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## Throwing Dirt on Doctor Frankenstein's Grave: Access to Experimental Treatments at the End of Life

Michael J. Malinowski

Louisiana State University Law Center, [mjmalin@lsu.edu](mailto:mjmalin@lsu.edu)

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# **Throwing Dirt on Doctor Frankenstein’s Grave: Access to Experimental Treatments at the End of Life**

**Michael J. Malinowski\***

## **Abstract**

All U.S. federal research funding triggers regulations to protect human subjects known as the Common Rule, a collaborative government effort that spans seventeen federal agencies. The Department of Health and Human Services has been in the process of re-evaluating the Common Rule comprehensively after decades of application and in response to the jolting advancement of biopharmaceutical science. The Common Rule designates specific groups as “vulnerable populations”—pregnant women, fetuses, children, prisoners, and those with serious mental comprehension challenges—and imposes heightened protections of them. This article addresses a question at the cornerstone of regulations to protect human subjects as biopharmaceutical research and development increasingly commingles clinical research and clinical care—as patients and physicians routinely reach into the drug development pipeline for treatment options. Given the vulnerabilities of those who confront end-of-life decision making, should the regulatory standard be raised to more effectively protect the terminally ill from additional suffering and the loss of quality time with family and friends, and to increase recognition of the opportunity to die with priority placed on comfort care and dignity? Alternatively, where death is the only existing option under standard of care, should the regulations be relaxed to promote access to experimental treatment alternatives? What importance should be placed on the overall advancement of biopharmaceutical research and development (R&D) in addressing these human health issues? This article proposes modifying the Common Rule to enhance human subject protection of the terminally ill, which the U.S. standard of care generally recognizes as a diagnosis of life expectancy of six months or less.

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\* Ernest R. and Iris M. Eldred Professor of Law, Paul M. Herbert Law Center, Louisiana State University; JD, Yale Law School; BA, summa cum laude, Tufts University. This article was improved immensely through the excellent research contributions of Andrea Bariant, the administrative input of April Smith, and the opportunity to address the core Food and Drug Administration issues as the B. F. Skinner Keynote presenter at the 39<sup>th</sup> Annual Applied Behavior Analysis International (ABAI) Convention in May 2013. Appreciation also is due to Professors Bartha Maria Knoppers and Mark Rothstein for taking the time to review an earlier draft of this article and their encouragement and support. This article is dedicated to those in my life who have endured terminal illness, their family members, health care providers, close friends, and other supporters.

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"It hath been often said that it is not death, but dying, which is terrible."

Henry Fielding<sup>1</sup>

## I. Introduction

Joe,<sup>2</sup> the self-employed owner of a small construction and demolition company and the father of two young children, one seven and the other nine, was just thirty-seven when he was diagnosed with extremely advanced hairy cell leukemia in 1973—a death sentence at the time.<sup>3</sup> When finally diagnosed definitively after repeated and often lengthy hospitalizations, gangrene had inflated his spleen, normally about the size of a tennis ball, to the equivalent of a football.

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<sup>1</sup> HENRY FIELDING, AMELIA 125 (2012).

<sup>2</sup> Joe was my father; his story as relayed is factual. I began writing this article several times in the past, but it has taken more than twenty years of work in health law for me to bring it to fruition.

<sup>3</sup> See Rose Kivi, *Hairy Cell Leukemia*, (Aug. 7, 2012), available at <http://ask.healthline.com/health/hairy-cell-leukemia> (last visited Mar. 20, 2013). Hairy cell leukemia (HCL) is a rare type of typically slow-growth blood and bone marrow cancer that produces a surplus of abnormal B-lymphocyte cells, a type of white blood cell that produce antibodies that fight infections. *Id.* These abnormal cells impede healthy ones, resulting in a low white blood cell count and a weakened immunity system. The production of these abnormal cells also can decrease red blood cells and platelets, and impede T-lymphocytes (“T-cells”) that help healthy B-lymphocytes fight infection. *Id.* According to the National Institutes of Health (NIH), as of 2012, treatments now allow patients with the disease to routinely live 10 years or longer after diagnosis. *Id.* See also Harvey M. Golomb, *Hairy Cell Leukemia: Treatment Successes in the Past 25 Years*, 26 J.CLINICAL ONCOLOGY 2607-2609 (2008), available at <http://jco.ascopubs.org/content/26/16/2607.short> (last visited Feb. 20, 2013). This improvement in treatment success is largely attributable to the outcome of the study Joe participated in, sponsored by Biogen Inc., which resulted in the development of Interferon Alpha. See Biogen Idec. Official Site, available at <http://www.biogenidec.com/> (last visited Mar. 30, 2013). The same pioneering science led to the development of AVONEX, a groundbreaking treatment for multiple sclerosis introduced to the market in 1996. See *id.* at [http://www.biogenidec-international.com/our\\_history.aspx?ID=11766](http://www.biogenidec-international.com/our_history.aspx?ID=11766) (last visited Jan. 14, 2013). Incidentally, John Moore, the plaintiff in the landmark intellectual property and bioethics case *Moore v. Regents of the University of California*, was diagnosed with hairy cell leukemia three years after Joe and contributed to research as well, though without his consent. See generally 51 Cal. 3d 120, 271 Cal. Rptr. 146; 793 P.2d 479 (1990).

Although uninsured, Joe had the good fortune of living within thirty-five miles of the Boston medical mecca, and a Harvard-affiliated doctor took over his care and put him on an experimental protocol. Overall, the treatment and related care gave Joe fourteen years of productive life—albeit with constant monitoring of his white blood cell counts (T-cells in particular), ingestion of potent medications, painful bone marrow tests, and frequent hospitalizations to fight infections and to raise his white blood cell levels.

However, in 1987, fourteen years after his spleen was removed, Joe’s health began to deteriorate rapidly. A growth behind his left ear was diagnosed as malignant melanoma. Although the hairy cell leukemia generally remained in remission, surgery to remove the melanoma was followed by a diagnosis of lymphoma—cancer that begins in the cells of the immune system.<sup>4</sup> Within months, Joe noticed a lump behind the same ear, which turned out to be an aggressive, external squamous cell tumor.<sup>5</sup> The tumor grew rapidly and engulfed his face and neck, devouring his flesh and literally opening his throat, which required painful cleaning and re-bandaging several times daily to combat infection.

Still, Joe was just fifty-three years old, with a strong heart and lungs and a muscular physique that reflected working heavy construction from the age of fourteen. Although he never completed the eighth grade (his reading comprehension was more realistically on a sixth-grade level), one of his sons had just entered Yale Law School, and he desperately wanted to see his youngest child, his fifteen-year-old son Scott, graduate from high school. So Joe, in spite of his prognosis, aggressively sought and received more experimental treatments—from drugs to a series of surgeries. The drugs worsened his health immediately; the side effects were horrific. The morphine, administered through a pump that enabled family to raise dosages to quell his coughing, attributable to his inability to swallow and made Joe delusional and paranoid. The surgeries paralyzed the right half of his face, to the point where he could not blink his right eye. His face was bandaged in stereotypical mummy fashion, and that entire side of his face operated on drooped. He had to hold a towel to his face constantly to catch drool. The spread of the squamous cell tumor required that Joe’s face and neck be completely bandaged for the rest of his life. Joe was too embarrassed about his appearance to ever leave his home again, and even close, life-long friends staggered visits and then eventually stopped visiting altogether. Many who are terminally ill are driven at the end of their lives by a final goal—perhaps one more wedding anniversary, a favorite holiday, or a visit from a family member or old friend separated by distance for an opportunity to say good-bye. After dropping his weight from two hundred and thirty to ninety-five pounds, Joe passed away at sunset on Father’s Day in 1989—more than seven months beyond what his doctors had predicted the year before.

Never during this saga was palliative care presented meaningfully as a treatment option.<sup>6</sup> As his health deteriorated, the physicians who had promptly returned calls personally over the

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<sup>4</sup> National Cancer Institute, NCI DICTIONARY OF CANCER TERMS, *available at* <http://www.cancer.gov/dictionary?CdrID=45368> (last visited Mar. 30, 2013).

<sup>5</sup> *Id.* at <http://www.cancer.gov/dictionary?CdrID=597171> (last visited Mar. 30, 2013). This is a “Cancer of the head and neck that begins in squamous cells (thin, flat cells that form the surface of the skin, eyes, various internal organs, and the lining of hollow organs and ducts of some glands).” *Id.*

<sup>6</sup> The objective of palliative care is to relieve suffering and to maximize the quality of life, with a focus on coordinating treatments with patient goals and providing collaborative care that draws from community resources and varied disciplines—e.g., interdisciplinary teams of physicians, nurses, social workers, chaplains, psychologists,

fourteen years of successful experimental treatments, and there were clusters of them at times, became essentially unreachable. Communication was shifted to their nursing staff. Joe's health care providers never confronted him about his imminent death, albeit largely because he did not want to hear and deal with that reality. He never fully accepted the inevitable until a month or so before it happened. Rather, in a state of denial, he aggressively sought out health care interventions, however experimental and painful, which he coupled with lots of prayer. Joe made no financial preparations, including the liquidation of his now over-extended construction business with a fleet of heavy equipment ranging from backhoes to cranes. He even took on a large contract during the final year of his life, which he finished to perfection but was never paid for; the client told him frankly that he was going to die and, given the client's legal staff, there was nothing Joe could do about it but accept a small payoff. His family was left with tremendous financial debt, and they were plagued by it for more than half a decade after his death. Joe's widow, who had handled administration of his business from payroll to billing and account management—down to writing all checks—in addition to raising a family and running and working at least fifty hours each week at her own business, was left with nothing after decades of hard work. She started over at the age of forty-six with the burden of settling debts totaling hundreds of thousands of dollars from Joe's company and a fifteen-year-old son to finish raising and educating by herself. During the final months of his life, Joe realized the situation he was leaving his family in, but it was too late to make any improvements. Joe died with that worry and a sickening sense that his life was a complete failure.

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and physical therapists. Kathleen Tschantz Unroe & Dr. Diane E. Meier, *Palliative Care and Hospice: Opportunities to Improve Care for the Sickest Patients*, 25 NOTRE DAME J. L. ETHICS & PUB. POL'Y 413, 415 (2011). Hospice care is limited to patients with a prognosis of six months or less of life, and who agree to forego potentially curative and life-prolonging therapies—e.g., when treatment options have been exhausted and the burdens of treatment outweigh benefits. Nat'l Consensus Project for Quality Palliative Care, Clinical Practice Guidelines for Quality Palliative Care 11 (2d ed. 2009) Dep't of Health & Human Servs., Ctrs. For Medicare & Medicaid Servs., Medicare Hospice Benefits 4 (2010), <http://www.medicare.gov/publications/pubs/pdf/02154.pdf> R. Sean Morrison & Diane E. Meier, *Clinical Practice: Palliative Care*, 350 NEW ENG. J. MED. 2582, 2587 tbl.2 (2004) (describing a review of the "benefit-to-burden ratio for disease modifying treatments"). Palliative care may be provided within the context of hospice services or outside of them; non-hospice palliative care may be provided with therapies intended to cure or otherwise prolong life. See generally Meier, *Palliative Care*, *supra*. The statutory criteria for the Medicare hospice benefit are certification by two physicians that the patient's prognosis is six months of life or less, and the patient must relinquish insurance coverage for life-prolonging treatments for the terminal illness. Medicare Hospice Benefit, 42 C.F.R. SS 418.22(b)(2002); Unroe & Meier, *supra*, at 418; Diane E. Meier, *The Development, Status, and Future of Palliative Care*, in ROBERT WOOD JOHNSON FOUND., SERIES ON HEALTH POLICY, PALLIATIVE CARE: TRANSFORMING THE CARE OF SERIOUS ILLNESS 3, 18 (2010). "Despite restrictions to the benefit, growth of hospice has been dramatic over the past few decades. In 2009, an estimated 1.56 million patients received hospice services, accounting for about 40% of all deaths in the United States." NAT'L HOSPICE & PALLIATIVE CARE ORG., NHPCO FACTS AND FIGURES: HOSPICE CARE IN AMERICA 4 (2010), available at [http://www.nhpco.org/files/public/Statistics\\_Research/Hospice\\_Facts\\_Figures\\_Oct-2-1-.pdf](http://www.nhpco.org/files/public/Statistics_Research/Hospice_Facts_Figures_Oct-2-1-.pdf). Both palliative care and hospice programs have been credited with improving outcomes while reducing costs:

Multiple studies of palliative care and hospice programs have shown that they improve physical and psychological symptoms experienced by patients, impact caregiver well-being, and improve patient, family, and physical satisfaction. Interdisciplinary palliative care and hospice teams reduce medical complications and expensive hospital utilization by identifying and treating distressing patient symptoms.

Unroe & Meier, *Opportunities*, *supra* note 6, at 418-419 (citing multiple sources for each claim). For palliative care resources, visit the Center to Advance Palliative Care, available at <http://www.capc.org/> (last visited Apr. 9, 2013); The Hertzberg Palliative Care Institute, available at <http://www.capc.org/old-tools-for-palliative-care-programs/marketing/sample-brochures/mt-sinai-hertzberg.pdf> (last visited Apr. 9, 2013). Discussion of palliative care and its general oversight in medical education is discussed *infra* at notes \_\_\_ and in the accompanying text.

Joe’s story illustrates common human reaction when death becomes defined, tangible, and must be confronted. Since Joe’s death in 1989, medicine has much more aggressively commingled clinical research with clinical care, and U.S. federal policy and regulation have promoted the same.<sup>7</sup> Part II of this article addresses the pulsating blending of clinical care with clinical research.

The question that is the focus of this article is the extent to which regulations to protect human subjects, and federal policy in general, should promote access to experimental treatments for the terminally ill or, alternatively, explicitly recognize this group as a “vulnerable population”<sup>8</sup> and protect it accordingly. Now is an opportune time to address this question: Decades after implementation, the U.S. is revisiting its fundamental law to protect human subjects known as the “Common Rule”<sup>9</sup> and is in the midst of implementing the Patient

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<sup>7</sup> See *infra* notes \_\_\_ and accompanying text.

<sup>8</sup> Special considerations apply to protecting the welfare of particularly vulnerable populations such as fetuses, children, prisoners, pregnant women, and mentally disabled or cognitively impaired persons. See 45 C.F.R. Pt. 46, §§ B-D. For example, the Common Rule imposes special procedures for obtaining consent and monitoring research for individuals with diminished mental capacity—e.g. patients with Alzheimer’s and traumatic brain injuries. See 45 C.F.R. § 46.107(a) (defining “handicapped or mentally disable persons” as within the scope of vulnerable populations). While the explicit regulatory requirement is limited to federally-funded research, it is common for institutions to elect consistent policies and procedures for all research and to represent the same to the Office for Human Subject Research Protections (OHRP) within the Department of Health and Human Services (DHHS) when they submit assurance applications to qualify for federal funding. See Christine G. Savage, *Research Compliance*, COLLEGE AND UNIVERSITY LAW MANUAL ch. 7, § 7.2.2 (2012).

<sup>9</sup> See *generally* Advanced Notice of Proposed Rulemaking, 76 Fed. Reg. 44512-44531 (July 26, 2011); Extension of Comment Period, 76 Fed. Reg. 54408 (Sept. 1, 2011). See Announcement, U.S. Dept. of Health and Human Servs., HHS Announces Extension of Comment Period on Proposal to Improve Rules Protecting Human Research Subjects (Sept. 1, 2011), available at <http://www.hhs.gov/?ohrp/?newsroom/?announcements/?2011.html>. The Department of Health and Human Services is contemplating substantial, fundamental changes to the Common Rule for the first time since it was introduced in the 1980s:

The impetus for the proposed changes to the Common Rule rests on the fact that the human subjects research landscape has undergone dramatic change since the 1980s, when the Common Rule was first developed. Human subjects research has increased in volume, scope, and application, reaching vast new areas of research activities. DHHS suggests that the changes seek to strike a balance by enhancing protections for human subjects who are involved with research while also facilitating research by reducing burden, delay, and ambiguity inherent in the current system of regulation.

76 Fed. Reg. at 44,512-44,513. Seven general features of the regulatory framework have been identified for reform:

- Utilization of a single IRB of record for all domestic sites on multisite studies;
  - Improvement of consent forms and the consent process;
  - Establishment of mandatory data security and information protection standards for all Studies that involve identifiable or potentially identifiable data;
  - Establishment of an improved, more systematic approach for the collection and analysis of data on unanticipated problems and adverse events;
  - Extension of federal regulatory protections to all human subjects research, regardless of funding source, conducted at institutions in the U.S. that receive some federal funding from a Common Rule agency for human subjects research; and
  - Improvement in the harmonization of regulations and related agency guidance.
- While DHHS has not yet published proposed rules, the July 2011 ANPRM signals that the Department is contemplating significant changes to the Common Rule in the areas outlined and discussed above.

*Id.* See *generally* Advanced Notice of Proposed Rulemaking, 76 Fed. Reg. 44512-44531 (July 26, 2011). In addition to the common rule, human subjects are protected by a somewhat parallel set of FDA regulations which apply to studies carried out under its supervision—e.g., studies to support new indications or uses of FDA-regulated

Protection and Affordable Care Act (PPACA).<sup>10</sup> The latter, recognition that cost increases in U.S. health care are unsustainable and more than forty million citizens are without health care insurance,<sup>11</sup> will draw tens of millions more people into the health care system—thereby exacerbating the policy significance of experimental treatment of the terminally ill, especially as baby-boomers approach the end of life.<sup>12</sup> The vast amount of health care cost is money spent for

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products. See 21 C.F.R. Parts 50, 54, and 56. See also Comparison of FDA and HHS Human Subject Protection Regulations, available at <http://www.fda.gov/oc/gcp/comparison.html>. See generally OFFICE FOR HUMAN RESEARCH PROTECTIONS, DEP'T HEALTH AND HUMAN SERV'S, SPECIAL CLASSES OF SUBJECTS: TERMINALLY ILL PATIENTS, INSTITUTIONAL REVIEW BOARD GUIDEBOOK VI.G (last updated 1993), available at [http://www.hhs.gov/ohrp/archive/irb/irb\\_chapter6.htm](http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm) (last visited Apr. 15, 2013). Therefore, fundamental changes to the common rule are likely to be incorporated into the FDA regulations. As summarized by DHHS, the FDA regulations:

[R]equire review and approval of protocols by IRBs, financial disclosures of potential conflicts of interest, and appropriate informed consent procedures. It is worth noting that the FDA conducts both for-cause and routine surveillance inspections of research institutions and the IRBs charged with reviewing FDA-regulated products. While the FDA typically issues warnings when compliance is unsatisfactory, the agency is also authorized to disqualify research programs or initiate criminal investigations when warranted.

Proposed Rulemaking, *supra*, at 44512. See 21 C.F.R. Parts 50, 54, and 56. Human subjects are protected additionally through direct regulation of conflicts of interest. As explained concisely by DHHS, concerns that conflicts of interest in research, derived from financial relationships or interests between the sponsor and the researcher, may affect the rights and welfare of human subjects. Beginning with the DHHS regulations on the topic in 1995, the federal government has taken the approach that not all financial interests in research being conducted are prohibited. For example, researchers and universities are permitted to patent and license the intellectual property developed in federally funded research. Examples of situations that would pose a conflict of interest, however, include scenarios where a patented product is tested in clinical trials by the inventor who stands to gain financially if the product is proven safe and effective. Specific concerns include the possibility that investigators may interpret data more generously than is warranted or ignore eligibility/exclusion criteria in order to generate more favorable results or obtain more rapid FDA approval of a product.

Proposed Rulemaking, *supra*, at 44512 (internal citation omitted). See 35 U.S.C. § 200 et seq.; BARBARA F. MISHKIN & MONIQUE V. NOLAN, "CONFLICTS OF INTEREST," IN HEALTH LAW HANDBOOK § 7.11 (West 2006). Rather than outright prohibition, the federal conflicts regulations generally require disclosure, independent review, and management of conflicts of interest. In 2011, DHHS issued the first substantive amendments to its conflicts of interest regulations since the Public Health Service (PHS) regulations on the Responsibility of Applicants for Promoting Objectivity in Research for which Public Health Service Funding Is Sought and Responsible Prospective Contractors, 42 C.F.R. pt. 50, were issued in 1995. These 2011 amendments, made effective on September 24, 2012, substantially strengthen the financial conflict of interest rules by lowering reporting thresholds, expanding reporting obligations, greatly increasing transparency, and requiring institutions that receive federal funding to develop and enforce policies on conflicts of interest that mandate disclosure, investigation, education, and training. See 42 C.F.R. § 50.604; Proposed Rulemaking, *supra*, at 44512-44531.

<sup>10</sup> Pub. L. No. 111-148, 124 Stat. 119 (2010).

<sup>11</sup> CONGRESSIONAL BUDGET OFFICE, THE LONG-TERM OUTLOOK FOR HEALTH CARE SPENDING (Nov. 2007), available at [http://moodle2.lsu.edu/pluginfile.php/175576/mod\\_resource/content/1/CBOHealthSpending.pdf](http://moodle2.lsu.edu/pluginfile.php/175576/mod_resource/content/1/CBOHealthSpending.pdf) (last visited Dec. 2012) [hereinafter "CONGRESSIONAL BUDGET OFFICE REPORT"].

<sup>12</sup> The already is a serious doctor shortage in many parts of the country. Editorial, *When the Doctor is Not Needed*, N.Y. TIMES, Dec. 16, 2012, at 10; Robert Pear, *Doctor Shortage Proves Obstacle to Obama Goals*, N.Y. TIMES (Apr. 27, 2009), at A1. The extent of the problem often correlates with poverty and disproportionate concentration of the approximately 50 million Americans without health insurance and the tens of million more who are underinsured. Editorial, *Not Needed*, *supra*, at 10. Louisiana is a prime example.



care at the end-of-life.<sup>13</sup> Part III of this article addresses this dilemma in a discussion of the competing perspectives of patient, clinical researcher, drug developer, and regulator at the end of life.

Part IV of the article introduces a law-policy proposal to modify human subject protection law and policy to enhance recognition of and responsiveness to the vulnerability of the terminally ill. This proposal is grounded in the seductiveness of science, especially when confronted by death, the care-at-all-costs culture of U.S. medicine, good medicine considerations, and the reality that health care resources are limited and the U.S. health care system must be rescued from a bleak financial future.<sup>14</sup>

## II. Comingling Clinical Research and Clinical Care at the End of Life

"Technological medicine sometimes seems to promote a view of death as an event that can be deferred indefinitely rather than as a normal, natural part of life."

Lynne Ann DeSpelder & Albert Lee Strickland<sup>15</sup>

From the 1980s to the present, in sync with advancement of the genomics revolution in the development of drugs and other therapeutics,<sup>16</sup> the U.S. has liberalized its experimental drug policies to increase access to clinical research as health care treatment.<sup>17</sup> In 1987, the U.S. codified and expanded a Compassionate Use Exemption which, at the FDA's discretion on a case-by-case basis, allows individuals to realize health care use of drugs and other therapeutics still in the midst of the FDA review process.<sup>18</sup> A Treatment IND Exemption was added to

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<sup>13</sup> Just 5 percent of the population is responsible for almost 50 percent of health care costs, and those costs are concentrated at the end of life. *See generally*, LONG-TERM OUTLOOK, *supra* note 10. *See* David Gruber & Paul Rundell, *Restructuring and PPACA*, 44 AM. BANKR. INST. J. 95, 96 (Sept. 2012).

<sup>14</sup> *See generally* CONGRESSIONAL BUDGET OFFICE REPORT, *supra* note 11.

<sup>15</sup> LYNNE ANN DESPEIDER & ALBERT LEE STRICKLAND, *THE LAST DANCE: ENCOUNTERING DEATH AND DYING* (1983).

<sup>16</sup> *See generally* Symposium, *The Genomics Revolution? Science, Law, and Policy*, 66 LA. L. REV. 1 (2005) (centennial issue).

<sup>17</sup> Linda Katherine Leibfarth, *Giving the Terminally Ill Their Due (Process): A Case for Expanded Access to Experimental Drugs through the Political Process*, 61 VAND. L. REV. 1281, 1282 (2008). Measures to increase access to experimental treatments were introduced in the context of broader efforts to accelerate drug review and approval. In 1992, the FDA issued regulations to codify acceptance of surrogate endpoints meaning that, in place of evidence of patient survival which may require considerable time to establish, the agency accepts evidence of physiological and biochemical data indicative of extended patient survival. 21 C.F.R. § 315.500. The same year, Congress enacted—and subsequently reauthorized in five-year intervals—the Prescription Drug User Fee Act (PDUFA), 21 U.S.C.A. Sec. Sec. 379g-379h. PDUFA established a cash flow of user fees from new drug sponsors that has enabled the agency to hire hundreds of additional reviewers. In 1997, Congress enacted FDAMA, which expanded the mission of the FDA to include efficiency along with safety and efficacy. *See infra* notes \_\_ and accompanying text. The net effect was a drop in the average new drug approval time from twenty-seven to fourteen months between 1993 and 2001. U.S. GEN. ACCOUNTING OFFICE, GAO-02-958, REPORT TO THE CHAIRMAN, COMMITTEE ON HEALTH, EDUCATION, LABOR, AND PENSIONS, U.S. SENATE, EFFECT OF USER FEES ON DRUG APPROVAL TIMES, WITHDRAWALS, AND OTHER AGENCY ACTIVITIES 3 (2002).

<sup>18</sup> 21 C.F.R. Sec. 312.34. Many credit this expansion to the onset of the AIDS epidemic in the 1980s. *See, e.g.*,



provide the same for groups.<sup>19</sup> While Compassionate Use applications are decided on a case-by-case basis, a Treatment IND (again, pertaining to groups of patients), adds a treatment protocol to an existing investigational new drug application (IND) that authorizes the clinical research drawn upon.<sup>20</sup> Patients who satisfy the protocol are, with physician support, candidates for the experimental treatment covered.<sup>21</sup> The FDA requires drug candidates to demonstrate meaningful potential of therapeutic benefit before approving use outside the scope of clinical trials, and the agency applies varying standards for serious and life-threatening diseases.<sup>22</sup> The standard for serious diseases is sufficient evidence of safety and effectiveness to support the use, which typically requires Phase III data.<sup>23</sup> The standard for *life-threatening* diseases is that data must be sufficient to reasonably conclude that the drug may be effective for the intended use in the target patient population without exposing those patients to an unreasonable and significant additional risk of illness or injury, which typically requires meaningful Phase II data.<sup>24</sup>

In addition, with enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA),<sup>25</sup> the U.S. introduced an internet site that tracks efficacy studies under FDA-approved investigational new drug (IND) applications and makes that information accessible to the general public.<sup>26</sup> Subsequently, the U.S. expanded the effort with enactment of section 801 of the Food and Drug Administration Amendments Act (FDAAA) of 2007.<sup>27</sup> Through this site and a range of other sites, including the NIH Cancer trial site and private sites, “Clinical research has

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Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U.J. LEGIS. & PUB. POL’Y, 295, 296-297 (2000); Leibfarth, *supra* note 17, at 1282. However, based upon this author’s work in the field during this time, there were several other important influences, including: (1) expansion of the number and volume of a range of political voices from patient advocacy, professional, and trade organization groups, including the Biotechnology Industry Organization, coupled with explosive advancement of information technology; (2) increased unification of the European pharmaceutical market through establishment of the European Medicines Agency; (3) reports that the U.S. lagged behind Europe in new drug approvals—the so-called “drug lag”; (4) frustration over the institutional memory of the FDA and lack of regulatory transparency; and (5) the rapid expansion of a meaningful biotechnology commercial sector and its integration with the pharmaceutical sector.

<sup>19</sup> 21 C.F.R. Sec. 312.34. The four conditions for a treatment IND to qualify are set forth at 21 C.F.R. Sec. 312.34: (1) the drug must be intended to treat a serious or life-threatening disease; (2) there cannot be a satisfactory alternative treatment; (3) the drug must be in advanced FDA trials (efficacy trials); and (4) the drug sponsor must be pursuing market approval. In recent years, there has been a major movement by patient advocacy groups to increase access yet further. *See infra* notes \_\_\_ and accompanying text (Abigail Alliance). The FDA also has a “parallel track” to increase access to drugs in the early stages of discovery, but the mechanism has been used very sparingly. *See generally* 57 Fed. Reg. 13259 (Apr. 15, 1992); OFFICE FOR HUMAN RESEARCH PROTECTIONS, TERMINALLY ILL PATIENTS, *supra* note 9.

<sup>20</sup> *See id.* at \_\_\_.

<sup>21</sup> *Id.* at \_\_\_.

<sup>22</sup> *See generally* OFFICE FOR HUMAN RESEARCH PROTECTIONS, GUIDEBOOK, *supra* note 19, at VI.G.

<sup>23</sup> 21 CFR 312.34(a).

<sup>24</sup> 312.34(b)(2), 312.34(b)(3).

<sup>25</sup> Pub. L. No. 105-115, 111 Stat. 2295 (1997).

<sup>26</sup> U.S. National Library of Medicine, Fact Sheet, ClinicalTrials.gov, *available at* <http://www.nlm.nih.gov/pubs/factsheets/clintrial.html> (last visited Mar. 30, 2013); Sarah K. Keitt, *Sex & Gender: The Politics, Policy, and Practice of Medical Research*, 3 253, 266-67 (2003) (observing that databases like [www.clinicaltrials.gov](http://www.clinicaltrials.gov), [www.womancando.org](http://www.womancando.org), and [www.centerwatch.com](http://www.centerwatch.com) identify ongoing trials, participation criteria, and participation considerations).

<sup>27</sup> Pub. L. No. 110-85, 121 Stat. 823, 904-905 (2007). *See infra* notes \_\_\_ and accompanying text.

entered an era of transparency, meaning that information about clinical trials is online and accessible to the general public, and the public is seeking access.”<sup>28</sup>

Moreover, in 2000, the U.S. introduced federal law and policy in favor of Medicare reimbursement for clinical research as care.<sup>29</sup> Specifically, “On June 7, 2000, the President of the United States issued an executive memorandum directing the Secretary of Health and Human Services to ‘explicitly authorize [Medicare] payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials.’”<sup>30</sup> Medicare funnels money into states’ private insurance markets, therefore Medicare reimbursement decisions often have broad impact on the private commercial insurance sector.<sup>31</sup> The “greying of America” suggests that this influence is bound to increase.<sup>32</sup>

The relevant government law and policy rests upon advancement of and the public’s faith in the underlying science, the primary fuel for the fusion of clinical research and clinical care,<sup>33</sup> and this trend is likely to continue.<sup>34</sup> The amount of advanced clinical research underway is unprecedented.<sup>35</sup> Over the last six years, the number of subjects typical for phase III trials, advanced trials leading into applications for new drug approvals, has increased from 3,000 to 20,000—doubling their cost (now typically \$50-100 million).<sup>36</sup> Given the specificity and complexity of human genetics and the industry’s reliance on group design—statistics, group averages and medians—in clinical research,<sup>37</sup> the scope of phase III trials likely will continue to

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<sup>28</sup> Michael J. Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 HOUS. J. HEALTH L. & POL’Y 31, 51 (2002). See, e.g., [www.cancer.gov/clinicaltrials](http://www.cancer.gov/clinicaltrials), [www.centerwatch](http://www.centerwatch.com) and [www.womancando.org](http://www.womancando.org).

<sup>29</sup> Health Care Financing Admin., Medicare Coverage Policy-Clinical Trials, Final National Coverage Decision, available at <http://www.hcfa.gov/coverage/8d2.htm> (last visited Jun. 2011); DEP’T OF HEALTH & HUMAN SERVS., HEALTH CARE FINANCING ADMIN., HCFA FACT SHEET, MEDICARE COVERAGE ROUTINE COSTS OF BENEFICIARIES IN CLINICAL TRIALS (2000), available at <http://www.hcfa.gov/medlearn/ctfs13.pdf> (stating that Medicare beneficiaries would not lose their coverage by enrolling in clinical trials in an effort to promote innovation).

<sup>30</sup> See generally Centers for Medicare and Medicaid Services, Medical Clinical Trial Policies, available at <http://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html?redirect=/ClinicalTrialPolicies/> (last visited Mar. 30, 2013). On July 10, 2006, CMS opened a reconsideration of its national coverage determination on clinical trials for clarification. *Id.*

<sup>31</sup> See PBS, HEALTHCARE CRISIS: WHO’S AT RISK? (2000).

<sup>32</sup> See generally CONGRESSIONAL BUDGET OFFICE REPORT, *supra* note 11.

<sup>33</sup> See Michael J. Malinowski, *Law, Policy, and Market Implications of Genetic Profiling in Drug Development*, 2 HOUS. J. HEALTH L. & POL’Y 31, 52 (2002).

<sup>34</sup> See *infra* notes \_\_ and accompanying text.

<sup>35</sup> See CTR. FOR HEALTH & PHARM. LAW & POLICY, SETON HALL LAW, WHITE PAPER: CONFLICTS OF INTEREST IN CLINICAL TRIAL RECRUITMENT & ENROLLMENT: A CALL FOR INCREASED OVERSIGHT 5-6 (2009); Michael J. Malinowski & Grant G. Gautreaux, *Drug Development—Stuck in a State of Puberty? Regulatory Reform of Human Clinical Research to Raise Responsiveness to the Reality of Human Variability*, 56 ST. LOUIS L. J. 363, 393-394 (2012). See generally Matthew Herper, *The Truly Staggering Cost of Inventing New Drugs*, FORBES, Feb. 10, 2012, available at <http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/> (last visited April 8, 2013); Appendices I & II. See also *infra* note 79 and accompanying text.

<sup>36</sup> Miho Nagano, *Big Pharma Looks for a Fix*, INVESTOR’S BUSINESS DAILY, Sept. 29, 2008, at A9.

<sup>37</sup> See generally Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35; Michael J. Malinowski & Grant G. Gautreaux, *All that is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development*, 45 CORNELL INT’L L. J. 185 (2012).

expand.<sup>38</sup> In any event, those who are terminally ill will seek access,<sup>39</sup> and existing government law and policy encourages them to do so. Manipulating the scope of trials under group design is a means to realize the desired averages and medians.

The law-policy challenge is to promote responsible clinical research and experimental treatments while grounding over responsiveness to experimental treatments by patients, providers, and researchers at the expense of quality of patient care, good medicine, and full voluntary informed consent. More than ninety percent of new drug candidates fail, and clinical research generally is a grasping reach from the equivalent of quality, tried and tested, clinical care. Clinical research is a transition from health care potential to quality treatment reality, which generally necessitates drug approval and years of physician-patient experience in the general population.<sup>40</sup>

The promotion of responsible clinical research is especially important today to transition drug development out of its doldrums and to realize the human health potential of the extraordinary advances of human genome-related basic research and enabling technologies over the last few decades (genomics, proteomics and myriad other disciplines).<sup>41</sup> In spite of new drug disappointments, there is ample proof of principle in the new drug pipeline—for example, drugs that target genetic aberrations fundamental to a range of cancers independent of where they originate, juxtaposed against “personalized” approaches to treating cancers. An example of the former are variations of a drug being developed in competition among Merck, Roche, and Sanofi to restore a mechanism that causes badly damaged cancer cells to self-destruct regardless of their origin.<sup>42</sup> A noted illustration of the latter is the work of Dr. Ralph Steinman, who with a colleague was co-awarded the 2011 Nobel Prize in Physiology or Medicine for his work battling his own pancreatic cancer through treatments generated from his body to reprogram his immune cells:<sup>43</sup>

Now doctors can scan each tumor for clues about its DNA and use those clues to determine its strengths and weaknesses. . . . This “personalized” approach to treating

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<sup>38</sup> This observation presumes adherence to the group design science standard and no dramatic science advancement intervention in the near future. Cf. Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35; Malinowski & Gautreaux, *All that is Gold*, *supra* note 37.

<sup>39</sup> See *infra* notes \_\_ and accompanying text.

<sup>40</sup> See Herper, *supra* note 35. See generally Barbara A. Noah, *Bioethical Malpractice: Risk and Responsibility in Human Research*, 7 J. HEALTH CARE L. & POL’Y 175, 176 (2004) (distinguishing research from treatment; describing research as transition from health care potential to actual medical treatment).

<sup>41</sup> See generally Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35; Malinowski & Gautreaux, *All that is Gold*, *supra* note 37.

<sup>42</sup> Gina Kolata, *New Drugs Aim to Make Cells Destroy Cancer*, N.Y. TIMES, Dec. 23, 2012, at 1, 23. Beyond the health care implications of multiplying treatment options for a broad range of major cancer patient groups and pooling research resources, from financial support to human subjects, treatment windfalls may reach those afflicted with rare cancers ignored by commercial drug makers. See generally *id.*

<sup>43</sup> Daniel Engber, *How One Scientist’s Losing Battle Against His Own Cancer Might Save the Rest of Us*, NEW YORK TIMES MAG., Dec. 23, 2011, 32-38. Dr. Steinman’s family was notified via a message delivered to Dr. Steinman’s BlackBerry three days after his death, which was years beyond his prognosis when diagnosed. *Id.* at 34. Although the Nobel Foundation does not allow posthumous awards, Dr. Steinman’s was allowed to stand. *Id.* Dr. Steinman served as both scientist and human subject in a clinical trial of one, but with broad human health implications: “It is known as cancer immunotherapy, and its offshoots have just now begun to make their way into the clinic, and treatments have been approved for tumors of the skin and of the prostate.” *Id.*

cancer, which subdivides the classic types according to distortions in their genes, has been growing at a rapid pace. In the past few years, laboratories financed by the government have set out to build a comprehensive atlas of the cancer genome—to collect 500 tumors from each of 25 kinds of the disease and then to analyze their DNA and RNA at a cost of more than \$100 million a year. The advent of inexpensive genome sequencing has produced a gold rush in the commercial sector too, with the promise that anyone’s tumor can be sliced and processed and analyzed, until its genetic fingerprint is decoded.<sup>44</sup>

FDAMA prioritizes research to develop therapeutics for treating life-threatening and otherwise seriously debilitating diseases that presently are untreatable, or for which no sufficient standard of care is available. Compassionate Uses and Treatment INDs, also responsive to these situations, are thereby reinforced through the priorities codified through enactment of FDAMA.<sup>45</sup>

### **III. The Competing Perspectives of Patient, Physician, Clinical Researcher, Drug Developer, and Regulator at the End of Life**

“How can it be coherent to insist on maintaining hope when life, the very object of the hope one is trying to maintain, will thereby be sacrificed?”

Paul T. Menzel<sup>46</sup>

Reducing matters literally of life and death in health care to law and policy inevitably raises controversy and debate—as they should. Patients, physicians, clinical researchers, drug developers, and regulators all have vested interests in law-policy that impacts access to experimental treatments for the terminally ill, as was illustrated vividly in recent years by *Abigail Alliance for Better Access to Developmental Drugs v. Von Eschenback*<sup>47</sup> and the controversy the case generated.<sup>48</sup>

Abigail Alliance (“the Alliance”) challenged FDA regulations that limited access to the experimental drugs Iressa and Erbitux for the named patient plaintiff, Abigail, and other

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<sup>44</sup> *Id.* at 35. The recent Supreme Court decision, *Assoc. For Molecular Pathology et al. v. Myriad Genetics, Inc.*, No. 12-398 (2013), now makes it possible to gather up clusters of allele (genetic variation) probes for particular diseases—for example, specific cancers—or even a range of diseases for genetic testing screens of medical value unprecedented thus far.

<sup>45</sup> See FDAMA, *supra* note 25 and accompanying text. See Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35, at 379-81 (addressing the codification of this presumption under section 506B and the “fast track” provisions of FDAMA).

<sup>46</sup> Paul T. Menzel, *The Value of Life at the End of Life: A Critical Assessment of Hope and Other Factors*, 39 J. L. MED. & ETHICS 215, 216 (2011).

<sup>47</sup> 495 F.3d 695 (D.C. Cir. 2007) (en banc), *aff’g* No. 03-1601 (RMU), 2004 WL 3777340 (D.D.C. Aug. 30, 2004), *rev’g* 445 F.3d 470 (D.D. Cir. 2006), *cert. denied*, 128 S. Ct. 1069 (2008).

<sup>48</sup> See generally Leibfarth, *supra* note 17; Priya Brandes, Comment, *Regulation of Drugs: A Death Sentence for the Terminally Ill?*, 46 U.S.F. L. REV. 1149, 1156-1163 (2012). See Linda Greenhouse, *Justices Won’t Hear Appeal on Drugs for Terminally Ill*, N.Y. TIMES, Jan. 15, 2008.

plaintiffs who were excluded from the clinical trials.<sup>49</sup> The Alliance asserted that drug sponsors should be permitted to make investigational drugs available to terminally ill patients with no other treatment options once Phase I clinical trials (trials for safety only, and conducted with healthy volunteers) have been completed.<sup>50</sup> Drawing from *Cruzan v. Dir., Mo. Dep't of Health*,<sup>51</sup> in which the Supreme Court recognized a fundamental liberty interest in the individual's right to refuse life-sustaining treatments even if that decision accelerates the end of life,<sup>52</sup> the Alliance alleged that terminally ill individuals have a similar liberty interest that entitles them to access experimental drugs. "Essentially, the panel argued that a liberty interest in choosing death by refusing treatment is akin to the right to choose a fighting chance at prolonged life."<sup>53</sup> The common denominator, according to the Alliance, is a right to control one's medical care at the end of their life. The Alliance also drew from the holdings in *Roe v. Wade*<sup>54</sup> and *Planned Parenthood v. Casey*<sup>55</sup> that a Woman has a right to terminate a pregnancy at any stage when necessary to preserve her life or health to propose a right to "medical self-defense."<sup>56</sup> In addition, the Alliance drew from *Gonzales v. Oregon*,<sup>57</sup> in which the Court, as in *Roe*, showed strong deference to the practice of medicine and medical choices made by individuals with their doctors, holding that physicians have a right to use FDA-approved drugs consistent with the approval even if the use hastens the death of patients.<sup>58</sup> Moreover, the Alliance argued that, "in connection with [their] own personal health-care, [the] FDA ha[d] offended the constitutional right of privacy."<sup>59</sup>

The Supreme Court denied the Alliance's petition for certiorari and thereby through silence affirmed the D.C. Circuit court's en banc holding that, although physicians are entitled to prescribe in accordance with FDA drug approvals (all that is on the pharmacy shelves is for use at doctor discretion provided they do not engage in known harm), there is no affirmative right to

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<sup>49</sup> Abigail lost her battle against cancer on June 9, 2001, years before the case in which she was the named plaintiff reached a final resolution. See Official Site, Alliance for Better Access to Development Drugs, available at <http://www.abigail-alliance.org/story.php> (last visited Apr. 1, 2013). The mission and work of the Alliance continue on. See *id.* at <http://www.abigail-alliance.org/> (last visited Apr. 1, 2013).

<sup>50</sup> *Abigail Alliance for Better Access to Developmental Drugs v. McClenllan*, No. 03-1601 (RMU) (D.D.C. Aug. 30, 2004), 2004 WL 3777340, at 27.

<sup>51</sup> 497 U.S. 261, 286-87 (1990) ("[W]e do not think the Due Process Clause requires the State to repose judgment on these matters with anyone but the patient herself...[T]he State may choose to defer only to those wishes [of the patient], rather than confide the decision to close family members.").

<sup>52</sup> The Court's decision recognized the doctrine of substituted judgment—an obligation to step into the life of the individual and make decisions about health care intervention based upon what the individual would have decided. See generally Louise Harmon, *Fall off the Vine: Legal Fictions and the Doctrine of Substituted Judgment*, 100 YALE L.J. 1 (1990).

<sup>53</sup> Leibfarth, *Expanded Access*, *supra* note 48, at 1296 (2008).

<sup>54</sup> *Roe v. Wade*, 410 U.S. 113 (1973).

<sup>55</sup> *Planned Parenthood of Southwestern Pa. v. Casey*, 505 US 833 (1992).

<sup>56</sup> See Leibfarth, *supra* note 17, at 1298-1300; see also Eugene Volokh, *Medical Self-Defense, Prohibited Experimental Therapies, and Payment for Organs*, 120 HARV. L. REV. 1913 (2007).

<sup>57</sup> 546 U.S. 243, 126 S.Ct. 904 (2006). The case was a Bush Administration challenge to an Oregon law allowing physicians, in response to patient requests and when certain requirements are satisfied, to prescribe prescription pain medications in a manner that accelerates the end of life.

<sup>58</sup> *Id.* at \_\_\_. Note that subsequently, in *Gonzales v. Carhart*, 127 S. Ct. 1610, 1633 (2007), the Court upheld a congressional ban on partial birth abortion even when a woman and her doctor conclude the procedure is medically necessary. *Id.* at 1633.

<sup>59</sup> 438 F. Supp. at 1301.

force the FDA to expand access to drug candidates under its review.<sup>60</sup> The Alliance's foundation argument, rejected by the D.C. Circuit, was that the FDA's standard for access to experimental pharmaceuticals interferes with fundamental rights, therefore is subject to a strict scrutiny standard of review, and imposes an undue burden on those who are terminally ill and could possibly benefit from experimental treatments blanketed under the regulatory protection.<sup>61</sup> The D.C. Circuit relied upon the Supreme Court's decision in *United States v. Rutherford*,<sup>62</sup> in which plaintiffs argued that drug regulations to protect the public did not have any reasonable application to terminally ill patients. The *Rutherford* Court disagreed, holding that "the concept of safety . . . is not without meaning for terminal patients. For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit."<sup>63</sup> The Court's rationale was that the language of the Food, Drug, and Cosmetic Act (FDCA) is plain and unambiguous, and whether there should be an exemption from protections for the terminally ill is a question of *statutory*, not judicial, interpretation.<sup>64</sup>

The *Abigail* litigation has and presumably will continue to inspire legislative proposals.<sup>65</sup> In 2005, the Access, Compassion, Care, and Ethics for Seriously Ill Patients Act was introduced in the U.S. Senate with Abigail Alliance support,<sup>66</sup> and an identical bill was introduced in the house.<sup>67</sup> The crux of these legislative proposals was to grant seriously ill patients a right to access experimental drugs after phase I testing, and provisions included a prohibition on placebo (no treatment) control groups in human clinical trials, a waiver of liability for providing the terminally ill with experimental drugs to provide an incentive for drug sponsor responsiveness, and restrictions on the marketing of experimental drugs to the terminally ill to quell opponents' concerns.<sup>68</sup>

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<sup>60</sup> *Abigail v. Von Eschenbach*, *supra* note 50. See Greenhouse, *Justices Won't*, *supra* note 35.

<sup>61</sup> *Abigail Alliance*, 495 F.3d at 701, *citing* 21 CFR sec. 312.34(b)(3) (2008). The Alliance also challenged FDA regulations that prohibit drug sponsors from profiting from the sale of experimental drugs; sponsors may recoup costs only. See *Abigail Alliance*, 495 F.3d at 701, *citing* 21 CFR sec. 312.7(d)(3) (2008).

<sup>62</sup> 442 U.S. 544 (1979).

<sup>63</sup> *Id.* at 555-56. The Court emphasized section 505 of the FDCA, which requires the FDA to assess "whether or not [a] drug is safe for use and whether such drug is effective in use" before approving its introduction into interstate commerce. 21 U.S.C. § 355(b) (2000).

<sup>64</sup> 442 U.S. at 551. The Court held that "Exceptions to clearly delineated statutes will be implied only where essential to prevent 'absurd results' or consequences obviously at variance with the policy of the enactment as a whole." *Id.* at 552. The D.C. Circuit held the same—that the issue is best debated through the political process, not the judiciary: *Abigail Alliance v. Von Eschenbach*, *supra* note 34, 495 F.3d at 713.

<sup>65</sup> Again, the Abigail Alliance continues its work. See *supra* note 49.

<sup>66</sup> S. 1956, 109th Cong. (2005). S. 1956, 109th Cong. (2005), available at <http://www.govtrack.us/congress/bill.xpd?bill=s109-1956>. The bill was reintroduced in May 2008. S. 3046, 110th Cong. (2008), available at <http://www.govtrack.us/congress/bill.xpd?bill=s110-3046> (tracking history of the bill).

<sup>67</sup> H.R. 6303, 109th Cong. (2005), available at <http://www.govtrack.us/congress/bill.xpd?bill=h109-6303>. The bill was reintroduced in June 2008. H.R. 6270, 110th Cong. (2008), available at <http://www.govtrack.us/congress/bill.xpd?bill=h110-6270>.

<sup>68</sup> See Leibfarth, *supra* note 17, at 1309-1315.

In the years since the *Abigail* decision, the scope of clinical research has unfolded over health care dramatically,<sup>69</sup> as has the public's perception that experimental therapeutics are an extension of clinical care options.<sup>70</sup> Joe's story is exponentially more prevalent today than when he passed away in 1989.<sup>71</sup> The U.S. population is greying and overcoming acute conditions to live longer with chronic ones demanding constant care.<sup>72</sup> Experimental treatment of the terminally ill and inclusion of the terminally ill in clinical research remain viable *legislative* matters and, in fact, ones much more compelling than in the past given the advancement and seduction of science. The varied and often competing perspectives of patient, physician, clinical researcher, drug developer, and regulator demand focused attention.

## A. The Patient's Perspective

Terminally ill individuals without standard of care treatment options generally weigh the risks and benefits of experimental treatments in a wholly distinguishable manner relative to the general population.<sup>73</sup> Often risks associated with experimentation are perceived as negligible provided there is *any* possibility of treatment and postponement of death.<sup>74</sup> Imminent death shifts the reference point for cost-benefit analysis: a premium is placed on a month of additional life that far exceeds the value placed on that same month tacked onto a period of years.<sup>75</sup>

[Ernest Becker] and colleagues suggest that four factors explain the high value people appear to put on life at the end of life. (1) Opportunity costs are low because assets that will prospectively remain after death have less value to the living [but terminally ill] patient than assets normally do. (2) Compromised quality of life has less effect in lowering one's perceived value of life when it is the only quality one's life can have yet. (3) Others, not only the person approaching death, see benefit in marginally longer life. In academic terms, the extended life has a "social value." People around the one whose life is ending are often heavily invested emotionally in extending life. More distant parties such as altruistic taxpayers and insurance subscribers, for example, can also see benefit in providing extended life in the face of death. Various interest groups benefit from the provision of care and perception of that. (4) Preserving hope by pursuing even unlikely and statistically small life extensions has value that is reflected in higher valuation of life. If hope is defined as "the *current* consumption of *future* survival," then "increased survival in the future is . . . [legitimately] 'double counted' as . . . having a current consumption value in addition to its traditional future consumption value."<sup>76</sup>

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<sup>69</sup> See *supra* note \_\_\_ and accompanying text (an increase from 3,000 to 10,000 for a typical phase III trial); See generally SETON HALL, WHITE PAPER, *supra* note 28.

<sup>70</sup> See generally *supra* Part II.

<sup>71</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>72</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>73</sup> The plaintiffs in *Abigail Alliance* articulated this argument. See *supra* notes \_\_\_ and accompanying text.

<sup>74</sup> *Id.* See also Leibfarth, *supra* note 17, at 1288.

<sup>75</sup> Paul T. Menzel, *The Value of Life at the End of Life: A Critical Assessment of Hope and Other Factors*, 39 J.L. MED. & ETHICS 216-17 (2011).

<sup>76</sup> *Id.* at 216-217 quoting BECKER K. MURPHY & T. PHIPSON, NATIONAL BUREAU OF ECONOMIC RESEARCH, THE VALUE OF LIFE NEAR ITS END AND TERMINAL CARE, NBER WORKING PAPER NO. 13333 (2007). See also KUHLMAN, *supra* note 106, at 4-5 ("The moment someone is told that their illness will likely result in death, time changes.").



U.S. culture prioritizes life, youth, and productivity, which feeds a fear of death and dying. Jolting advances in medical technology, actual and perceived, give many who are terminally ill hope, and it has created the concept of “invisible death.”<sup>77</sup> There is a belief, drawing masses in search of hope in ever-expanding numbers, that death is avoidable through investment in research and science. This faith stigmatizes death as failure, something to be hidden and avoided, and creates compulsion to exhaust all medical science resources—escalating pressure to undertake whatever can be done medically to fend off death.<sup>78</sup>

If it is presumed that death can be defeated by science, then when it does occur it theoretically could have been prevented and thus must reflect a failure—of the family to find the right doctor; of the patient to take care of himself; of the doctors or hospitals to know and provide the right treatments; and of society to invest enough in research. . . . This stigma of death as failure, the widely held belief that modern medicine can perform miracles in the battle against death, and the multi-year course of the chronic illness responsible for 75% of deaths in the United States have fostered an environment where over 70% of deaths in the United States occur in institutions—hospitals and nursing homes. The hospital is believed to have the people and technology needed to keep death at bay. Further, the hospital and the nursing home offer respite for families from the difficult, often many years long, work of caring for a seriously ill person.<sup>79</sup>

Consequently, death in the U.S. has become a ritual encompassing prolonged hospital stays, many in intensive care units.<sup>80</sup> This ritual gives families and health care providers comfort—a sense that “We did everything possible.” A “We cannot do more for you medically” from a health care provider triggers confrontation with mortality and a self-preservation instinct.<sup>81</sup> This fear of death has a legacy as long as humankind, and one that lingers in perpetuity: “[M]an has not basically changed. Death is still a fearful, frightening happening, and the fear of death is a universal fear even if we think we have mastered it on many levels.”<sup>82</sup> As observed by Pulitzer Prize recipient Ernest Becker, “And so we can understand what seems like an impossible paradox: the ever-present fear of death in the normal biological functioning of our instinct of self-preservation, as well as our utter obliviousness to this fear in our conscious life . . . .”<sup>83</sup> As explained by Becker, the human condition of denying death is reinforced by science and narcissism:

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<sup>77</sup> PHILLIPE ARIES, *THE HOUR OF OUR DEATH* 575 (1981). This point is sharpened when one compares the fear of death in contemporary U.S. culture with ancestral celebration of death as the ultimate rite of passage to elevate to a higher existence. ERNEST BECKER, *THE DENIAL OF DEATH* ix (1973) (Pulitzer Prize Winner for General Nonfiction 1974).

<sup>78</sup> *Id.* at 575.

<sup>79</sup> Kathleen Tschantz Unroe & Dr. Diane E. Meier, *Palliative Care and Hospice: Opportunities to Improve Care for the Sickest Patients*, 25 *NOTRE DAME J. L. ETHICS & PUB. POL’Y* 413, 416 (2011).

<sup>80</sup> See generally BECKER, *supra* note 77.

<sup>81</sup> *Id.* at 15-17.

<sup>82</sup> KUBLER-ROSS, *DYING*, *supra* note 82, at 4.

<sup>83</sup> BECKER, *supra* note 77, at 17. For discussion of the unconscious attitude towards death, see SIGMUND FREUD, *Thoughts for the Times on War and Death*, *COLLECTED PAPERS*, vol. 4, pp. 316-317 (1959).

As Aristotle somewhere put it: luck is when the guy next to you gets hit with the arrow. Twenty-five hundred years of history have not changed man's basic narcissism; most of the time, for most of us, this is still a workable definition of luck. It is one of the meaner aspects of narcissism that we feel that practically everyone is expendable except ourselves. Our organism is bred to fill the world all alone, even if our mind shrinks at the thought. This narcissism is what keeps men marching into point-blank fire in wars: at heart one doesn't feel that *he* will die, he only feels sorry for the man next to him. Freud's explanation for this was that the unconscious does not know death or time: in man's physiochemical, inner organic recesses he feels immortal.<sup>84</sup>

Folded into daily life, a major weakness in this narcissistic analysis in the health care context is that it assumes equal durations of lifetime are comparable in content and quality, which typically is not the case—as illustrated vividly by the last nine months or so of Joe's life.<sup>85</sup> Another is distortion of the health care market attributable to a disconnection between the costs and value of services and patients' end-of-life perspectives, and often those of their providers as well. Experimental treatments widen this disconnect, and profoundly so in many cases. When coverage is a beacon in the bleak, enveloping shadow of death, there tends to be demand for invasive care at all costs, regardless of the actual impact on care and the quality of life:

Insured patients and often their providers as well, have the incentive to use every bit of care that has even the slimmest, pie-in-the sky prospect of benefit, regardless of its cost. People see themselves as having paid their insurance “dues” already, and their future premiums will not increase by more than micro-pennies because of *their one current use* of marginal care. . . . Since providers are seen to be the jury expert professionals in delivering care, patients tend to defer to their recommendations, allowing them to create much of their own demand.<sup>86</sup>

Congress is attempting to address this problem under PPACA through establishment of an Independent Payment Advisory Board (IPAB) to assess health care outcomes, but a segment of the public and providers alike have balked at the effort—labeling the measure as “death panels.”<sup>87</sup> An at times cult-level faith in science and technology drives the need for regulatory intervention to communicate the realities of treatment and quality of life implications—so that individuals are better positioned to make rational decisions and to control the end of their lives with grounded insight.<sup>88</sup> Such an intervention is essential to improve end-of-life decision

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<sup>84</sup> Ernest Becker elaborated on the impact of narcissism on the human condition. BECKER, *supra* note 77, at 2-3.

<sup>85</sup> See *supra* notes 4-6 and accompanying text.

<sup>86</sup> Menzel, *supra* note 75, at 17.

<sup>87</sup> ALIGN America, *Does the Independent Payment Advisory Board = “Death Panels”?*, available at <http://www.alignamerica.com/node/63> (last visited Apr. 6, 2013). Many in the public and press have commingled IPAB with another “death panel” provision on palliative care directly removed from the final version of the PPACA. See *infra* note 194 and accompanying text.

<sup>88</sup> See generally DOROTHY NELKIN & MARTY SUSAN LINDEE, *THE DNA MYSTIQUE: THE GENE AS CULTURAL ICON* (1996); DOROTHY NELKIN & MARY SUSAN LINDEE, *SELLING SCIENCE: HOW THE PRESS COVERS SCIENCE AND TECHNOLOGY* (1995). With the success of the Human Genome Project (a rough draft of the map of the human genome was announced in 2003, and the map has been improved substantially since), faith in medical technology has been enhanced. See Press Release, Nat'l Human Genome Research Inst., *International Consortium Completes*

making—to infuse realistic decision making with thoughtful consideration of quality of life and comfort at the end-of-life. This intervention is essential in a society that, where the individual holds a contractual obligation to provide insurance coverage, promotes the possibility of extending the duration of life at all health care and quality of life costs—a society that breeds and feeds a vulnerability to live fates worse than death in which experimental treatment is embraced regardless of the associated suffering and at the cost of life resolution and closure. Even with the FDA’s portfolio of market failures such as Vioxx, Avandia, and Accutane after several years on the market and scathing evaluations from the Institutes of Medicine and Government Accountability Offices of the FDA’s regulatory performance once drugs are on the market,<sup>89</sup> faith in technology endures. Fear of death is coupled with at times desperate belief in medical technology. In the U.S., epicenter of the global genomic revolution in biomedical science, the uncertainty associated with “experimental” fuels hope—a “beat death” lottery ticket with odds inflated by perception—especially when conditions are terminal and standard of care treatments fail, are limited, or simply do not exist. Factors such as fear and faith certainly are not mutually inclusive with or exclusive of hope, but these influences often inflate the latter to the point of skewing patient intake of information and overall judgment.<sup>90</sup> At the very least, death is more difficult to confront in an age of technology.<sup>91</sup> Coupled with an explosion in the amount of clinical research underway,<sup>92</sup> FDAMA introduced a presumption in favor of putting new drugs on the market with clinical trial conditions that often are not enforced.<sup>93</sup> The prevalence of technology and its promise skews perception and appreciation of the clinical research reality that most drugs will fail—meaning that they will not prove helpful and, in fact, often prove harmful.<sup>94</sup> As illustrated by the last year of Joe’s life,<sup>95</sup> comfort and quality time often are sacrificed for invasive care, hospitalizations, and increased human suffering.

## B. The Perspectives of Physician and Clinical Researcher

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*Human Genome Project* (Apr. 14, 2003), Nicholas Wade, *A Decade Later, Gene Map Yields Few New Cures*, N.Y. TIMES, June 13, 2010, at A1.

<sup>89</sup> See U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-06-402, DRUG SAFETY: IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS (2006) [hereinafter GAO FDA REPORT]; INST. OF MED., THE FUTURE OF DRUG SAFETY: ACTION STEPS FOR CONGRESS (2006) [hereinafter IOM FDA REPORT], [http://www.iom.edu/~media/Files/Report%20Files/2006/The-Future-of-Drug-Safety/futureofdrugsafety\\_reportbrief.pdf](http://www.iom.edu/~media/Files/Report%20Files/2006/The-Future-of-Drug-Safety/futureofdrugsafety_reportbrief.pdf).

<sup>90</sup> See generally Menzel, *supra* note 61, at 218-219.

<sup>91</sup> KUBLER-ROSS, *supra* note 82, at 7 (“I think there are many reasons for this flight away from facing death calmly. One of the most important facts is that dying nowadays is more gruesome in many ways, namely, more lonely, mechanical, and dehumanized; at times it is even difficult to determine technically when the time of death has occurred.”).

<sup>92</sup> See *supra* notes 36 and accompanying text.

<sup>93</sup> See *infra* III.D. Michael D. Greenberg, *AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process*, 3 N.Y.U. J. LEGIS. & PUB. POL’Y 295, 296-297 (2000), *citing* Sheila R. Shulman & Jeffrey S. Brown, *The Food and Drug Administration’s Early Access and Fast-Track Approval Initiatives: How Have They Worked?*, 50 FOOD & DRUG L.J. 503, 505 (1995). 506(b)

<sup>94</sup> “Right now fewer than one in ten medicines that begin testing in human clinical trials succeed.” Herper, *Staggering Cost*, *supra* note 28. The average pharmaceutical company cost for developing a new drug ranges from \$4 billion to \$11 billion. *Id.* For company-by-company data on new drug spending, see Appendices I and II. See Leibfarth, *supra* note 17, at 1303.

<sup>95</sup> See *supra* notes 4-6 and accompanying text.

The legislation that empowers and enables the FDA embodies assurances of deference to the practice of medicine—a reflection of the medical profession’s profound influence throughout most of the 20<sup>th</sup> century.<sup>96</sup> Although the discretion of the medical profession has been checked increasingly over the last few decades by conditions on reimbursement, health care management, and consumer pressures, physicians have and continue to enjoy “an especially persuasive claim to authority. Unlike the law and the clergy, [the medical profession] enjoys close bonds with modern science, and at least for most of the last century, scientific knowledge has held a privileged status in the hierarchy of belief.”<sup>97</sup> Physicians hold extraordinary discretion to prescribe drugs that reach pharmacy shelves off label regardless of limits to the scope of clinical data that puts them there.<sup>98</sup> The FDA’s standard for efficacy is to be better than nothing (beat a placebo or sugar pill), new drug sponsors decide what uses they will apply for and control the core breadth of their clinical research knowing that reaching market invites off label uses, and the end result is heavy reliance on actual physician-patient experience over several years to meaningfully understand pharmaceuticals.<sup>99</sup> This reliance is dangerous given physician aversion to reporting adverse events.<sup>100</sup> Doctors do not speak out enough when treatments go badly due to the administrative burden of doing so, conflicts of interest in an age of industry-academia-government collaboration, and fear of professional and legal ramifications driven by awareness that drug sponsors will protect their investments.<sup>101</sup>

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<sup>96</sup> For discussion of the strength, influence, and independence of the medical profession throughout most of the twentieth century, *see generally* PAUL STARR, *THE SOCIAL TRANSFORMATION OF AMERICAN MEDICINE* (1982). *See also* Michael J. Malinowski, *Doctors, Patients, and Pills—A System Popping Under Too Much Physician Discretion? A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Health Care*, 33 *Cardozo L. Rev.* 1085, 1090-99 (2012). The check on FDA authority to ensure deference to the practice of medicine is addressed in *Ass’n of Am. Physicians and Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 218 (D.D.C. 2002) (quoting former FDA Commissioner David Kessler, FDA Comm’r, Address to the American Academy of Pediatrics on Oct. 14, 1992). The House Report that accompanied FDAMA enacted in 1997 (*see supra* note 25 and accompanying text), expressly states that “FDA has no authority to regulate how physicians prescribe approved drugs in the context of their medical practice. Physicians prescribing off-label uses of approved drugs is not within the jurisdiction of the FDA.” H.R. Rep. No. 105-310, at 60 (1997).

<sup>97</sup> STARR, *supra* note 96, at 4.

<sup>98</sup> *See generally* Malinowski, *Doctors, Patients, and Pills*, *supra* note 96.

<sup>99</sup> *See generally id.*

<sup>100</sup> Barry Meier, *Doctors Who Don’t Speak Out*, N.Y. TIMES, Feb. 17, 2013, at 5 (“Doctors also have an aversion to reporting. For instance, while the Food and Drug Administration relies on physicians to help monitor product safety by alerting the agency to adverse patient reactions, doctors usually do not make such filings, saying they are too busy for the paperwork.”). *See also* 60 Minutes, *Prescription Disaster*, Nov. 14, 2004 (interview with clinical researchers who published negative data about Vioxx in peer-reviewed literature and were subjected to professional attacks from Merck, the drug’s manufacturer). An alternative to FDA reporting is to gather data and publish concerns in peer-reviewed medical journals such as *The Journal of the American Medical Association (JAMA)*, the *New England Journal of Medicine*, and *The Lancet*, but discovery and exposure in this manner is piecemeal and takes years, and each of these publications has struggled with conflicts of interest controversies that raise questions about reliability in an age of academia-industry integration. *See Meir* at 5. Congress, with enactment of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Pub. L. No. 110-85, 121 Stat. 823 (codified as amended in scattered sections of 21 U.S.C.), is trying to improve physician reporting of adverse events through the introduction of Sentinel, a more formal surveillance system. *See* Barbara J. Evans, *Congress’ New Infrastructural Model of Medical Privacy*, 84 *NOTRE DAME L. REV.* 585631-32 (2009). However, successful establishment of Sentinel is questionable because of the cost of creating such a system and the requisite change in physician culture to make it work. *See id.*

<sup>101</sup> *See generally supra* note 100. *See* Nathaniel Popper & Bill Vlasic, *Quiet Doctor and Inside Man: In Trading Case, a Parallel Life*, N.Y. TIMES, Dec. 16, 2012, at 1, 20 (financial conflicts of interest raise concerns about the

The FDAMA presumption in favor of putting new drugs on the market conditioned with follow-on clinical research, which the FDA has been lax in enforcing,<sup>102</sup> exacerbates this reliance.<sup>103</sup> Also, clinical medical service (the delivery of care) remains heavily shielded from regulatory intrusion—for example, assisted reproduction procedures which encompass novel technology and use innovation but overall are deemed clinical service (the practice of medicine) and escape regulation as experimentation.<sup>104</sup>

The medical profession, and especially clinical researchers, embrace technology and contribute to the concept of invisible death—the belief that death may be trumped through science, as addressed above.<sup>105</sup> The medical profession’s mission is to treat and heal, so it is understandable that “Some doctors may feel that the moment they break the bad news about a terminal illness is the point at which they have nothing more to offer.”<sup>106</sup> As observed by Dr. David Kuhl based upon more than fifteen years of end-of-life palliative care of patients, “One of the most difficult times in the doctor-patient relationship is the moment when the doctor breaks the news that the disease process will likely result in death. Both suffer, and each has his own coping mechanisms.”<sup>107</sup> As illustrated by Joe’s experience,<sup>108</sup> general practitioners and clinical

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extent to which release of negative clinical data is delayed and its overall integrity). Drug and device manufacturers often interact with physicians in an ongoing manner, including through consulting and sponsored research agreements that may create a sense of loyalty and even impose a silence obligation. *See generally* Meir, *Don’t Speak*, *supra* note 85. Accordingly, these manufactures hold considerable influence, which is exacerbated in many medical specialties:

For example, when Dr. Lawrence D. Dorr, an orthopedic specialist, warned fellow surgeons in an open letter in 2008 that a hip implant made by Zimmer Holdings was flawed, he became the subject of a whisper campaign that questioned his skills as a surgeon. “The first thing that a company does is to put out a campaign that a surgeon does not know how to operate,” said Dr. Dorr, who was a consultant to Zimmer when he wrote the letter. “It hurt my practice for a year.”

*Id.* at 5. Researchers who published data questioning Vioxx also experienced professional attacks, which reached their employers. *See Prescription Disaster*, *supra* note 85.

<sup>102</sup> *See generally* GAO FDA REPORT, *supra* note 89; IOM REPORT, *supra* note 89.

<sup>103</sup> *See* Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35, at 379-81 (addressing the codification of this presumption under section 506B and the “fast track” provisions of FDAMA).

<sup>104</sup> *See generally* Symposium, *A Law-Policy Proposal to Know Where Babies Come from During the Reproductive Revolution*, 9 IOWA J. RACE & GENDER 549 (2006) (live and published symposium); Michael J. Malinowski, *Choosing the Genes of Children: Our Eugenics Past—Present and Future?*, 36 CONN. L. REV. 125 (2003).

<sup>105</sup> *See supra* note 77 and accompanying text.

<sup>106</sup> KUHL, WANT, *supra* note 106, at 61.

<sup>107</sup> *Id.* at 53.

<sup>108</sup> *See supra* note 4-6 and accompanying text. Autologous bone marrow transplants in thousands of breast cancer patients during the 1990s provides another vivid example of patients subjected to fates worse than death through experimental treatments that actually accelerated the end of their lives:

The most noted recent example is the use of autologous bone marrow transplants in women with breast cancer, an extraordinarily dangerous, painful, and costly treatment given to thousands of women in the 1990s. The study supporting the assumption of the efficacy of the treatment and relied on for more than a decade while contrary data was slowly compiled now has been discredited and is accompanied by allegations of scientific misconduct and research fraud.

Michael J. Malinowski, *Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities, and Lost Opportunities*, 41 JURIMETRICS J. 23 (2000), citing Gina Kolata & Kurt Eichenwald, *Insurer Drops a Therapy for Breast Cancer*, N.Y. TIMES, Feb. 16, 2000, at A24; *Cancer Study Shuns Bone Marrow Therapy*, N.Y. TIMES, Mar. 4, 2000, at A16, 24. The treatment involved extracting healthy stem cells from the patient’s bone marrow,

researches alike frequently disengage and shift interface with the patient to nurses and other health care providers.<sup>109</sup> In such situations, general practitioners often are eager to refer patients they cannot treat to clinical researchers and experimentation—thereby moving situations from confrontation with death to treatment options, however unlikely to result in positive outcomes and in spite of the risk of adverse events, considerably more pain and suffering, and the lost opportunity for comfort and closure at the end of life. When these opportunities are presented, many terminally ill patients are eager to exchange quality of life and endure even significantly more pain and suffering and acceleration of life’s end for any opportunity to fend off death through science.<sup>110</sup>

U.S. medical education and medical practice center on science at a cost to the doctor-patient relationship:

What happens in a changing field of medicine, where we have to ask ourselves whether medicine is to remain a humanitarian and respected profession or a new but depersonalized science in the service of prolonging life rather than diminishing human suffering? Where the medical students have a choice of dozens of lectures on RNA and DNA but less experience in the simple doctor-patient relationship that used to be the alphabet for every successful family physician?<sup>111</sup>

Too often experimental treatments are embraced as a substitute for palliative care, meaning comfort care at the end of life, rather than presented as an alternative with palliative care defined and explained as a legitimate treatment option.<sup>112</sup> Palliative care, mistakenly, often is equated with acceleration of the end of life by both physicians and patients. In fact, palliative care is about focusing on the patient. To be specific, priority is placed on communication with the patient and maximizing comfort—the avoidance of human suffering when possible, not necessarily accelerating death.<sup>113</sup> There are ample instances where comfort care has extended life beyond other treatment alternatives.<sup>114</sup> Often quality palliative care gives those who are terminally ill an incentive to fight harder and to live longer, and to decline invasive treatment

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bringing the patient to the brink of death through radically high doses of chemotherapy or radiation that wiped out their bone marrow, and then reintroducing the bone marrow extracted earlier. *See generally* Kolata & Eichenwald, *supra*; *Cancer Study, supra*. Given the depletion of their immunity systems, these patients often spent the end of their lives in a state of isolation from family and friends and in excruciating pain, and by most accounts the end of life was accelerated. *See generally id.* It is important to note, however, that advances in stem cell research subsequent to the controversy in the 1990s has introduced reconsideration of the treatment. *Cf.* Owen C.B. Hughes, Alan L. Jakimo, & Michael J. Malinowski, *United States Regulation of Stem Cell Research: Recasting Government’s Role and Questions to be Resolved*, 20 HOFSTRA L. REV. 101-161 (2009).

<sup>109</sup> KUHLMAN, *supra* note 106, at 38 (“People expect their doctors to be there for them through their illnesses, but it doesn’t always happen. In fact, for some it’s the opposite.”).

<sup>110</sup> *See generally supra* part III.A. *Cf.* NELKIN & LYNDÉE, *DNA MYSTIQUE, supra* note 88.

<sup>111</sup> *See* KUBLER-ROSS, *DYING, supra* note 82, at 10.

<sup>112</sup> *See generally* Kathleen Tschantz Unroe & Dr. Diane E. Meier, *Palliative Care and Hospice: Opportunities to Improve Care for the Sickest Patients*, 25 NOTRE DAME J. L. ETHICS & PUB. POL’Y 413 (2011). For general discussion of palliative care inside and outside of the context of hospice care, *see supra* note \_\_\_ and accompanying text.

<sup>113</sup> *See generally* Unroe & Meier, *Palliative Care, supra* note 95; Palliative Care Center, *supra* note 95; Hertzberg Institute, *supra* note 95.

<sup>114</sup> *See supra* note \_\_\_ and accompanying text.

more likely to accelerate death than to postpone it.<sup>115</sup> Palliative care is not possible unless the patient is humanized, and the individual patient and their comfort are the epicenter for treatment decision making, albeit with the option of gambling with experimental treatments still available.

### C. The Drug Developer's Perspective

Drug developers are under crushing pressure to continue decades of high performance for investors,<sup>116</sup> but the transition from traditional drug development to biotechnology-based R&D with all of its specificity, complexity, and environmental influence is proving difficult, to say the least.<sup>117</sup> “The average drug developed by a major pharmaceutical company costs at least \$4 billion, and it can be as much as \$11 billion.”<sup>118</sup> In spite of this enormous investment, 2007 was the worse year in a quarter of a century for new drug approvals, and the following years have not been much more fruitful.<sup>119</sup> Commercial drug development is struggling in a stage of puberty.<sup>120</sup> The situation is dire enough for the federal government to propose an intervention.<sup>121</sup> The crude FDA standard for new drug approvals (shared among the top global pharmaceutical markets through the International Conference on Harmonisation, ICH)—group design based upon mathematical abstracts encompassing statistics, averages, and medians—is driving drug developers to engage in voluminous human clinical trials in an effort to make medical sense out of the human genome.<sup>122</sup> Over the last six years, the typical phase III trial has ballooned from 3,000 to 10,000 subjects at enormous expense.<sup>123</sup>

Industry received what it bargained for through FDAMA, and the end result is a race to the bottom for the major players.<sup>124</sup> Based upon drug development performance over the last

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<sup>115</sup> *See id.*

<sup>116</sup> “Throughout much of the twentieth century and into the present one, pharmaceutical research and development (“R&D”) has been *the* most profitable sector.” Malinowski & Gautreaux, *Drug Development*, *supra* note 28, at 386, quoting MARCIA ANGELL, *THE TRUTH ABOUT DRUG COMPANIES*, at xv (2004).

<sup>117</sup> *See generally* Malinowski & Gautreaux, *Drug Development*, *supra* note 28; Malinowski & Gautreaux, *All that is Gold*, *supra* note 30. *Cf.* G. Steven Burrill, *Polishing the Crystal Ball: G. Steven Burrill Predicts What's Ahead for Biotech in 2009*, BURRILL REP. (Jan. 2, 2009), <http://www.burrillreport.com/article-980.html>. The FDA approved eighteen innovative new drugs in 2007, twenty-four in 2008, and twenty-six in 2009. Ed Silverman, *How Many New Drugs Did FDA Approve Last Year?*, PHARMALOT (Feb. 18, 2011, 9:35 AM), <http://www.pharmalot.com/2011/02/how-many-new-drugs-did-fda-approve-last-year>; New Drug Approvals on Pace to Exceed 2008 Total, Res. Recap (June 9, 2009), <http://www.alacrastore.com/blog/index.php/2009/06/09/new-drug-approvals-on-pace-to-exceed-2008-total>. But see Miho Nagano, *Big Pharma Looks for a Fix*, INVESTOR'S BUS. DAILY, Sept. 29, 2008, at A9 (stating seventeen approvals in 2007).

<sup>118</sup> Matthew Herper, *The Truly Staggering Cost of Inventing New Drugs*, FORBES MAG., Feb. 10, 2012, available at <http://www.forbes.com/sites/matthewherper/2012/02/10/the-truly-staggering-cost-of-inventing-new-drugs/> (last visited Apr. 11, 2013).

<sup>119</sup> Jared A. Favole & Jennifer Corbett Dooren, *FDA Approved More Drugs in 2008*, WALL ST. J., Jan 2009, at A9; Asher Mullard, *2010 FDA Drug Approvals*, 10 NATURE REVIEWS: DRUG DISCOVERY 82, 84 tbl. 1 (2011) (listing CDER's 2010 approvals in chart form).

<sup>120</sup> *See generally* Malinowski & Gautreaux, *Drug Development*, *supra* note 28; Malinowski & Gautreaux, *All that is Gold*, *supra* note 30.

<sup>121</sup> Gardiner Harris, *A New Federal Research Center Will Help to Develop Medicines*, N.Y. TIMES, Jan. 23, 2011, at A1 (quoting Dr. Francis S. Collins, Director of the National Institutes of Health, in a story on the federal government's decision to launch a billion-dollar drug development center to help industry create new pharmaceuticals).

<sup>122</sup> *See supra* notes \_\_\_ and accompanying text.

<sup>123</sup> *See supra* notes 29 and 103 and accompanying text.

<sup>124</sup> *See generally supra* note 99 and accompanying text. *Cf.* Herber, *Cost*, *supra* note 28.



decade in spite of the infusion of a universe of advancement in basic genetic science, myriad enabling technologies, and enormous financial investment, the critics are right—the proof is in the outcome: “[S]ome critics have taken issue with the amount of regulatory liberalization already taken by the FDA since the late 1980s, suggesting that the FDA and the public have misplaced their faith in science.”<sup>125</sup> The group design base science standard for FDA review—efficacy approval based upon the mathematical abstracts of means, medians, averages, and statistics, which actually may not reflect any individual who participated in the studies, followed by at times carte blanche off label use by the medical profession—is antiquated and no reflection of the technical specificity of biotechnology which centers on understanding disease pathways, gene and environment interactions, and fundamentally why disease happens.<sup>126</sup>

Treatment IND applications and Compassionate Uses allow the sponsors of potential new drugs to recoup some manufacturing costs, and they may generate additional data that helps to advance clinical trials.<sup>127</sup> However, increased access to experimental drugs has led to an inability to separate the scope of recovery from the reality that almost all experimental drugs never will prove effective, at least not effective enough to overcome safety concerns, and many may prove extremely harmful. The failure rate of new drug candidates in clinical trials exceeds ninety percent, and that is just against a science standard to beat a placebo based upon group design and mathematical abstracts—be better than nothing, with a level of adverse events that is deemed acceptable.<sup>128</sup> Even drugs that complete the FDA clinical trial process and are approved for market use cause enormous harm to human health: Adverse drug reactions cause more than 100,000 deaths and more than two million hospitalizations annually in the United States—meaning that more people in the United States die from legal use of prescription medications than from automobile accidents.<sup>129</sup> Basic science has been delivering—a map of the human genome is in hand and basic science continues to explode with progress—so faith in science has elevated legitimately, while drug development lingers and disappoints. Drawing potential subjects away from clinical trials through alternative access to experimental treatments and increasing pre-approval manufacturing pressures by added demands on supply will only

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<sup>125</sup> Leibfartha, *supra* note 35, at 1303. See Appendix I & II; Herber, *Cost*, *supra* note 28.

<sup>126</sup> See generally Malinowski & Gautreaux, *Drug Development*, *supra* note 28; Malinowski & Gautreaux, *All that is Gold*, *supra* note 30; *Doctors, Patients and Pills*, *supra* note 81. For discussion of the potential utility of a single subject study design approach to end-of-life decision making (drawn from the field of applied behavior analysis), see generally LAWRENCE E. FRALEY, *DIGNIFIED DYING—A BEHAVIOROLOGICAL THANATOLOGY* (2012).

<sup>127</sup> CITE FROM MY BIOTECH TREATISE—CITES THAT COVER RECOUPING ACTUAL COSTS. *Charging for Treatment Use of Investigational Drugs*. Ordinarily, sponsors or investigators may not charge for investigational drugs involved in clinical trials. FDA considers the cost of distributing drugs for investigational purposes to be part of the normal cost of doing business (unless the sponsor can show that charging subjects for the cost of the drug is necessary to enable the sponsor to undertake the clinical trial) [21 CFR 312.7(d)(1)]. Treatment use, however, is not part of a clinical trial and is therefore not considered to be a normal cost of doing business. Rather, the Treatment IND was created to encourage drug manufacturers to make potentially lifesaving drugs available to those desperately in need of them while the FDA review process is in motion. The prerequisite for charging for investigational drugs is that, in addition to approval of treatment IND status, the sponsor must notify FDA in writing in an information amendment submitted under §312.31. The FDA may withdraw authorization to charge for treatment use drugs if it finds that the requirements of §312.7 are no longer being met [21 CFR 312.7(d)(4)].

<sup>128</sup> See Herper, *supra* note 28. See generally *supra* note 79 and accompanying text.

<sup>129</sup> Malinowski, *Pills*, *supra* note 81, at 115, citing Barkur Sriram Shastry, *Pharmacogenetics and the Concept of Individualized Medicine*, 6 *PHARMACOGENOMICS J.* 16, 16-21 (2006); Robert Pear, *New Plan for Patients to Report Medical Mistakes*, *N.Y. TIMES*, Sept. 23, 2012, at 22.

complicate the drug development challenge.<sup>130</sup> Using experimental drugs outside of the controls of clinical trials also increases the risk of adverse events, which require inquiry and may delay market approval.

Drug developers need a jolt to snap into the realities of contemporary science and deliver new drugs accordingly. In the meantime, the terminally ill in the U.S. with health care coverage and their health care providers continue to scour all possibilities to postpone death. The challenge is to intervene and to promote consideration of the quality of life and comfort over a possibility of some added duration of life accompanied by the risk of accelerated death and grave human suffering unless a fully informed patient opts for the latter after considering the former.

#### **D. The Regulator's (FDA's) Perspective**

FDAMA expanded the mission of the FDA to include efficiency along with efficacy and safety, meaning to speed things up through more cooperation with drug sponsors.<sup>131</sup> There lingers a misconception among many in the general public, scholars, government officials, and industry representatives that the FDA imposes a paternalistic gold standard for new drug approvals and market entry: "Historically, the American Public clamored for increased FDA regulation of new drugs; however, more recent criticism has focused on how the FDA's 'gold standard' impedes consumer access to new, potentially lifesaving treatments."<sup>132</sup> In fact, the FDA science standard, based up group averages, medians, means and other mathematical abstracts lingers as a remnant from the pharmaceutical past, with its focus on taking away symptoms, rather than a reflection of the drug development present and future centered on the specificity of human genetics and intervention in disease pathways.<sup>133</sup> The proof is in the outcome: a troubling drop-off in new drug approvals in spite of an enormous increase of financial investment in biopharmaceutical R&D and the infusion of myriad enabling technologies, including a map of the human genome.<sup>134</sup> The FDA's regulation of drugs it puts

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<sup>130</sup> See, e.g., ROBERT BAZELL, *THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER* (1998). Genentech faced tremendous consumer demand from terminally ill breast cancer patients while Herceptin still was being evaluated by the FDA. Accordingly, the company shifted the supply it could provide after meeting its FDA clinical trial requirements to the National Cancer Institute, which distributed Herceptin through a national lottery system. See generally *id.*

<sup>131</sup> See *supra* note 17 and accompanying text (PDUFA discussion); James L. Zelenay, Jr., *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 *FOOD & DRUG L.J.* 261, 295 (2005) ("PDUFA II[, enacted in conjunction with FDAMA,] shifted the agency's focus from one based solely on protecting the public from unsafe and ineffective products, possibly at the cost of expediency, to one that must balance this interest in safety with an interest in providing patients with speedy access to new drugs."); Christopher D. Zalesky, *Considering Changes to CMS's National Coverage Decision Process: Applying Lessons Learned from FDA as a Regulator of Access to Healthcare Technology*, 57 *FOOD & DRUG L.J.* 73, 74-75 (2002).

<sup>132</sup> Leibfarth, *supra* note 35, at 1286. See, e.g., RICHARD A. EPSTEIN, *OVERDOSE: HOW EXCESSIVE GOVERNMENT REGULATION STIFLES PHARMACEUTICAL INNOVATION* (2006); DAVID GRATZER, *THE CURE: HOW CAPITALISM CAN SAVE AMERICAN HEALTH CARE* (2006).

<sup>133</sup> See generally Michael J. Malinowski & Grant G. Gautreaux, *All that is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global "Gold Standard" for Drug Research and Development*, 45 *CORNELL INT'L L. J.* 185 (2012); Malinowski & Gautreaux, *State of Puberty?*, *supra* note 35.

<sup>134</sup> In spite of enormous increases in R&D investment, new drug approvals slumped to a twenty-five year low in 2007; 2008 and 2009 were not much better. See Malinowski & Gautreaux, *State of Puberty*, *supra* note 78, at 392-399. See *supra* note 111 and accompanying text.

on the market also leaves much to be desired as exemplified by the recalls of drugs on pharmacy shelves for years such as the COX-2 inhibitors Vioxx and Bextra,<sup>135</sup> and as concluded by both the Institutes of Medicine (IOM) and Government Accountability Office in their 2006 assessments of the FDA.<sup>136</sup> This poor performance inspired Congress to enact the sweeping FDAAA.<sup>137</sup>

The issue of access for those terminally ill to experimental treatments is regulatory and legislative at its core, not a judicial matter, as recognized by the Supreme Court in *Rutherford*,<sup>138</sup> by the D.C. Circuit in *Abigail Alliance*, and by the Supreme Court again in 2008 through its denial of *Abigail Alliance*'s petition for certiorari.<sup>139</sup> Therefore, Congress, DHHS (through OHRP), the FDA, and arguably CMS given the health care finance implications and implementation of PPACA, must work through this matter, individually or collectively.<sup>140</sup> The FDA clinical trial process, albeit open too wide with its better-than-nothing efficacy standard coupled with a showing of tolerable safety, is at least a gate providing some quality control that distinguishes approved and experimental treatments.<sup>141</sup> While adverse events caused by FDA-approved pharmaceuticals that have completed the clinical trial process raise serious concerns, the greater than ninety-percent failure rate of experimental drugs demands extreme caution in comingling them with patient care.<sup>142</sup> In addition to complicating compliance with the informed consent requirements under the Common Rule and FDA regulations to protect human subjects, processing compassionate use and treatment IND applications draws from the FDA's resources—especially when adverse events outside of clinical trials raise concerns that spill into them.

#### **IV. A Law-Policy Proposal to Modify Human Subject Protection of the Terminally Ill**

“[B]irth, and lust, and illness, and death are changeless things, and when one of these harsh facts springs out upon a man at some sudden turn of the path of life, it dashes off for the moment his mask of civilization and gives a glimpse of the stranger and stronger face below.”

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<sup>135</sup> Consumer Guide, *Vioxx Recall and Vioxx Side Effects*, available at <http://www.vioxxconsumerguide.com/> (last visited Apr. 11, 2013) (Merck recall); CNN Money, *Pfizer Pulls Bextra Off the Market*, available at <http://money.cnn.com/2005/04/07/news/fortune500/bextra/> (last visited Apr. 11, 2013).

<sup>136</sup> See generally GAO FDA REPORT, *supra* note 75; IOM FDA REPORT, *supra* note 75.

<sup>137</sup> Pub. L. No. 110-85, 121 Stat. 823, 904-905 (2007). See *supra* note 20 and accompanying text. See generally Evans, *New Model*, *supra* note 85.

<sup>138</sup> See *supra* note \_\_ and accompanying text.

<sup>139</sup> See *supra* notes \_\_ and accompanying text.

<sup>140</sup> See *supra* notes \_\_ and accompanying text.

<sup>141</sup> “The FDA regulatory scheme, mandating three phases of clinical trials as well as evidence of safety and effectiveness, provides information on which an individual can base a meaningful choice.” Leibfarth, *supra* note 35, at 1304. See George J. Annas, *Faith (Healing), Hope and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771, 773, 786 (1989) (discussing tensions between the research agendas of medical researchers and therapeutic hopes of patients confronting terminal illness); Michael D. Greenberg, *Information, Paternalism, and Rational Decision-Making: The Balance of FDA New Drug Approval*, 13 ALB. L.J. SCI. & TECH. 663, 333 (2003).

<sup>142</sup> See *supra* note 109 and accompanying text. See e.g., Daniel Engber, *How One Scientist's Losing Battle Against His Own Cancer Might Save the Rest of Us*, NEW YORK TIMES MAG., Dec. 23, 2011, 32-38 (Bayer's refusal to allow its experimental drug to be comingled with a vaccine).

Joe’s story illustrates the best and worst health care outcomes for the terminally ill who access experimental treatments.<sup>144</sup> More than fourteen years of productive life shifted into nine months of enduring what Joe himself ultimately referred to as a fate worse than death during his final days. Belief in science and medicine runs deep in U.S. culture,<sup>145</sup> but the reality of drug development is a greater than ninety-percent failure rate of new drug candidates,<sup>146</sup> and only one-third of medications that satisfy the FDA safety and efficacy standards perform as anticipated when prescribed to patients.<sup>147</sup> According to the Institute of Medicine, there are approximately two million serious adverse drug reactions each year that require hospitalization and cause 100,000 deaths—more than from work-place and motor vehicle accidents.<sup>148</sup>

This time of sweeping federal and state health care reforms through PPACA implementation, reconsideration of the Common Rule, and expansive, ongoing clinical research presents an opportunity to improve health care decision making at the end of life fundamentally and substantially. The following discussion proposes law and policy reforms to heighten protection of the terminally ill who seek experimental treatments without unduly impeding clinical research and responsible access to experimental treatments.

### **A. Classification of the Terminally Ill as a “Vulnerable Group”**

The terminally ill should be directly and fully recognized as a “vulnerable group” under the Common Rule and FDA regulations in a manner on par with pregnant women, fetuses, children, prisoners, and those who are cognitively impaired; review and oversight of research on them should be subjected to stricter scrutiny; and more protections tailored to the specific vulnerabilities of the terminally ill should be introduced.<sup>149</sup> The protections should be especially strong and encompass multiple sets of vulnerable group considerations where patients are both terminally ill and a member another recognized protected group—for example, terminally ill children. As explained by Professor George Annas, “Incapacitated and hospitalized because of illness, frightened by strange and impersonal routines, and fearful for his health and perhaps life,

<sup>143</sup> SIR ARTHUR CONAN DOYLE, *The Curse of Eve*, in *ROUND THE RED LAMP* 82 (2011).

<sup>144</sup> See *supra* notes \_\_ and accompanying text.

<sup>145</sup> See *supra* notes \_\_ and accompanying text.

<sup>146</sup> See *supra* note \_\_ and accompanying text.

<sup>147</sup> Jeffrey P. Braff et al., *Patient-Tailored Medicine, Part Two: Personalized Medicine and the Legal Landscape*, 2 *J. Health & Life Sci. L.* 1, 9, 16-17 (2009). See also Jeffrey P. Braff et al., *Patient-Tailored Medicine, Part One: The Impact of Race and Genetics on Medicine*, 2 *J. HEALTH & LIFE SCI. L.* 1 (2008).

<sup>148</sup> See *supra* note \_\_ and accompanying text. While some of these adverse reactions derive from errors when prescribing and dispensing the medications, many of them are attributable to variations among individuals, such as how they metabolize the drugs. Braff, *Personalized Medicine*, *supra* note 128, at 9. B.S. Shastry, *Pharmacogenetics and the Concept of Individualized Medicine*, 6 *PHARMACOGENOMICS J.* 16, 16 (2006). For a discussion of the tremendous variability in the practice of medicine for the same diagnoses, see John Carey, *Medical Guesswork: From Heart Surgery to Prostate Care, The Health Industry Knows Little About Which Common Treatments Really Work*, 3989 *BUS. WK.* 72 (2006). See also Petra A. Thürmann, *Prescribing Errors Resulting in Adverse Drug Events: How Can They Be Prevented?*, 5 *EXPERT OPINION ON DRUG SAFETY* 489, 489-93 (2006); Kathryn A. Phillips et al., *Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review*, 286 *JAMA* 2270, 2270-79 (2001).

<sup>149</sup> See *supra* note \_\_ and accompanying text. Karen J Schwenzer, *Protecting Vulnerable Subjects in Clinical Research: Children, Pregnant Women, Prisoners, and Employees*, 53 *RESPIRATORY CARE* 1342-1349 (2008).

[the patient] is far from exercising a free power of choice when the person to whom he anchors all his hopes asks [him to help] . . . carry out some very important research . . . .”<sup>150</sup> The Department of Health and Human Services acknowledged the particular human subject vulnerabilities of those who are terminally ill in a 1993 guidance, but the same guidance also supports expanded access outside of controlled trials, and it has not been formalized into regulations or even updated in two decades.<sup>151</sup> Although the Alliance and its supporters continue to propose reductions of regulatory standards to increase access to experimental treatments for those who are terminally ill,<sup>152</sup> heightened protection of research subjects and access to experimental treatments are not mutually exclusive. For instance, relative to clinical research overall, more biomedical research on pregnant women and children takes place today than any time in the past.<sup>153</sup> As recognized in *Rutherford*, “the concept of safety . . . is not without meaning for terminal patients. For the terminally ill, as for anyone else, a drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit.”<sup>154</sup>

During the informed consent process with those who are terminally ill, human subject protection regulations should mandate the presentation of palliative care inside and outside of hospice care as a treatment option in a manner comparable with the experimental treatment option.<sup>155</sup> In addition to the quality of life and other benefits of palliative care,<sup>156</sup> there is evidence that palliative care prolongs life:<sup>157</sup>

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<sup>150</sup> George J. Annas, *Faith (Healing), Hope and Charity at the FDA: The Politics of AIDS Drug Trials*, 34 VILL. L. REV. 771, 773 (1989) (discussing tensions between the research agendas of medical researchers and therapeutic hopes of patients confronting terminal illness); *id.* at 777 (inequality in bargaining power).

<sup>151</sup> See generally OFFICE FOR HUMAN RESEARCH PROTECTIONS, TERMINALLY ILL PATIENTS, *supra* note \_\_ (“Two important reasons for concern regarding research involving terminally ill persons are: (1) they tend to be more vulnerable to coercion or undue influence than healthy adult research subjects; and (2) research involving the terminally ill is likely to present more than *minimal risk*.”).

<sup>152</sup> See *supra* notes 36-42 and accompanying text; see *infra* Part IV.B.

<sup>153</sup> Legislative and regulatory initiatives, namely the Best Pharmaceuticals for Children Act, Best Pharmaceuticals for Children Act of 2002, Pub. L. No. 107-109, 115 Stat. 1408 (codified as amended in scattered sections of 21 and 42 U.S.C.); Orphan Drug Act, Pub. L. No. 94-414 § 526(a)(2), 96 Stat. 2049 (1983) (revised 2000) (codified as amended at 21 U.S.C. §360bb (2006)), and the NIH’s Women’s Health Initiative, <http://www.nhlbi.nih.gov/whi/> (last visited Apr. 12, 2013), have incentivized research on these groups. See Malinowski, *Pills*, *supra* note 81, at n.213 and accompanying text; Malinowski, *Drug Development*, *supra* note 28, at 35, 263-268 and accompanying text. Prior to the introduction of these incentives, industry often failed to engage in research tailored to women and children even for pharmaceuticals obviously prescribed to them. This research was avoided by industry for decades—even for pharmaceuticals obviously prescribed to women and children (e.g., use of asthma drugs in a child patient population). Similar to the approach used often by veterinarians, pediatricians were forced to guesstimate prescription dosages based upon weight.

<sup>154</sup> *Rutherford v. United States*, 442 U.S. 544, 5555-56 (1979). The Court emphasized section 505 of the FDCA, which requires the FDA to assess “whether or not [a] drug is safe for use and whether such drug is effective in use” before approving its introduction into interstate commerce. 21 U.S.C. sec. 355(b) (2000).

<sup>155</sup> For discussion of palliative care inside and outside the context of hospice care, see *supra* note \_\_ and accompanying text.

<sup>156</sup> See *id.*

<sup>157</sup> Unroe & Meier, *Opportunities*, *supra* note \_\_, at 420 (citing multiple sources). More U.S. government-sponsored palliative care research is necessary: three Institute of Medicine report, two National Institute of Health state-of-science conferences, and a report from the research committee of the American Academy of Hospice and Palliative Medicine simply is not enough data to maximize quality in end-of-life care and medicine. See *id.* at 425.

In contrast to many assumptions that palliative care and hospice care may hasten death, recent studies have demonstrated that palliative care and hospice may be associated with prolongation of life. An analysis of nearly 4,500 Medicare patients with heart failure or cancer found that survival of patients who received some hospice services was nearly a month longer than patients who did not receive hospice. A recent study randomized patients with advanced lung cancer to receive palliative care along with standard oncology care as compared with patients receiving only standard oncology care. Although the patients receiving palliative care along with best cancer care were less likely to receive aggressive care, they had an improved survival benefit of 2.7 months compared to the best cancer care only control group.

Despite the association between hospice and giving up on treatment for the terminal illness, a precondition to qualify for the Medicare Hospice benefit,<sup>158</sup> there has been a surge in use of hospice services during the last decade: approximately forty percent of all deaths in the U.S. in 2009 (1.56 million patients) involved use of hospice services.<sup>159</sup> Unfortunately, these hospice stays are brief (the median duration of stay is just twenty to twenty-one days),<sup>160</sup> which “reduce[s] the opportunity for patients and their families to receive the full benefit of hospice services and also limit[s] the ability of hospice care to have a positive impact upon the use of other health care resources, i.e., reducing avoidable hospitalizations and other intensive services or procedures near the end of life.”<sup>161</sup>

The presentation of palliative care as a treatment option in research and a mandatory component of the informed consent process would require that the institutional review boards (IRBs) overseeing research on the terminally ill include members with substantial palliative care professional expertise and experience.<sup>162</sup> The American Board of Internal Medicine has recognized palliative medicine as a subspecialty since 2006, and the American Board of Nursing Specialties has accredited a master’s-level hospice and palliative care certification program since 2007.<sup>163</sup> The first physician palliative subspecialty exam was administered in 2008 and, as of

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<sup>158</sup> See *supra* note \_\_ and accompanying text. However, in Medicare and the Medicaid and Children’s Health Insurance Program, Concurrent Care Demonstration Projects are underway. These projects allow patients to receive potentially life-prolonging treatments with hospice services, and outcomes are studied for quality of life, patient care, and cost-effectiveness. Unroe & Meier, *Opportunities*, *supra* note \_\_, at 426, citing PPAC, Pub. L. No. 111-148, § 3004, 124 Stat. 440 (2010).

<sup>159</sup> Nat’l Hospice & Palliative Care Org., NHPCO Facts and Figures: Hospice Care in America 4 (2010), *available at* [http://www.nhpc.org/files/public/Statistics\\_Research/Hospice\\_Facts\\_Figures\\_Oct-2-1-.pdf](http://www.nhpc.org/files/public/Statistics_Research/Hospice_Facts_Figures_Oct-2-1-.pdf).

<sup>160</sup> *Id.* at 5.

<sup>161</sup> Unroe & Meier, *Opportunities*, *supra* note \_\_, at 421 .

<sup>162</sup> IRBs, prescribed under the Common Rule, enforce the protection of human subjects in all federally funded research. See 21 CFR Part 56, 21 CFR 312.34(c). See *infra* notes \_\_ and accompanying text. Ideally, though often not practicable, IRBs overseeing research on the terminally ill also will including individuals who have faced terminal illness themselves and survived:

Only people with a terminal illness know what it is like to live with such an illness. They are the people who hold the knowledge, who know the lived experience of having a terminal illness. They are our best teachers. They are the ones who could answer my questions. How might they be heard and understood? How could I learn to listen, to really listen to what people were saying rather than to listen for the information I wanted to hear?

KUHL, WANT, *supra* note 106, at xix.

<sup>163</sup> Unroe & Meier, *Opportunities*, *supra* note \_\_, at 423-424.

2011, there were approximately seventy certified post-graduate fellowship-training programs in palliative medicine—which supports the feasibility of this proposal.<sup>164</sup> However, in spite of the inevitability of death and pervasiveness of terminal illness within the scope of delivery of care, palliative care training has not become a staple in medical education or residency programs.<sup>165</sup>

While the increasing availability of clinical palliative care programs represents forward progress in the field, workforce development lags behind. Multiple national reports have called attention to this issue. The 2001 Institute of Medicine (IOM) report *Improving Palliative Care for Cancer* states that “[m]ost new physicians leave medical school and residency program with little training or experience in caring for dying patients. It reports that appropriately trained nurses and social workers are also in short supply. The IOM report makes the following recommendations to improve training in medicine, nursing, and social work: (1) faculty development; (2) education materials and curriculum development; (3) coordination among training programs for the variety of professionals involved in the care of dying patients; (4) guidelines for residency programs and increased palliative and end-of-life content in licensing and certifying examinations; and (5) improving the research base for palliative care education.

Standard of care, professional liability, and market forces—especially in an age of increased privatization of and commercialization of hospitalization and delivery of care—suggest that recognizing and utilizing palliative care professionals under the Common Rule and through PPACA implementation as proposed below<sup>166</sup> should enhance demand for palliative care expertise, increase overall recognition of the field, and improve the relevant professional education and training.

The informed consent process should be rigorous enough to convey the risk that access to an experimental treatments will mask the real possibility of death and sacrifice an opportunity to make “invisible death” visible—meaning to accept death and, relative to the alternative, to find considerable comfort in the final phase of life.<sup>167</sup> “For some people, learning that they have a terminal illness is a gift of time to pay close attention to who they really are, discover the sense of a high power, and grow in self-acceptance and love. As this spiritual discovery unfolds, the fear of death is diminished or even eliminated.”<sup>168</sup> As observed by Elisabeth Kubler-Ross in *On Death and Dying*, a compilation of insights culled from decades of personal experience working with the terminally ill:<sup>169</sup>

If a patient is allowed to terminate his life in the familiar and beloved environment, it requires less adjustment for him. His own family knows him well enough to replace a sedative with a glass of his favorite wine; or the smell of a home-cooked soup may give him the appetite to sip a few spoons of fluid which, I think, is still more enjoyable than an

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

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

<sup>166</sup> See *infra* Part IV.D.

<sup>167</sup> See *supra* notes 63, 90 and accompanying text.

<sup>168</sup> KUHLMAN, *supra* note 106, at 269; *id.* at 227 (“Because they know that they cannot escape death, they embrace life—their own life. The ‘prescription’ of how to live given by family, culture, profession, religion, or friends loses its grasp. Perhaps, in this way, knowing that you have a terminal illness is of value.”).

<sup>169</sup> KUBLER-ROSS, *DYING*, *supra* note 82, at 5-6.



infusion. I will not minimize the need for sedatives and infusions and realize full-well from my own experience as a country doctor that they are sometimes life-saving and often unavoidable. But I also know that patience and familiar people and foods could replace many a bottle of intravenous fluids given for the simple reason that it fulfills the physiological need without involving too many people and/or individual nursing care.

As a prerequisite for consideration, IRBs reviewing research proposals that expose the terminally ill to experimental treatments should require investigators and research sponsors to establish clear criteria necessitating removal of subjects from the studies and encouragement to transition into palliative care treatments with options to do so fully identified and accompanied by administrative support to make such transitions both doable and as non-stressful as possible under the circumstances. They also should mandate provisions to maximize ongoing IRB oversight with periodic reassessment of the subjects' conditions accompanied by disclosure to them and renewed consultation about the palliative care alternative options. Moreover, the investigators and sponsors of such studies should be required to establish with specificity an obligation to cover the costs of palliative care treatments not otherwise reimbursed by the subjects' health insurances—or to make such coverage a prerequisite for study participation—for those who withdraw from or who are otherwise removed from these studies at any time. Study sponsors should be required to put the resources needed to meet this obligation in trust prior to commencement of the studies.

Discussion of end-of-life scenarios should be accompanied by execution of legal instruments recognized in the relevant jurisdictions that formalize final wishes, ensure the individual's control over the end of their life, avoid judicial intervention under the doctrine of substituted judgment,<sup>170</sup> and spare family members and close friends from speculation and the stress of life-and-death decision making for loved ones.<sup>171</sup> Living wills, directives, and proxies now are being shored up by adding medical orders signed by a doctor, known as Physician Orders for Life Sustaining Treatment (POLST), which are entered in the medical record.<sup>172</sup> “With these physician orders, the doctor, or in some states a nurse practitioner or physician assistant, leads conversations with patients, family members and surrogates to determine whether a patient with advanced illness wants aggressive life-sustaining treatment, a limited intervention or simply palliative or hospice care.”<sup>173</sup> Such deliberation with a health care provider committed to delivery of care, directly serving the patient, and removed from a vested (conflict of) interest in the research protocol and research outcome would provide a meaningful added caution for one who is terminally ill and considering an experimental treatment.

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<sup>170</sup> See generally Harmon, *supra* note 39.

<sup>171</sup> Editorial, *Care at the End of Life: An Enlightened Approach to Giving Patients More Say in the Medical Interventions they Want*, NY TIMES, Nov. 25, 2012, at 10.

<sup>172</sup> See generally Editorial, *Care at the End of Life*, N.Y. TIMES, Nov. 25, 2012, at 10; SUSAN NELSON, IMPROVING THE QUALITY OF CARE FOR PATIENTS WITH SERIOUS ADVANCED ILLNESS THROUGH ADVANCED CARE PLANNING AND LAPOST (Nov. 7, 2012) (unpublished presentation slides and manuscript). Louisiana Physician Orders for Scope of Treatment (LaPost), Official web site, *available at* <http://lhccf.org/lapost-home> (last visited Apr. 14, 2013). Fifteen states have enacted laws to authorize the use of POSTS, and 28 more are considering legislation. Editorial, *Care at the End of Life*, N.Y. TIMES, Nov. 25 2012, at SR-10.

<sup>173</sup> *Id.* at SR-10.

## B. Additional Conditions for Compassionate Use and Treatment IND Applications

The Abigail Alliance litigation and the organization's ongoing lobbying have inspired multiple legislative proposals to exempt the terminally ill from full FDA drug review and approval protections through expansion of Compassionate Use and Treatment IND venues for access to experimental treatments.<sup>174</sup> The underlying rationale, articulated through the Abigail Alliance litigation, is that those who are terminally ill and without health care options other than experimental treatments are, with support from their physicians, entitled to access them—at least to the extent that FDA standards for safety and efficacy as preconditions for general market access should not be imposed on them and impede a patient-doctor choice to assume risks for the only opportunity to save one's life.<sup>175</sup>

The protection of individuals who are terminally ill and seek access to experimental treatments outside of the clinical research context should be heightened, not lessened. Experimental treatments under study are a transition from health care potential to health care reality, far from the equivalent of health care reality given the greater than ninety-percent failure rate of new drug candidates.<sup>176</sup> Patients receiving them share the vulnerability of research subjects, and more risk is introduced when research self-awareness is pushed to the side of patient and treatment norms. DHHS recognized as much over three decades ago:<sup>177</sup>

Informed consent is especially important in Treatment IND situations because the subjects are desperately ill and particularly vulnerable. They will be receiving medications, which have not been proven either safe or effective, in a clinical setting. Both the setting and the recipients' desperation may work against their ability to make an informed assessment of the risk involved. IRBs must ensure that potential subjects are fully aware of the risks involved in participation.

In addition, although experimental treatments delivered through the Compassionate Use and Treatment IND mechanisms may contribute to the progress of the clinical trials they are drawn from, delivery of care is the primary focus and social justification.<sup>178</sup> These treatment uses draw from clinical research, but they offer no comparable counterpart to the primary social justification for exposing human subjects to risks in clinical trials—the advancement of human health science, furthering the transition from health care potential to health care reality, and the improvement of human health.<sup>179</sup> In fact, Treatment INDs may impede their clinical trial counterparts by drawing potential subjects away from them. “As one scientist put it, ‘Why would patients who are sophisticated, demanding, and willing to participate in experiments take a chance on receiving a placebo when they want the active compound?’”<sup>180</sup>

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<sup>174</sup> See *supra* notes \_\_\_ and accompanying text for full discussion of Compassionate Use and Treatment IND applications, see *supra* notes \_\_\_ and accompanying text.

<sup>175</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>176</sup> See *supra* note 34 and accompanying text. See generally Noah, *Bioethical Malpractice*, *supra* note 39.

<sup>177</sup> DHHS, GUIDEBOOK, *supra* note \_\_\_, at \_\_\_.

<sup>178</sup> CITATION: BIOTECH TREATISE.

<sup>179</sup> See *supra* note 39 and accompanying text. See generally Noah, *Bioethical Malpractice*, *supra* note 39.

<sup>180</sup> DHHS, GUIDEBOOK, *supra* note \_\_\_, at \_\_\_.

The FDA standard for market approval is too low: Out perform nothing (a placebo) with tolerable levels of risk based upon mathematical abstracts—group means and averages which may not reflect reality for any individual actually in the study—coupled with broad physician discretion to use approved drugs off label.<sup>181</sup> Nevertheless, en masse market use of FDA-approved drugs contrasts with Compassionate Uses isolated to individuals and with Treatment INDs limited to small groups.<sup>182</sup> The check on efficacy and safety provided by physician-patient experience through market use, relied upon heavily (arguably too heavily<sup>183</sup>) with FDA-approved pharmaceuticals and recognized in the provisions of FDAAA to establish the Sentinel reporting system,<sup>184</sup> is removed when experimental treatments are delivered as health care prior to market approval and general population use.

Standing law and policy extends safety and human subject protections inside the context of clinical trials under FDA supervision to health care delivery applications of the experimental treatments under Compassionate Uses and Treatment INDs. The sponsor and investigators must comply with all applicable provisions governing INDs, including distribution of the drug through qualified experts, maintenance of manufacturing facilities with sufficient quality assurance, and submission of IND safety reports.<sup>185</sup> Compassionate Use approvals are case-by-case add-ons to ongoing clinical research, which the FDA typically conditions on adherence to the human subject protections implemented in the clinical research trials they are drawn from.<sup>186</sup> Treatment INDs must be reviewed by an IRB prior to submission to the FDA, and they must comply with the regulations governing IRBs<sup>187</sup> and informed consent.<sup>188</sup> The responsibility of IRBs remains consistent: prohibit unreasonable and unnecessary risks, monitor the sufficiency of informed consent forms and processes, and oversee progress.<sup>189</sup>

Accordingly, contrary to the Alliance’s position, recognition of the terminally ill as a “vulnerable group” and associated reforms must be applied to experimental treatments beyond the scope of clinical trials.<sup>190</sup> In fact, IRB scrutiny should be *enhanced* to account for the added risks of deviating from the express research context. For example, in addition to the added risks discussed above, the option of recouping the costs of manufacturing drugs for experimental uses outside of clinical trials may tempt sponsors to market them aggressively to the terminally ill to subsidize the cost of manufacturing supply for clinical trial use and to generate additional data

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<sup>181</sup> See *supra* notes \_\_\_ and accompanying text. See generally Malinowski & Gautreaux, *Drug Development Puberty?*, *supra* note \_\_; Malinowski & Gautreaux, *All that is Gold*, *supra* note \_\_.

<sup>182</sup> Even when the FDA responds favorably to applications for Treatment IND status, sponsors of the potential new drugs cannot be compelled to risk the supply they need to conduct their clinical research before the FDA or to scale up to a manufacturing capacity that would only be economically feasible in the event of market approval and successful market uptake. CROSS REFERENCE TO HERCEPTIN EXAMPLE.

<sup>183</sup> See generally Malinowski, *Doctors, Patients, and Pills*, *supra* note 93.

<sup>184</sup> CROSS REFERENCE—FDA, SENTINEL.

<sup>185</sup> 21 CFR Part 312.

<sup>186</sup> See generally OHRP, TERMINALLY ILL, GUIDEBOOK, *supra* note \_\_.

<sup>187</sup> 21 CFR Part 56, 21 CFR 312.34(c).

<sup>188</sup> 21 CFR Part 50.

<sup>189</sup> CROSS REFERENCE.

<sup>190</sup> See generally *supra* part IV.A.

without the cost of manufacturing and under their discretion to submit for FDA consideration depending on data outcomes.<sup>191</sup>

### C. End-of-Life Decision Making Under PPACA

PPACA is a sweeping legislative response to the unsustainable escalation of health care costs.<sup>192</sup> A major impetus for the legislation was a 2007 Congressional Budget Office report that documented the problem with numbers even bleaker than most anticipated and a firm, resonating conclusion that the escalation of health care finance costs in the U.S. is unsustainable.<sup>193</sup> The health care reform mandated by PPACA presents an opportunity to substantially improve end-of-life decision making. Realizing the fundamental factors that drove enactment of PPACA,<sup>194</sup> the need to contain health care costs and improve access to and the quality of health care, requires nothing less.

PPACA contained a provision that encouraged consultations with Medicare patients to discuss treatment options at the end of life including palliative care, but it was denounced as a “death panel provision” and left out of the final bill.<sup>195</sup> However, PPACA as enacted contains other provisions which are a means to promote palliative care through research and reimbursement. In fact, PPACA mandated the federal government to publish quality measures for hospice.<sup>196</sup> A Patient-Centered Outcomes Research Institute (PCORI) and a Center for Medicare and Medicaid Innovation have been established, and formation of an Independent Payment Advisory Board (IPAB) is underway.<sup>197</sup> Each of these mechanisms is intended to improve health care decision making and to reduce escalation of health care costs—objectives that necessitate responsiveness to palliative care.<sup>198</sup>

Responsiveness to palliative care in PPACA implementation will demand its inclusion in medical school curricula and improve the supply of sorely needed palliative care expertise in reasonable time. Changing physician and patient culture to alter end-of-life decision making systemically is a much more challenging matter—as exemplified by the aggressive challenges to IPAB, including one from the American Medical Association.<sup>199</sup> Care-at-all-costs health care norms are deeply embedded. When there is insurance coverage, physicians and patients are

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<sup>191</sup> See *supra* note \_\_\_ and accompanying text; Leibfartha, *supra* note \_\_\_, at 1306.

<sup>192</sup> See generally PPACA, Pub. L. No. 111-148, 124 Stat. 119 (2010); Government Accountability.

<sup>193</sup> Congress of the United States, Congressional Budget Office, The Long-Term Outlook for Health Care Spending (2007), available at <http://www.cbo.gov/publication/41646> (last visited Apr. 22, 2013).

<sup>194</sup> The Congressional Budget Office’s conclusions were an inspiration for PPACA, as acknowledged in the legislation’s legislative history. See [CITE].

<sup>195</sup> See generally Editorial, *Care at the End of Life*, N.Y. TIMES, Nov. 25, 2012, at 10.

<sup>196</sup> PPACA, *supra* note \_\_\_, at § 3004, 124 Stat. at 368 (2009). See Unroe & Meier, *Opportunities*, *supra* note \_\_\_, at 426.

<sup>197</sup> See generally *id.* The official Internet site of PCORI is available at <http://www.pcori.org/> (last visited Apr. 22, 2013), and the official site for the CMS Innovation Center is available at <http://innovation.cms.gov/> (last visited Apr. 22, 2013).

<sup>198</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>199</sup> See AMA, *Independent Payment Advisory Board*, available at [http://www.ama-assn.org/ama/pub/advocacy/topics/independent-payment-advisory-board.page?](http://www.ama-assn.org/ama/pub/advocacy/topics/independent-payment-advisory-board.page) (last visited Apr. 22, 2013).

reactionary to imminent death and reach broadly for intervention.<sup>200</sup> Nevertheless, the social needs that drove passage of PPACA and implementation of the resulting legislation demand the change: “If purchasing affordable basic insurance or paying taxes to support a society-wide insurance pool is a citizen’s obligation, then delivering insurance and care efficiently and with a cost-worthy scope is a concomitant obligation of insurers and providers.”<sup>201</sup> Joe’s care during the last ten months of his life, especially the aggressive experimental surgeries, was beyond wasteful—as Joe came to appreciate during his final weeks of his life. Unfortunately, where there is access to care, Joe’s story is far too common, and the stories accumulate in terms of both good health care decision making and cost.<sup>202</sup> When per year of life (YOL) actuarial calculations are introduced (life extension comparisons where there are aggressive added health care interventions at the end of life with scenarios where there are not),<sup>203</sup> the waste in our health care system attributable to end-of-life decision making is undeniable and extraordinary:<sup>204</sup>

## D. Global Implementation

The endeavor of biopharmaceutical research and development (R&D) crosses borders, markets, and governments. Clinical research, the setting for experimental treatments, has globalized through escalating reliance on contract research organizations (CROs) and the shear

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<sup>200</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>201</sup> Paul T. Menzel, *The Value of Life at the End of Life: A Critical Assessment of Hope and Other Factors*, 39 J.L. MED. & ETHICS 215 (2011).

<sup>202</sup> For example, consider the late Senator Kennedy’s end-of-life surgery:

The treatment options were the standard radiation treatment developed in the 1980s, which averaged 4.5 months from the time of detection and cost approximately \$100,000. Subsequently, treatment was expanded to often include chemotherapy as well at a cost of \$150,000. The combination of these therapies have expanded the average survival rate to 14 months (a 9-10 month increase over radiation alone). Experimental surgery is another option at a cost of \$250,000. Senator Kennedy opted for the full course of treatment and died 15 months from his diagnosis—the average survival rate for standard radiation and chemotherapy treatment alone. The standard cost per [added year of life, or YOL] for the standard treatment is approximately \$300,000.00 (\$250,000 for 9-10 months). Senator Kennedy’s experiment surgery of course doubled that cost. Similarly, a generation of innovative cancer drugs have reached the market but at enormous cost with marginal life extensions

*Menzel, Value, supra* note \_\_\_, at 216.

<sup>203</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>204</sup> Consider the following illustration:

Several well-known drug treatments for various cancers are more expensive than radiation and chemotherapy for glioblastoma [both the most common and most aggressive malignant primary brain tumor in humans]. Avastin at \$90,000 adds only an additional 1.5 months, also within a fairly narrow range of variation; Erbitux at \$80,000 adds 1.2 months. Avastin extends life at a cost of \$720,000/YoL, Erbitux at \$800,000/YoL. One can extrapolate: if a tumor retarding a drug like Erbitux were used to treat all of the 550,000 Americans who die of cancer annually, then \$440b would be spent each year to add only an average of one-tenth of a year -- and for even the luckiest users, little more than that. Such expenditure would add another 18% to the \$2.4 trillion the U.S. spends annually on health care already, and would be 100 times the annual research budget of the National Cancer Institute. Provenge, a new drug for prostate cancer approved by the FDA in April 2010, is more cost effective than Avastin or Erbitux but still pricey: \$93,000 for a treatment regimen adding an average 4.0 months survival, a rate of \$279,000/YoL. This spending rate, similar to that for radiation and chemotherapy for glioblastoma, may be more typical in spending at the end of life than the rate of Avastin and Erbitux; many new oncology treatments at the end of life cost \$300,000 per YoL.

*Menzel, supra* note \_\_\_, at 16. See also FRALEY, DIGNIFIED DYING, *supra* note \_\_\_, at 55.

increase in volume of clinical research—both in the number and scope of clinical trials.<sup>205</sup> Over the last two decades, the world’s three largest pharmaceutical markets—those of the U.S., Europe, and Japan—have integrated officially to create shared science standards and to avoid research duplication through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), which embodies government and industry representation from these markets.<sup>206</sup>

U.S. regulatory reforms to better protect the terminally ill contemplating experimental treatments should be incorporated into the ICH standards for good clinical practice. In fact, the U.S. would benefit from this integration and application given that Europe and Japan are much more receptive to and experienced in palliative care and the realities of health care resource rationing that inspired enactment of PPACA and are at the core of its implementation.

## V. Conclusion

“[T]he idea of death, the fear of it, haunts the human animal like nothing else; it is a mainspring of human activity—activity designed largely to avoid the fatality of death, to overcome it by denying in some way that it is the final destiny for man.”

Ernest Becker<sup>207</sup>

Joe’s story relays the best and worst scenarios when clinical research and clinical care are comingled. Experimental care is just that—experimental, meaning the possibility of a transition from health care potential to health care reality.<sup>208</sup> The over-arching message of this article is that the terminally ill are vulnerable and should be recognized and protected as such during this possible transition.

Two misconceptions drive end-of-life care in the U.S., and law and policy governing experimental treatments for the terminally ill must be modified to address them for the sake of protecting human subjects. First, palliative care is not intentional acceleration of the end of life, or even dismissal of the hope of continuation of life.<sup>209</sup> Rather, it is acceptance of the limits of and consequences of continued aggressive health care intervention inconsistent with the priority of patient comfort and recognition of the practical limits of health care.<sup>210</sup> With priority on

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<sup>205</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>206</sup> For more information about the ICH, visit the official Internet site ICH, <http://www.ich.org> (last visited Oct. 3, 2011). See generally International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline: Guideline For Good Clinical Practice E6(R1) (1996), available at [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf); Michael J. Malinowski & Grant G. Gautreaux, *All that is Gold Does Not Glitter in Human Clinical Research: A Law-Policy Proposal to Brighten the Global “Gold Standard” for Drug Research and Development*, 45 CORNELL INT’L L.J. 185 (2012). See also Michael J. Malinowski, *Ethics in a Global Pharmaceutical Environment*, 5 SANTA CLARA J. INT’L L. 57, 70-71 (2006).

<sup>207</sup> BECKER, DENIAL, *supra* note 78, at ix (Pulitzer Prize Winner for General Nonfiction 1974).

<sup>208</sup> See generally Noah, *Bioethical Malpractice*, *supra* note 39.

<sup>209</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>210</sup> Adam Ross, Book Review, *40 Days and 40 Nights*, NY TIMES, Dec. 23, 2012 (reviewing ANTOINE WILSON, PANORAMA CITY (2012)).

patient comfort, palliative care also often extends the duration of life deemed terminal.<sup>211</sup> Second, while health care capabilities have expanded enormously, human clinical trials have multiplied exponentially, and the potential for treatment applications churned from the research underway is simply breathtaking. Unfortunately, as self-evident in the greater than ninety-percent failure rate of new drug candidates,<sup>212</sup> potential is not reality in the vast majority of terminal cases. Moreover, that potential is accompanied by the realities of accelerated death and imposition of additional suffering in many cases, and the too often realized danger of doing harm within the scope of research. The “DNA mystique”<sup>213</sup> is intoxicating for all involved—especially for the terminally ill who must confront the reality of death.

Acceptance of mortality is a struggle for patients and the health providers caring for them. The tendency to deny death must be checked during the process of end-of-life decision making. Human subject protections are recognition that the gate to access experimental treatments must be closed enough to prevent medical interventions that impose excessive harm, albeit with the intention to help and responsiveness to the compelling want of hope. Joe’s story is just one of many thousands in a given year. There are fates worse than death, even with the best of intentions to reach into imminent death with science to create additional life. Doctor Frankenstein has no place in contemporary health care in spite of the seduction of genomic science.<sup>214</sup>

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<sup>211</sup> See *supra* notes \_\_\_ and accompanying text.

<sup>212</sup> See *supra* note \_\_\_ and accompanying text.

<sup>213</sup> See generally NELKIN & LYNDEE, DNA MYSTIQUE, *supra* note 88.

<sup>214</sup> See generally MARY WOLLSTONECRAFT SHELLY, FRANKENSTEIN (2010).

**APPENDIX I.**<sup>215</sup>

**Research Spending Per New Drug**

Company	Ticker	Number of drugs approved	R&D Spending Per Drug (\$Mil)	Total R&D Spending 1997- 2011 (\$Mil)
AstraZeneca	AZN	5	11,790.93	58,955
GlaxoSmithKline	GSK	10	8,170.81	81,708
Sanofi	SNY	8	7,909.26	63,274
Roche Holding AG	RHHBY	11	7,803.77	85,841
Pfizer Inc.	PFE	14	7,727.03	108,178
Johnson & Johnson	JNJ	15	5,885.65	88,285
Eli Lilly & Co.	LLY	11	4,577.04	50,347
Abbott Laboratories	ABT	8	4,496.21	35,970
Merck & Co Inc	MRK	16	4,209.99	67,360
Bristol-Myers Squibb Co.	BMY	11	4,152.26	45,675
Novartis AG	NVS	21	3,983.13	83,646
Amgen Inc.	AMGN	9	3,692.14	33,229

*Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems*

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<sup>215</sup> Herper, *Staggering Cos*, *supra* note 101.



**APPENDIX II.**<sup>216</sup>

**Research Spending Per New Drug**

Company	Number of drugs approved	R&D spending 1997-2011	
		per drug (\$BIL)*	total (\$BIL)*
<b>AstraZeneca</b>	5	\$11.80	\$59.00
<b>GlaxoSmithKline</b>	10	8.2	81.7
<b>Sanofi</b>	8	7.9	63.3
<b>Roche Holding</b>	11	7.8	85.8
<b>Pfizer</b>	14	7.7	108.2
<b>Eli Lilly &amp; Co</b>	11	4.6	50.3
<b>Merck &amp; Co</b>	16	4.2	67.4
<b>Novartis</b>	21	4	83.6

\*All figures are adjusted for inflation. *Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems.*

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<sup>216</sup> Herper, *Staggering Cos*, *supra* note 101.