

The Two-Faced Angel: Do Phase I Clinical Trials Have a Place in Modern Hospice?

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Abstract

Increasingly, bioethicists have been exploring the possibility of making phase I clinical trials available to hospice patients. Phase I clinical trials are designed to test a drug's safety and dosage, not its effectiveness. Participants in these studies generally do not understand that the purpose of the investigation is not to benefit them, thus challenging the notion of informed consent. But furthermore, the idea that patients believe experimental drugs will help them is contrary to the principles of hospice. Also, the very nature of the research in phase I conflicts with hospice's methods. For these reasons, this paper finds that the two models must remain distinct.

Death is an angel with two faces:

To us he turns

A face of terror, blighting all things fair;

The other burns

With glory of the stars, and love is there.

—Theodore Chickering Williams

The appalling work of “Dr.” Josef Mengele was probably the lowest point in the history of medical research. A “physician” at Nazi Germany’s infamous Auschwitz concentration camp, Mengele contributed to the executions of 400,000 people—a flick of his wrist meant the difference between life and death—while at the same time directing the suffering of countless others over the course of his notorious investigation. Gruesome experiments to his name include tolerance studies of electric shock and radiation exposure on live subjects who were either killed instantly or left severely scarred. Mengele never expressed remorse for his actions, citing the fact that all of his human Guinea pigs were amongst the walking dead, already condemned by Hitler. Who cares what we do to people who are going to die anyway? For his “contributions” to

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medical knowledge, this “doctor” lives on by way of his well-known pseudonym, the “Angel of Death” (Pence, 1990).

But in contrast, while Mengele and his experiments define “a face of terror, blighting all things fair,” modern American medicine has a care model that “burns/ With glory of the stars”: hospice. Unlike the Nazi, whose shocking exploits evoke images of the Grim Reaper, hospice reminds us of Hermes, the Greek god whose charge was to lead the souls of the dead to Hades. According to the National Hospice and Palliative Care Organization (2002), hospice is “support and care for persons in the last phase of an incurable disease so that they may live as fully and comfortably as possible.” It functions as a comforting guide to the ill and their families as they progress through the process of dying, respecting life though understanding death as its natural terminus. Hospice patients have chosen to accept their fate, forego curative treatment, and thus spend their final days in palliative care, attending only to the comfort of themselves and those close to them—“and love is there.” This brand of healthcare clearly is a different side of the angel of death.

But what happens when we attempt to look at both of the seraph’s faces simultaneously. What happens when we attempt to conduct research on the dying, particularly those who have made the hospice decision, who have therefore accepted that they are “going to die anyway?” Truth be told, the initial juxtaposition of Mengele and hospice is unfair to the scientist’s perspective, but bringing the sociopath into this discussion is not wholly inappropriate in that researchers do want to use hospice patients to test treatments, not for efficacy, but for toxicity and dosage—they want to execute phase I clinical trials on these subjects (Byock, 2005). Ethically, this could not be more askew. As we will see, enrolling hospice patients in phase I trials compromises and contradicts the goals of palliative care and is thus an unethical medical practice.

Interestingly, both early clinical tests of pharmaceuticals and hospice are linked by a common goal: altruism. Phase I trials are most often associated with oncology and chemotherapy, and “agents and interventions that are tested in phase I may have substantial side effects” (Casarett et al., 2002, p. 1601). In these situations scientists have discovered a compound that might be a Holy Grail, a miraculous cure for cancer. But their invention might also be dangerous, so researchers conduct a Phase I trial, defined by the

FDA as “initial studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness” (ClinicalTrials.gov, 2005). As an ethical necessity, participants are informed that their involvement “offers no meaningful chance of direct medical benefit”—the purpose of their participation is to test a therapy’s safety, not its value (Casarett et al., 2002, p. 1601-1602). A survey of hospice patients conducted by Dr. David Casarett, Dr. Cordt Kassner, and Dr. Jean S. Kutner (2004) indicated that this perception of selflessness is the most popular motivation for which they would consider joining a clinical trial: 66% of those who expressed willingness to be approached about research said they desired this to “help others” (p. 857).

The modern hospice is founded on a separate sense of this same humanity. In a pamphlet provided by the Hospice Association of America, the organization describes its model of care as “[reaffirming] the right of every person and family to participate fully in the final stage of life” (Hospice Association of America, 2002). Hospice focuses on palliative care and symptom management, providing services that support the medical, social, emotional, and spiritual needs of the dying and their loved ones. Since 1982, Medicare has offered a hospice benefit, subsidizing all costs for those who enter certified hospice programs, subject to the condition that their prognosis be terminal within six months or less and that they terminate curative care, including Phase I clinical trials. This new policy, through its financial incentive to enroll in and provide hospice care, drove the number of registered hospice program in the United States from 31 in 1984 to 2,265 in January 2002 (Hospice Association of America).

But besides economics, key to the success of hospice is the understanding reached by all parties that life-sustaining treatment will cease—besides “comfort first,” do-not-resuscitate (DNR) is the golden rule in hospice care. This principle is the root of the first major ethical conflict between hospice and research: researchers have a stake in the life and death of their subjects. More data can be collected if the subject is kept alive longer, thus doctors might be inclined to override a DNR order in order to elongate their study. Margaret Edson’s *Wit*, a play turned HBO movie, highlights this distressing possibility. Vivian Bearing, the main character, is a former English professor diagnosed with terminal ovarian cancer. At the behest of a doctor at her university, she decides to enroll in what was most likely a phase I trial, but after eight months of suffering through a volatile course of chemotherapy, she decides that if her heart stops, she’d like it to stay that way. The last scene, however, portrays one of the researchers violating this decision, calling in a “code blue” to bring her back because “she’s research.” Fortunately in the end, the blue team leaves Dr. Bearing in peace, but this fictional

picture is not so far from reality (Nichols, 2001).¹

In another study by Dr. Casarett (1999), this time with Dr. Carol Stocking and Dr. Mark Siegler, a survey of 358 physicians showed that the 29% of them “certainly would” resuscitate a patient who had experienced a cardiopulmonary arrest if the arrest was due to a complication in treatment. Furthermore, on a 7-point Likert scale, with 1 being “certainly would not” and 7 being “certainly would”, the mean response to that question was 5.24, “likely” (Stocking et al., 1999, p. 36). Consider that phase I clinical trials are those most likely to exhibit the types of complications that would cause heart stoppage—in the movie, as Vivian whispers with her characteristic wit, it’s not her cancer has so ravaged her body that she is required to be in immunonological isolation—it’s her treatment (Nichols, 2001). How, then, would a researcher react to a cardiac arrest when faced with the inherent DNR of hospice, the therapeutic misconception, and the fact that his research depended on his subject living as long as possible—which of the angel’s masks would he wear? The truth is that no one can be trusted to make the ethical decision under these circumstances, and for this reason alone, it’s clear that research ethics and the hospice model don’t mix well.

It’s also apparent, revisiting Mengele, that research on those “are going to die anyway” raises some complicated moral questions. In an August 2000 article in the *Journal of Pain and Symptom Management*, Dr. Casarett and Dr. Jason Karlawish outlined and discussed four considerations that are particular to research in hospice: that “these patients are especially vulnerable,” that “investigators must obtain consent from patients and families,” that “balancing research and clinical roles is particularly difficult,” and that “the risks and benefits of palliative research are difficult to assess” (p. 131). The first concern is acknowledged by the National Institutes of Health, the principal research regulatory body in the United States, which “defines people near the end of life as a ‘special class’ of research subjects” because of their lack in decision-making capacity and questionably voluntary choices (Karlawish et al., 2000, p. 131). This issue is clearly related to the second concern regarding informed consent, and the combined problem is fairly sticky: can terminal patients reasonably give consent to enroll in clinical trials?

The answer is no: dying people enrolled in phase I research do not understand that the purpose of the investigation is not their own benefit. In a study on Phase I research participants at the University of Chicago, surveyors found that 85% of patients decided to participate because of possible therapeutic benefit and that 93% said that they understood all (33%) or most (60%) of the information

¹ At many points in the film, her physicians indicate their surprise that she lasted as long as she did, acknowledging that the drug was being tested for safety.


given to them; the same study found that only 33% could actually state the purpose of the trial: dose-escalation and dose-finding studies (Daugherty, 1999, p. 1607). Also, in the same study in which Dr. Casarett (2004) observed that two thirds of hospice patients would participate in research for altruistic reasons, 55% also responded that they'd participate to in an attempt to help themselves (p. 857). Unfortunately, these views are horribly misguided because, according to the Mayo Clinic (2005), 30% of experimental therapies aren't even safe enough to make it out of phase I, and only 6% eventually come before the FDA for approval.² Clearly these statistics, coupled with the results of both surveys, indicate a surprising amount of ignorance amongst those participating in studies for which they are supposed to have given "informed" consent. This is because the consent they have given is not truly informed. To present terminal patients with the option to enroll in phase I research is to tantalize them with a terribly false hope for their own survival. And unfortunately there's no better way to say that this hope is completely contrary to the idea of hospice other than to state it bluntly: hospice patients have accepted their impending deaths, and those enrolled in phase I clinical trials cling to the thought that their participation will cure them. Thus it is absolutely unethical to offer a hospice patient the opportunity to enter a phase I clinical trial because doing so would undermine the basis of the palliative model.

While the false hope of patients enrolled in phase I trials contradicts the foundations of hospice, the other two ethical concerns enumerated by Dr. Casarett and Dr. Karlawish compromise its goals. Hospice care's approach is primarily focused on providing comfort for both patient and family, and the difficulties that arise in defining the roles of caregivers and in assessing the perils and profits of research directly inhibits this end (Karlawish et al., 2000 p. 134-135). First of all, enrolling a patient in both research and hospice involves constant contact with quite a few physicians, each with a different agenda. Who, then, helps patient and family make the important decisions that arise at the end of life? Adding a research team into the mix makes the already stressful process of dying all the more hectic for all parties by giving voice to perspective that might not necessarily have the best interests of patient and family in mind. That said, the same criticism could be charged against hospice practitioners, but the very possibility of such confusion in an already nerve-racking situation demonstrates that the natural tension that would exist between the two healthcare teams would be a barrier to good end-of-life care. Second of all, the side effects of

² According to the website, 20% of all treatments make it from phase I to FDA approval, but after analysis of the other statistics provided, this is impossible. 70% of drugs pass phase I, 33% of those pass phase II, and 25-30% of those pass phase III. Multiplying those odds yields 6%, and that doesn't even factor in the odds of receiving FDA approval after phase III.

these drugs are counter-productive to the goal of alleviating physical pain. That nearly a third of phase I therapies are too dangerous to continue testing indicates just how volatile these substances can be. A disease that puts a person in hospice is obviously bad enough as it is; do caregivers really need the added responsibility of controlling the symptoms of something that can so easily be avoided? Finally, the very nature of a phase I trial is to assess the hazards of a drug, an end that also opposes to the goal of comfort. Researchers want to know how uncomfortable the drug makes the subject: how much vomit heaved, how many pounds lost, or how few hairs left (Nichols, 2001). Doctors whose objective is to measure pain have a most unfortunate aim that opposes the fundamentals of palliative care, and for this reason it seems that their presence can do nothing but hinder the hospice course. For these reasons, phase I research trials have, intrinsically, no place in a true hospice program.

Still, it seems rather unfair to deprive participants in phase I research trials of the hospice's resources. In fact, it seems rather ludicrous that any person would be denied the means of attaining a more comfortable healthcare experience. But this is the status quo in American medicine. For example, at the Hospital of the University of Pennsylvania, the 14th best hospital in the country according to U.S. News and World Report, only 1.5 nurse practitioners provide only 20 of 680 (3%) patients with palliative care, while 20-30% could be assisted by their expertise (McMamamen, 2005). This is general symptom management, not just for the dying, to which everyone should have access.

Therefore, the objections to allowing hospice patients to enroll in phase I research outlined in this paper are not grounded in the notion that participants in clinical trials should be restricted from the services of hospice—everyone should have those. Rather, the goals of the two approaches are so divergent that to utter "experimental drug" and "hospice" in same breath seems sacrilegious. The government's current policy on the matter is thus correct: those participating in clinical trials should not be eligible for Medicare's benefit. But a happy-medium paradigm for care should be established that permits those who partake in phase I trials access to the suffering management resources that make hospice so popular. Currently, phase I research and hospice characterize the two-faced angel of dying in America. But death should be an angel with only one expression, a gaze that "burns/With glory of the stars, and love is there." 

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