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AUTONOMY, DESPERATION, AND CONSENT IN EXPERIMENTAL MEDICINE

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Abstract The most salient bioethics principle in American medical care is respect for autonomous decision-making. This principle of autonomy is established in law through 'informed consent' rules, which have been refined in American law for more than a century. Desperately ill individuals who enroll in research trials often believe they are accessing new therapies that will benefit them personally, even when the consent forms they sign explicitly state that no benefit is promised. This 'therapeutic misconception' and related autonomy-based concerns cast doubt on the genuineness of informed consent obtained from desperately ill patients enrolling in research trials. Related concerns about comprehension and consent have shaped debates about whether terminally ill patients should have access to experimental medical products outside of research trials. Suggestions are offered for enhancing informed consent by desperately ill patients and for alternatives to steering them towards research trials.

Keywords
terminal illness, respect for persons, clinical trials, experimental drugs, surgical advances, retrospective medical studies

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1 Introducton

My mother was a brilliant and respected judge and a pioneer for women in the legal profession. She had extensive legal experience with the principles of medical ethics and the importance of patient autonomy. However, when she became ill and faced a choice about an experimental medical treatment, she refused to read the consent form and refused to allow me to read it or speak with her doctor. She worried that asking questions would alienate the doctor and jeopardize her access to the experimental treatment. She consciously chose to make an emotional, uninformed decision. This unexpected and astonishing choice typifies the issues at the heart of this paper, in which I present two sides of the same coin. Can desperately ill patients truly exercise autonomy when consenting to serve as clinical research subjects? Conversely, should government policy permit desperately ill patients to exercise autonomy by choosing to use experimental drugs? Below, I will identify key issues and offer proposals for addressing them.

1.1 Principles of Medical Ethics

Four principles of medical ethics have long been widely accepted in the United States (Gillon, 2015). These were initially laid out by Tom Beauchamp and James Childress in their 1979 Book Principles of Biomedical Ethics (Beauchamp & Childress, 1979). Sometimes called the bioethics mantra, the four principles are: autonomy (see more Michałowska & Magoń, 2018), beneficence, non-maleficence, and justice. Beneficence is physicians' familiar duty to act for the benefit of the patient. Nonmaleficence is the physician's duty to avoid harming the patient. In medical ethics, justice is concerned primarily with distributive justice (Varkey, 2020). Autonomy derives from respect for individual liberty (Mill, 1859). "The only part of the conduct of anyone for which he is amenable to society is that which concerns others. In the part which concerns himself, his independence is, of right, absolute. Over himself, over his own body and mind, the individual is sovereign" (Mill, 1859). The bioethics mantra has been used for many years to provide a framework for addressing issues that arise in medicine and human research. In the United States, the autonomy principle in particular plays a key role in the legal rules that have developed around medical decision-making and consent to medical treatment and research (see for example Bazzano, Durant & Brantley, 2021; Pugh, 2020).

1.2 Respect for Persons, Autonomy, Informed Consent

Schloendorff v Society of New York Hospital (211 NY 125 (1914)) is a foundational case. In 1908, Ms. Schloendorff came to the Society of NY hospital suffering from a stomach disorder. After a few weeks of hospitalization, Dr. Bartlett found that Ms. Schloendorff had a lump, a fibroid tumor. According to Ms. Schloendorff, Dr. Bartlett told her the "character of the lump could not … be determined without an ether examination". She agreed to the ether examination but insisted that "there must be no operation". Ether was administered and the tumor was removed without her consent or knowledge. Following the operation, gangrene developed and some of her fingers had to be amputated. She sued the hospital. The court held in favor of the hospital according to the (now defunct) rule that charity hospitals were exempted from liability. Nevertheless, in its ruling the court famously stated that the removal of the tumor had been a trespass, because "Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault, for which he is liable in damages." (211 NY at 129).

Another famous consent case, Canterbury v. Spence, 464 F.2d 772 (1972) involved Dr. Spence, a neurosurgeon who treated a 19-year-old FBI clerk, Canterbury, for back pain. Dr. Spence told Canterbury that he would need a laminectomy. Canterbury gave Dr. Spence his mother's phone number, and when they communicated, Mrs. Canterbury asked Dr. Spence if the operation was "serious". Dr. Spence replied, "not any more than any other operation". Mrs. Canterbury traveled to Washington D.C., where the operation took place, but arrived after the laminectomy was over. At that time, she signed a consent form. "The laminectomy revealed several anomalies: a spinal cord that was swollen and unable to pulsate, an accumulation of large tortuous and dilated veins, and a complete absence of epidural fat… [I]n suturing the wound, Dr. Spence attempted to relieve the pressure on the spinal cord by enlarging the dura – the outer protective wall of the spinal cord – at the area of swelling." Following the operation, young Canterbury initially recovered normally but then suffered a fall, which left him unable to move his legs and caused breathing difficulties. Dr. Spence rushed to the hospital and Mrs. Canterbury signed another consent form. Dr. Spence reopened the wound and "created a gusset" to allow the spinal cord greater room to pulsate. After the second surgery, Canterbury regained some function but needed crutches to walk and was incontinent. He had trouble finding employment and sued for medical expenses, pain and suffering, and

loss of wages, claiming that Dr. Spence had inadequately disclosed information about the risks of a laminectomy.

The court found that the physician has a duty of "reasonable disclosure of the choices with respect to proposed therapy and the dangers inherently and potentially involved". The mother's signature on two consent forms did not satisfy the consent requirement if she did not have adequate information to make a true consent. The court stated: "True consent to what happens to one's self is the informed exercise of a choice, and that entails an opportunity to evaluate knowingly the options available and the risks attendant upon each. The average patient has little or no understanding of the medical arts and ordinarily has only his physician to whom he can look for enlightenment with which to reach an intelligent decision. From these almost axiomatic considerations springs the need, and in turn the requirement, of a reasonable divulgence by the physician to patient to make such a decision possible" (464 F.2d at 772). This landmark ruling established the idea of informed consent in medical procedures and thereby fundamentally reshaped medical malpractice law in the U.S.

Later cases, along with statutes, regulations, and professional codes, have confirmed the elements of medical 'informed consent'. These include the patient's ability to understand the relevant medical information and the treatment alternatives, the medical caregiver's presentation of accurate information including risks and benefits of all the options, and the patient's voluntary consent to the proposed action. (American Medical Association, n.d., Opinion 2.1.1; Varkey, 2020).

Courts have carved out some exceptions to the requirement of informed consent, including in the context of an emergency in which a patient is unable to give consent because he is unconscious and where harm from failure to treat is imminent and outweighs the harm threatened by proposed treatment. But the general rule requires that a patient be allowed to make an informed and autonomous choice about his own medical care. This informed consent rule extends to a research subject's consent to participate in medical research as well.

2 Autonomy and Consent to Participate in Human Research Studies

2.1 Human Research Trials

Clinical trial activity has grown dramatically over the past two decades, since the ClinicalTrials.gov began collecting data and posting registry counts in 2000. The current clinical trial workforce numbers in the millions (Society for Clinical Research Sites, 2022). It is difficult to estimate how many individuals enroll as research subjects. One study estimates that more than 7% of cancer patients enroll in clinical trials (Unger et al., 2024). At present, ClinicalTrials.gov includes more than 566,000 clinical trials registered worldwide. Approximately 432,000 of those are interventional treatment trials. How many of these involve terminally ill or desperately ill research subjects is difficult to determine. One report ranks the top ten clinical trial areas. It concludes that 25% of the trials address cancer, more than 15% address mental health, more than 12% address nervous system disease, 10 % address cardiovascular diseases, and so on (Definitive Healthcare, 2025). Most of the illnesses studied appear to be serious illnesses, but it is difficult to determine how many are the kind that involve desperately ill individuals. Nevertheless, it is clear that clinical trial activity has become an enormous industry with many stakeholders.

2.2 Human Research Protections and Informed Consent

The United States Department of Health and Human Services regulates human subjects research at 45 CFR 46. Subpart A, known as the 'Common Rule', applies to "all research involving human subjects conducted, supported, or otherwise subject to regulation by any Federal department or agency … including research … subject to regulation by the Federal Government outside the United States" (Section 46.101). Institutions engaged in research covered by the policy must provide written assurance to the relevant federal agency that they will comply with the policy requirements, including certifying that proposed research studies will be reviewed by Institutional Review Boards (IRBs) before enrolling in human research subjects. IRBs have the authority to approve, disapprove, or require modifications to most research activities. IRBs require that research subjects receive information that is necessary for informed consent, information that "would meaningfully add to the protection of the rights and welfare of subjects." (Section 46.109(b)). The criteria for IRB approval of research include the following provisions:

> ***§ 46.111 Criteria for IRB approval of research.***
>
> *(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:*
> *(1) Risks to subjects are minimized:*
> *(i) By using procedures that are consistent with sound research design and that do not unnecessarily expose subjects to risk, and*
> *(ii) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.*
> *(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (e.g., the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.*
> *(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted. The IRB should be particularly cognizant of the special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons.*
> *(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, § 46.116.*
> *(5) Informed consent will be appropriately documented or appropriately waived in accordance with § 46.117.*
> *…*
> *(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects. (Section 46.111).*

Of note among these requirements is the instruction that the IRB "should not consider possible long-range effects of applying knowledge gained in research (e.g., the possible effects of the research on public policy)." (Section 46.111(a)(2)). IRBs should focus on the risks and benefits faced by prospective research subjects and the quality of their consents to participate. The benefit to society of the knowledge gained from research may not be used to offset any risks or problems with consent.

IRBs must determine whether the regulatory requirements are satisfied, with special attention to vulnerable research participants, "subjects who are vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons." The pertinent requirements of informed consent in research are as follows.

§ 46.116 General requirements for informed consent.

*(a) **General.** General requirements for informed consent, whether written or oral, are set forth in this paragraph and apply to consent obtained in accordance with the requirements set forth in paragraphs (b) through (d) of this section. … Except as provided elsewhere in this policy:*

(1) Before involving a human subject in research covered by this policy, an investigator shall obtain the legally effective informed consent of the subject or the subject's legally authorized representative.

(2) An investigator shall seek informed consent only under circumstances that provide the prospective subject or the legally authorized representative sufficient opportunity to discuss and consider whether or not to participate and that minimize the possibility of coercion or undue influence.

(3) The information that is given to the subject or the legally authorized representative shall be in language understandable to the subject or the legally authorized representative.

(4) The prospective subject or the legally authorized representative must be provided with the information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information.

(5) Except for broad consent obtained in accordance with paragraph (d) of this section:

(i) Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

(ii) Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

(6) No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

(b) Basic elements of informed consent. Except as provided in paragraph (d), (e), or (f) of this section, in seeking informed consent the following information shall be provided to each subject or the legally authorized representative:

(1) A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures that are experimental;

(2) A description of any reasonably foreseeable risks or discomforts to the subject;

(3) A description of any benefits to the subject or to others that may reasonably be expected from the research;

(4) A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject;

(5) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained;

(6) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained;

(7) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject;

> *(8) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled; and*
> *(9) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:*
> *(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or*
> *(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies* (Section 46.111).

The purpose of these IRB criteria is to support the autonomy and dignity of the individual research subjects enrolling in research studies. True volunteerism is vital in research with human subjects. Without it, research exploits human beings and reduces them to the moral equivalent of laboratory animals.

2.3 Historical Abuses and the Moral Foundations of Human Research Protections

Historically, governments have been among the worst offenders against human research subject autonomy. For example, the reader should consider the Nazi medical research experiments and the U.S Public Health Service's Tuskegee Syphilis Study, both perpetrated by governments. The Nazi medical research trials used concentration camp prisoners during World War II to study, among other things, human tolerance to extreme cold, infectious diseases such as malaria, methods of sterilization, wound treatment, chemical weapons, and the limits of starvation. These experiments were marked by cruelty, absence of consent, and profound violations of ethical norms. The Tuskegee Syphilis Study, conducted by the U.S. Public Health Service from 1932 to 1972, deliberately left Black men with syphilis untreated for decades without their consent in order to observe the natural course of the disease. Both examples involved research ostensibly intended to advance science for the public good. Both sets of experiments were morally corrupt, disgraced by the lack of volunteerism of the research subjects (see Auschwitz-Birkenau State Museum, n.d.; Centers for Disease Control and Prevention, 2024).

In 1979, the U.S. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued the Belmont Report, Ethical Principles and Guidelines for the Protection of Human Subjects of Research (National

Commission for the Protection of Human Subjects or Biomedical and Behavioral Research, 1979). The Commission reviewed past abuses of human subjects in biomedical experiments, especially the Nazi abuses of World War II, and identified basic ethical principles that "should assist in resolving ethical problems that surround the conduct of research with human subjects." As summarized by the Belmont Report, "scientific research has produced substantial social benefits. It has also posed some troubling ethical questions" (National Commission for the Protection of Human Subjects or Biomedical and Behavioral Research, 1979, introduction). The Belmont Report serves as a statement of the U.S. Department of Health and Human Services' policy. The basic ethical principles identified by the Belmont Report fall into three categories: respect for persons, beneficence, and justice, mirroring the bioethics mantra (embedding the principle of 'non-maleficence' in the broader principle of beneficence). Respect for persons includes the ethical principles that "individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection" (National Commission for the Protection of Human Subjects or Biomedical and Behavioral Research, 1979, Part B: Respect for Persons, 'Basic Ethical Principles' section).

Because the purpose of research is to create generalizable knowledge for the good of society rather than to provide treatment to the research subject himself, one of the key ethical issues in human research is how to avoid the use of human beings as means rather than as ends in themselves. Philosopher Immanuel Kant's 'Formula of Humanity', one of the formulations of his Categorical Imperative, commands that persons ought never to be treated 'merely as a means' to an external end. Morality requires that individuals should not be exploited or manipulated merely for the sake of others. This formulation permits individuals to give free, informed, non-coerced consent to be used for the sake of others, as long as their own rational agency is fully respected, so that their actions remain compatible with treating them as ends in themselves rather than as means for others (Robeyns, 2020). Consistent with this formulation, the Belmont Report and later ethical and legal determinations condoned the idea that people may volunteer to serve as research subjects, even to their own possible detriment, to create generalizable knowledge that will benefit others. Accepting genuinely voluntary participation is consistent with the bioethics mantra's principles of autonomy and respect for persons.

According to the principle of respect for persons, true volunteerism requires the exercise of autonomous decision-making; that is, true volunteerism requires informed consent, exercised by a person with capacity to understand the choices presented to him. It is this respect for persons that distinguishes acceptable human research from abusive human research typified by the Nazi medical research experiments and the Tuskegee Syphilis Study. Having considered the principle of respect for persons and these historical abuses, we now consider several issues associated with consent in desperately ill patients.

2.4 Desperately Ill Research Subjects, Autonomy, and Consent

Recall that the US human research protections, in Section 46.111(a)(3) note "special problems of research that involves a category of subjects who are vulnerable to coercion or undue influence, such as … individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons." An example of true volunteerism by a desperately ill person would be a reasonable decision to devote the remainder of his life to serving as research subject to help future patients avoid the suffering he has endured, made with full awareness and without coercion or illusion. But autonomous consent by desperately ill individuals may be undermined by the same special problems anticipated in the human research protections for other categories of vulnerable subjects.

2.4.1 Desperately Ill Research Subjects – Information and Power Asymmetry

The consent of a person who is desperately ill may be compromised by the information and power asymmetry inherent in the doctor/researcher – patient relationship. Patients often learn about research studies from their own treating doctors, upon whom they rely for personal care. Indeed, doctors may recruit patients for research studies in which they are themselves the principal investigators or research partners. Physician-researchers are often specialists who conduct clinical trials related to their own specialty. Most patients are not research scientists or doctors. As The Canterbury court pointed out, "the average patient has little or no understanding of the medical arts." Even more, many if not most patients have limited ability to assess the risks and benefits of the research protocols proposed to them. In this sense, they suffer from an 'educational disadvantage', as compared with the researchers conducting the trial. In addition, their illnesses may confine them to

hospital or leave them physically depleted, thereby limiting their practical ability to engage fully and reflectively in decision-making. Because patients often place deep trust in their physicians' intention to benefit them personally, they may confuse research participation with treatment. This confusion may be exacerbated by the research trial marketing materials that one often finds in medical waiting-rooms, advertising trials as cutting-edge 'treatments'. While these marketing materials may not be intended to confuse medical patients about the purposes of the research trial, they may undermine a desperately ill patient's ability to discern the difference between research and treatment.

2.4.2 Desperately Ill Research Subjects – Influence or Implicit Coercion

The consent of desperately ill patients may also be unwittingly undermined by influence or implicit coercion even if not intended by the treating physician. Medical patients may fear that refusing to participate will alienate their physicians or reduce the quality of the care they will receive from the one or few specialists who know most about their disease. Research trials do offer professional benefits to physician-researchers, giving rise to potential conflicts between the physician's intention to benefit patients and his intention to produce generalizable knowledge that will help others and support his own career. At least one study has identified the desire to advance scientific knowledge as a motivation that oncologists have reported for enrolling their medical patients in clinical trials (Manley et al. 2022).

2.4.3 Desperately Ill Research Subjects – Irrationality and Therapeutic Misconception

In addition, a person's ability to make an autonomous decision may be compromised by desperation itself. Alexandr Solzhenitsyn said it best in his 1968 novel, The Cancer Ward. The novel tells the story of a small group of cancer patients in Uzbekistan in 1955, in the post-Stalinist Soviet Union. The protagonist, Kostoglotov, reflects on his life and illness:

> *"How he craved to be healed!---despite those harrowing months and years of by now hopeless treatments, he would suddenly recover completely. His back would heal and he would stand up straight and walk with a firm step, feeling like a new man…*
>
> *How they all craved to hear of such a wonder-working doctor, of a medicine unknown to the doctors here! These people might have admitted or denied that they believed in such a thing, but all of them, to a man, felt, deep in*

> *their hearts, that there really was such a doctor, such a dispenser of herbs or such an old village woman living somewhere, and that they only had to learn where, take that medicine, and they would be saved.*
>
> *It was impossible that their lives were already doomed!*
>
> *Laugh as we may at miracles as long as we are strong, healthy and flourishing, let life become hopelessly wedged and crushed so that only a miracle can save us—and we shall believe in that one and only and altogether extraordinary miracle."* (Solzhenitsyn, 1991).

When life becomes 'hopelessly wedged and crushed' by illness and the desperation for relief, experimental procedures may seem like potential miracles, or at least cutting-edge medical treatments. The tendency of research subjects to view research participation as an opportunity for treatment, rather than as an effort to participate in the production of generalizable knowledge, is sometimes called 'therapeutic misconception'. Some critics have argued that therapeutic misconception makes research subject consent invalid, because a desperate patient does not have the capacity to make rational choices (Fried, 2001; de Melo-Martin & Ho, 2008; see also McCormick, 2018; Jacobs et al., 2020). If a person is compromised by his own illness and desperation, he may not use his reason to assess the risks and benefits of the proposed research, or even to discern whether the proposed research is intended to benefit him personally. Recall that U.S. human research protections identify 'special problems' when research involves a category of 'individuals with impaired decision-making capacity'. Whether desperately ill patients have 'impaired decision-making capacity' placing them into this category should be considered.

One may argue that rational decision-making is not necessary for human dignity or for exercising autonomy. Perhaps respect for autonomy requires that desperate people be allowed to be irrational in their decision-making. Most civic institutions do not require rational decision-making, even for the most important decisions. For example, choosing whom to marry is often an emotional decision, and marriage rules do not require marriage decisions to be rationally weighed. In fact, we celebrate the emotional aspect of marriage decisions. On the other hand, adolescents are generally not allowed to marry (or to make contracts, vote, or purchase alcohol or tobacco) in the U.S. without parental permission, because they are not considered capable of making fully informed decisions and may be susceptible to influence, emotion, and irrational thinking. These same concerns may apply to desperate patients facing choices about research participation.

Human research protections do require that research investigators ensure research subjects have the information necessary to make rational, reasoned decisions when agreeing to participate in medical research. The regulatory protections require that researchers provide research subjects with "information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information" (Section 46.116(a)(4)). One might question whether a desperately ill person can make the sort of decision a 'reasonable person' would make. If the potential research subject is not able to make the sort of decision a reasonable person would make, one could argue that respect for persons principle has not been satisfied.

2.5 Suggestions for Enhancing Autonomous Consent for Desperately Ill Individuals – in Research

Whether or not rationality is required for valid autonomous consent, there are ways to enhance a desperately ill person's ability to make a valid autonomous choice. Consider these additional procedures that could support and enhance autonomous decision-making:

1. Imposing a waiting period after the research protocol is presented to the potential subject, before the subject is allowed to consent to participate. Such a waiting period might be considered analogous to the waiting periods that some countries impose prior to sterilization procedures or abortions, ostensibly to ensure full and informed consent (see Curhan & Sherman, 2025; Rowlands & Thomas, 2020, arguing, however, that in some cases, these waiting periods undermine agency and autonomy as they relate to sterilization and abortion). Another example, in a context that is less contentious but also less personal, is the example of the Right of Withdrawal or 'cooling off period' as applied to consumer protections in the European Union. European Commission, 2025). The 'cooling off period' gives consumers time to ameliorate the information asymmetry and vulnerability to pressure that are inherent in consumer agreements (Consumer Law Ready, n.d.).

2. Another suggestion to promote rational decision-making is to ask potential research subjects what they would advise a child or a parent faced with the same choice. This reframing exercise shifts the evaluative perspective away from the subject's immediate personal stakes and toward the role of a rational advisor,

one who is expected to weigh risks, benefits, and uncertainties more dispassionately. By encouraging subjects to consider what they would recommend to another person rather than what they hope for themselves, this approach may reduce the influence of desperation, optimism bias, or therapeutic misconception. In doing so, it offers a structured way to support more reflective judgment and, ultimately, more meaningful informed consent.

3. A third procedural mechanism to help promote autonomy and true volunteerism is to include time during the consent process for the potential research subject to consult with a family doctor (unaffiliated with the researchers), family member, clergy, advisor, or attorney before consent is requested or given. In other words, the consent process should be designed so that outside counseling of the potential research subject is possible and encouraged. This consent process structure is consistent with at least one appellate court's analysis in an analogous case (addressing the programmatic requirements for good decision-making, but not human research). *Stiver v Parker, 975 F.2d 261* (6th Cir. 1992), a leading Sixth Circuit case addressing duty of care in the context of a commercial surrogacy program. The case involved a Michigan surrogate mother who contracted cytomegalovirus (CMV) during artificial insemination, possibly from the intended father's semen that was used to inseminate the surrogate (Note that commercial surrogacy has since been criminalized by the Michigan legislature.) The surrogate gave birth to a child who suffered birth defects resulting from the CMV infection. Although the contract signed by the surrogate listed risks of several hundred infections and diseases, including CMV, the court still found that the surrogacy program design raised:

> *clear issues of negligence: there was no meeting or counselling possible in a program designed so that the prospective surrogate mother sees all the professionals for the first time only seven or eight days before she is to be inseminated. On that same day she sees the contract for the first time, is expected to sign it after a very brief consultation with a participating lawyer provided by the program and is given a copy only after the insemination.* (975 F.2d at 269).

As in the Stiver case, explication of risk alone may not be enough to provide a potential research subject with the opportunity to make an informed decision. Establishing procedures that allow and encourage potential research subjects to

consult advisors external to the program may be helpful in protecting the autonomous decision-making necessary for true informed consent.

Even if these suggestions were implemented and even with human research protections as in 46.116, which aim to promote enhancing autonomous decision-making, critics have argued that ultimately, the research subject is at the mercy of the "researcher's conscience and compassion" (Ingelfinger, 1972: "The subject's only real protection, the public as well as the medical profession must recognize, depends on the conscience and compassion of the investigator and his peers.") Given the informational and power asymmetry between patients and doctors, the possibility of implicit coercion and undue influence, and the potential for hope-tainted impairment of decision-making capacity, it is questionable whether most desperately ill individuals are capable of giving truly autonomous informed consent to serve as human research subjects.

3 Autonomy and Consent to Use an Experimental Drug Outside of Clinical Trials

A companion issue is whether desperately ill patients have the capacity to give true autonomous consent to use experimental, unapproved drugs or procedures outside of research trials. The question here concerns experimental treatments intended to benefit the patients themselves, rather than experiments in which patients become the subject of research intended to benefit others.

3.1 United States Food and Drug Administration Regulations for Medical Products

The goal of the United States FDA regulatory regime is 'to protect the public health' (U.S. Food and Drug Administration, n.d. - c). FDA requirements for the approval of new drugs, biologics, and devices (as a group, 'medical products') has given rise to the massive human research infrastructure described in section 2.1 of this paper. The FDA regulates the safety and effectiveness of medical products pursuant to federal legislation, the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301–399i (1938) (FFDCA) and the Public Health Service Act, 42 U.S.C. §§ 201–300mm-61 (1944) (PHSA). The requirements for approval of drugs, biologics, and devices vary. In general, with some exceptions, medical products may not be marketed in the US unless they have been approved by the FDA. To receive approval, a drug

manufacturer must submit "a new drug application (NDA) demonstrating that the drug is safe and effective for its proposed use". FDA officials evaluate the drug based on clinical trials that have been conducted to prove its safety and efficacy. A parallel approval program exists for FDA evaluation of biologics and medical devices. Even after approval, drugs, biologics, and devices are subject to additional requirements once they are on the market (see Sarata & Sheikh, 2023).

As an example, and for clarity, this paper will focus on drug approval, with the understanding that other medical products undergo comparable regulatory reviews. Before the FDA approves a new drug for market, a company submitting a new drug application must test the drug and submit evidence that it is safe and effective. A drug sponsor needs FDA permission to ship a new drug to various states for this testing. Ordinarily, such permission is obtained when the sponsor submits an Investigational New Drug (IND) application. As part of the IND application, the drug sponsor must submit to the FDA: "Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks … [and] … commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations" (U.S. Food and Drug Administration, n.d. - b). The drug sponsor conducts clinical trials, with consenting human research subjects, to produce data for FDA evaluation. The FDA then reviews the results of human clinical testing "to determine if the product … is safe and effective". According to the FDA, "at the heart of all of the FDA's medical product evaluation decisions is a judgment about whether a new product's benefit to users will outweigh its risks" (U.S. Food and Drug Administration, n.d. - a).

Clinical trials generally proceed in three phases:

Each phase has a different purpose and helps researchers answer different questions.

- *"Phase I trials: Researchers test a drug or treatment in a small group of people (20–80) for the first time. The purpose is to study the drug or treatment to learn about safety and identify side effects.*
- *Phase II trials: The new drug or treatment is given to a larger group of people (100–300) to determine its effectiveness and to further study its safety.*

- *Phase III trials: The new drug or treatment is given to large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it with standard or similar treatments, and collect information that will allow the new drug or treatment to be used safely.*
- *Phase IV trials: After a drug is approved by the FDA and made available to the public, researchers track its safety in the general population, seeking more information about a drug or treatment's benefits, and optimal use"* (National Institutes of Health, n.d.).

Best scientific practice demands double-blind randomized clinical trials (RCTs) to establish a medication's effects. Some RCTs compare a new drug to a placebo, and some compare a new drug to an existing standard therapy. Double-blind studies are those in which neither the researcher nor the research subject knows which research subjects are assigned to which study arm. In the case of a placebo-controlled trial, this means that some research subjects are assigned randomly to receive a placebo, and some are assigned randomly to receive the new drug. In a study that compares a new drug with an existing therapy, some research subjects are assigned randomly to receive the existing therapy, and some are assigned to receive the new drug. Randomization and double-blinding are both intended to reduce bias and enhance the scientific value of the clinical trial. Randomization avoids bias in the assignment of which volunteers receive which drug or placebo. And blinding avoids bias in measurement of research trial results. The dispensing pharmacist knows which research subject is receiving which drug and can unmask the information when medically necessary or when it is time to compare the results of the trial arms.

3.2 Historical Abuses and the Foundations of Drug Regulations

FDA approval processes, like human research protections, were informed by a long history of abusive and unsafe medical practices. In the 19th century, infamous 'snake oil' salesmen, marketed unproven medicines, often making fraudulent claims about their safety and effectiveness (Friedman & Freelance Writer, 2024).

Even before the founding of the United States, Colonial governments tried to protect people from dangerous medical products. For example, the Colony of Virginia banned dispensing more drugs than 'necessary or useful', because that practice had become 'dangerous and intolerable' (*Abigail Alliance v Eschenbach,* 495 F.3d 695, 704 (DC Cir. 2007) (en banc)).

These risks persisted into the 20th century. In 1937, sulfanilamide, a potential treatment of streptococcal infections, was formulated into a liquid by Harold Cole Watkins, chief pharmacist for S.E. Massengill Co. Watkins used diethylene glycol (antifreeze) as a solvent. He did not test the resulting Elixir Sulfanilamide for toxicity or conduct pharmacological studies on the new sulfanilamide preparation before distribution. Disastrously, Elixir caused the deaths of more than 100 people around the country (Ballentine, 1981).

The following year, Congress passed The Federal Food, Drug, and Cosmetic (FDC) Act of 1938. While the federal government's initial efforts were designed to protect people from dangerous medical products, Congress expanded FDA protections in 1962, with the Kefauver-Harris Drug Amendments. This required drug makers to prove their products were effective as well as safe.[64]

The expansion of federal protections curtailed patient access to drugs that the FDA had deemed unsafe or ineffective, as well as to new drugs the FDA had not yet approved. For desperately ill patients, the FDA's refusal to allow access to certain drugs based on efficacy alone became controversial and contentious. With some exceptions, a U.S. patient who wanted to try a new (unapproved) drug generally did not have access to that drug except as a clinical trial participant, and even then, only if he was randomly assigned to the new drug arm of the clinical trial.

3.3 Expanded Access to Experimental Drugs

In the 1980s, as the AIDS crisis claimed the lives of many young patients, activists sought access to HIV/AIDS antiretroviral medications that the FDA had not yet approved. They demonstrated, negotiated, and engaged with regulators, eventually permanently reshaping FDA drug regulation. The FDA improved patient access to drugs outside of RCTs and reduced the time to final FDA authorization (Manley et al., 2022). The FDA Modernization Act of 1997 later codified these changes into the Expanded Access Program (Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997)). However, even the new FDA expanded access program remained lengthy and administratively burdensome. The

64 For more on this history, see the FDA's chronological history of its expanding regulations – available at https://www.fda.gov/files/drugs/published/A-History-of-the-FDA-and-Drug-Regulation-in-the-United-States.pdf (accessed: January 20, 2026); see also Meadows, 2006.

FDA's regulatory requirements continued to prevent patients, including desperately ill patients, from accessing experimental medications without FDA approval.

3.4 *Abigail Alliance v Eschenbach* and Arguments About Additional Expanded Access

In 2006, the landmark case, *Abigail Alliance v Eschenbach*, addressed whether terminally ill patients had a constitutional right to access drugs that had the potential to save their lives, without government interference. Abigail Alliance is a nonprofit organization that advocates for terminally ill patients' access to experimental treatments. It sued the FDA, claiming that the Fifth Amendment of the U.S. Constitution protected persons from being 'deprived of life, liberty, or property without due process of law', and that the right to attempt to preserve one's life by taking a potentially life-saving drug was protected from government interference without proof of a compelling government interest that overcomes that right. Abigail Alliance argued that the FDA's lengthy clinical trials, combined with the "FDA's restrictions on pre-approval availability [of drugs] amount to a death sentence for these [terminally ill] patients" (*Abigail Alliance v Eschenbach*, 495 F.3d 695, 700). The district court dismissed the case, holding that no such constitutional right existed. The DC Circuit found that the district court had erred in dismissing Abigail Alliance's case and held that "a terminally ill, mentally competent adult patient's informed access to potentially life-saving investigational new drugs determined by the FDA after Phase I trials to be sufficiently safe for expanded human trials warrants protection under the Due Process Clause" (*Abigail Alliance v Eschenbach*, 445 F3d 470, 486 (D.C. Cir 2006).

In his dissent, Judge Griffiths argued that terminally ill patients could not give informed consent to use experimental drugs because they did not have knowledge about the potential risks and benefits (445 F.3d at 495). Critics of the Circuit Court's decision agreed. Several wrote about the decision, including oncologist and bioethicist Ezekiel Emanuel, later a key health care policy advisor to both the Obama and Biden administrations, arguing that access to unapproved drugs should not be expanded for terminally ill patients (Emanuel, 2006). Emanuel and others who opposed the DC Circuit's 2006 decision argued that unapproved medications provide little benefit to terminally ill patients beyond false hope, and indeed, these medical products and procedures could lead to harm. Emanuel pointed to the harm caused by expanded access in the 1980s and 1990s, which allowed more than 20,000

women suffering from metastatic breast cancer access to grueling bone marrow transplants. According to Emanuel, these experimental bone marrow transplants caused suffering and did not prove effective compared to standard chemotherapy. In addition, Emanuel and other critics argued that expanded access delayed research, because desperately ill patients who had unfettered access to unproven drugs would refuse to participate in RCTs that determined which drugs were useful (see for example, Manley et al., 2022).

Legal scholar Richard Epstein disagreed with the critics of expanded access. He noted that the FDA errs by focusing its review on averages. "By placing its focus on the average use, the FDA ignores the variation in individual responses… It could well be that on average a particular drug does not perform as well as a placebo. But so what? That only shows that most people should not take the drug, not that it should be banned." (Epstein, 2006).

Ultimately, in a rehearing *en banc*[65], the DC Circuit court sided with criticis of expanded access, including several medical associations that filed a joint amicus brief (CancerNetwork, 2007). The court held that the U.S. Constitution provides terminally ill patients no right of access to experimental drugs, even those that have passed the first, limited phase of safety trials, and even when terminally ill patients have no alternative treatments available to save their lives. (495 F.3d 695 (DC Cir. 2007) (*en banc*). The Court concluded "there is no fundamental right 'deeply rooted in this Nation's history and tradition" of access to experimental drugs for the terminally ill." In a strong dissent, Judge Rogers decried the denial of "a terminally ill patient her only chance to survive" as "a dangerous brand of paternalism" (495 F.3d at 728).

The majority opined in a footnote: "…we do not suggest that the law can never strike a balance between access to experimental drugs and risk that the Alliance suggests. We limit our analysis to whether the Constitution demands the balance they desire." (495 F.3d at 710, fn 17). In fact, Abigail Alliance and others continued to advocate in the elected branches for expanded access to potentially life-saving drugs for terminally ill patients.

[65] Normally, a case in the U.S. Court of Appeals is heard by a three-person panel of judges. Matters are reheard *en banc*, as an additional review, when they are exceptionally important. A rehearing "*en banc*" is heard by all of the court's active judges.

3.5 Right to Try

The democratic branches responded. Several states and the federal legislature enacted Right to Try laws. In 2018, President Trump signed into law the federal Right to Try Act, which "allows eligible patients to have access to eligible investigational drugs"[66] (U.S. Food and Drug Administration, 2024; 21 U.S.C. § 360bbb-0a).

> *A patient who is eligible for Right to Try is a patient who has:*
>
> – *Been diagnosed with a life-threatening disease or condition;*
> – *Exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug (this must be certified by a physician who is in good standing with their licensing organization or board and who will not be compensated directly by the manufacturer for certifying); and*
> – *Provided, or their legally authorized representative has provided, written informed consent regarding the eligible investigational drug to the treating physician.*
>
> *An eligible investigational drug is an investigational drug:*
>
> – *For which a Phase 1 clinical trial has been completed;*
> – *That has not been approved or licensed by FDA for any use;*
> – *For which an application has been filed with FDA or is under investigation in a clinical trial that is intended to form the primary basis of a claim of effectiveness in support of FDA approval and is the subject of an active investigational new drug application (IND) submitted to FDA; and*
> – *Whose active development or production is ongoing, and that has not been discontinued by the manufacturer or placed on clinical hold by FDA* (U.S. Food and Drug Administration, 2023).

The non-codified part of the federal act notes that it is the 'sense of the Senate' that adding the Right to Try Act "expands the scope of individual liberty and agency among patients, in limited circumstances" (Pub. L. No. 115-176, § 3(3), 132 Stat. 1372, 1374 (2018)).

It remains unclear whether the federal Right to Try Act has in practice expanded access significantly since it became law in 2018 (Sheikh, 2021). Continuing obstacles to access may include administrative hurdles and manufacturer-imposed costs. Although the Right to Try legislation may improve patient access to experimental

[66] Also known as Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.

drugs, one may argue that it does not cure the regulatory defect identified by Epstein. The FDA still bans drugs from market based on averages and centers the decision about which drugs may be used in the government rather than placing it in the hands of the people most affected and their physicians. Desperately ill patients still face practical hurdles accessing experimental drugs outside of RCTs. These hurdles are due, at least in part, to the regulatory environment. For example, confusion exists among doctors about the pathways that can be used to access unapproved drugs, and some physicians still may encourage their patients to enter clinical trials for reasons unrelated to the patients' own care (Manley et al., 2022).

3.6 Suggestions for Enhancing Autonomous Consent for Desperately Ill Individuals – in Expanded Access

If one accepts the argument that terminally ill patients lack sufficient information to make a genuinely informed choice about unapproved experimental drugs, the suggestions offered in section 2.5 of this paper for enhancing autonomous decision-making could be helpful. Taking each of the earlier suggestions in turn:

1. Imposing a waiting period after presenting an unapproved drug as an option to a desperately ill patient: A de facto waiting period exists between the time a drug is proposed for Phase 1 trials and its availability for Phase 2 testing. Even if the patient had not been exposed to information about the new drug during the Phase 1 period, it is certainly true that an analogous waiting period could be imposed. One might argue that any waiting period conflicts with the core purpose of Right to Try legislation. However, a brief, disease-specific waiting period aimed at improving decision-making could be far shorter than regulatory delays that last months or years (Kane et. al., 2002).
2. Reframing the question about taking the unapproved drug in a way that allows the patient to consider the choice more dispassionately: This suggestion could work to enhance decision-making in the treatment context in the same way it works in the research context.
3. Including time during the consent process for consultation: This suggestion could be as equally valuable for a desperately ill medical patient as for a desperately ill potential research subject.

These suggestions could enhance autonomous decision-making for patients considering unapproved medications in much the same way they could enhance autonomous decision-making for desperately ill patients contemplating enrollment in research trials.

4 Respect for Desperately Ill Patients

4.1 Moral Inconsistency in Consent Standards for Research and Treatment

The same potential for false hope that may compromise a desperate patient's consent to use an unapproved drug may also compromise a desperate patient's consent to serve as a research subject. Why are these two consents treated differently by research rules and by critics of expanded access?

Critics of expanded access to unapproved investigational drugs argue that desperately ill patients cannot give genuine, reasoned informed consent. In the 2007 Abigail Alliance rehearing dissent, Judge Rogers called the denial of expanded access 'a dangerous brand of paternalism'. Paternalism is a form of beneficence.

However, it appears that beneficence and respect for persons, though these are central to human research protections, are not priorities for critics of expanded access to experimental drugs. If desperately ill patients are deemed capable of consenting to participate in research for the benefit of future patients, then a fortiori they must be capable of consenting to experimental treatments intended to benefit themselves. Yet critics of expanded access, while claiming to protect patients, endorse and even encourage patients' participation in research trials – apparently treating consent as valid when it serves societal goals but questioning it when it serves patients' own interests. In other words, if the validity of desperately ill patients' consent were an issue, then these critics would not condone enrolling desperately ill people in research trials. On the contrary, they assert that terminally ill individuals can volunteer to serve as research subjects, seemingly regardless of any reduced capacity to give true, voluntary informed consent.

Those who would deny desperately ill patients access to experimental drugs while allowing their enrollment as research subjects disregard Kant's admonition that people ought not to be used merely as means. Their focus on advancing science for

the common good reflects utilitarian and distributional justice concerns rather than concern for patient autonomy or beneficence (see above, Emanuel, 2006; American Society of Clinical Oncology, Association of American Medical Colleges, & National Coalition for Cancer Survivorship, 2007).

4.2 Expanded Access to Experimental Drugs and Additional Safeguards to Enhance Autonomous Consent in Research for Desperately Ill Patients

The Belmont Report and the U.S. Human Research Protections require true volunteerism to distinguish ethically defensible human subjects research from the immoral research conducted by the Nazis in World War II. Whether desperately ill people can give genuine, autonomous informed consent may be questionable, but that genuine consent is the criteria necessary to distinguish morally justified human research from the transgressions of the past. If desperately ill patients had free access to experimental treatments, we could be sure that, when they volunteered for research trials, they were genuinely volunteering to serve as human research subjects for the benefit of future patients rather than choosing to participate in research as a way to access experimental treatments. Restricting access to experimental drugs risks undermining the integrity of research subject consent because it channels desperately ill patients who seek experimental drugs toward research participation rather than treatment. Justifying restricted access on utilitarian grounds, to ensure that desperately ill patients sign up to be human research subjects 'for the greater good', echoes the same moral logic that underpinned the Nazi medical research experiments and the Tuskegee Syphilis Study.

Precisely to avoid these moral transgressions, U.S. human research protections, and U.S. common law emphasize autonomy as the core normative principle in medical legal circumstances. Prioritizing autonomy in research subject and patient decision-making may conflict with the goal of advancing science and collecting generalizable knowledge, but autonomy nevertheless trumps social utility in U.S. law.

One approach to addressing the potentially diminished decision-making capacity of desperately ill individuals would be to include them expressly among the categories of subjects who need to be protected by additional safeguards. Recall that section 46.111(b) of the Common Rule states: "When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners,

individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects." Section 46.111(b) could be amended to include desperately ill persons. These individuals are vulnerable to coercion and implicit undue influence, they are educationally disadvantaged as compared with the researchers who would use them as research subjects, and they would benefit from additional safeguards to protect their welfare and rights. Additional safeguards to protect desperately ill subjects may include the enhancements proposed in this paper, along with any pertinent analogous requirements among the additional safeguards that have been created for research with children, prisoners, and pregnant women (see U.S Department of Health and Human Services, 2025).

4.3 Alternatives for Supporting Medical Advances

In addition, there may be alternatives to RCTs for gathering generalizable knowledge. Prospective research studies may not be the only way to advance science, especially with the advent of robust information technology. Retrospective data collection might serve to replace or at least reduce the need for prospective RCTs.

One promising development is the advent of enhanced data collection and analysis methods. For example, researchers at the Harvard Medical School and the Division of Pharmacoepidemiology and Pharmacoeconomics at Brigham and Women's Hospital have published methods for using insurance data to complement RCTs and enhance understanding of how medications work in clinical practice (Wang, Schneeweiss & RCT-DUPLICATE Initiative, 2023). The research group "aims to demonstrate the validity of using data routinely collected in clinical practice to produce meaningful conclusions". Although the researchers admit that "randomized clinical trials remain the gold standard for establishing a medication's effect," they note that clinical trials are expensive, time consuming and difficult to conduct (Sweet, 2026). Perhaps collection of real-world data can reduce the numbers of people enrolled in clinical trials, even if it cannot eliminate the need for these trials (see also Retsas, 2023).

It may also be helpful to consider an example of surgery. Unlike medical products (drugs, biologics, and devices), surgical techniques have developed without heavy regulation. Researchers seeking to develop new surgical techniques are not required

to conduct RCTs using human research subjects before a regulator allows them to market their new techniques. Scholars have argued for and against surgical procedures regulation, and some have distinguished surgical techniques from drugs, devices, and biologics on the basis that it is not possible to standardize measurements of surgeons' skills (in favor of surgical regulation see Andreoletti & Bina, 2022; against it: Rhodes, 2004). Based on the example of surgery, an argument may be made that if RCTs are not required, medical improvements can still occur.

5 Conclusion

Desperately ill patients who face choices about experimental treatments are vulnerable, not only because they are overwhelmed by disease, but also because their agency as autonomous individuals can be undermined by the bureaucracies that govern their choices. The legal and moral rules that justify using humans as research subjects are founded on respect for persons, autonomy, and informed consent. To satisfy the moral imperative of respect for persons, we must be careful about steering desperately ill patients into research trials, especially when we know therapeutic misconception is likely.

I have long been troubled by the tension between my opposition to my mother's agreement to undergo experimental treatment and my support for Right to Try legislation. Why did I oppose the exercise of autonomy in one circumstance and not the other? Was my reaction simply the product of concern for my mother, or a belief that autonomous consent must be grounded in reasoned deliberation, or was something deeper at stake?

Reflecting on these issues, I have come to two conclusions. First, desperately ill people may require special protection to ensure that their consents are genuinely informed and reasoned. More troubling, however, is the conclusion that a system that steers desperately ill patients towards research trials risks transgressing the important moral principle of respect for persons. Although I suspected my mother's emotionally driven decision to undergo experimental treatment was tainted by therapeutic misconception, what likely disturbed me most was the possibility that she was being used to advance her doctor's career or to produce generalizable knowledge. Desperately ill people should not be used for the benefit of others unless they clearly understand the request and freely volunteer to assume that role.

Legal Acts, Legal Cases

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About the author

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Povzetek v slovenskem jeziku

Najpomembnejše bioetično načelo v ameriškem zdravstvu je spoštovanje avtonomnega odločanja. Načelo avtonomije je zakonsko urejeno s pravili o „informiranem soglasju“, ki je v ameriškem pravu uveljavljeno že več kot stoletje. Neozdravljivo bolni posamezniki, ki se vključijo v raziskovalne študije, pogosto verjamejo, da bodo imeli dostop do novih terapij, ki jim bodo osebno koristile, čeprav v soglasju, ki ga podpišejo, izrecno piše, da jim nobena korist ni obljubljena. Ta »terapevtska zmota« in z njo povezane skrbi glede avtonomije vzbujajo dvom o pristnosti informiranega soglasja, pridobljenega od neozdravljivo bolnih pacientov, ki se vključijo v raziskovalne študije. S tem povezane skrbi glede razumevanja in soglasja so oblikovale razprave o tem, ali naj imajo neozdravljivo bolni pacienti dostop do eksperimentalnih medicinskih izdelkov zunaj raziskovalnih študij. Članek predlaga ukrepe za izboljšanje informiranega soglasja neozdravljivo bolnih pacientov in alternative za njihovo usmerjanje v raziskovalne študije.