

End-of-life Care for Terminally Ill Participants in Clinical Research

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ABSTRACT

Efforts to improve end-of-life care in the United States have paid little attention to the unique concerns of participants in clinical research who are terminally ill. In this paper we focus attention on and offer an analysis of how to meet the needs of these individuals. To address their concerns, we consider how to reconcile two important tasks: providing optimal end-of-life care and conducting clinical research. First, we examine the inherent tension between the goals of medicine and the goals of science. Second, we focus more specifically on the tensions between a good death and conducting clinical research in patients with a short life expectancy. We examine six domains that have been suggested for measuring a good death: physical symptoms; psychological and cognitive symptoms; economic and caregiving needs; social relationships; spiritual beliefs; hopes and expectations. For each of these domains we examine how the goals of clinical research may conflict or coincide with taking care of a patient with a terminal illness. Finally, we offer suggestions to address these tensions: (1) modify the informed consent discussion for terminally ill participants in research; (2) build a palliative care component into clinical trials; (3) attend to the needs of family caregivers of terminally ill research subjects; (4) arrange for continuity of care so that dropping out of a trial does not jeopardize medical care; (5) train clinical investigators in end-of-life care; (6) develop a counseling strategy for terminally ill participants in clinical research.

INTRODUCTION

THERE HAS BEEN A CONCENTRATED effort to improve end-of-life care in the United States yet little attention has been paid to the unique concerns at the end of life for participants in clinical research. In this paper we focus attention on and offer an analysis of the needs of these individuals and how to address them. The care of patients with a short life expectancy who are enrolled in

clinical trials is particularly compelling because research will always likely focus on illnesses that remain untreatable with extant conventional therapy and hence life-threatening. The valuable information learned from conducting phase 1 clinical trials will primarily benefit future patients whose illnesses would otherwise be fatal. For the patient who chooses to participate in a trial, there is no guarantee of benefit and there is the possibility of harm and discomfort. Given that these

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patients/subjects may have terminal illnesses, they deserve the benefit of all the information that we have learned about how to care for patients at the end of life.

Thus, in this paper we consider how to reconcile the two tasks of providing optimal end-of-life care and conducting clinical research. First, we briefly examine the inherent tension between the goals of medicine and the goals of science. Second, we focus more specifically on the tensions between a good death and conducting clinical research in patients with a short life expectancy. Third, we offer some suggestions and solutions to address these tensions. The patients who are the focus of this paper are individuals with metastatic cancer—those whose advanced disease affords no cure. These individuals are likely to have a good performance status with a life expectancy of more than 3 months when entering a clinical trial but are likely to die of their illness. While many disease processes shorten life expectancy, metastatic cancer has a more predictable course and will be the focus of this paper, but the discussion may be applicable to other disease processes as well. The type of clinical research that is most applicable to our discussion are phase 1 trials. Our goal is to facilitate clinical research that advances medical practice while also being sensitive to the needs of dying patients. In so doing we explore the ethical tensions in conducting research with terminally ill patients and offer suggestions to resolve them.

THE GOALS OF CLINICAL MEDICINE AND SCIENCE

The essence of clinical medicine is contained in the doctor–patient relationship that obligates the physician to relieve suffering in the unique patient confronted in the clinical encounter.¹ The goal of the physician is the achievement of the particular patient's good, "a good decision must be grounded in some sense of the meaning of illness to this patient. A patient's biography is at stake in any serious illness. Healing is impaired without some attention to that biography."² Because a central feature of the doctor–patient relationship involves alleviating suffering by taking into account the particularities of an individual patient and choosing what is good for that patient, the interaction between a doctor and patient

becomes a moral encounter.² While the clinician must be familiar with and have a command of the scientific basis of medical practice, he or she does so in service of the individual patient, by tailoring care to the individual.

This individualized approach of clinical practice stands in contrast to the nature of science and its ends. The goal of scientific research is to contribute to generalizable knowledge³ that often requires the minimization of individual particularities. Furthermore, there is no guarantee of direct benefit to the research subject. Hence, the focus of science is not to meet individual patient needs.

TENSIONS BETWEEN A GOOD DEATH AND CLINICAL RESEARCH

The ethical issues for the physician-investigator can become particularly prominent and problematic when he or she is conducting research on patients with short life expectancies. Patients with terminal illnesses are especially vulnerable in the sense of feeling wounded and needing care from others and thus have many unique needs in coping with their disease.⁴ The cornerstone of care at the end of life is to tailor treatment to the specific needs of the particular patient in order to fulfill his or her personal goals. A good death involves establishing clinical and personal goals with patients and those close to them, and fitting care strategies—physical, psychological, spiritual, and practical—to patient goals and circumstances.⁵ At the same time, many patients with terminal disease need and want new innovative therapies. In the absence of effective standard therapy, clinical trials offer them hope for a potential cure. However, the benefit profile for participants is particularly limited if we consider the outcomes of phase 1 clinical trials. DeCoster and colleagues⁶ conducted a review of phase 1 clinical trials using cytotoxic compounds from 1972 to 1987. A total of 211 trials with a total of 6639 patients were evaluated. They found 23 (0.3%) complete responders and 279 (4.2%) partial responders for an overall response rate of 4.5% among all entries. Estey and colleagues⁷ report a similar overall response rate of 4.2% in 187 phase 1 trials of 54 anticancer drugs introduced into National Cancer Institute-sponsored clinical trials from 1974 to 1982. Given the inevitable need for the early phases of research with human subjects

and the high likelihood that many participants will die, it is essential to find approaches for a "good death" that are attentive to the needs of particular patients and reconcilable with the nature of the scientific enterprise.

A GOOD DEATH

Efforts to make clinical trials compatible with the needs of patients with life-threatening illnesses can be facilitated by current understanding of a good death. The Institute of Medicine's definition of a good death is "one that is free from avoidable distress and suffering for patients, families, and caregivers; in general accord with the patients' and families' wishes; and reasonably consistent with clinical, cultural, and ethical standards."⁵ Emanuel and Emanuel⁸ have suggested six domains for measuring and modifying a good death: physical symptoms; psychological and cognitive symptoms; economic and caregiving needs; social relationships and support; spiritual and existential beliefs; and hopes and expectations. These domains are useful in examining the tensions between the goals of achieving a "good death" and generating scientific knowledge. For each of these domains we will examine whether the goals of clinical research may conflict or coincide with taking care of a patient with a terminal illness.

PHYSICAL SYMPTOMS

The vast majority of terminally ill patients will suffer from physical symptoms. An essential component of their care involves minimizing the physical symptoms of pain, fatigue, drowsiness, insomnia, dyspnea, and anorexia, which are common at the end of life.⁹⁻¹¹ The impact of participation in clinical trials on physical symptoms can be complex,¹² although publication regarding the extent of these symptoms is currently lacking. Similar to well-established cancer therapy, experimental therapy causes side effects. But given the novelty of experimental therapy, some of its side effects cannot be fully anticipated. The primary goal of phase 1 trials is to determine the profile of side effects of a drug and to increase the dose of the drug until the dose limiting toxicity level is achieved. Patients undergoing exper-

imental therapy frequently have to undergo monitoring, including regular needle sticks for blood draws, biopsies, and long-term indwelling venous catheter as part of the protocol. In short, participants frequently experience physical symptoms in the course of their participation in experimental research.

Experimental therapy may possibly ameliorate the underlying disease and decrease physical symptoms. Alternatively, it may possibly increase physical symptoms transiently for the sake of longer term remission of symptoms, or possibly provide a trade-off of a known set of symptoms for another set of less predictable symptoms. At the other extreme, the experimental intervention may lead to life-threatening complications that require intensive care. In sum, there is uncertainty about what the effect of experimental treatment will be on a particular patient.

The structure of clinical research can be well equipped to care for these patients. Because one of the major goals of clinical trials is to measure symptoms, patients are generally well monitored using a comprehensive symptom list and meticulously followed during a clinical trial. Symptoms are graded according to severity and numerous stopping points are determined for each physical symptom before the clinical trial starts. There is usually a treatment strategy in place to treat possible physical symptoms, and if patients do not respond to treatment, they can be withdrawn from the trial. Thus there is the potential for terminally ill patients in clinical trials to have their physical needs well cared for.

PSYCHOLOGICAL AND COGNITIVE SYMPTOMS

The psychological and cognitive symptoms of a dying patient may include depression, sadness, anxiety, or irritability.^{9-11,13} Whether patients experience more or less psychological symptoms while participating in a research study varies. While some individuals may have no inclination to enroll in research, others may be distressed to be told they do not meet eligibility criteria and cannot participate. These psychological symptoms also have predetermined stopping points for withdrawing patients from a clinical trial. One potential advantage for all patients participating in clinical trials is that several members of the re-

search team care for them. Regular visits and attention are likely to be psychologically beneficial for patients involved in clinical research. This extra scrutiny may also lead to a quick detection of psychological symptoms, and thus, more prompt treatment. Alternatively, subtle changes in mood or behavior might be more readily detected by those individuals who have more longstanding relationships with the participants than the research team does.

Research subjects may also have differing psychological responses to the options of ongoing participation or withdrawal from a protocol. Some subjects will be powerfully motivated to remain in a study; some may feel that the research team expects cooperation and ongoing participation but may not wish to continue; some may feel pressured by their families to continue; others may have conflicted feelings. Yet another possibility is that if the experimental treatment fails, the research team may consider it necessary to withdraw the patient from the protocol and the patient may feel abandoned in the process.

ECONOMIC DEMANDS AND CAREGIVING NEEDS

The economic demands and caregiving needs of terminally ill patients can be overwhelming. Lack of insurance and loss of income along with substantial nursing and personal needs in patients with terminal illness may impose significant economic demands and caregiving burdens on patients and those who take care of them.¹⁴⁻¹⁶ Participating in a research trial may increase some of the economic burden because although the experimental drug is usually paid for there is usually more intensive monitoring and testing which can increase the costs of travel, room, and board. Additionally, patients with terminal illnesses need family members to accompany them, thus increasing the economic burden.

Terminally ill patients require care and have tremendous personal needs that can be overwhelming for a patient's family. Participation in funded research offers the possibility that caregiving needs may decrease because there are more caregivers available to absorb the needs of the dying patient. A multidisciplinary team of caregivers can help reduce the psychological distress of caring for a loved one.

SOCIAL RELATIONSHIPS AND SUPPORT

Having social supports such as people to talk to, to help reflect on one's life, or simply to have fun with is an important part of making the process of dying less burdensome and more meaningful. Participating in a clinical trial may be helpful either by directly involving more people in the provision of social support or by helping identify other sources of social support needed by patients. Alternatively, if a patient must be hospitalized, or be in a research institution far from home, then participation in a trial may remove him from his family, friends, and community at a crucial time near the end of life and hence diminish crucial sources of support.

SPIRITUAL AND EXISTENTIAL BELIEFS

Attending to spiritual and existential concerns can be an important part of the experience of a patient with a terminal illness regardless of whether or not the patient participates in a clinical trial. Some patients who recognize that they have little hope of surviving find solace in the possibility of contributing to the advancement of science through their participation in research. Others may find the process too burdensome because it takes away from the precious time they have left to focus intently on those spiritual concerns that matter to them most.

HOPES AND EXPECTATIONS

The hopes and expectations of terminally ill patients regarding their prognosis, future health status, and quality of life can be a profoundly important part of their experience. It can be argued that participating in a clinical trial would increase the hope and expectations of survival or other benefits in patients with a terminal illness. Participation in a clinical trial offers the possibility, albeit uncertain, of palliation of symptoms or extension of life. Patient understanding of these possibilities involves a complex mix of cognitive and emotional reactions. Most terminally ill cancer patients overestimate their survival time, and this can be associated with preferences for more medical interventions.¹⁷ This denial of a terminal

prognosis may lead to unrealistic requests for treatment. Patients with cancer that has failed conventional treatment may be so eager to find alternatives that they misunderstand the intent of research.¹⁸ Several studies of informed consent have found that advanced cancer patients who have been offered the opportunity to enroll in a phase 1 trials were motivated by hope for improvement or a lack of other alternatives.¹⁹⁻²¹ Thus, for many researchers, the difficulty lies not in convincing patients to participate in trials, but rather in explaining to patients that they are too sick to qualify for participation. Some patients approach researchers and are already well informed about clinical trials from the Internet and other sources. These patients may entertain unrealistic hopes and deny their poor prognosis. They may insist on participating on the basis of inflated expectations and misconceptions about the benefits to be gained from participation in a clinical trial. At the other extreme, the potential exists for investigators to recruit unsuspecting or desperate patients into clinical trials. Investigators can at times find it difficult to convey the risks and benefits accurately to obtain truly informed consent, and may hesitate to give a realistic picture in the face of the inclination of patients to deny the reality of their situation. This can lead to patients becoming involved in research trials without their clear understanding that there is a low benefit/risk ratio.

At times, because of the tendency of patients, families, and investigators to view the trial as giving some hope of avoiding or delaying death, the task of confronting the reality and imminence of death may be deferred, often indefinitely. Enrolling a patient in a research protocol may thus make the possibility of coming to terms with death harder that it might be otherwise.

SUGGESTIONS FOR SOLUTIONS

Given the need to involve terminally ill patients in clinical research, we suggest the following strategies be used to assist in providing ideal end-of-life care for participants in clinical trials.

1. *Modify the informed consent discussion.* Obtaining truly informed consent for participation in research has proven to be an elusive task.¹⁸ Efforts to improve consent forms have not en-

tirely succeeded in improving subject understanding of research protocols.^{22,23} Techniques such as educational audiotapes, videotapes, computer aids, and supplemental written material offer modest improvements.¹⁸ But despite much effort at improving the consent process, little of it has focused on the tensions that exist for terminally ill patients participating in clinical trials who must understand that enrollment in a trial offers little or no hope of altering the outcome of their cancer. Patients with untreatable malignancies are expected to have a realistic understanding of the likely outcome of their participation in a trial even in the face of their hopes for some gain, be it a sense of purpose, of struggling or carrying on in the face of death, or of altruism. In this light it is important to find strategies for honestly conveying the improbability of therapeutic benefit in the course of participation while supporting patients' sense of meaning, purpose, and hope in the course of their enrollment. Better ways need to be developed to discuss the possibility of death in spite of participation. Often patients have the therapeutic misconception that the research being conducted is primarily for their own benefit rather than for generalizable knowledge for the sake of future patients.²⁴ Explicitly discussing the end of life in as supportive a fashion as possible during the consent process might help avoid the misconception about the benefits they are likely to derive from the trial. A potential research subject might be asked how much he understands and how he is feeling about his illness and treatment options. Then a discussion can ensue about how the research fits in with the patient's overall goals and options. If the discussion has included some give and take about the patient's circumstances and what can be expected from the research, it should be possible to have an exchange that is respectful of the patient's unique needs and informative enough to yield properly informed consent. In addition, as Sachs²⁵ suggests, posing comfort care only as a real alternative during the informed consent process and in consent documents might diminish the inclination of some potential participants to enroll because it avoids the misapprehension that that there is no alternative to enrollment.

2. *Build a palliative care component into clinical trials.* Research subjects with terminal illnesses should not have to forgo the standard of care in palliative medicine in the course of enrolling in research. There are both attitudinal and financial obstacles to incorporating palliative care into clinical trials, but we would suggest that such an incorporation would yield an ideal strategy for addressing the end-of-life issues that participants in phase 1 trials must almost inevitably face. The attitudinal obstacles are complex. One attitudinal obstacle is the belief that administration of chemotherapy or enrollment in a phase 1 clinical trial is antithetical to the goals of palliative care. This is an attitude that is difficult to overcome in both patients and physicians. As the discipline of palliative care medicine has matured and evolved, the ideal model has incorporated the recognition that patients need palliation of symptoms long before they may be perceived as terminally ill. As the Institute of Medicine suggests in describing a new model for care at the end of life called Mixed Management, the traditional categories of therapy as either curative or palliative do "not capture or support the reality of simultaneously pursuing a broad array of desired ends."⁴ Palliative care and life-prolonging care are not mutually exclusive. In the same way, palliative care and research participation are not mutually exclusive. A given therapy may sometimes prolong life, sometimes palliate, and sometimes do both. As with other terminally ill patients, participants in clinical trials need palliative care. Thus, a palliative care component should be incorporated into clinical trials. This would allow research to go on, while at the same time palliating symptoms and preparing the patient and the family for the dying process. A second attitudinal obstacle is dealing with end of life issues, when it is clear that the patient is indeed terminally ill. Phase 1 clinical trials are not intended to deal with emotional or existential difficulties at the end of life. The complexities of administering a compound of unknown toxicity and unknown therapeutic index, intensely monitoring symptoms, and managing medical problems that invariably arise do not leave much time for discussion of end-of-life issues. These issues usually arise at the end of a clinic visit as the doctor is walking out, or while the nurse

is administering chemotherapy. It is difficult for the phase 1 investigator to address all the complexities for all the issues for each patient at every visit. Incorporating palliative care specialists into phase 1 trials would afford the resources and inclination to address the needs of dying patients.

In addition, there are financial obstacles to palliative care. We touch here on a controversy about the ethical advisability of providing collateral benefits to patients while they participate in clinical trials. From one point of view, to provide a benefit like palliative care that some participants might otherwise have little access to, might create an undue inducement to participate in a trial. Furthermore, some might argue that research funds ought not be spent on the provision of routine clinical care. At the other extreme, some might argue that a trial ought to be designed with some attention to direct benefit to research subjects. While it is beyond the scope of this paper to address this controversy fully, we would suggest that palliative care ought to be financed for participants in phase 1 clinical trials and this could be accomplished using strategies that are in keeping with either of these points of view. In keeping with the first perspective, the investigator ought to arrange with the subject's primary care provider for delivery of palliative care through the usual sources of health care delivery and financing. For those clinical investigators who serve both as investigator and health care provider, the issue may become one of justifying to an insurer that terminally ill patient/subjects deserve coverage for the cost of their palliative care through their insurance even while being enrolled in research because, as we have argued, research participation and palliation need not be mutually exclusive. From the alternative perspective, funding for a phase 1 trial should include resources for providing palliative care in the study protocol.

In suggesting the provision of palliative care for research subjects, we recognize that the organization and delivery of palliative care services vary from one clinical setting to another. Comprehensive interdisciplinary palliative care teams are more likely to be available in large cancer centers. For patients enrolled in clinical trials in community oncology practices, a single palliative care specialist or a hos-

pice program in the local community may be the most likely available providers of palliative medicine. Research participants with far advanced disease, like other terminally ill individuals, would benefit from provision of palliative care regardless of how it is delivered, so long as it is coordinated with the investigational effort.

This suggestion contrasts with and complements the suggestion of Sachs²⁵ to offer palliative care as an alternative to enrollment in a clinical trial. The intent in our suggestion is to try as much as possible to have the agendas of research and optimal end-of-life care coincide.

3. *Attend to the needs of family caregivers of terminally ill research subjects.* Ethicists and investigators justifiably focus on the rights of human subjects when thinking about clinical research. However, when research subjects are terminally ill, the needs of their family members, which are so substantial under these circumstances, warrant more attention. It would be useful to adopt the model of palliative care in which the patient and family are considered one unit that requires support for psychological and physical needs, and help in anticipation of loss and grief. As currently conceived, there is little way to address their needs. If attention to palliative care were incorporated into phase 1 trials, either through direct funding or through advocacy of insurance coverage, these family needs could be incorporated into the research scheme.
4. *Arrange for continuity of care so that dropping out of a trial does not jeopardize medical care.* The importance of continuity of care has been well recognized in clinical practice. But while efforts have been made to clarify and measure the concept of continuity of care,^{26,27} and to assert and examine its importance for cancer patients in the clinical setting,^{28,29} there is little parallel attention to the fact that participants in research are also likely to need continuity of care. Participants will sometimes have to leave a trial because they are no longer eligible because of progression of their disease, or will leave a trial because they choose to do so. For those participants who enroll in trials in which their health care provider is not the investigator, the tendency may develop to identify the clinical investigator as their care provider. It is important that the affiliation with the original clinician not be lost and that

there be good communication between investigators and clinicians so that if and when it is necessary or desirable for participants to withdraw from research, they perceive that they have options for medical management and do not feel a sense of abandonment.

5. *Train clinical investigators in end-of-life care.* As knowledge about the dying process grows, end-of-life care becomes an increasingly complex skill. Just as clinical investigators receive training in conducting good research, they need training in end-of-life care. Caring for dying patients requires skills in communication, symptom management, coordination of care, and preparation of the family for what to expect.²⁵ While these are a different set of skills than those considered necessary to be a good researcher, studies that include patients with life-threatening illnesses, require that the investigator be skilled in addressing the needs of this patient population. Talking to a patient about dying, breaking bad news, and managing symptoms are complex tasks that need to be formally taught. Therefore, it is necessary that investigators receive education about care at the end of life.^{5,30}
6. *Develop a counseling strategy for terminally ill participants in clinical research.* We have alluded to the fact that terminally ill individuals who participate in research may approach their participation from various emotional and cognitive standpoints. Some may recognize the limited likelihood of benefit and be comfortable with slim odds of benefit, some may deny their poor prognosis and have high expectations of benefit from participation in a trial, and some may not have any expectations of benefit but wish to participate because it is an altruistic act that gives additional meaning to their lives as they face death. Regardless of what expectations and rationale each participant has, subjects might benefit from counseling that recognizes the unusual circumstances they face as they choose to participate in research near the time of death. Without such assistance, they are more likely than most patients to die without ever having come to terms with the end of their lives. Such counseling would take into account the fact that these individual have chosen a path that differs from the usual hospice care. While they have chosen to end their lives tethered to the most aggressive medical interventions or the most untested experimental protocols, their

need for caring and comfort is as great as it is for any other dying individual. In keeping with our arguments for the need to recognize each individual patient's unique needs, this counseling must be tailored to each individual's expectations and rationale for being a research subject. Some may want to discuss their medical situation more explicitly than others, but all would benefit from acknowledgement of the difficulties they face, learning how they can overcome these difficulties, and becoming aware of the help they could use in facing their situation. All would benefit from discussing their life accomplishments and their unfinished business. All could use help identifying the important priorities in their lives and finding strategies for attending to them. It would help them negotiate the experience of participating in a standardized experimental regimen with the unique practices or customs of their particular religious or cultural background, and their own personal beliefs and wishes during sickness and dying.

CONCLUSION

The dramatic improvement in survival for patients with life-threatening illnesses would not be possible without the participation of those terminally ill patients who have participated in early phase clinical trials. Patients who choose to enroll in such phase 1 trials when they have illnesses with short life expectancy deserve to receive the routine standard of care that has now developed for terminally ill patients. It behooves clinical investigators to assure these research participants of this type of care whether it be through the research protocol or through coordination of care with other clinical providers. Concern about undue inducement should not dissuade us from guaranteeing this standard of palliative medicine. It will facilitate the ethical conduct of phase 1 trials and the compassionate care of participants enrolled in them. In so doing it will reduce the possible conflicts that arise between research and medical practice that we have outlined here.

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