

Ethical Considerations and Barriers to Research in Surgical Palliative Care

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There are many distinctive ethical characteristics, dilemmas, and potential barriers for surgeons involved in palliative care research. Although some of these issues might not be unique to patients facing the end of life, they are often magnified in this population. Because of the inherent stresses for patients, families, and caregivers in treating terminally ill patients, many ethical concerns are magnified in this patient group. These concerns compound the potential ethical issues present in all clinical research trials. In addition, when considering surgical interventions, the risk-benefit analyses warranted in all clinical research require special attention. Ethical dilemmas and barriers to research for surgeons might be similar to those noted for palliative care in general,¹ but there are several distinctive characteristics that must be considered.

Ethical concerns not exclusive to palliative research

Clinical research has many ethical concerns that are not exclusive to the patient facing the end of life, although these concerns might be more obvious and complex in this patient population. These concerns include a vulnerable population, problems in the consent process, ability of the researcher–clinician to balance dual roles, the invasiveness of assessments (notably evaluations for eligibility and a greater number of and different tests than are usually performed in standard clinical practice), and the scientific value of the study.

Vulnerability

All patients for whom there is no standard of care or conventional efficacious treatment for their disease process are, by nature, vulnerable. Dying patients can be seen as especially vulnerable.² Decision-making capacity

can be limited. Patients might feel compelled to participate if they depend on a research institution for their care.³ Although these concerns are valid, they are not unique to palliative research. As with all research projects, it must be stressed that care will not be altered if the patient does not participate in the research project. Decision-making capacity must be carefully scrutinized. If possible, a lead-in time should be implemented to reduce the risk that severe symptoms can lead to desperate decision making.³

Informed consent

Adequate informed consent can be particularly difficult to obtain from subjects at the end of life,⁴ and one cannot always assume that consent remains valid after patients deteriorate physically and mentally.⁵ Although proxy consents for treatment are valid if the treatment is considered in the best interests of the adult patient, the use of a proxy decision maker to give consent for participation in a research protocol is much more problematic. In fact, Warren and colleagues⁶ discovered that proxy decision makers are likely to allow a relative to participate in a trial they thought the patient would not agree to or would be unwilling to enter. It is imperative to involve caretakers in the consent process whenever necessary. Casarett and Karlawish³ believe, “In palliative care research there should be a presumption that all those involved as subjects, whether they are patients, family members, or providers, should give informed consent for research participation.” This might be a difficult criterion to meet, but it does highlight the need to be inclusive whenever possible in the consent process, especially for patients facing a terminal disease.

Coercion is a major potential problem in the consent process, especially in the hospital environment. This is true of all clinical research, but patients facing the end of life may have fewer perceived options and might feel more inclined to please their caregivers. Researchers must confront this potential problem with clear explanations and allow time to ensure patients make their own decisions. Followup is important with the caveat that overwhelming the patient with multiple visits can

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also be deemed coercive and must be considered by the prospective researcher. Educating patients is a key role of any consent process, but allowing maintenance of autonomy and self-respect throughout the course of illness are imperative.

Patients can present on an emergency basis with symptoms causing them both physical and psychological distress. In this state, they are in no position to fully understand the research that they are asked to participate in, and proxy consent might not be considered legal or ethical.⁵ The consent process mandates an understanding of the proposed medical treatment, risks, benefits, and alternatives, and patient competency might make such decision making difficult or impossible. Research without consent, even with minimal risk, leaves too much to doubt and will not be accepted by most Human Subjects Committees or published by medical journals.⁷

Another potential concern might occur when patients no longer understand or remember that research is taking place. This might be problematic in all observational research, but certainly will occur in many palliative care settings. As patients deteriorate physically and mentally, would they continue to have agreed to the ongoing research program? How does this affect the designated decision maker's perceived responsibilities? Researchers must consider these important questions when designing research trials involving patients at the end of life.

Finally, the compelling question of how truly informed "informed consent" can be is crystallized in the patient facing the end of life. Many studies have shown that a high percentage of patients have limited recall of the risks of various surgical procedures after consenting to a procedure.⁸⁻¹⁶ This will certainly also be true of patients who undergo a palliative procedure, whether for research- or nonresearch-related procedures. Clear, comprehensive discussions must be held, with the option of stopping and returning later if necessary because of fatigue or confusion.² As always, the investigator or research nurse must use sound judgment to ensure an ethical consent process.

Role of the clinician-researcher

There is inherent conflict and ambiguity when one individual is required to work simultaneously as a patient's doctor and as an investigator. Balancing these roles can be particularly difficult in the palliative care setting, but it is not exclusive to palliative care research.³ The need to intervene when things are not going as postulated can

cause considerable stress that is highlighted in the end-of-life setting, but these are dilemmas that all researchers must face. Clear algorithms of care must be addressed before initiation of a trial in anticipation of all potential issues to minimize patient suffering.

Research-related testing

As medical research attempts to show an improvement in new therapeutic modalities, it mandates a number of tests, frequently invasive, to document progress in care. Research usually necessitates a greater number of measurements than normally performed in clinical practice.¹⁷ This can be problematic in patients for whom decisions have been made to limit interventions in an effort to improve patient comfort. Subjects and families should be clearly warned when interventions are necessary for research, but have no benefit to the patient. It is imperative that tests should be limited to those that are absolutely essential. The relevance of measurements should be considered carefully. Every radiologic examination, blood test, or questionnaire carries the burden of time and discomfort, which can be enhanced for patients with limited life expectancy and multiple symptoms that already impact on their quality of life.

Scientific value

Ensuring the scientific value of a study is an ethical dilemma in itself. In a quote from Gary Ellis, chief of the Office for Protection Against Research Risks, overseer of ethics at the National Institutes of Health and 3,500 local review panels around the nation, "Bad science is bad ethics."¹⁸ It is imperative that the rationale and study construct be sound. Clearly, this issue is of importance to all clinical research, but can be especially scrutinized for studies involving patients known to be facing the end of life. Studies must have clearly defined questions with clearly defined outcomes to ensure that the data gathered can answer the questions raised.

Ethical dilemmas unique to palliative care research

Palliative care research can have particular ethical dilemmas that differ from other types of clinical research. These can include difficulty in assessing risks and benefits, randomization, especially if there is a "no treatment arm," and the unstable mental status of patients.

Risk-benefit analysis of proposed interventions

The risks and benefits of palliative research are difficult to assess. This issue might be more clearly unique to palliative care research.³ Outcomes measurements focus-

ing on improvement in quality of life and the relief of symptoms are difficult to design and administer, yet are potentially more meaningful than more objective outcomes measures such as length of survival. It might be difficult for physicians and Institutional Review Boards (IRBs) to determine an ethical balance of risks and benefits.³ This is made particularly difficult because the course of a terminal illness is characterized by gradual or sudden changes in health status, followed by corresponding changes in goals of care for patients and their families. Treatment and selection bias by the primary physicians, IRBs, and researchers themselves play a role in determining whether a palliative care trial will be able to lead to meaningful results.

The principle of nonmaleficence can be thought to apply at physical, psychosocial, and spiritual levels.¹⁹ Patients who participate in trials, such as phase I studies in particular, can have a high degree of physical suffering with a low likelihood of benefit. Participation in a research trial can potentially inhibit the natural dying process by forcing patients "to remain within the medical circuit."¹⁹ In other words, patients might be kept in the hospital longer than might otherwise be necessary. This can diminish critical time with loved ones or settling one's affairs. Participation in a research protocol may encourage a false hope of cure, even when the goals of therapy are adequately described, notably altering the dying process. In fact, providing honest information without destroying hope is the most common ethical dilemma for surgical oncologists.¹ A potentially positive benefit of palliative care research might be the perception that, although the patient and family might not directly benefit, their participation can add meaning to their illness.²⁰ It is imperative to consider these broad issues when constructing palliative care research protocols to ensure that patients die according to their preset desires, while still eliciting the information needed to improve medical care for future patients.

Randomization to placebo or sham treatments

Although randomization might be considered the cornerstone for clinical trials, it is far from commonplace in surgical or other medical literature.²¹ In fact, it has been shown that only 33% of clinical trials in prestigious medical journals adequately described a valid randomization process.²¹ That percentage can be anticipated to be lower in palliative care journals. That said, no other

study design provides as unbiased a research methodology,²² and randomized trials will remain an important part of clinical research that palliative care research must strive to reach. Samuel A Wells, MD, FACS, implores surgeons to participate in surgical trials as "a primary component of evidence-based medicine."²²

The mandate for palliative care research is that "as long as the randomized control trial is the standard by which effectiveness is judged, a field whose interventions have not been proved by this test is at risk of being relegated to second-class status in the medical hierarchy."²³ Clearly, randomization is a major limitation of palliative research, especially if there is a "no treatment" arm. Researcher bias plays a key role in that there often is a perceived advantage of one therapy. Although this is frequently an issue with clinical research, in the case of palliative care research, it is often more difficult. Importantly, one cannot prescribe a placebo versus a medication that is known to have efficacy in the palliative setting.

For surgical procedures, sham operations by their nature might be seen as unethical.²⁴ There might be a placebo effect of the surgical experience, but it is unethical to undertake an operation without performing any procedure.²⁵ In deference to this opinion, La Vaque and Rossiter²⁶ conclude, "Sham-placebo-controlled studies are ethically acceptable for those disorders for which no effective treatment is available." For the patient facing the end of life, there might always be an effective treatment choice through the use of aggressive pain medications and sedation. Without adequate comparisons, ineffective techniques, surgical or otherwise, will continue to go untested. Recently, the use of a sham arm in a surgical trial has questioned the common practice of arthroscopic surgery for osteoarthritis.²⁷ In addition, one must consider that a surgical procedure that provides no benefit to a patient might be deemed unethical.²⁸ As with all clinical research, it is acceptable to expose patients to treatments with some risk and no benefit if the potential gain to future patients outweighs the potential harm to research subjects, the risk to the subject is minimized, and there is no other way to obtain the information.²⁹ Clearly, it is more difficult to have an arm where there is no treatment in a palliative surgery trial. Ingenuity must be used to ensure that one can truly test the usefulness of an established treatment and ensure the patient's needs are constantly anticipated and met.

Unstable mental status

Although comprehension of a research protocol is always a concern, unstable mental status is a feature of palliative research that might be quite different. Patients might be lucid during the consenting process, but soon after might not be coherent. This might wax and wane throughout their course and bring trepidation to the researcher and family. As discussed previously, deterioration of patients can bring the consent issue into question. The fact that patients with advanced disease might be intermittently lucid because of multiple possible medical issues (eg, hypoxia, dehydration, and medications such as opioids) leads to somewhat different concerns than the typical research protocol.

Ethical dilemmas particular to surgical palliative research

There are ethical dilemmas that are particular to surgical research. First and foremost, the invasiveness of a surgical procedure and the potential morbidity and mortality directly related to these procedures can make decision making especially difficult. Other therapies, such as chemotherapy and radiation therapy, have their own treatment-related complications, but the intimacy and magnitude of operations are quite different and necessitate special consideration. A second difference related to surgery is the loss of decision-making control during and sometimes for prolonged periods after a procedure. So designation of a proxy decision maker, and clear advance directives, are mandatory before surgical intervention. Next, when comparing a surgical approach to a nonsurgical approach to a specific problem, there must be clear equipoise to the researcher to initiate such a study. In other words, the researcher must believe that there is no clear evidence that one intervention is markedly better than the other. Although equipoise is mandatory for all research, it might be more difficult when treatments are so vastly disparate. Finally, ethical research mandates the freedom to withdraw from a study. Obviously, there is little means to withdraw from a surgical procedure, especially if general anesthesia is used. The patient might opt out of multiple followup testing, though.

Barriers to research in surgical palliative care **Ethical dilemmas as a barrier to palliative care research**

Closely aligned with ethical dilemmas are ethical barriers to palliative care research. In fact, ethical dilemmas

themselves might be the greatest barrier of all. There is frequently the belief that no such research is morally justifiable in this patient population.³⁰ Although others find the arguments to this conclusion unacceptable,³¹ this still might be a prevailing belief among many practitioners. The paternalistic nature of the medical specialty might breed this viewpoint. Although the optimal treatment modalities for specific problems might not be truly elucidated, the best therapeutic approaches often seem obvious, so practitioners are unwilling to refer or enroll patients in the terminal phase of their illness to research protocols. Such bias is a problem with all clinical research, but might be much more steadfast for physicians of patients facing the end of life. Even experienced researchers can have difficult psychological and emotional concerns with the complexities of research in the patient with terminal disease.³² In fact, it can be argued, based on the Declaration of Helsinki and the generally accepted ethical code of practice in clinical research, that *not* offering patients at the endstage of life the opportunity to take part in clinical research is unethical.³³ One approach that has been suggested to help with this problem is to identify support personnel to confidentially counsel researchers undergoing psychological stress related to research trials.³²

Barriers inherent to surgery

There are many barriers inherent to surgical trials. These include: 1) structural, cultural, and psychological resistance to randomization; 2) the inherent variability of surgery requires precise definition of interventions and close monitoring of quality; 3) equipoise might be more difficult for both the surgeon and the patient; 4) the urgency of mandatory operations causes difficulty with recruitment, consent, and randomization; and 5) surgical learning curves cause difficulty in timing and performing randomized trials of new techniques.³⁴ In addition, surgeons can choose a particular operation based on commercial competition, such as newer minimally invasive techniques.³⁵ These problems might be confronted by improved quality control, larger cooperative trials, consideration of learning curves, and adequate preliminary data before randomized trials.³⁵ Goals might be quite difficult to reach, but one should strive to meet these ideals.

Barriers related to palliative surgery

There are many barriers to palliative research for surgeons that are likely related to barriers to care for patients

with advanced disease in general. These include patient and family reluctance to agree to surgery, financial constraints for care, reluctance to refer to surgeons (or other palliative care specialists), and cultural factors influencing the care of patients with terminal illness.¹ These might be based on surgeon education, training and experience, ethnicity of patients and surgeons, and type of surgical practice.³⁵ Palliative surgical decision making is often complex and there might be inadequate financial compensation offered to surgeons for their expertise. These issues must be taken into account when considering any surgical research protocol.

Funding barriers

Funding deficiencies are a major barrier to palliative care research. Recently, the National Cancer Advisory Board issued a clear statement declaring the need for advancing palliative care research in cancer.³⁶ They point out that only 0.9% of the total 1999 National Cancer Institute budget went to palliative and hospice care research. In addition, a recent statement from the National Cancer Institute's Director's Consumer Liaison Group, Survivorship Working Group appeals for end of life to be a major research focus in the comprehensive approach to cancer survivorship.³⁷ Although statements from these groups are extremely vital, and the importance of palliative care research is increasingly being recognized, it is imperative that major funding sources support meritorious projects to improve palliative care.

Consent process as a barrier

The consent process is not only an ethical dilemma for clinical research, but it is also a barrier. This is true for various reasons. First, the lack of ability to get consent may be seen as a barrier to research. The absence of a functional surrogate decision maker was found to be a major barrier to research for patients with advanced dementia.³⁸ Lack of understanding or agreement by patients themselves can also be seen as a barrier. The inability to help the patient see the reality of their illness in the consenting process may lead to misunderstandings.³⁹ Of course, this does not minimize the importance of a clear, thoughtful consent process for patients who might undergo a palliative procedure study.

Inaccessibility of palliative care

There are limited palliative care services and hospices,⁴⁰ which ultimately leads to fewer opportunities for palliative care research. Only 19% of hospices actively partic-

ipate in research, with a lack of staffing resources being the most common barrier.⁴¹ It is vital that hospices participate in research to provide innovative interventions that can improve quality of life; allow their patients to help others; ensure end-of-life research is generalizable to their patients; and provide indirect benefits of research, such as increased attention.⁴² Hospice and palliative care teams must be integrated with all specialties, including surgery, to provide alternative approaches of care and palliative research.

In conclusion, to ensure that current palliative treatments are the most superior alternatives to care, they must undergo the same scrupulous investigation as other medical research. As with all treatments of uncertain benefit, we must "overcome ethical objections to research and ingrained beliefs in established treatments."²⁸ Although surgical ethical dilemmas and barriers pose their own difficult and novel problems for palliative care research, they can often be overcome with well-constructed studies carried out by thoughtful research teams. Researchers in surgical palliative care are challenged to define clear questions that can be answered by the data, to obtain fully informed consent that involves not only the subject, but also the family members, and to minimize the interventions so that the goals of palliation need not be obscured by participation in research.

Author contributions

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