains no exception for terminally ill patients and its caution that finding otherwise would subject these "highly vulnerable patients" to the "vast range of self-styled panaceas that inventive minds can devise."[128] In one such case, *Cowan v. United States*, the plaintiff, a terminally ill AIDS patient seeking to gain access to an experimental goat neutralizing antibody drug, did not challenge the applicability of the FDCA, but asserted that he meets an exception to it and asked the Court to prohibit the FDA from interfering with the administration of the unapproved drug.[129] Following *Rutherford*, the court rejected plaintiff's claim and reaffirmed the Supreme Court's statement of the law under the current statutes and regulations, declaring that "[p]laintiff's physician may not administer the goat neutralizing antibody absent prior approval of the FDA."[130] Adding that although it was sympathetic to plaintiff's situation, the required course of action for plaintiff and his physician was to "pursue approval of his Investigational New Drug application as quickly as possible" and "obtain appropriate approval through the proper regulatory authorities."[131] Lastly, the court made clear that the decision whether to grant such exemptions from the IND process for terminally ill patients is one that rests properly with Congress and not with the courts.[132]

Since *Rutherford*, lower courts have wrestled with claims by terminal patients that they have a right under the Constitution to access unapproved medicines, and have consistently struck down such claims, reasserting the basic principles in *Rutherford*. While the Supreme Court in *Rutherford* did not directly address the claim by plaintiffs that they had a constitutionally protected "privacy" right to use laetrile, on remand the Court of Appeals for the Tenth Circuit rejected that claim, finding that, "although a decision by a patient whether to have a treatment or not is a protected right, the 'selection of a particular treatment, or at least

[128] *Cowan v. United States*, 5 F. Supp. 2d 1235, 1242-43 (N.D. Okla. 1998) (citations omitted).
[129] *See id.* at 1239.
[130] *Id.* at 1242 (adding that "to permit terminally ill patients to seek any type of treatment regardless of the effectiveness of such treatment would create a cottage industry existing solely to provide potential panaceas to highly vulnerable patients").
[131] *Id.* at 1243.
[132] *See id.*

a medication, is within the area of governmental interest in protecting public health."'[133] Likewise, other federal courts have followed the Tenth Circuit's lead in holding that the selection of a particular treatment or medicine is not a protected right under the Constitution.[134] State courts have similarly rejected terminally ill patients' claims based on a constitutionally protected right to privacy, concluding that the right to obtain unapproved drugs whose efficacy has not been proven is not a fundamental right.[135]

As a final illustration, in *Garlic v. Food and Drug Administration*, plaintiffs suffering from Alzheimer's disease challenged the FDA's failure to approve the drug tetrahydroaminoacrinine (THA) as a treatment for their severely debilitating disease.[136] Asserting that the Ninth and Fourteenth Amendments guarantee them a right to follow a course of medical treatment designed to "prolong and improve" one's life, they argued that the FDA was unconstitutionally interfering with the private importation of the drug.[137] While acknowledging that several courts have recognized that decisions concerning medical treatment are "essentially personal, and therefore may affect an individual's right to liberty or privacy,"[138] the District Court for the District of Columbia cited *Rutherford* and held that plaintiffs had not stated a valid claim under the Constitution.[139] Expressing sympathy for plaintiffs' "sense of exigency and frustration," the court reaffirmed *Rutherford*'s well-established tenet that "the Federal Food, Drug, and Cosmetic Act makes no special provision for drugs

[133] *Seeley v. State of Washington*, 940 P.2d 604, 612 (Wash. 1997) (quoting *Rutherford v. United States*, 616 F.2d 455, 457 (10th Cir.), *cert. denied*, 449 U.S. 937 (1980)).

[134] *See Seeley*, 940 P.2d at 613; *See, e.g., Carnohan v. United States*, 616 F.2d 1120 (9th Cir. 1980) (finding that constitutional rights of privacy and personal liberty did not give plaintiff the right to get access of laetrile free of lawful exercise of government police power); *Kulsar v. Ambach*, 598 F. Supp. 1124 (W.D.N.Y. 1984) (holding that patients had no constitutional right to a drug treatment which the FDA ordered removed from commerce); *United States v. Burzynski*, 819 F.2d 1301, 1314-15 (5th Cir. 1987) (finding unsupportable plaintiffs' claim for injunctive relief against interference with interstate distribution of an unapproved cancer drug, antineoplastons, based on the asserted "constitutional right to obtain medical treatment that is encompassed by their right to privacy").

[135] *See, e.g.*, *People v. Privitera*, 591 P.2d 919, 925-26 (Cal. 1979), *cert. denied*, 444 U.S. 949 (1979) (applying a rational basis analysis where terminally ill cancer patients asserted a right to be treated with an unapproved drug, and finding that the state statute met this standard and therefore did not violate the federal constitutional right of privacy); *Seeley*, 940 P.2d at 613-14 (applying the rational basis standard of review and upholding the challenged legislation categorizing marijuana as a schedule I controlled substance).

[136] 783 F. Supp. 4 (D.D.C. 1992).

[137] *See id.* at 5.

[138] *See, e.g., Whalen v. Roe*, 429 U.S. 589 (1976); *New York State Ophthalmological Soc'y v. Bowen*, 854 F.2d 1379 (D.C. Cir. 1988).

[139] *See Garlic*, 783 F. Supp. at 5.

used to treat terminally ill patients."[140]

D. The Plight of Dr. Burzynski in the War on Cancer

The constant interplay between the courts, Congress, the FDA, and the interested public with respect to the issue of access by terminally ill patients to unapproved and experimental drugs and treatments is a testament to the very heated debate that has been kept alive, and, indeed, re-fueled, for much of the twentieth century and into the twenty-first. An illustrative example of the powerful interaction among these key players is one that began when Stanislaw Burzynski, a Polish-born physician with a doctorate in biochemistry, discovered a reportedly non-toxic cancer therapy in 1967.[141] Escaping communist oppression in his home country, Burzynski came to the United States in 1970 and began work on his discovery, an alternative cancer drug called antineoplaston, which simply means "anticancer."[142] Desperately ill cancer patients flocked to Burzynski and his cancer research institute, seeking to obtain his experimental therapy as a last hope after traditional chemotherapy and radiation had failed or only intensified their illnesses.[143]

Despite the benefits reported by many patients, who claimed that the antineoplastons actually reduced their tumors and that they had gone into complete remission, without experiencing the dreadful toxic side effects typically associated with many anticancer drugs, the American Cancer Society added Burzynski's treatment to its "unproven methods" blacklist in 1983.[144] The FDA entered the ring several months later when it

[140] *Id.* (quoting *Rutherford*, 442 U.S. at 552) (leaving no doubt that "plaintiffs must wait for THA to pass the rigorous statutory and regulatory process designed to ensure that a medication is safe as well as effective before it is marketed to the public").
[141] *See* Sue A. Blevins, *FDA: Keeping Medication from Cancer Patients*, Regulation, Cato Institute, Vol. 20, No. 1 (1997); *see also* David Wagner, *Friend or Enemy?*, Insight on the News, at 8 (Aug. 17, 1998).
[142] *See* Blevins, *supra* note 141.
[143] *See id.* (noting that since 1977 more than 2,500 Americans have sought out Burzynski's experimental therapy).
[144] *See id.*

sought an injunction against Burzynski's use of the drug to treat patients because it had not been approved in accordance with the agency's new drug approval process under the FDCA. Refusing to issue a broad injunction against the drug's use, which would effectively shut down Burzynski's clinic, the federal judge allowed the doctor to continue treating patients in Texas, but prohibited him from shipping the drug across state lines.[145] As expected, out-of-state patients came to Texas to be treated by Burzynski and shipped the drug interstate, leading to a fierce battle between the doctor and the federal government that lasted more than a decade.

In July of 1985, the government applied for and obtained a warrant to search Burzynski's clinic as part of a criminal investigation based on the FDA's referral to the Department of Justice.[146] Patient records and other property were seized as evidence to show that antineoplastons had been shipped outside the state and were being distributed in interstate commerce in violation of several federal mandates as well as the district court's initial injunction.[147] In addition to federal raids on his research facilities, Burzynski was subjected to three federal grand jury investigations between 1986 and 1994, although none led to an indictment.[148]

In 1994, the doctor's endeavor seemed to be looking up, with the FDA even approving his manufacturing facility and granting him permission to conduct clinical research trials, until Burzynski welcomed a chance to publicly endorse his treatment by appearing in March of 1995 on the CBS television show "This Morning" with three of his patients who had apparently beaten terminal cancer after receiving antineoplastons.[149] Later that same day federal agents again raided Burzynski's clinic, and eight months later a federal grand jury, the fourth to be convened within a span of nine years, handed down an indictment against the doctor, charging him with 40 courts of distributing an unapproved drug in interstate commerce, 34 counts of mail

[145] *See id.*
[146] *See United States v. Burzynski*, 819 F.2d at 1305.
[147] *See id.*
[148] *See* Blevins, *supra* note 141.
[149] *See id.*

fraud, and one count of contempt of court.[150]

While the battle waged on in the courtroom, Congress entered the scene the same year when Representative Joe Barton and his Subcommittee on Oversight and Investigations of the House Commerce Committee held hearings during July of 1995 to probe charges that the U.S. Attorney's office in Houston and the FDA had acted improperly and harassed Burzynski through investigations that began in 1983.[151] During the hearings, which addressed alleged abusive and retaliatory practices by the FDA, one of Burzynski's patients, who had successfully undergone antineoplaston therapy after being diagnosed with an inoperable brain tumor, offered dramatic testimony in support of the experimental therapy, asserting, "[i]t's like I'm at war against cancer, and the government keeps trying to take away the only weapon I have."[152] Responding to the allegations of abuse, then-FDA chief David Kessler testified in November of 1995, denying that any pattern of retaliation or abuse existed, and, ironically, the 75-count indictment against Burzynski was handed down just five days later.[153] As the saga continued on multiple fronts, the Burzynski case went to trial in January of 1997, but ended with a hung jury just two months later, with the judge dismissing the mail fraud charges and federal prosecutors dropping the 40 counts of unauthorized distribution.[154] In May of 1997, a second federal trial to address Burzynski's lone remaining contempt charge resulted in an acquittal after just three hours of jury deliberation.[155]

While Burzynski's 14-year battle with the FDA may have appeared to be over, the "miracle" doctor and

[150] *See id.*; *see also* Wagner, *supra* note 141, at 8 (noting that the doctor's appearance on television is when "[t]hings took a turn for the worse for Burzynski, when he seized an opportunity to promote his cause the American way – through the media").
[151] *See* Wagner, *supra* note 141, at 8; *see also* Blevins, *supra* note 141.
[152] *See* Wagner, *supra* note 141, at 8.
[153] *See id.*
[154] *See id.*; *see also* Sue A. Blevins, *FDA's War on Dr. Burzynski and His Patients: Physician and Patients Win!*, Medical Sentinel, Vol. 3, No. 4 (1998), at 135.
[155] *See id.*

his experimental "cure" finally victorious, the controversy rages on, as Burzynski's patients, as well as other desperately ill patients in search of a last chance at life, continue to plead with Congress to reign in the FDA's control over terminally ill patients' access to experimental drugs.[156] For example, in 1998 Representative Barton led a new set of hearings concerning FDA abuses before the House Committee on Government Reform and Oversight. Addressing the Committee, the father of a 6-year-old patient of Burzynski dramatically asserted, "[f]rom the time we went to Dr. Burzynski [for antineoplaston treatment], the biggest threat to [my son's] life was not cancer, it was the FDA," and scolded the FDA's "cold disregard for the life of [his] son and Dr. Burzynski's other terminal cancer patients," as well as the "legal maneuvers" it employed to stop them from receiving the treatment.[157] Such tactics, he claimed, were both "un-American and unconstitutional," and it was Congress' job to put an end to them once and for all.[158]

Since the unfolding of the case of Dr. Burzynski, similar allegations of abuse and calls for action have been recorded in congressional hearings, and an increasing number of members of Congress have joined the debate, many of whom have expressed concern over the "inherent injustice in preventing cancer victims from having the medical freedom to try to save their lives."[159] For example, one Congressman, prompted by the many phone calls and letters his office had received regarding the plight of Dr. Burzynski, testified that "[w]hatever the FDA's concerns are, the problem remains they are denying patients with life-threatening diseases access to this [experimental] therapy," and "fail to recognize that people's lives and rights are being trampled in this process."[160] In an emotional appeal for change in the face of life-or-death circumstances, he pleaded that "as we continue down the path toward FDA reform, let us be mindful of patients with life-threatening diseases who are grasping at their last hopes to continue to live."[161]

[156] *See* Blevins, *FDA's War on Dr. Burzynski and His Patients*, *supra* note 154, at 135.
[157] *Id.* (citing the congressional testimony of Jack Kunnari, the father of 6-year-old Dustin Kunnari).
[158] *Id.*
[159] Horwin, *supra* note 7, at 201.
[160] *FDA Does Not Serve Public By Denying Treatment of Last Resort Pursued by Terminally Ill Patients*, 142 Cong. Rec. H. 4115 (daily ed. Apr. 29, 1996) (statement of Rep. Pallone).
[161] *Id.*

Even after Burzynski had been cleared of all charges his story remained a heated backdrop for continued congressional debate regarding patient access to experimental treatments and legislation to promote it.[162] Accompanying such discussions has been an undying concern for the protection of human subjects in experimental clinical research. For example, in a 1997 hearing before the House Subcommittee on Human Resources, the Deputy Commissioner and Senior Advisor to the FDA Commissioner, Mary Pendergast, discussed the FDA's policies concerning the protection of human research subjects and emerging issues involving access to experimental treatments and informed consent.[163] Setting out the basic structure for human research protection in the U.S. and the interconnection between the FDA and Department of Health and Human Services (DHHS) regulations,[164] Pendergast highlighted the FDA's vigilance in protecting the rights and welfare of human research subjects, asserting that the "[FDA] take[s] no human right more seriously than the protection of people enrolled in clinical trials."[165]

E. Legislative Proposals for Expanded Access: *The Access to Medical Treatment Act*

In 1998, a series of hearings were held to address ways to expand access to investigational and alternative therapies for seriously ill and dying patients, including new "legislation that would give all Americans the

[162] *See, e.g.*, *The Plight of Dr. Stanislaw Burzynski*, 143 Cong. Rec. H. 5176 (daily ed. July 11, 1997) (statement of Rep. Pallone) (calling the government's conduct in Burzynski's case "disturbing" and its treatment of Burzynski "reprehensible," adding that the government "placed cancer patients at jeopardy at one point" and "badly utilized" taxpayer money and resources).

[163] *See Biomedical Ethics: Hearing Before the Subcomm. on Human Resources of the House Comm. on Government Reform and Oversight*, 105th Cong. (May 8, 1997) (statement of Mary K. Pendergast, Deputy Commissioner and Senior Advisor to the Commissioner of Food and Drugs, U.S. Food and Drug Administration) (hereinafter "Pendergast testimony").

[164] Both the FDA and the Department of Health and Human Services (HHS) have regulations addressing the protection of human research subjects (20 C.F.R. Parts 50 and 56 for FDA; 45 C.F.R. Part 46 for HHS). While the HHS regulations apply to research that is conducted or supported by HHS and are implemented by the National Institutes of Health (NIH), the FDA regulations apply to human subject research involving products regulated by the FDA, whether the research is privately or publicly funded. Although the FDA and HHS regulations are essentially identical, the two agencies apply them in ways that reflect their distinct missions (*e.g.*, NIH implements the HHS regulations through assurances made by the institutions where the research is done, while FDA regulates the investigators who conduct the research and the IRBs that review proposed research studies). Both sets of regulations apply where a research project is conducted or supported by HHS and involves a product regulated by FDA. In sum, they are "complementary and together they set forth criteria that are needed to protect research subjects." Pendergast testimony at 6.

[165] *Id.* at 4.

freedom to choose their own medicines."[166] One piece of proposed legislation, entitled "The Access to Medical Treatment Act" ("AMTA"), has been repeatedly introduced in Congress since 1993.[167] Generating much debate over the years since its first introduction in Congress, AMTA provides that patients may be treated by any licensed healthcare practitioner with any method of medical treatment the patient desires, even if the treatment has not yet been approved by the FDA, and provided that a comprehensive list of requirements are met.[168] For example, Section 3 of the proposed legislation requires the healthcare practitioner to use "generally accepted principles and current information" to conclude that the unapproved drug, when used as directed, will not cause a danger to the patient, to inform the patient that the drug is not approved by the FDA, to allow the patient sufficient opportunity to consider whether or not to use the drug and to minimize the possibility of coercion or undue influence when making a recommendation to the patient, to disclose any financial interest that he or she may have in the drug, and to adhere to stringent informed consent procedures set forth in the legislation.[169]

The increased access to experimental treatments available under AMTA has been applauded by groups such as the American Association for Health Freedom, which claims that the legislation is necessary "to stop the legal harassment many alternative practitioners face from the FDA and state medical boards."[170] Other advocates assert that AMTA is necessary "because of the FDA's—and the pharmaceutical industry's—

[166] *Clinical Trial Subjects: Adequate FDA Protections: Hearing Before the House Comm. on Government Reform and Oversight,* 106th Cong. (Apr. 22, 1998) (statement of Dan L. Burton, Chairman, House Comm. on Government Reform and Oversight).

[167] *See* S. 1955, 106 Cong. (1999); H.R. 746, 105 Cong. (1997); S. 578, 105 Cong. (1997); H.R. 2019, 104 Cong. (1995-96); S. 1035, 104 Cong. (1995-96); H.R. 4696, 103 Cong. (1993-94); H.R. 4499, 103 Cong. (1993-94); *see also* Horwin, *supra* note 7, at 201 (presenting the comments of Senator Bob Dole, an original co-sponsor of the legislation: "In a free market system, it seems to make sense to make available non-harmful alternative medical treatments to individuals who desire such treatments, without the Federal Government standing in the way.").

[168] *See* "Access to Medical Treatment Act," 2001 H.R. 1964, S. 1378, 107th Cong. (2001); *see also* Blevins, *FDA: Keeping Medication from Cancer Patients*, *supra* note 141 (maintaining that the Access to Medical Treatment Act addresses the issue which stands at the crux of the problem with most regulations today, namely, that "they restrict the freedom of individuals to engage in voluntary transactions").

[169] *See* "Access to Medical Treatment Act," 107th Cong. § 3; *see also* Horwin, *supra* note 7, at 201 (outlining the requirements of the legislation).

[170] Sue A. Blevins, *Legalize Alternative Medicine*, Christian Science Monitor (Boston, MA) (Mar. 28, 1996), at 20.

entrenched hostility to new treatments."[171] These proponents attack the increasing influence of the drug industry over the FDA, particularly through the use of user fees that pharmaceutical companies must pay to file new drug applications with the FDA under the Prescription Drug User Fee Act.[172] Other advocates focus on the FDA's "unnecessary and unwanted" interference in the personal health decisions of Americans. House Representative Dan Burton voiced this objection succinctly during a congressional hearing on alternative medicines, asserting, "Americans do not need the government, in this case the FDA, telling them how to treat their illnesses, especially when state-level protections are already in place to safeguard the public from those who might do harm to patients."[173] Moreover, Burton characterized the FDA's process for patient access to unapproved and experimental treatments as "a good example of the nature of the federal government to micromanage the lives of individual Americans, often unnecessarily."[174]

On the other side of the debate, critics respond by arguing that the AMTA would pose serious risks to consumers who will have access to possibly dangerous treatments and therapies. Thus, critics remain steadfast in their belief that all drugs should be required to go through the FDA's approval process before consumers can gain access to them.[175] During a series of congressional hearings in 1998 addressing clinical trials and patient safety, one FDA insider aptly voiced his concerns with AMTA, warning that the proposed legislation "would lower the standard for safety, thus putting patients at unnecessary risk," and would have at least three unintended and severe consequences: (1) the bill would reduce, or wholly eliminate, the critical pro-

[171] Wagner, *supra* note 141, at 8.

[172] *See id.* Those opposed to the imposition of user fees claim that industry funding of the FDA through such fees undermines the credibility and independence of the FDA. They argue that the imposition of user fees has made the FDA too close to the pharmaceutical industry, which has pressured the FDA to approve drugs too quickly, and that the industry is essentially "buying" drug approvals, and thus compromising the entire review and approval process.

[173] *Alternative Medicines: Hearing Before the House Comm. on Government Reform and Oversight*, 105th Cong. (Feb. 12, 1998) (statement of Dan L. Burton, Chairman, House Comm. on Government Reform and Oversight).

[174] *Id.* Burton explained that access to unapproved drugs and therapies in the development process generally requires participation in a clinical trial. However, if a patient does not meet the strict guidelines established for a trial, his or her access may be entirely "shut off, with no appeal," with the FDA making the "life or death decision as to whether a patient can have the treatment under a special exception."

[175] *See* Wagner, *supra* note 141, at 8.

cess of scientific data collection necessary to establish the safety and effectiveness of a product; (2) the bill would diminish any assurance of appropriate informed consent and human subject protection; and (3) the bill would make it extremely difficult to protect consumers against health fraud.[176] Moreover, this AMTA critic stressed the FDA's efforts to balance two compelling factors: the controlled study necessary to identify treatments that may improve patients' health, and the desire of terminally and seriously ill patients, with no effective options available, to have the earliest access to unapproved and experimental drugs and treatments that could be the best therapy for them.[177] Emphasizing the former factor, another critic concerned with AMTA's potential implications offered this plea for more rigorous drug testing:

> Without extensive drug testing we just can't tell which hand holds a dangerous poison, and which conceals the life saving drug. Without proper testing even a potentially life saving treatment may be harmful if given in the wrong dose, or to the wrong patients. I want people to have choices too. But they should have real choices, involving scientific data about how much harm and good various treatment alternatives can be expected to achieve. We have a [sic] only one proven solution. We need public policies to promote more drug testing, not still more new loopholes that could endanger the health and safety of millions of people.[178]

After several unsuccessful attempts to pass AMTA in Congress, it seems clear thus far that the majority of congressman and senators believe that the risks outweigh the potential benefits in permitting patients the freedom to access the medical treatments of their choice.[179] But while critics remain staunchly opposed, AMTA advocates will undoubtedly continue to focus their energies on achieving its passage, most likely invoking emotional pleas by terminally ill patients and their families who view AMTA as a giant step toward increased access to treatments that offer one last hope for survival.[180] For example, testifying at yet another congressional hearing addressing access to experimental and alternative treatments, one impassioned

[176] *Clinical Trials and Patient Safety: Hearing Before the House Comm. on Government Reform and Oversight*, 105 Cong. (Apr. 22, 1998) (testimony of Michael A. Friedman, M.D., Lead Deputy Commissioner, Food and Drug Administration).

[177] *Id.* (adding that the FDA's primary concern with the AMTA is that it would weaken the protections of the FDCA, and, specifically, that it would limit the FDA's ability to ensure "reasonable safety, effectiveness, informed consent, and scientific data collection").

[179] *See* Horwin, *supra* note 7, at 201.

[180] *See, e.g., Legislative Priorities for the 107th Congress: Access to Medical Treatment Act – HR 1964/S1378*, American Association for Health Freedom, at http://healthfreedom.net (last visited Mar. 31, 2003).

supporter of expanded access recounted her battle against a fatal cancer and the successful, yet experimental and unapproved, treatment she received from Dr. Burzynski only after several physicians had issued her a death sentence and absolutely no hope under conventional therapies. Speaking from personal experience, she poignantly questioned the FDA's policy toward experimental drug approval for the terminally ill, asking the committee convened that day, "Who gave FDA the right to play God? Was it the intent of Congress to give FDA the kind of power it exercises over life and death with no accountability? By denying terminally ill cancer patients access to antineoplastons, this agency literally decides 'who shall live and who shall die."'[181] Whether one is a proponent or a critic of expanding access to experimental drugs and therapies for terminally ill patients, there is one issue of concern upon which all participants in the debate can agree: there must be adequate safeguards in place for the protection of subjects who take part in clinical research and trials. In the next section I will explore the federal regulations governing research involving human subjects, and, specifically, research involving certain "vulnerable" classes, as well as the application of the current regulatory framework to one class in particular: the terminally ill.

VI. The Terminally Ill as a "Vulnerable" Population?

The regulations governing clinical research, in addition to the provisions applicable to all research, provide additional safeguards for certain "vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons."[182] Citing the same "special" populations, the regulations additionally provide that "[w]hen some or all of the subjects, . . . , are likely to be vulnerable to coercion or undue influence," the IRB involved must ensure that "addi-

[181] *Alternative Medicines: Hearing Before the House Comm. on Government Reform and Oversight*, 105th Cong. (Feb. 4, 1998) (statement of Mary Jo Siegel).
[182] 21 C.F.R. § 56.111(a)(3).

tional safeguards have been included in the study to protect the rights and welfare of these subjects."[183] The additional protections available to these subjects can generally be separated into three types: (1) structural provisions addressing how IRBs will be comprised and who will make decisions; (2) substantive provisions governing the types of research that will be allowed; and (3) procedural provisions to guarantee that no research is done without the voluntary and informed consent of subjects.[184]

In order to ensure that members of the IRBs adequately represent the interests of certain "vulnerable" subjects, the regulations provide that "[i]f an IRB regularly reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, or handicapped or mentally disabled persons, consideration shall be given to the inclusion of one or more individuals who are knowledgeable about and experienced in working with those subjects."[185] In addition, the types of research that are approved by IRBs will depend on the presence of vulnerable populations. Similarly, the presence of vulnerable subjects signals a requirement of heightened scrutiny to guarantee the informed consent before research may begin, as well as throughout the research process.[186]

Although the regulations use the term "vulnerable" to identify subjects who may need additional protections, they do not explicitly define the term. Rather than providing specific criteria with which to define "vulnerable" populations, the regulations instead offer examples of the types of subjects who may be considered vulnerable.[187] However, it is possible to divide into two groups the types of "vulnerability" to which the regulations seem to apply: vulnerability due to *circumstances* and vulnerability due to *cognitive defects*.[188] For

[183] *Id.* § 56.111(b).
[184] *See* Addicott, *supra* note 19, at 485.
[185] 21 C.F.R. § 56.107(a).
[186] *See id.* § 56.111; *see also* Addicott, *supra* note 19, at 486-88 (describing some of the "general provisions designed to protect any human subject who may be vulnerable to coercion or undue influence").
[187] *See* Addicott, *supra* note 19, at 486-87 (noting that even when the current regulations were first proposed after an extensive review of the then-existing regulatory scheme, neither the Department of Health and Human Services nor the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research provided any specific guidance or criteria with which to define vulnerable populations).
[188] *See* Jessica W. Berg et al., Informed Consent: Legal Theory and Clinical Practice 266-67 (2d ed., Oxford University Press, 2001).

example, the former category includes prisoners, pregnant women, and economically disadvantaged persons, while the latter category encompasses children and mentally disadvantaged persons.[189] While such classifications may plausibly be made, the categories may frequently overlap and any lines drawn undoubtedly will become blurred.[190]

While the regulations provide explicit protections for certain "vulnerable" populations, terminally ill subjects must seek any additional safeguards in the general provisions applicable to all "vulnerable" populations, and whether and to what extent these rules apply is open to question.[191] Those who oppose the inclusion of terminally ill subjects as a "vulnerable" population emphasize the fact that the relevant regulatory framework and the official government documents neither list nor discuss the terminally ill in such terms. Moreover, they claim that characterizing the terminally ill as vulnerable would further stigmatize those already suffering from loss of personal dignity and autonomy.[192]

Responding to the above arguments against the inclusion of the terminally ill as a "vulnerable" population in the regulations, one IRB member notes that "[m]any research subjects are vulnerable simply because they are ill," and adds that the vulnerability of ill patients "depends on the gravity of their illness and their level of desperation."[193] Similarly, advocates for this position have continued to point to characteristics shared by the terminally ill and "vulnerable" populations such as prisoners and children. For instance, Jay Katz asserts, "[l]ike children, [terminally ill patients'] ability to make informed decisions is often either impaired or disregarded, and, like soldiers and prisoners, they are . . . 'captives' of their disease, their physicians and

[189] *See id.* at 266.
[190] *See id.* at 266-67 (citing as an example of overlapping categories a 1999 case that involved psychiatric research on teenage prison inmates).
[191] *See* Addicott, *supra* note 19, at 492 (asserting that the terminally ill, unlike children, pregnant women, fetuses, and prisoners, have no dedicated regulations to guarantee that they are not victimized in unethical research).
[192] *See id.* at 492-93 (noting, however, that to conclude that their judgment is impaired by these factors would demean them as well as discredit reality).
[193] *See* Moore, *supra* note 22, at 565-66.

hospital, and their enforced isolation."[194] Likewise, a former editor of the New England Journal of Medicine expressed well the source of the vulnerability of terminally ill subjects when he noted that "[t]he thumb screws of coercion are most relentlessly applied . . . [to] the most used and useful of all experimental subjects, the patient with disease."[195]

While the regulations fail to define the term "vulnerable," leaving the category open-ended allows IRBs to assess the vulnerability of the subjects involved and to determine whether or not the regulations are applicable. One commentator notes that the fact that the examples of vulnerable populations provided in the regulations vary from provision to provision suggests that the types of subjects listed were "meant to be illustrative, rather than denominative."[196] Indeed, the regulations refer to vulnerable subjects in several provisions and offer a slightly different image of who these subjects are in each provision.[197] For example, the section addressing the rules of IRB membership lists as vulnerable categories of subjects "children, prisoners, pregnant women, or handicapped or mentally disabled persons."[198] Meanwhile, the section setting forth the criteria for IRB approval of research lists as vulnerable populations "children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons."[199] Lastly, the regulations provide explicit guidelines and additional safeguards for research with three specific categories of subjects: pregnant women and fetuses, prisoners, and children.[200]

In addition, while formal government publications lack explicit references to additional protections for termi-

[194] Jay Katz, Experimentation with Human Beings 1053 (1972); *see* Joni N. Gray et al., Ethical and Legal Issues in AIDS Research 52 (1995) (stating that "[t]o be sure, research participants with fatal illnesses are vulnerable in many ways").
[195] Franz J. Ingelfinger, *Informed (but Uneducated) Consent*, 287 New Eng. J. Med. 465, 466 (1972).
[196] Addicott, *supra* note 19, at 493.
[197] *See* Moore, *supra* note 22, at 568 (adding that the sources of these groups' vulnerabilities, including institutionalization and diminished decision-making capacity, vary).
[198] 21 C.F.R. § 56.107(a).
[199] *Id.* § 56.111(a)(3).
[200] 45 C.F.R. §§ 46.201-46.211, 46.301-46.306, 46.401-46.409.

nally ill subjects,[201] there are indications in early publications that regulators were cognizant of the special concerns related to research with this population. The *Belmont Report*, for example, specifically mentioned the terminally ill as a potentially "incompetent" group, providing that "[e]ach class of subjects that one might consider as incompetent (*e.g.*, infants and young children, mentally disabled patients, the *terminally ill* and the comatose) should be considered on its own terms."[202]

As a result, many commentators claim that the terminally ill do in fact fall into the "vulnerable" population category under the regulations, and point to a number of features shared by the terminally ill with the vulnerable populations explicitly mentioned in the provisions. Such characteristics, in turn, make terminally ill patients who may be considering whether to take part in clinical research extremely vulnerable to coercion, exploitation, and undue influence.[203] As one commentator noted in his discussion on patients' perceptions of illness and suffering, "[i]t is natural for a sick person to perceive that he or she has become isolated from the rest of the community, to feel vulnerable and mortal."[204] This feeling of isolation and estrangement from relationships with others leads the terminal patient to question his or her own capacity to act autonomously with regard to others. In this way, recognizing that illness is a source of diminished autonomy, terminal patients may be more willing to entrust their doctors with significant decision-making authority, believing that they themselves are incapable of rational, independent decision-making.[205]

While the regulations provide specific guidelines for certain "special" populations, including pregnant women

[201] *See* Addicott, *supra* note 19, at 492-93; *see generally, e.g.*, President's Commission for the Study of Ethical Problems in Medicine and Biomedical Research, *Implementing Human Research Regulations: The Adequacy and Uniformity of Federal Rules and of Their Implementation* (1983); Food and Drug Administration, *Current Issues in Human Subject Protection* (1996).

[202] *Belmont Report* at 13 (emphasis added).

[203] *See* Addicott, *supra* note 19, at 496.

[204] Robert M. Timko, Clinical Ethics: Due Care and the Principle of Nonmaleficence 85 (University Press of America, Inc., 2001).

[205] *See id.* at 86 (emphasizing the "anomie, depression, and sense of estrangement from one's life-plan that occur with the onset and development of illness," and which lead to a loss of autonomy); *see also* Addicott, *supra* note 19, at 496 (noting that the psychological response of terminal patients after diagnosis may be exacerbated by the physiological symptoms of the illness, and patients may be reluctant to question the authority of their doctors).

and fetuses, prisoners, and children, the common thread that seems to run through these groups is the concern that their vulnerability to coercive pressures and undue influence limits, if not wholly eradicates, their ability to give truly voluntary consent. The terminally ill share characteristics with these groups that render them more susceptible to coercion and outside influence, which should call into serious question the sufficiency of the informed consent model as applied to research with terminally ill subjects. Given these concerns, two elements of informed consent must be considered in order to understand the protections accorded to vulnerable populations: information and voluntariness.[206] As applied to children or the mentally handicapped, for example, the issue is whether they can adequately understand the information provided in order to rationally decide whether to participate in the research. As applied to prisoners, on the other hand, the question is whether their consent can in fact be given voluntarily due to the inherently confining and coercive nature of prison.[207] These two concerns, in turn, may both be present in the case of research with terminally ill subjects. Like children or the mentally handicapped, terminally ill patients are often considered incapable of making rational, informed decisions; and like prisoners, they are often seen as not "really" free, but instead as "captive" to their illness and the coercive circumstances in which they find themselves.[208] Viewed in these terms, such analogies suggest that similar procedural protections as those provided to children and prisoners should also be available to the terminally ill.

In order to fully explore the vulnerabilities shared by terminally ill patients and the "vulnerable" populations explicitly mentioned in the regulations, it may be useful to consider more closely the reality experienced by terminally ill individuals. One writer has suggested that cancer and AIDS have perhaps become linked as

[206] *See* Addicott, *supra* note 19, at 485.
[207] *See id.* at 485-86.
[208] *See* Garnett, *supra* note 87, at 482 (expressing concerns that terminally ill patients "might submit to quackery in a hopeless and desperate attempt to beat the inevitable," or "out of misplaced or entirely genuine altruism," and the fear that the "ritual of informed consent" is often viewed as a mere formality rather than "an opportunity for choice or a vehicle for empowerment").

the two most feared ways to die, and notes that cancer, like AIDS, "leads to a hard death," adding that "[t]he most terrifying illnesses are those perceived not just as lethal but as dehumanizing, literally so."[209] The "universal fears" of cancer patients have been termed "the six Ds: death, dependency, disfigurement, disability interfering with normal life functions, disruption of relationships, and discomfort or pain resulting from the disease itself."[210] Moreover, the prevalence of psychiatric disorders in terminal cancer patients has been well documented. In one study in which 215 cancer patients were selected at random, forty-seven percent of the patients suffered from psychiatric disorders.[211]

In addition to the psychological symptoms of illness, the physiological symptoms may further impair the cognitive function and mental status of the terminal patient. For instance, with cancer patients, "fatigue, recovery from surgery and radiation, [and] toxicity from drugs (including antibiotics and pain medicine) may all alter thinking ability, dampening the sharpness, rapidity, and productivity of the [patient's] thought processes."[212] Frequent hospitalization, not uncommon for terminally ill patients, may also contribute to their diminishing sense of control over their environment and decision-making ability. Similar to prisoners, a "vulnerable" population under the regulations, hospitalized patients become entirely dependent on the institution's staff and undoubtedly develop a sense of helplessness and apathy with respect to their situation and any treatment decisions that must be made.[213] The hopelessness that often blurs the terminal cancer patient's cognitive abilities likely strikes at the heart of the informed consent model. As one commentator notes, terminally ill patients who become depressed may be more likely to consent to take part in research

[209] Susan Sontag, Illness as Metaphor and AIDS and its Metaphors 126 (1990).
[210] Addicott, *supra* note 19, at 499.
[211] *See id.* at 499-500 (noting that of the patients with disorders, sixty-eight percent had "adjustment disorder with depressed, anxious, or mixed mood; 13% had major depression; 8% had an organic mental disorder; 7% had a personality disorder; and 4% had anxiety disorder") (footnotes omitted).
[212] *See id.* at 500 (quoting Stephen P. Hersh, *Death From The Cancers*, *in* Living With Grief When Illness is Prolonged 100 (Kenneth J. Doka & Joyce Davidson eds., 1998)).
[213] *See id.* at 501.

because the concept of risk is meaningless to them. In particular, "they become malleable and vulnerable to coercion precisely because they do not care whether they live or die."[214]

As this utter hopelessness leads many terminally ill patients to latch on to the mantra that they have "nothing to lose," it is not surprising that they frequently ignore the potential risks and blindly consent to participate in research due to a phenomenon known as "therapeutic misconception." In particular, desperate patients often fail to understand that they are taking part in research that may not be intended primarily for their benefit, perhaps completely unaware that the research is meant to study toxicity levels of drugs and dose schedules, not to cure their illnesses.[215] One commentator focuses on the "self-deception inherent in seeing experimentation as treatment, especially in terminally ill cancer patients" who participate in Phase I drug studies with anticancer agents.[216] While researchers at the National Cancer Institute refer to such studies as "potentially therapeutic," FDA regulations provide that Phase I studies are intended to have no therapeutic content, but rather are to determine "toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range."[217] As a result, Phase I trials are transformed into "experimental therapy," eradicating altogether the distinction between experimentation and therapy.[218] Not surprisingly, a number of commentators have criticized the conflation of research and treatment, the doubling of researchers and physicians, subjects and patients, and have little, if any, regard for the distinction, exemplified in the Helsinki Declaration, between therapeutic and

[214] *Id.* at 502-03 (asserting that terminally ill patients may, in their desperation, fail to even attempt to evaluate the risks and benefits of experimental research, "having already made up their minds to try any available treatment).

[215] *See id.* at 503-04. Addicott describes one study in which investigators examined the motivation and understanding of patients participating in Phase I cancer trials. The results of the study showed that patients were motivated to take part in the research almost exclusively because of a belief that it would make them better. *See generally* Christopher K. Daugherty et al., *Perceptions of Cancer Patients and Their Physicians Involved in Phase I Trials*, 13 J. Clin. Oncol. 1062-72 (1995).

[216] Annas, *supra* note 83, at 310.

[217] *Id.* at 310-311 (quoting *The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research*, Protecting Human Subjects 65 (1981)).

[218] *Id.* at 311 (adding that roughly 94% of researchers admit that adult patients enroll in Phase I studies largely for the possible medical benefit); *see* Eric Kodish et al., *Ethical Issues in Phase I Oncology Research: A Comparison of Investigators and Institutional Review Board Chairpersons*, 10 J. Clinical Oncology 1810, 1812 (1992); Mortimer B. Lipsett, *On the Nature and Ethics of Phase I Clinical Trials of Cancer Chemotherapies*, 248 JAMA 941, 941-42 (1982).

non-therapeutic research.[219]

VII. Terminal Patients Speak for Themselves: Advocates for a "Right of Access"

Although the vulnerabilities shared by the terminally ill and certain groups explicitly mentioned in the regulations may support the calls for additional safeguards for terminally ill subjects who choose to participate in research trials, perhaps one of the groups that most vigorously opposes regulatory restrictions is the one they are intended to protect: the terminally ill. Not only are terminally ill patients, who often view experimental therapies as their last chance to beat the inevitable, generally willing to take part in research, but they often compete for the chance to do so.[220] Desperately ill cancer patients, for example, may believe that it is in their interest to gain access to experimental treatments, and, indeed, in some cases it is rational to want to try an unapproved drug when, compared with the alternative, the potential benefits justify the risks involved.[221]

Advocates for expanded access to experimental treatments for the terminally ill claim that the freedom of each patient to choose his or her weapons of choice is critical to each patient's personal dignity, autonomy, and control over his or her body.[222] The calls for a comprehensive "right of access" to experimental therapies raise two distinct issues: (1) whether the current FDCA regulations should apply without modification to the terminally or seriously ill, and (2) whether constitutionally protected liberty or privacy interests exist to

[219] *See* Annas, *supra* note 83, at 310-312; *see also* Robert J. Levine, Ethics and Regulation of Clinical Research 8-10 (2d ed., Urban & Schwarzenberg, 1986).

[220] *See* Addicott, *supra* note 19, at 493-94.

[221] *See* Robert M. Veatch, *From Nuremberg Through the 1990s: The Priority of Autonomy*, *in* The Ethics of Research Involving Human Subjects: Facing the 21st Century 55-56 (Harold Y. Vanderpool ed., 1996) (posing the question whether a priority for autonomy gives terminally ill individuals a right of access to experimental agents, not only over-the-counter agents such as aspirin, but also restricted drugs controlled by investigational new drug research).

[222] *See, e.g.,* Perrin, *supra* note 39, at 121 (noting that when the desperately ill patient exhausts all available conventional therapies cannot gain access to an experimental or investigational therapy, his or her plight is clear: the "patient is destined to suffer or die").

protect the right to choose unapproved or experimental treatments.[223] As Marshall's opinion in *Rutherford* illustrates, the FDCA makes no exception for experimental or unapproved drugs used to treat the terminally ill, and thus the safety and efficacy requirements are applicable to such patients without exemption or modification.[224]

With respect to the second issue, whether a constitutionally protected privacy interest encompasses the right of access to unapproved or experimental treatments, some advocates have embraced the claim that the right to privacy is fundamental and "protects the individual from unwarranted governmental intrusions into certain personal decisions ... that have some relation to child rearing and education, contraception, marriage, family relationships and procreation."[225] Specifically, advocates for this reading to support a right to experimental therapies assert that the right to privacy should include the personal therapeutic choices of the seriously or terminally ill for three reasons: (1) the freedom to care for one's health is of a highly personal nature that should ultimately rest with the individual; (2) a regulation denying access to unapproved drugs severely interferes with the lifestyle of the terminally ill patient; and (3) only the terminally ill person is affected by the decision to choose experimental and unapproved drugs.[226]

In addition to expanding the privacy argument to encompass the right of access, some commentators have pointed to the Fifth and Fourteenth Amendments to the Constitution to support their claim that the freedom of each citizen to choose a treatment of choice in fighting a terminal illness is a basic liberty to which they cannot be deprived. In the words of one commentator, the U.S. government, "through the FDA, deprives [terminally ill patients] of their interests in life and liberty by precluding them from obtaining life-extending drugs or by coercing them to participate in placebo studies."[227] Embracing the Fifth and Fourteenth Amend-

[223] *See id.* at 123.
[224] *See* 442 U.S. 544.
[225] Scott H. Power, *The Right of Privacy in Choosing Medical Treatment: Should Terminally Ill Persons Have Access to Drugs Not Yet Approved by the Food and Drug Administration?*, 20 J. Marshall L. Rev. 693, 703-04 (1990) (footnotes omitted).
[226] *Id.* at 705.
[227] Bret L. Lansdale, *A Procedural Due Process Attack on FDA Regulations: Getting New Drugs to People With AIDS*, 18 Hastings Const. L.Q. 417, 419 (1991); *see* Perrin, *supra* note 39, at 151 (citing as support for advocate's calls for a "right to

ments' due process guarantees, courts should therefore acknowledge a terminally ill patient's "due process right of access to new, potentially life-extending drugs."[228] Following that line of reasoning, another proponent of the "right of access" asserts that "[i]t would be illogical in the extreme to hold, on the one hand, that a person has a constitutional right to refuse treatment needed to sustain life (*Cruzan v. Director, Missouri Dep't of Health*, 497 U.S. 261 (1990)) and, on the other, that a person has no constitutional right to receive a treatment that may sustain life."[229] Seizing upon language from Justice O'Connor's concurring opinion in *Cruzan*, where the Court held that the Due Process Clause does not require the state to repose judgment on matters concerning the right to refuse treatment with anyone but the patient herself,[230] one commentator finds support in the analogy between the terminally ill patient who chooses to *refuse* life-saving treatment and the terminally ill patient who wishes to *receive* a treatment that may sustain life, offering as support O'Connor's powerful words in that opinion: "A seriously ill or dying patient whose wishes are not honored may feel a captive of the machinery required for life-sustaining measures or other medical interventions. Such forced treatment may burden that individual's liberty interests as much as any state coercion."[231]

Finally, the calls for a comprehensive "right of access" have embraced autonomy as an "absolute priority," a liberty right enjoyed both by researchers and patients, which must be respected.[232] Speaking to this proposition, one commentator asserts, "[i]f investigators were willing to cooperate with subjects who had rational, subjective preferences for [investigational new drug] agents, then their autonomy as well as that of the subjects would support their providing the agents to them."[233] Moreover, labeling certain patients, including

access" the Fifth Amendment's guarantee that no person shall be deprived of life, liberty, or property without due process of law).

[228] Lansdale, *supra* note 227, at 419.

[229] *Government v. The Terminally Ill*, Letter from Jonathan W. Emord, Attorney, Emord & Associates, P.C., Counsel to the Burzynski Patient Organization, *in* Regulation, The Cato Review of Business and Government, Vol. 20, No. 2 (1997), *available at* http://www.cato.org/pubs/regulation/reg20n2-let.html (hereinafter "Letter from Jonathan W. Emord") (asserting that "[w]hen the state denies a terminally ill patient freedom to elect a course of treatment, deprives that patient of bodily integrity, robs that patient of control over his or her person, and effectively dictates one therapy, there is little left of liberty").

[230] *See Cruzan v. Director, Missouri Dep't of Health*, 497 U.S. 261 (1990).

[231] *See* Letter from Jonathan W. Emord, *supra* note 229 (quoting O'Connor's concurring opinion in *Cruzan*, 497 U.S. at 288).

[232] *See* Veatch, *supra* note 221, at 56-57.

[233] *Id.* at 56.

metastatic cancer patients, as "among the worst-off members of society," this advocate for access declares that "these patients have an entitlement-right claim to access to experimental agents," and, furthermore, "[i]f they are plausible among the least well-off, they have claims of justice that may override the autonomy of the investigators."[234] Thus, in such circumstances, the principle of autonomy effectively disappears and the investigators' "moral duty to help the least well-off gain access to experimental treatments" takes center stage in the patient's fight to live.[235] It is *justice*, and not mere *social beneficence*, that guides this view; in sum, "[i]t is what we *owe* to the least well-off among us."[236]

VIII. Conclusion

The FDA, through the development of the current regulatory regime and ethical guidelines, has attempted to strike an appropriate balance between two compelling values: promoting access to new, experimental and potentially life-saving therapies for the terminally ill, and protecting this unique class of subjects from research abuse and coercion. Advocates for increased access may ask, "[w]hy should terminal patients, who according to orthodox medicine will die, be prevented from accessing non-orthodox therapies through their medical doctors?"[237] In particular, if a patient understands that the treatment has not been approved by the FDA and that the risks and benefits cannot be fully identified or quantified, and nonetheless gives his or her informed consent to participate in the research, why should he or she be prevented from making that choice?[238]

[234] *Id.* at 56-57.
[235] *Id.* at 57.
[236] *Id.* (emphasis added).
[237] Horwin, *supra* note 7, at 222.
[238] *Id.* at 222-23.

On the other side of the spectrum, those concerned with the particular vulnerabilities that often characterize the terminally ill urge that more stringent regulatory protections should be in place for such patients, who frequently are individuals "desperate for a cure and [who] often suffer from depression, anxiety, or other psychological disorders that may be exacerbated by the physiological symptoms of their illnesses."[239] As a result, proponents of heightened standards for research involving the terminally ill have proposed a number of additional safeguards and regulatory reforms to better ensure the safety and protection of terminally ill subjects, including an explicit recognition in the regulations of the terminally ill as a "vulnerable" population, which at a minimum would alert researchers and IRBs "to familiarize themselves with the unique difficulties their subjects face," as well as a requirement in the regulations that psychological evaluations and subject advocates are employed to protect the integrity of the informed consent process.[240]

While rational individuals will come to different conclusions as to how the balance should be struck, perhaps one primary benefit to be gained from engaging in the debate is that through such discussions we will undoubtedly become more aware of the diverse interests and values at stake, and therefore better able to design research programs to accommodate these interests. The current regulatory regime, including recent federal initiatives and proposed reforms, seems to emphasize three essential values: protecting vulnerable research subjects, promoting access to new and much-needed therapies, and satisfying the "social need for research to validate new needed therapies."[241] However, with the ebb and flow of scientific and medical advances, as well as the inevitable setbacks, history has demonstrated that policy shifts and regulatory reforms must adapt to the changing times. For example, citing the "proliferation of new and deadly diseases,"

[239] Addicott, *supra* note 19, at 524.

[240] *See id.* at 524 (adding to the list of proposed regulatory reforms a requirement that IRBs that work with the terminally ill have at least one member who is a representative of the terminally ill, a requirement that researchers who work with terminally ill patients undergo psychological training, and a mandate providing that research generally should involve the terminally ill only if it is intended to benefit them).

[241] Brody, *supra* note 6, at 45.

one commentator notes that "*[r]esearch* over the past decade has shifted in the public's mind from an enterprise in which subjects need protection to one in which subjects demand access."[242]

Nevertheless, it seems clear from the constant back and forth wrangling over the potential benefits and risks of clinical research and access to experimental therapies that "there are [still] serious deficiencies in the current system for the protection of the rights and interests of human subjects."[243] As depicted in the preceding pages, the interplay between Congress, the courts, the medical and scientific communities, as well as terminally ill patients themselves, has continued to play an essential role in the debates surrounding clinical research involving human subjects. Perhaps only by maintaining a constant dialogue between these key participants will terminally ill patients get the benefits they deserve from clinical research, enjoying the protections provided under the regulations while at the same time gaining access to potentially life-saving new therapies – both goals, although seemingly irreconcilable at times, tailored to respect the dignity and autonomy of those individuals who stand at the heart of the debate, battling their illnesses armed with promising new weapons as well as appropriate shields of protection.

[242] Berg et al., *supra* note 188, at 273.
[243] *Id.* (citation omitted).

Epilogue and Dedication

This paper is dedicated to a very dear friend of mine who is currently battling ovarian cancer and who recently began a twelve-week Phase II clinical trial at a major medical institution. When I first began researching the topic for this paper, my friend had just enrolled in the trial and was filled with extreme hope that the experimental treatment would be successful in beating the insidious disease. Sadly, painfully aware that her cancer was not responding to the treatment, my friend dropped out of the trial after just six weeks and returned once again to try more conventional chemotherapy treatments instead. As I researched the federal regulations and policies governing clinical research involving terminally ill patients, and as I explored the emotionally-charged and dire circumstances in which many such individuals find themselves, I remained constantly mindful of the experience of my friend, as she continues to search for an effective treatment to beat the disease – a final hope in her painful battle against cancer.