

Protecting the Terminally Ill: Is Present Medical Research Structure to Credit or to Blame?

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Every medical treatment is based on a foundation of medical research supporting its efficacy and credibility. Scientific research must adhere to guidelines developed to ensure that all research is ethically and scientifically sound. Institutional Review Boards (IRBs) are committees composed of a diverse group of medical, legal, and general members. The role of IRBs is to evaluate whether research is ethical. Ezekiel Emanuel outlines the seven requirements of ethical research in his article "What makes clinical research ethical?" (1) He argues that the principle of beneficence must not be violated; the benefit to risk ratio of the research must be positive (1). The present debate is about whether or not the current structure of the research process for potential new treatments is harmful or unfair for terminally ill patients. Should the manner in which the risk/ benefit ratio is determined in terminally ill patients be different than for that of a healthy volunteer? Is society allowing an emotionally charged debate that may impinge upon a system that was developed to protect human subjects; or does this system create "unnecessary paternalistic barriers?" (2)"

To gain approval, experimental treatment must progress through three phases of study, often completing a fourth for marketing purposes. The Phase I study seeks to determine the maximum tolerated dose, as well as to discover any toxicity that was not detected during animal research (3). Phase II and III test the efficacy of the proposed treatment. Once the safety data, side effects, and effectiveness are confirmed, the drug can be marketed (4). Following marketing, a phase IV trial can be used to look at efficacy in a broader patient group and also to observe longer-term side effects (4). At each stage, research may not proceed without first obtaining approval from an IRB.

The regulation of research and the focus on research ethics exist for good reasons. The aftermath of World War II revealed the atrocities committed by the Nazi regime, which used concentration camp prisoners as human "guinea pigs", testing cruel and often futile treatments (5). The Nuremberg Code asserts that the priority of human subjects' protection is to protect the patient from the overzealous investigator; meaning human safety and autonomy cannot be sacrificed for the purpose of scientific gain (2). Included in the Nuremberg Code is the acknowledgment that consent from the research subject is essential, and that one of the things that can render consent invalid is "duress" (6). Following this trend

towards regulating research practices is the publication of the World Medical Association's Declaration of Helsinki. The Declaration of Helsinki was adopted in 1964, and has been revised as recently as 2004 (7). It is a list of guidelines for medical research, and includes those principles contained in the Nuremberg Code. The 32nd clause of section C, titled "Additional Principles for Medical Research Combined with Medical Care," states that: "In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures.... Where possible, these measures should be made the object of research...." (7)

When did a regulatory system designed with the intention of being ethical come to be seen as restrictive? In the late 1980's and early 1990's, diagnosis with Acquired Immunodeficiency Syndrome (AIDS) was an imminent and painful death sentence. In the presence of little hope, AIDS activists began to challenge the system with which proposed treatments



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were being tested and regulated (2). The question for debate was whether or not the Nuremberg code had created a research system with "unnecessary paternalistic barriers," which were slowing down the discovery of potentially life saving treatments (2). The Federal Drug Administration (FDA) did react to pressure from activists, responding by allowing drug fast tracking for AIDS related treatments (2). Fast tracking allows for clinical trials to proceed with less safety data accrued (2). In a similar response to pressure from the cancer patient population, cancer drugs may now also be fast-

tracked (2). For example, Gleevec, a drug indicated for the treatment of cancer, which was put through FDA priority review and approved in four months (8). In fact, the drug approval time for a potential cancer treatment has been reduced from over twelve months to a time period of less than six months (2).

The research regulatory system continues to be questioned by sick patients who want to do "everything possible," even if it means taking risks with regards to the research system (9). In her report on how palliative patients forgo hospice care in the interests of entering a phase I trial, Dr. Ira Byock reaffirms that patients with far-advanced illness frequently enter clinical trials in the

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hope that the experimental treatments will extend their lives (10). In fact, in a study of surveyed phase I cancer participants published in 2006, 90% of respondents indicated that they would still enter a phase I trial even if the risk of death was quantified at 10% (11).

Frank Burroughs of the Abigail Alliance, a prominent patient advocacy organization, said that the FDA "block(s) the life, liberty and pursuit of happiness for patients who cannot get into clinical trials" (3). The debate has been further complicated by the proposal of Bill S.1956, titled "Access, Compassion, Care and Ethics for Seriously Ill Patients Act" (12). If this bill is passed, patients who have no further possibility of conventional treatment would have legal access to any phase I drug with some minimal accumulated evidence of efficacy, not necessarily obtained through a phase II trial (12). This regulation would make primitive treatments more readily accessible to terminally ill patients who are "fed up with waiting on the medical community to get through their red tape" (3).

Actions by very sick patients to dodge this perceived "red tape" have been met with resistance. In a response to the proposal of Bill S.1956, the Board of Directors of the Society for Clinical Trials cite their reasons for resistance to the proposed legislation saying that the law's "effect would be to undermine the system of scientifically valid testing of new drugs" (12). There is a profound therapeutic misconception associated with Phase I trials. One survey study of phase I oncology trial participants reported that 85% reported their reason for participation as therapeutic benefit (13). This is contrasted with the reality that fewer than 5% of Phase I trials typically yield a response rate (11, 13). As W. Glannon reports, the distinction between "a rational therapeutic optimism consisting in weighing low probable benefit against risk," is very different from "an irrational therapeutic misconception (9)." Are patients, indeed as cancer patient Professor George Zimmer claims, looking to "maximize potential benefit," and "struggle" against cancer? Or are they vulnerable, their judgment leading them to place faith in unproven treatments (2)? The New York Times featured the story of Todd Hendrickson, a father of three, two years shy of

his forty-fifth birthday, and near death due to intestinal cancer (14). Todd Hendrickson chooses to accept the risks of and participate in a clinical trial for Gleevec (14). He considers his experience a success: his cancer has been reduced in size by 80% and he "feel[s] the best he has in three years" (14).

The role of the physician is also crucial when questioning the research regulatory structure. Firstly, should the government provide terminally ill patients with access to new treatments, there will still be the need of an available physician to monitor and concur that this alternative treatment is in their patient's best interest (15). An unproven and experimental treatment could pose potential harm to a patient, and the first role of the physician is "to do no harm" (15). Currently, when treatments are offered to patients for compassionate use, they are offered pro-bono (12). If new legislation extends this compassionate use to anyone who has failed traditional forms of treatment and wishes to have access to an experimental treatment, there will be no more pro-bono lending of treatment solutions (12). Additionally, the efficacy of the evidence based research system is threatened when people other than enrolled research subjects are taking experimental drugs, and thereby not contributing to the accumulation of scientific knowledge (15).

Success stories like Todd Hendrickson's inspire faith in the utility of research; however, it is essential to remember that in research there are also potentially less favorable outcomes. Suggestions to better accommodate terminally ill patients while maintaining the security of the research structure have been made. These include increasing dosages closer to the maximum tolerated dose in Phase I trials, and making more liberal risk/benefit ratio calculations (9, 15). Society needs to come to a consensus on whether the correct answer is to change research practice or instead to decide to trust regulation bodies and IRBs as a group of neutral and experienced individuals with the expertise to make rational and informed decisions, however difficult the outcomes may be to face.

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