

Daniel J. Hurst*

Does the Distinctiveness of Palliative Care Research Require Distinct Ethical Guidelines?

ABSTRACT

Palliative and end of life care is changing, becoming more widespread and improving for patients. Yet, the current literature in the field suggests that the evidence for palliative and end of life care is somewhat limited. Research on treatment decisions, family care, and advance directions are just a few of the areas that need rigorous research efforts. Palliative care research is essential in order to continue providing effective treatments to those suffering in the last stages of life. Indeed, the goal of good palliative care research is to relieve suffering and to improve quality of life. Similar to any other field, palliative care programs must develop on a research base, and patient care will suffer if it is not backed by sound research. However, weighted against this need are some who maintain that the ethical and practical challenges of palliative care research are unique and insurmountable. This analysis considers if distinct ethical guidelines are needed for palliative care research.

Keywords: palliative care; palliative sedation; vulnerability; end-of-life care; risk-benefit analysis; decision-making capacity.

Introduction

Palliative and end of life care is changing in many parts of the world, becoming more widespread and improving for patients. The current literature in the field of palliative medicine suggests that the evidence for palliative and end of life care is limited.¹ The American Academy of Hospice and Palliative Medicine released a statement

* Correspondence Address: Daniel Hurst, Cahaba Family Medicine Residency, 405 Belcher Street, Centreville, AL 35042, United States. Email: hurst.danielj@gmail.com.

1 Marcia Grant, Ronit Elk, Betty Ferrell, R. Sean Morrison, and Charles F. von Gunten, "Current Status of Palliative Care—Clinical Implementation, Education, and Research," *CA: A Cancer Journal for Clinicians*, 59 (2009), 332.

in late 2014 emphasizing that many palliative care decisions and interventions lack sufficient evidence to either recommend or not recommend.² Research on treatment decisions, family care, and advance directions are just a few of the areas that need rigorous research efforts. Resources for such research, although limited, have begun to fund needed studies.³ Palliative care research is essential in order to continue providing effective treatments to those suffering in the last stages of life. Indeed, the goal of good palliative care research is to relieve suffering and to improve quality of life.⁴ Similar to any other field, palliative care programs must develop on a research base, and patient care will suffer if it is not backed by sound research.⁵ However, weighted against this need are some who maintain that the ethical and practical challenges of palliative care research are unique and insurmountable.⁶

While we must not take lightly the fact that palliative care researchers confront an array of ethical dilemmas, does the distinctiveness of palliative care research require distinct ethical guidelines? That is, do the ethical issues that arise in palliative care research extend beyond those of standard research trials? Thus, at the heart of this debate is the question of whether palliative care research creates new or unique ethical challenges. The answer to this question will have significant implications for the design and conduct of palliative care research.⁷

This analysis will consider three arguments that may be raised to support the claim that palliative care research raises distinct ethical issues. The three arguments that will be considered are that: 1) Palliative care patients are especially vulnerable; 2) Research investigators must obtain consent from patients and families; and 3) The risks and benefits of palliative research are difficult to assess. These three arguments are considered here because the literature suggests they are the issues that are most disturbing to investigators, healthcare providers, and the public.⁸ All three of the arguments outlined above may create considerable challenges for palliative care investigators. Nonetheless, the central thesis of this analysis is that the

2 American Academy of Hospice and Palliative Medicine, Statement on Palliative Care Research, November 2014: <http://aahpm.org/positions/research-ethics>

3 Grant, et. al., "Current Status of Palliative Care—Clinical Implementation, Education, and Research," 332.

4 David Casarett, "Ethical Issues in Palliative Care Research," in *Oxford Textbook of Palliative Medicine*, 4th edition, edited by Geoffrey Hanks, Nathan Cherny, Nicholas Christakis, Marie Fallon, Stein Kaasa, and Russell Portenoy, 416-21, (New York: Oxford University Press, 2011) 416.

5 Neil MacDonald and Charles Weijer, "Ethical Issues in Palliative Care Research," in *Oxford Textbook of Palliative Medicine*, 3rd edition, edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny and Kenneth Calman, 76-83. (New York: Oxford University Press, 2004), 77.

6 A.M. Jubb, "Palliative Care Research: Trading Ethics for an Evidence Base," *Journal of Medical Ethics* 28, no. 6 (2002): 342.

7 David J. Casarett and Jason H.T. Karlawish, "Are Special Ethical Guidelines Needed for Palliative Care Research?" *Journal of Pain and Symptom Management* 20, no. 2 (2000): 130-31.

8 Casarett and Karlawish, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 131.

issues of vulnerability and informed consent do not merit requiring distinct ethical guidelines. However, there does appear to be distinct ethical challenges in analyzing risks and benefits in palliative care research, though it does appear these challenges are surmountable. This analysis will proceed by initially providing an overview of the research process and its relation to palliative care. It will then analyze the human rights concerns of vulnerability and informed consent that come into focus when conducting research on palliative care patients. An examination of the argument that assessing risks and benefits in palliative care research is difficult, which is somewhat distinct to this field, follows. Lastly, further considerations to protect research participants, including the ideas of compassion and vigilance, are brought forward.

Research Ethics

The development of contemporary research ethics has been quite difficult. From a historical perspective, paternalism has held a prominent place in healthcare for the majority of its past. Further, the crimes against humanity committed by the Nazi regime under the guise of human research, and more recent offenses such as the Tuskegee syphilis experiments that were not concluded until 1972, still resound clearly in the field of research ethics. It is against this challenging background that research ethics evolved.⁹ This section considers the research process and its application to palliative care.

The Research Process and Palliative Care

Clinical trials provide the strongest evidence for the effectiveness, efficiency, and acceptability of clinical interventions. Without evidence from clinical trials, clinicians lack an important source of information to guide their practice. This may be a particular issue in palliative medicine where clinical research has not evolved at the same pace as palliative care programs. The result of this has been limited evidence for many of the interventions used in palliative care. Indeed, many pharmacological interventions that are in common use in palliative care have not been robustly tested in broad clinical trials.¹⁰ Yet, as in any other healthcare field, clinicians have

9 Franz-Josef Illhardt and Henk ten Have, "Research Ethics in Palliative Care," In *The Ethics of Palliative Care: European Perspectives*, edited by Henk ten Have and David Clark, 198-211, (Buckingham, England: Open University Press, 2002), 202.

10 Yolanda Zuriarrain Reyna, Michael I. Bennett, and Eduardo Bruera, "Ethical and Practical Issues in Designing and Conducting Clinical Trials in Palliative Care," in *Research Methods in Palliative Care*, edited by Julia M. Addington-Hall, Eduardo Bruera, Irene J Higginson, and Sheila Payne, 27-41, (New York: Oxford University Press, 2007), 27.

an obligation to provide the best possible treatment and care to patients at the end of their lives. The only way to ensure that high medical standards are established and maintained is through an understanding of the pathophysiological processes in patients with advanced disease and by evaluating the treatments that are employed using the most robust methodology possible.¹¹ Therefore, if palliative care patients are to receive the best imaginable care, an appropriate evidence base that is grounded in clinical research must be furthered. Hence, clinical trials are a key part of good clinical practice, even in the palliative care setting.¹²

The first question that palliative care investigators face in designing an ethical research study is whether it is research or quality improvement (QI). This decision is very significant and has profound implications for both the study's design and the ethical standards to which it will be held. For example, US federal law requires research projects be approved by local IRBs to ensure that informed consent is obtained from each subject, that research risks are reasonable in relation to expected benefits, and that subjects are recruited in an equitable fashion. In comparison, there are few widely accepted standards that govern QI. In many situations this delineation is clear. However, QI activities often share many of the characteristics of research. For instance, both QI and research involve systematic data collection methods, both may apply statistical methods to test hypotheses, establish relationships among variables, and evaluate outcomes, and both are designed to produce knowledge that could benefit patients other than those directly involved in the activity. Therefore, QI and research activities can at times be difficult to distinguish, and may be particularly difficult in end-of-life research. This may result in confusion and conflicting opinions from IRBs that review study protocols.¹³

The research process in the healthcare setting unfolds within a series of particular stages. The basic idea and hypothesis must first be elaborated. Despite having a clear hypothesis about the outcome of the trial, it is essential that this is merely an assumption and the investigator does not have evidence or an overwhelming belief to the contrary. Indeed, there is a consensus that at the beginning of a trial that compares two or more treatments, an honest null hypothesis must exist.¹⁴ This state of not knowing the outcome is called "equipoise," and it is an essential component

11 Geoffrey Hanks, Stein Kaasa, and Karen Forbes, "Research in Palliative Care," in *Oxford Textbook of Palliative Medicine*, 4th edition, edited by Geoffrey Hanks, Nathan Cherny, Nicholas Christakis, Marie Fallon, Stein Kaasa, and Russell Portenoy, 361-74 (New York: Oxford University Press, 2011): 362.

12 Reyna, et. al., "Ethical and Practical Issues in Designing and Conducting Clinical Trials in Palliative Care," 27.

13 David Casarett, "Ethical Considerations in End-of-Life Care and Research," *Journal of Palliative Medicine* 8, no. supplement 1 (2005), S149.

14 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 80.

of ethical research.¹⁵ Once a research goal has been identified, it is then necessary to work out how to achieve it in a reliable way.¹⁶ This is followed by the design of the methodological procedure and creating the research study protocol. An ethics review board must then approve the research protocol. The purpose of these reviews is to safeguard the rights and welfare of human research subjects. They examine risks to human subjects, ensure that consent is properly attained, and certify that the overall design of the study is scientifically sound.¹⁷ Once the protocol has been approved it may then be carried out. The results of the study, which may take a significant amount of time to collect, will be analyzed. New medical interventions and treatments may be developed on the basis of what is learned by the study.¹⁸ Palliative research does present unique issues over other forms of medical research. The end result of palliative care is always the same: a deceased patient, and family and friends that are left in mourning. In palliative research, it is unlikely that the patient and his family would experience any benefit from presumed new interventions as patient's lifespan is very limited, and this perspective should be described in detail in the research design. For healthcare providers, one of the hardest questions in palliative medicine is how to tell the truth but leave room for hope.

Research in healthcare is distinguished from research in other areas because it has a particular objective and because it typically involves the participation of human subjects. The objective of research in healthcare is focused on finding novel or better methods of treatment. To achieve this aim, there must be a continual effort within the healthcare sector to generate new data that can be applied to the medical care of patients who are suffering due to limited treatment options and a deficiency of medical knowledge. Thus, new studies must be constantly initiated in order to improve the current standards of treatment and better patient care. Further, the participation of human subjects is a distinguishing mark of medical research. Prior to clinical research on humans, animal experiments are performed and their results are analyzed and the drug or new therapy must be approved for clinical trials in human subjects.¹⁹

As this analysis shifts to palliative care research in particular, it is important to clarify what is meant by the term. The World Health Organization defines palliative care as “an approach that improves the quality of life of patients and their families facing the

15 Michael I. Bennett, “Principles of Designing Clinical Trials in Palliative Care,” in *Research Methods in Palliative Care*, edited by Julia M. Addington-Hall, Eduardo Bruera, Irene J Higginson, and Sheila Payne, 13-26, (New York: Oxford University Press, 2007), 14.

16 Claire Foster, *The Ethics of Medical Research on Humans*, (New York: Cambridge University Press, 2001), 21.

17 U.S. Food and Drug Administration. “Institutional Review Boards Frequently Asked Questions – Information Sheet.” <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm>

18 Illhardt and ten Have, “Research Ethics in Palliative Care,” 200.

19 Illhardt and ten Have, “Research Ethics in Palliative Care,” 200-01.

problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”.²⁰ This article is particularly concerned with the physical aspect of palliative care and its research. The benefits of palliative care research to future patients seem fairly obvious, for palliative care research is designed to produce knowledge that will advance end of life care, then implicit in this goal is the expectation that this knowledge will improve care for future patients. These benefits to future patients may be described in terms of the study’s validity and value. Palliative care researchers must use methods in their research that can be agreed upon by peer reviewers; thus, their study methods must be valid. All studies must further be designed in such a way as to produce knowledge that is generalizable. That is, the research findings need to be able to be extended to the population at large. Validity is a threshold requirement for all research, because, as it has been recognized, it is unethical to expose participants to research risks that peer reviewers agree cannot answer a research question.²¹

Moreover, the study’s value must be taken into account. As defined broadly, value can be taken as the likelihood that the study’s results will improve the health and wellbeing of future patients. Validity is an important measure of both a study’s scientific and ethical quality. One reason why patients participate in research is to generate knowledge that will benefit those patients who come after them. Because subjects are willing to accept risks and burdens of research in order to benefit future patients, investigators have an ethical responsibility to maximize the possibility that a research study will do so.²² However, it must also be considered whether there are benefits to those who participate in research, which will be examined in section 4 of this analysis.

Nonetheless, some commentators, such as Jeanne Quint Benoliel, suggest that there is merit in raising the general question as to whether dying patients should ever properly be subjects for scientific study.²³ Similarly, Munhall argues that all research turns people into mere means, regardless of whether or not the research participant is expected to benefit from the experience.²⁴ Additionally, Louise de Raeve has supported the argument that strong moral grounds exist for objecting to research in

20 <http://www.who.int/cancer/palliative/definition/en/>

21 Casarett, “Ethical Issues in Palliative Care Research,” in *Oxford Textbook of Palliative Medicine*, 416.

22 Casarett, “Ethical Issues in Palliative Care Research,” in *Oxford Textbook of Palliative Medicine*, 416.

23 Jeanne Quint Benoliel, “Research with Dying Patients,” in *Patients, Nurses, Ethics*, edited by A. J. Davis, J. C. Krueger (New York: American Journal of Nursing, 1980): 119-28.

24 P. L. Munhall, “Ethical Considerations in Qualitative Research,” *Western Journal of Nursing Research* 10, no. 2 (1988), 150-56.

palliative care. De Raeve argues from both a Kantian and risk-benefit perspective.²⁵ While the Kantian argument will not be addressed in this analysis, the question of risk-benefit will be examined at length. At this juncture it should be noted that it is currently generally accepted that, whatever the sensitivities around palliative care research, in the long run palliative care patients will be disadvantaged if there is a lack of evidence to support improvements and initiatives in palliative care. Therefore, though palliative care research poses many challenges from an ethical point of view, this should not discourage researchers from undertaking research in this field. The remainder of this analysis will consider these ethical issues.²⁶

Universal Human Rights Considerations

Numerous ethical concerns are present in palliative care research, which should not be diminished. Indeed, there have been concerns raised from several commentators about whether it is ever appropriate to allow patients near the end of life to participate in research.²⁷ These arguments have considerable intuitive appeal and must be seriously addressed.²⁸ However, it must also be understood that overly strict limits on palliative research can also cause harm by impeding the establishment of new knowledge that will improve future patient care.

In order to be valid, arguments against research in a palliative setting must demonstrate that dying patients constitute a special class of research subjects, for whom research raises distinct ethical challenges that are insurmountable. From this stance, one may argue that special, distinct restrictions, protection, and guidelines are necessary to direct research. In contrast, if patients near the end of life are not subject to unique ethical constraints, then research may be acceptable within the context of strategies devised to protect subjects who pose similar challenges.²⁹ This section examines the two major human rights considerations in the context of research ethics, and specifically, palliative care research: vulnerability and informed consent.

Vulnerability

One reason to consider special ethical guidelines for palliative care patients is that they may be considered a vulnerable population. Surely palliative care patients are

25 Louise de Raeve, "Ethical Issues in Palliative Care Research," *Palliative Medicine* 8, no.4 (1994), 298-305.

26 Scottish Partnership for Palliative Care, *A Beginner's Guide to Successful Palliative Care Research*, (Edinburgh: Scottish Partnership for Palliative Care, 2011), 17.

27 de Raeve, "Ethical Issues in Palliative Care Research," 298-305.

28 David Casarett, "Ethical Issues in Palliative Care Research," in *Oxford Textbook of Palliative Medicine*, 416.

29 Jubb, "Palliative Care Research: Trading Ethics for an Evidence Base," 343.

not a homogenous group, yet they are a group for whom there is often no second opportunity to improve care.³⁰ Due to disease processes and the effects of palliative medicines there also may be some degree of decisional impairment. The Institutional Review Board Guidebook developed by the Department of Health and Human Services lists terminally ill patients as a special class of subjects, along with children, prisoners, and the mentally handicapped.³¹ A simplistic definition of vulnerability is that, it describes a group of subjects who may be relatively or absolutely incapable of protecting their own interests.³² The UNESCO *Universal Declaration on Bioethics and Human Rights* has provided an expanded definition of vulnerability. Article 8 asserts that when applying scientific knowledge and medical practice to individuals, the vulnerability of men and women must be taken into account. That is, individuals and groups of distinct vulnerability should be protected and respected. UNESCO defined vulnerability broadly as the susceptibility of being wounded.³³

The notion of human vulnerability should not merely be applied to individuals in lower income lands. It is now widely accepted that vulnerability is universal in scope. That is, at some time in life, all humankind is vulnerable, regardless of social status, intelligence, authority, or economic power.³⁴ For many, the state of vulnerability is transient or contextual rather than inherent. However, it is to those individuals, groups, or communities for whom vulnerability is not a transient state that attention is particularly important.³⁵ For example, by definition, being a terminal patient is not a transient state, until death occurs. To be certain, the notion of vulnerability is a criticism of the conventional emphasis on individual autonomy as insufficient, and that attention should be directed towards the conditions for humanity's flourishing.³⁶ What is more, the principle of respect for human vulnerability should be linked to that of human dignity, which reinforces the notion of the unconditioned value of humankind by demanding their inviolability.³⁷

Palliative care patients may encounter vulnerability because they lack decision-making capacity or because their choices are not truly voluntary. Decision-making capacity describes the ability of a person to understand given information and make

30 Reyna, et. al., "Ethical and Practical Issues in Designing and Conducting Clinical Trials in Palliative Care," 28.

31 U.S. Department of Health and Human Services, "Institutional Review Board Guidebook, Chapter VI, Special Classes of Subjects," http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm

32 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?," 131.

33 H. ten Have, Michèle Jean, *The UNESCO Universal Declaration on Bioethics and Human Rights*, 155-64.

34 ten Have and Jean, *The UNESCO Universal Declaration on Bioethics and Human Rights*, 158.

35 Sheila A.M. McLean, "Respect for Human Vulnerability and Personal Integrity," in *Handbook of Global Bioethics*, edited by Henk ten Have and Bert Gordijn (New York: Springer, 2013), 108.

36 Henk ten Have, "Vulnerability as the Antidote to Neoliberalism in Bioethics." *Revista Redbioetica* 2014; 1 (9): 87-92.

37 ten Have and Jean, *The UNESCO Universal Declaration on Bioethics and Human Rights*, 161-62.

a cogent choice. The concern is that this capacity may be impaired in patients near the end of life, which is based largely on observations that terminal patients regularly have evidence of cognitive impairment. To be sure, this has the ability of leading to impaired decision-making capacity and inadequate informed consent. Though not all patients with cognitive impairment will lack decision-making capacity, informed consent for these patients will be more difficult or impossible. Since cognitive impairment appears to be quite common in this population, palliative care researchers may often have difficulty identifying those patients who lack decision-making capacity and cannot provide consent.³⁸

It must be recognized that this is a real challenge; however, the challenge is not unique to palliative care research. Hence, because it is not unique to palliative care research, it does not appear to provide grounds for distinct ethical guidelines. Investigators working in fields of research involving patients with dementia, psychiatric illness, and similar settings have developed strategies for assessing the decision-making capacity of such patients. Guidelines such as those provided by the National Bioethics Advisory Committee (NBAC) can be applied to palliative care research studies. The NBAC recommends that capacity should be assessed formally whenever research subjects are likely to be cognitively impaired and the research poses greater than minimal risk. Risks are determined to be greater than minimal if they are greater than those encountered in everyday life, or routine medical care. Indeed, as research risks increase and the chance of benefit decreases, decision-making capacity becomes increasingly essential. For instance, in high risk, low benefit research, to incorrectly assume that a patient is competent would be a grim mistake. This strategy is reasonable in palliative care research because the risks to which subjects are exposed are highly variable. While some studies involve only questionnaires or surveys, others involve experimental medications or risky procedures. When palliative care research involves only minimal risks, such as those posed by questionnaires, formal capacity assessments may not always be required. However, capacity assessment is more significant for studies that carry greater risks, such as those that involve a placebo when an effective agent is available, or an invasive intervention.³⁹

Voluntariness is a second concern about vulnerability that must be considered. The voluntariness of a subject to consent to research participation has been at the forefront of research ethics since the Nuremberg Trials. In general terms, a choice is said to be voluntary if it is made without significant controlling influences.⁴⁰ The issue with palliative care research is that a subject's choice to participate may

38 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 131.

39 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 131-32.

40 Casarett, "Ethical Issues in Palliative Care Research," in *Oxford Textbook of Palliative Medicine*, 419-20.

be limited if their suffering has created a sense of desperation. If this concern is legitimate, voluntary consent in palliative care research may be confounded by the uncontrollable symptoms that are common in patients near the end of life.⁴¹ What is more, a patient may feel some compulsion or obligation to participate in a research study, especially if they rely on a research institution or investigator for their care. This influence may be powerful in a palliative care setting and constitute some manner of involuntariness on the part of the patient.⁴²

Though it is reasonable to suspect that these influences exist in palliative care settings, it is not at all clear that they present more of a danger than they do in other fields of human research. As has been recognized in the prevailing literature, a sense of desperation is not unique to palliative care patients. Oncology patients may feel a similar manner of desperation that influences their decision to enroll in phase I oncology clinical trials, even though the likelihood of attaining a medical benefit is remote. Therefore, it does not appear that these risks are unique to palliative care research. Further, the principle of respect for patient autonomy supports the potential involvement of patients in research that may not be of immediate benefit to themselves.⁴³ The voluntariness of a participant can be protected by ensuring that a participant's decision to enroll in a study is made with full knowledge of available alternatives and with the knowledge that he or she may withdraw at any time without penalty.⁴⁴ This is required by US law and the regulations of many other states, though it may not be emphasized sufficiently. Even more, palliative care researchers may find it beneficial to recruit participants through a third party. This serves to underscore the distinction made between research and clinical care, and may clarify to patients that they can decline participation without jeopardizing their clinical care.⁴⁵

Informed Consent

A second reason to support the claim that palliative care research raises unique ethical issues is that investigators must obtain consent from patients. The notion of informed consent, similar to voluntariness, has been near the forefront of the concerns of medical ethics since at least the Nuremberg Trials in 1945-46. Informed consent refers to an individual's autonomous authorization of a medical procedure or of involvement in research. This involves more than a simple agreement or complying

41 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 132.

42 Russell Portenoy and Mitchell Max, "Pain Research—The Design of clinical trials," in *The Oxford Textbook of Clinical Medicine*, 3rd edition, edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny and Kenneth Calman, 144-53, (New York: Oxford University Press, 2004), 143.

43 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 80.

44 Casarett, "Ethical Issues in Palliative Care Research," in *Oxford Textbook of Palliative Medicine*, 419-20.

45 Casarett and Karlawish, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 132.

with a proposed medical intervention, for informed consent is a process, not a document. Explicit authorization of a medical intervention or research involvement through an act of informed and voluntary consent is essential. This can occur only if the patient or human research subject has gained substantial understanding of the proposed action and are void of substantial control by others.⁴⁶

Even after the establishment of the Nuremberg Code, it has been shown that certain medical experiments in the US were conducted without the informed consent of patients. Examples of this abound and include the Willowbrook State School experiments in Staten Island of the 1950s and 1960s⁴⁷, as well as open-air tests of biological weapons over the US cities from 1949 to 1969 which resulted in the death of a man from San Francisco.⁴⁸ Subsequently, the principle of informed consent was incorporated into the Declaration of Helsinki, and the World Medical Association proposed the need for ethics review committees to evaluate and control medical research. Thus, the Declaration of Helsinki was revised in 1975, in part, to urge the scientific community to look to ethics review committees for guidance prior to beginning a research project.⁴⁹

Palliative care researchers may face a number of challenges in the area of informed consent, however, none of these challenges are unique to palliative care.⁵⁰ Some have attempted to argue that informed consent in palliative care research is problematic because the stability and duration of consent are uncertain.⁵¹ Patients nearing the end of life may lack decisional capacity or may experience fluctuating and/or declining capacity.⁵² The issue of whether patients are competent to give informed consent is one that needs to be taken seriously by all palliative care researchers.⁵³ The dying person's freedom to choose their own course of treatment should be protected as long as they are competent to decide such matters. Several commentators have noted that the medical profession itself may complicate this. The weaker and more ill a patient becomes, the more they will require the assistance of a caregiver. The

46 Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 7th ed. (New York: Oxford University Press, 2013), 120-25.

47 Frederick Adolf Paola, Robert Walker, Lois Lacivita Nixon, ed.. *Medical Ethics and Humanities*, (Sudbury, MA: Jones & Bartlett Publishers, 2009), 185–186.

48 Jonathan D. Moreno, *Undue Risk: Secret State Experiments on Humans*, (New York: Routledge, 2001) 233-34.

49 Illhardt and ten Have, "Research Ethics in Palliative Care," 202.

50 Meera Agar, Danielle N. Ko, Caitlin Sheehan, Michael Chapman, and David C. Currow, "Informed Consent in Palliative Care Clinical Trials: Challenging but Possible," *Journal of Palliative Medicine* 16, no. 5 (2013), 485.

51 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 79.

52 Susan Hickman, Juliana C. Cartwright, Christine A. Nelson, and Kathleen Knaf, "Compassion and Vigilance: Investigators' Strategies To Manage Ethical Concerns in Palliative and End-of-Life Research," *Journal of Palliative Medicine* 15, no. 8 (2012): 882.

53 Reyna, et. al., "Principles of Designing Clinical Trials in Palliative Care," 31-33.

medical profession tends to create a paternalistic attitude in such circumstances. For irreversibly ill patients, treatment generally involves both the compensation for lost functions and the mobilization of remaining functions. Hence, while some paternalistic intervention may be necessary, many patients retain the freedom to choose and act, though this range may become increasingly restricted as the illness progresses. Although personal autonomy may gradually diminish, patients will rarely lose freedom completely. Hence, medical research in the field of palliative care should acknowledge the freedom of a patient, and the research ought to be compatible with it, otherwise it ought not to be done.⁵⁴

Furthermore, obtaining informed consent for palliative care research may be particularly delicate because participants may find it difficult to make such decisions at such a distressing point in their lives. Deciding how to describe the research trial also presents challenges, for certainly not all patients and families will have had full and open conversations with the physician about the patient's current condition and prognosis. Another complication and reason why it has been suggested that palliative care research deserves distinct ethical guidelines is that investigators must often obtain consent not simply from patients, but also from families. Including families as subjects in the clinical research is a logical extension of hospice and palliative care, for the aim is often to provide family-centered care. Studies have explored not only new drugs or therapies on the patient, but also include issues such as family functioning, family perceptions, and the effect of the patient's illness on the family. Indeed, there is reason to believe that families may become increasingly involved in palliative care research studies in the coming years. The Institute of Medicine and the National Institutes of Health have each called for more research on the experience of the families in distress.⁵⁵

In these types of studies, both the patient and the family are "subjects" because they are the focus of the research. These studies may create complex administrative challenges because of the need for investigators to generate an effective informed consent process tailored to meet the difficult needs of both patients and families. It is important to note, though, that these are administrative challenges created by the ethical obligation to obtain informed consent, and are not created by palliative care research itself. Indeed, investigators may look to the field of dementia research for some solutions. In dementia research studies, investigators often obtain a "dual consent". That is, investigators obtain informed consent from both patients and family members simultaneously. This dual consent has the ability of assuring that family members understand the research and what is required of them to fulfill their

54 Illhardt and ten Have, "Research Ethics in Palliative Care," 202-03.

55 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 133.

responsibilities. In dementia research, as in palliative care research, the responsibilities of the family or caregiver can be substantial, including transportation to the study site, giving medications, and assessment participation.⁵⁶

Thus, though the informed consent process in palliative care research may be challenging, overcoming these difficulties is possible. Each clinical trial in palliative care must carefully develop an appropriate protocol to solve the specific problems the trial will bring.⁵⁷ What is more, although research that includes multiple subjects does pose a real challenge for palliative care investigators, these are administrative challenges rather than purely ethical challenges. The situation of dementia research shows that the informed consent process in palliative care research is not unique in its complexity. Hence, palliative care researchers may learn from other fields of research, such as dementia research, the strategies to obtain consent from multiple subjects.⁵⁸

In summary, though issues of vulnerability, voluntariness, and informed consent may present ethical challenges to research in the palliative care milieu, it does not appear that they raise distinct challenges that merit distinct ethical guidelines. Though none of these challenges is unique to palliative care research, the combination and frequency with which they are encountered does require systematic and considered solutions.⁵⁹ Thus, while these issues must not be taken lightly, it appears that the principles of research ethics are sufficient to protect human research participants from harmful practices.⁶⁰

Distinct Research Considerations for Palliative Care

Above has been presented that issues of vulnerability and informed consent, though raising significant challenges for IRBs and investigators, are not unique to palliative care research. Further, there seems to be manners of overcoming these challenges. Therefore, neither issues of vulnerability nor informed consent appear to justify special restrictions, protections, or guidelines, as the principles of research ethics can protect patients. However, this section examines the question of risk-benefit analysis, which may provide such a justification.

56 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 133.

57 Reyna, "Ethical and Practical Issues in Designing and Conducting Clinical Trials in Palliative Care," 31.

58 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 134.

59 Agar, et. al., "Informed Consent in Palliative Care Clinical Trials: Challenging but Possible," 485.

60 Illhardt and ten Have, "Research Ethics in Palliative Care," 207.

Risk-Benefit Analysis is Difficult to Assess

Estimation of the anticipated risks and benefits is critical in the evaluation of any research project, but it is also one of the least developed areas in research ethics.⁶¹ This issue may be more clearly unique to palliative care research.⁶² To be sure, clearly articulating expected risks and benefits in palliative care research poses specific challenges.⁶³ Indeed, the NBAC has affirmed that properly assessing risk versus benefit is difficult in research studies.⁶⁴ One issue with risk-benefit analysis in palliative care research is the distinction between therapeutic and non-therapeutic medical research. This distinction was made in order to differentiate the scope, the participants involved, and the context in each of the two categories. In therapeutic research, the goal is to treat an individual's illness with the hopes he/she will recover. The context is usually in the hospital, utilizing the hospital's equipment and the experience of the research team. Non-therapeutic research involves the use of healthy subjects and seeks to obtain basic scientific data. This is often done for financial compensation and the context is the research site, such as a laboratory.⁶⁵ Thus, therapeutic research is designed with the intention of yielding benefit to participants, while non-therapeutic research seeks to derive knowledge without direct benefit to participants. This distinction can be useful in the ethical assessment of an acceptable balance for research participants, between the benefits and the risks of research.⁶⁶ Further, it has been recognized that when the distinction between therapeutic and non-therapeutic research with respect to the irreversibly ill patient disappears, the principle of beneficence may be in danger. Thus, we must ask whether palliative care patients can ethically be involved in non-therapeutic research trials.⁶⁷

Moreover, another reason that the risks and benefits of palliative care research are often hard to assess comprehensively is due to limited preexisting evidence. The frequent heterogeneity of study populations has also been perceived as making the weighing of

61 M. Agrawal, "Voluntariness in Clinical Research at the End of Life," *Journal of Pain and Symptom Management* 25 (2003), S25–S32.

62 Robert S. Krouse, Alexandra M. Easson, and Peter Angelos, "Ethical Considerations and Barriers to Research in Surgical Palliative Care," *Journal of the American College of Surgeons* 196, no. 3 (March 2003), 470.

63 M. Masso, *Ethical Research in Palliative Care: A Guide Through the Human Research Ethics Committee Process*, (Canberra: National Palliative Care Program, 2004), 18.

64 National Bioethics Advisory Committee, "The Assessment of Risk and Potential Benefit," in *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*, 1998, <https://bioethicsarchive.georgetown.edu/nbac/capacity/Assessment.htm>

65 Illhardt and ten Have, "Research Ethics in Palliative Care," 203.

66 Masso, *Ethical Research in Palliative Care: A Guide Through the Human Research Ethics Committee Process*, 18–19.

67 Illhardt and ten Have, "Research Ethics in Palliative Care," 203.

risks and benefits difficult.⁶⁸ To be certain, it is an ethical duty of all investigators to maximize research benefits and minimize research risks. This obligation is expressed in US federal guidelines as the requirement that risks to subjects are reasonable in relation to anticipated benefits and to the anticipated value of knowledge generated by the study.⁶⁹ For example, this requirement is clearly stated in the Department of Health and Human Services IRB guidelines.⁷⁰ Nonetheless, this goal is often difficult to achieve, but is crucially important because the balance of risks and potential benefits is a main reason why subjects participate in clinical research. When palliative care investigators attempt to meet this challenge they may encounter difficulties in two issues: defining research risks and benefits, and measuring them against an appropriate standard.⁷¹ Each of these will be examined in this section.

In the majority of research studies that involve either healthy participants or patients with a known and well-defined medical problem, the benefits and risks of research are fairly clear. Medical ethicist and physician David Casarett illustrates this by providing an example of a clinical trial comparing two forms of treatment for an acute myocardial infarction that might offer potential benefits of improved survival or improved cardiac function. The risks of such a trial might include bleeding, infection, or death. There ought to be general agreement that these are important risks and benefits to be balanced, and should be dutifully explained to the patients. However, the issue in palliative care research is that the benefits and risks that are important to patients near the end of life may be difficult to assess and define because an individual's goals may change as they near death. It has been suggested that, broadly defined, these changes can be characterized by a decreased emphasis on survival, and an increased push for pain management, symptom relief, retention of dignity, and maintaining social relationships and a semblance of control in their lives. Thus, it may be likely that patients' preferences regarding the potential risks and benefits of research may change as well.⁷²

As patients approach the end of life, they may increasingly emphasize qualities such as pain management, dignity, social relationships, and control, as noted above. For instance, patients close to death may perceive the time spent answering questionnaires, surveys, or doing interviews for research as detrimental to the time

68 Jonathan Koffman and Fliss Murtagh, "Ethics in Palliative Care Research," in *Textbook of Palliative Medicine*, edited by Eduardo Bruera, Irene Higginson, Charles F. von Gunte, 192–201 (Boca Raton, FL: Taylor and Francis, 2006), 196.

69 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 135.

70 U.S. Department of Health and Human Services, "Institutional Review Board Guidebook. Chapter III, Basic IRB Review," http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm

71 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 135.

72 Casarett, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 135.

they could spend strengthening social relationships and addressing any “unfinished business” with family members, friends, and associates, while the identical protocol may not prove so onerous to patients with a curative disease.⁷³ Thus, palliative care patients may prefer to spend their time in ways other than research and may even be reluctant to impose any additional burdens on family members.⁷⁴ Additionally, a dying patient’s emphasis on control may have important implications for their assessment of research risks and benefits. If the patient’s control over medications and dosing is very important to them, any loss of control may be viewed as a significant risk. Conversely, a trial that gives patients an increased control over “as needed” medication dosing may be viewed as beneficial by patients who value control.⁷⁵

The second issue is that measuring the risks and benefits in palliative research against an appropriate standard may prove especially challenging for IRBs. IRBs, per US federal guidelines, are required to measure the risks of research against the risks encountered in daily life or during the performance of routine physical or psychological examinations or tests.⁷⁶ Therefore, even if patients clearly understood the risks and benefits of research, it is not clear how investigators and ethics committees should balance them in determining whether a proposed research study offers an ethical balance of risks and benefits. This task may prove difficult in palliative care research because it may be either overly permissive or overly restrictive. For example, questionnaires or surveys that are time-consuming may cause little discomfort and pose a minimal risk in most research settings. However, for patients near the end of life who wish to spend quality time with family members rather than completing lengthy surveys, such research may become quite burdensome. Further, it has been suggested that judging risks to terminally ill patients by the standards of risks encountered in daily life may be misleading and unhelpful, because patients who are terminally ill face daily risks of death and suffering that are far greater than those faced by other research subjects.⁷⁷ What is more, in a 2015 research survey of the delegates at the 7th Pediatric Palliative Care Conference, approximately one-third of respondents in the study identified the IRB approval process as a major barrier

73 Jubb, “Palliative Care Research: Trading Ethics for an Evidence Base,” 344.

74 Blair Henry and Damon C. Scales, “Ethical Challenges in Conducting Research on Dying Patients and Those at High Risk of Dying,” *Accountability in Research* 19, no. 1 (2012): 7.

75 Casarett, “Are Special Ethical Guidelines Needed for Palliative Care Research?” 135-36.

76 U.S. Department of Health and Human Services, “Institutional Review Board Guidebook. Chapter III, Basic IRB Review,” http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm

77 Casarett, “Are Special Ethical Guidelines Needed for Palliative Care Research?” 136.

to palliative care research, citing the approval process as “arcane”, “challenging,” and “restrictive”.⁷⁸ This would be worth examining in further research.

Response to the Difficulty of Assessing Risk-Benefit Analysis

As stated briefly above, Louise de Raeve has argued that strong moral grounds exist for objecting to palliative care research based on a risk-benefit perspective. De Raeve asserts that it is not clear from the outset of the study that participants will get anything out of the experience, which may be unethical. The author couples this argument with describing the “seductiveness” of palliative care research. That is, the researcher often provides a nonjudgmental listening ear, interest, and close attention to the patient, which is something the patient may not have received in a very long time, making a continued relationship with the investigator very enticing.⁷⁹ However, this second issue is not unique to palliative care research and, thus, should not be grounds for disqualifying research in that field. Further, it is not altogether clear that palliative care patients do not benefit from research.

At least two benefits of palliative care research to participants have been identified. During the course of the research study, investigators may have several opportunities to maximize the potential benefits of research to participants. In an interventional study, participants may be free to choose their own intervention. While, ideally, a new intervention should have a reasonable chance of success, more important may be that it offers to participants a significant potential benefit or improvement over other interventions that are available to patients outside the study. Further, potential benefits of a study can be enhanced by choosing an active control design, rather than a placebo. It must be noted that these suggestions ought to be tempered by realizing that potential benefits of research are never certain. If they were completely certain, equipoise could not be maintained. Nonetheless, investigators generally design trials of interventions for which there is at least some evidence of effectiveness. Moreover, palliative care studies may also benefit participants by the data gathering that occurs. This data collected during a descriptive study may identify inadequately treated pain, dissatisfaction with pain management, or related problems such as depression or anxiety. Investigators can then use this data to improve the participant’s care. Therefore, it does not seem true that palliative care patients cannot benefit at all from research studies.⁸⁰

78 Emma Beecham, Briony F. Hudson, Linda Oostendorp1, Bridget Candy, Louise Jones, Vickey Vickerstaff, Monica Lakhnpaul, Paddy Stone, Lizzie Chambers, Doug Hall, Kate Hall, Thines Ganeshamoorthy, Margaret Comac, and Myra Bluebond-Langner, “A call for increased paediatric palliative care research: Identifying barriers,” *Palliative Medicine* 30, no. 10 (2016): 979-80.

79 de Raeve, “Ethical Issues in Palliative Care Research,” 303.

80 Casarett, “Ethical Considerations in End-of-Life Care and Research,” S-152-53.

Therefore, as has been identified in the above section, the weighing of risks and benefits in palliative care settings may present distinct ethical considerations that merit special attention. This judgment seems correct, especially when we consider that the risks and benefits that are important to patients near the end of life may be much more difficult to define because their goals may change significantly as they near death. Further, as has been explained above, it can be difficult to measure risks and benefits against the risks of everyday life because palliative care patients are in a unique phase of life. However, it should not be concluded that these challenges are insurmountable.⁸¹ Robert Krouse, Ira Byock, and others have echoed this sentiment by affirming that barriers in palliative care research can be overcome with well-constructed studies carried out by thoughtful research teams. Indeed, the methodological difficulties in palliative care research are all surmountable through existing techniques and appropriately careful scientific design.⁸²

In order to demonstrate that these concerns are surmountable, at least two strategies are essential to this endeavor. First, in order to define and weigh risks and benefits properly, data that describe how patients perceive the risks and benefits of research are necessary.⁸³ If palliative care researchers hope to find a balance between risks and benefits that participants will find acceptable then these data are essential. Researchers should also try to consider these risks and benefits in relation to those that patients near the end of life typically experience in their daily routines. A second strategy is that when IRBs review the protocols for palliative care research studies examining the physical aspects of palliative care, they will be better prepared to assess and weigh the risks and benefits of research if they include at least one healthcare professional with expertise in the field of palliative care. Indeed, IRB reviews have been considered to be a significant impediment to conducting quality research in palliative care because they are often ill-equipped to handle such protocols and, thus, promote a natural protectiveness towards what is perceived to be a vulnerable population.⁸⁴ Involving a healthcare professional with expertise in this area might curtail this. The Common Rule recommends that this be done for other vulnerable populations such as children. The IRB guidelines of the NIH extend this suggestion to palliative care research as

81 Jubb, "Palliative Care Research: Trading Ethics for an Evidence Base," 344.

82 Robert Krouse, Kenneth E. Rosenfeld, Marcia Grant, Noreen Aziz, Ira Byock, Jeffrey Sloan, and David Casarett, "Palliative Care Research: Issues and Opportunities," *Cancer Epidemiology, Biomarkers & Prevention*, 13, no. 3 (March 2004): 337-39.

83 J.H.T. Karlawish, "Permissible Risk and Acceptable Benefit (The Ethics of Research Involving the Cognitively Impaired)," *Forum* 7 (1997): 277-285.

84 P.W. Keeley, "Improving the Evidence Base in Palliative Medicine: A Moral Imperative," *Journal of Medical Ethics* 34, no. 10 (2008), 758.

well. Thus, this person may be very helpful in focusing the IRB on the risks and benefits that are likely to be most important to patients in their stage of life.⁸⁵

In summary, palliative care research does seem to be unique because the evaluation and parameters of the risk benefit analysis, as well as the burden of the research upon the patient, may change significantly as patients near death. What is sure is that physicians and caregivers have the moral duty to support research, but in each case this must be done on the basis of a concrete risk-benefit analysis. The greater the risks are predicted to be, the greater the concrete benefits for the involved participant should be. Hence, studies that are likely to provide small benefit can only be justified if they bear low risk. While these concerns may be difficult to manage, the majority of literature appears to conclude that they are surmountable because of medicine's commitment to regarding irreversibly ill patients as autonomous and capable of freely consenting to research participation.⁸⁶

Further Considerations to Protect Research Subjects

As has been presented in this analysis, there does not appear to be a compelling case for believing that research in palliative care is significantly more distinct than research in other fields as to require distinct ethical guidelines. Thus, patients suffering from an irreversible disease can be involved in medical research because the principles of research ethics seem to be appropriate for their protection.⁸⁷ However, this does not mean that there are no serious ethical concerns that need to be taken into consideration. This section will consider how further to safeguard palliative care patients who are involved in research and mitigate ethical concerns. The first subsection will consider specific suggestions to enhance ethical conduct and protect patients, and the second will look at the notion of compassion and vigilance as strategies to manage ethical concerns in palliative care research.

Specific Suggestions to Enhance Ethical Conduct

Franz-Josef Illhardt has recognized that, commonly, pharmaceutical companies will enroll critically ill patients into clinical trials if they meet the following criteria: 1) a life expectancy of more than three months, 2) informed consent for the trial, and 3) no other concomitant life-threatening diseases. As has been reported, these criteria have been applied frequently to studies in the second-line treatment of cancer.

85 Casarett and Karlawish, "Are Special Ethical Guidelines Needed for Palliative Care Research?" 136.

86 Illhardt and ten Have, "Research Ethics in Palliative Care," 209-10.

87 Illhardt and ten Have, "Research Ethics in Palliative Care," 207.

However, there are many items to consider, for we must question whether these guidelines are sufficient to protect vulnerable persons such as the incurably ill.⁸⁸

When analyzing the first criterion regarding the life expectancy, problems may arise as we recognize that patients who come close to the threshold of three months of life expectancy should be protected against any kind of exploitation. This is true both in the research context and out of it. Indeed, caregivers have the moral and legal obligation to safeguard the interests of the patients. As death draws near, patients require the devotion and support of their families and other professionals to help them in coping with their fate. We must question whether they also need the progress of science from which they may never receive benefits.⁸⁹

The second criterion also poses problems. Physicians have reported that many terminally ill patients agree to participate in research trials simply out of a sense of altruism. However, an altruistic attitude can be a sign of moral pressure when patients in the last stages of life opt for this moral mechanism. Patients may believe that they are burdens to their family and caregivers, and that they can enhance the value of their lives by participating in research. To be certain, this is not a mark of moral freedom. It is the duty of the caregiver to make the differentiation between a free altruistic attitude and the fear of not being free disguised as altruism.⁹⁰

The final criterion that has been presented was an absence of concomitant life-threatening diseases. This is also often problematic. While only having the disease that is the prerequisite of the research aids the investigator in gaining control over the project, those patients who are incurably ill typically have multiple diseases and affected organs. It has been recognized that, due to this, research with patients in palliative care facilities can easily create situations in which the endpoints of research put risks upon the patient's process of treatment or bring about more inconveniences to the patient than the caregivers can ethically accept.⁹¹

There are a variety of ways to enhance the ethical conduct of palliative care research. This section will discuss specific suggestions in regards to how patients are enrolled, how the study is designed, and how it is conducted. In regards to patient enrollment, potential palliative care research participants ought to be advised to discuss their participation in a research trial with family members or other close friends. As has been briefly mentioned, palliative care stresses the importance of families and that they represent the fundamental unit of care. Because of this, the patient's family

88 Illhardt and ten Have, "Research Ethics in Palliative Care," 207-08.

89 Illhardt and ten Have, "Research Ethics in Palliative Care," 208.

90 Illhardt and ten Have, "Research Ethics in Palliative Care," 208.

91 Illhardt and ten Have, "Research Ethics in Palliative Care," 208.

or close friends should be involved in discussions on the decision to participate in research trials to the degree the patient will allow. It is also not uncommon that the family members will share research burdens due to the transport needs of the patient, medication arrangements, and other qualities of the study. It is reasonable for the family members or close friends who share these burdens to have their input recognized and honored as well. Further, as has been held throughout this analysis, there does not seem to be a valid reason to exclude potential research participants on the basis of age, frailty, or mental or physical disability. Members of society should not be unfairly excluded from the potential benefits of research participation. It is not ethically acceptable to stigmatize or stereotype an individual's rights because of a perceived attribute.⁹²

The design of the clinical trial should also be formulated in such a way as to maximize ethical conduct. Research protocols should be written in such a manner as to encourage understanding and participation by members of the palliative care team who work with the research participant. This is grounded in the basic principle of palliative care as a multidisciplinary activity. Further, the trial methodology must emphasize the maintenance of patient comfort and dignity through the routine inclusion of assessments of the factors which contribute to this goal. Certainly, the recognition and alleviation of suffering is the primary reason for palliative care. Clinical trials that reflect this goal must be designed. Practical expressions of this concept include routine use of symptom control and quality of life assessments.⁹³

During the conduct of clinical trials, particularly in studies that involve greater-than-minimal risk, it is recommended that tests of cognitive status be repeated at regular intervals. Palliative care patients may become incompetent subsequent to enrollment in a research trial and their continued participation should be dependent upon a surrogate's consent and the demonstration of continued patient benefit while on the experimental therapy, as well as the evidence that the therapy is not the cause of their development of incompetence. Conversely, if an incompetent patient should gain competency during a study, they should only continue in the study upon directly attaining their informed consent.⁹⁴

Compassion and Vigilance as Strategies to Manage Ethical Concerns

In a recent empirical study, investigators found that when clinical researchers and their protocols reflected an environment of both compassion and vigilance, ethical concerns can be managed. In the study, the concept of compassion was reflected

92 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 82.

93 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 82.

94 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 82.

in strategies that represented heightened sensitivity to the needs of the research participants, such as allowing extra time to solicit consent, gently building up to sensitive questions, developing backup protocols, careful attention to the use of language, and methodological flexibility. Further, compassion was coupled with exercising heightened vigilance during every step of the research process about the possible effects of study participation on the participants' emotional and physical well-being, ensuring the research did not interfere with clinical care.⁹⁵

Compassion has been recognized by numerous commentators to be a great virtue, if not a duty, of all physicians.⁹⁶ This easily transfers to the clinical trial investigator. The compassionate behavior of a physician or investigator is not only desired because it is nice for the patient; it is taken as a sign of an authentic attitude that underlies the fiduciary relationship between physician and patient.⁹⁷ When one examines the definition of compassion, we see how important this is to ethical palliative care research. The relevant literature on the etymology and meaning of the word provides slightly nuanced conclusions. The etymology of the two Latin roots suggests that the term means the ability to share or to enter into another's experience of suffering.⁹⁸ While it has been described as the participation in the suffering of others, it can also be thought of as something spontaneous and benevolent.⁹⁹ Working with this definition in mind, it seems desirable to have compassionate healthcare professionals who sense that compassion is one of their professional virtues.

To be a concerned, compassionate physician or investigator means to be involved, and to say that compassion is a physician's duty, a point that will be elaborated below, is to assert an obligation to employ some of humankind's natural ability to feel with the sufferings of others.¹⁰⁰ The obligation to relieve human suffering is virtually synonymous with the practice of medicine, and the suffering of the patient and the compassion of the physician are intimately related. Eric Cassell has asserted that there are three goals which would, if met by the actions of physicians, promise better care and result in lessened suffering for patients. The first goal is that all diagnostic or therapeutic plans be made in terms of the sick, suffering person, not the disease. The second goal is to maximize the functions of the patient, their quality of life, not

95 Hickman, et. al., "Compassion and Vigilance: Investigators' Strategies To Manage Ethical Concerns in Palliative and End-of-Life Research," 888.

96 C.J. Dougherty, and R. Purtilo, "Physicians' Duty of Compassion," *Cambridge Quarterly of Healthcare Ethics* 4, no. 4 (Fall 1995): 426.

97 P. Gelhaus, "The Desired Moral Attitude of the Physician: (II) Compassion," *Med Health Care Philos* 15, no. 4 (Nov 2012): 403.

98 Dougherty and Purtilo, "Physicians' Duty of Compassion," 427.

99 Gelhaus, "The Desired Moral Attitude of the Physician: (II) Compassion," 401.

100 Eric J. Cassell, *The Nature of Suffering and the Goals of Medicine*. 2nd ed. (New York: Oxford University Press, 2004), 290.

length of life. The third goal is to minimize both the patient's and family's suffering. As Cassell affirms, these aims are interlocking in that they arise from the more basic idea that physicians and other healthcare professionals should focus primarily on the best interests of the patient rather than treatment of the disease.¹⁰¹

The physician's duty to provide due care requires them to maintain a judicious range of professional skills and use them with appropriate diligence. Due care bars the deliberate or negligent imposition of unreasonable risks on patients. Although compassion provides no guarantees in this arena, compassion certainly makes it more likely that a healthcare provider will act with due care as changing circumstances require. Indirect evidence for this claim can be found in the legal arena where lawsuits for malpractice, which is the alleged violation of a standard of due care, often seem more closely linked to failed relationships with patients than to inadequate technical skills.¹⁰²

While there are exceptions to nearly every rule, generally speaking, a physician's or investigator's duties are more readily satisfied when they bring a sense of compassion to their encounters with patients and research subjects. To contrast this, the physician or investigator who lacks compassion is more likely to be unaware of a patient's interest and less motivated to place it first in situations of conflict. Due care that is void of compassion is subject to compromise in various scenarios in which standards are implicit and unenforceable, and the uncompassionate physician or investigator is less likely to appreciate and protect patient's vulnerability. It can be assessed that the connection of compassion to the satisfaction of the core duties of physicians and investigators is so close as to make compassion itself a duty.¹⁰³ Indeed, principles of medical ethics are sterile if not applied within a compassionate environment by wise, charitable, and moral investigators.¹⁰⁴ Therefore, provided investigators compassionately apply ethical principles to their work, there is no justification for not endeavoring to improve the quality of palliative care through research.¹⁰⁵

Conclusion

This analysis has examined the question of whether the distinctiveness of palliative care research requires distinct ethical guidelines. The analysis first provided an

101 Eric J. Cassell, *The Nature of Suffering and the Goals of Medicine*. 2nd ed. (New York: Oxford University Press, 2004), 282.

102 Dougherty and Purtilo, "Physicians' Duty of Compassion," 429.

103 Dougherty and Purtilo, "Physicians' Duty of Compassion," 429.

104 MacDonald and Weijer, "Ethical Issues in Palliative Care Research," 80.

105 Jubb, "Palliative Care Research: Trading Ethics for an Evidence Base," 345.

overview on the history of the research process. Then, three arguments were presented that have been used to support the conclusion that palliative care does in fact raise distinct ethical questions that may merit distinct ethical guidelines. The issues of vulnerability and informed consent were examined in detail, and it was determined that though these topics are serious, the principles of research ethics are sufficient to protect participants. Section 4 examined the issue of risk-benefit analysis and discussed the difficulties of this assessment. It was concluded that risk-benefit analysis in palliative care research might be distinct from other fields of research. However, these issues appear to be surmountable. Lastly, section 5 examined further considerations to protect research subjects, including the notions of compassion and vigilance.

To be certain, research is essential to improve medical care and increase our knowledge base. Dying patients or those at high risk of dying should not be denied the valuable opportunity to participate in such research. However, such research should always adhere to accepted ethical principles. Research must respect the dignity of patients, it must be scientifically valid, it should have the potential to benefit the targeted population, and it should minimize any potential for harm. Research involving patients that are at the end of life should be designed considering their emotional, social, physical, and spiritual taxing situations. Particularly, provisions should be taken to ensure that informed consent is obtained from patients who are capable, free from coercion, and not harboring false expectations about the likelihood of benefiting from the study intervention. Adhering to these principles will help ensure that patients can ethically participate in research that has the potential to advance knowledge and improve future patient care.

BIBLIOGRAPHY:

Agar, Meera, Danielle N. Ko, Caitlin Sheehan, Michael Chapman, and David C. Currow. "Informed Consent in Palliative Care Clinical Trials: Challenging but Possible." *Journal of Palliative Medicine* 16, no. 5 (2013): 485-91.

Agrawal, M. "Voluntariness in Clinical Research at the End of Life." *Journal of Pain and Symptom Management*. 25 (2003): S25-S32.

American Academy of Hospice and Palliative Medicine, Statement on Palliative Care Research, November 2014: <http://aahpm.org/positions/research-ethics>

Beauchamp, Tom L., and James F. Childress. *Principles of Biomedical Ethics*. 7th ed. New York: Oxford University Press, 2013.

- Beecham, Emma, Briony F. Hudson, Linda Oostendorp¹, Bridget Candy, Louise Jones, Vickey Vickerstaff, Monica Lakhmanpaul, Paddy Stone, Lizzie Chambers, Doug Hall, Kate Hall, Thines Ganeshamoorthy, Margaret Comac, and Myra Bluebond-Langner. "A call for increased paediatric palliative care research: Identifying barriers." *Palliative Medicine* 30, no. 10 (2016): 979-80.
- Bennett, Michael I. "Principles of Designing Clinical Trials in Palliative Care." In *Research Methods in Palliative Care*. Edited by Julia M. Addington-Hall, Eduardo Bruera, Irene J Higginson, and Sheila Payne, 13-26. New York: Oxford University Press, 2007.
- Benoliel, Jeanne Quint. "Research with Dying Patients." In *Patients, Nurses, Ethics*. Edited by A. J. Davis, J. C. Krueger. New York: American Journal of Nursing, 1980: 119-28.
- Casarett, David J, and Jason HT Karlawish. "Are Special Ethical Guidelines Needed for Palliative Care Research?". *Journal of Pain and Symptom Management* 20, no. 2 (2000): 130-39.
- Casarett, David. "Ethical Considerations in End-of-Life Care and Research." *Journal of Palliative Medicine* 8, no. supplement 1 (2005): S148-60.
- Casarett, David. "Ethical Issues in Palliative Care Research." In *Oxford Textbook of Palliative Medicine*, 4th edition, edited by Geoffrey Hanks, Nathan Cherny, Nicholas Christakis, Marie Fallon, Stein Kaasa, and Russell Portenoy. New York: Oxford University Press, 2011: 416-21.
- Cassell, Eric J. *The Nature of Suffering and the Goals of Medicine*. 2nd ed. New York: Oxford University Press, 2004.
- de Raeve, Louise. "Ethical Issues in Palliative Care Research." *Palliative Medicine* 8, no.4 (1994): 298-305.
- Dougherty, C. J., and R. Purtilo. "Physicians' Duty of Compassion." *Cambridge Quarterly of Healthcare Ethics* 4, no. 4 (Fall 1995): 426-33.
- Foster, Claire. *The Ethics of Medical Research on Humans*. New York: Cambridge University Press, 2001.
- Gelhaus, P. "The Desired Moral Attitude of the Physician: (II) Compassion." *Med Health Care Philos* 15, no. 4 (Nov 2012): 397-410.
- Grant, Marcia, Ronit Elk, Betty Ferrell, R. Sean Morrison, and Charles F. von Gunten, "Current Status of Palliative Care—Clinical Implementation, Education, and Research," *CA: A Cancer Journal for Clinicians*, 59 (2009): 327-35.
- Hanks, Geoffrey, Stein Kaasa, and Karen Forbes. "Research in Palliative Care." In *Oxford Textbook of Palliative Medicine*, 4th edition. Edited by Geoffrey Hanks, Nathan Cherny, Nicholas Christakis, Marie Fallon, Stein Kaasa, and Russell Portenoy. New York: Oxford University Press, 2011: 361-74.
- Henry, Blair, and Damon C. Scales. "Ethical Challenges in Conducting Research on Dying Patients and Those at High Risk of Dying." *Accountability in Research* 19, no. 1 (2012): 1-12.
- Hickman, Susan, Juliana C. Cartwright, Christine A. Nelson, and Kathleen Knaf. "Compassion and Vigilance: Investigators' Strategies To Manage Ethical Concerns in Palliative and End-of-Life Research." *Journal of Palliative Medicine* 15, no. 8 (2012): 880-889.
- Illhardt, Franz-Josef, and Henk ten Have. "Research Ethics in Palliative Care." In *The Ethics of Palliative Care: European Perspectives*, edited by Henk ten Have and David Clark, 198-211. Buckingham, England: Open University Press, 2002.
- Jubb, A. M. "Palliative Care Research: Trading Ethics for an Evidence Base." *Journal of Medical Ethics* 28, no. 6 (Dec 2002): 342-46.

- Karlawish, J.H.T. "Permissible Risk and Acceptable Benefit (The Ethics of Research Involving the Cognitively Impaired)." *Forum* 7 (1997): 277–285.
- Keeley, P.W. "Improving the Evidence Base in Palliative Medicine: A Moral Imperative." *Journal of Medical Ethics* 34, no. 10 (2008): 757–60.
- Koffman, Jonathan, and Fliss Murtagh. "Ethics in Palliative Care Research." In *Textbook of Palliative Medicine*. Edited by Eduardo Bruera, Irene Higginson, Charles F. von Gunte, 192–201. Boca Raton, FL: Taylor and Francis, 2006.
- Krouse, Robert S, Kenneth E Rosenfeld, Marcia Grant, Noreen Aziz, Ira Byock, Jeffrey Sloan, and David Casarett. "Palliative Care Research: Issues and Opportunities." *Cancer Epidemiology Biomarkers & Prevention* 13, no. 3 (March 2004): 337–39.
- Krouse, Robert S., Alexandra M. Easson, and Peter Angelos. "Ethical Considerations and Barriers to Research in Surgical Palliative Care." *Journal of the American College of Surgeons* 196, no. 3 (March 2003): 469–74.
- MacDonald, Neil, and Charles Weijer. "Ethical Issues in Palliative Care Research." In *Oxford Textbook of Palliative Medicine*, 3rd edition, edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny and Kenneth Calman, 76–83. New York: Oxford University Press, 2004.
- Masso, M. *Ethical Research in Palliative Care: A Guide Through the Human Research Ethics Committee Process*. Canberra: National Palliative Care Program, 2004.
- McLean, Sheila A. M. "Respect for Human Vulnerability and Personal Integrity." In *Handbook of Global Bioethics*. Edited by Henk ten Have and Bert Gordijn. 105–117. New York: Springer, 2013.
- Moreno, Jonathan D. *Undue Risk: Secret State Experiments on Humans*. New York: Routledge, 2001.
- Munhall, P. L. "Ethical Considerations in Qualitative Research." *Western Journal of Nursing Research* 10, no. 2 (1988): 150–56.
- National Bioethics Advisory Committee. "The Assessment of Risk and Potential Benefit." In *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity*. 1998. <https://bioethicsarchive.georgetown.edu/nbac/capacity/Assessment.htm>
- Paola, Frederick Adolf, Robert Walker, and Lois Lacivita Nixon, ed. *Medical Ethics and Humanities*. Sudbury, MA: Jones & Bartlett Publishers, 2009.
- Portenoy, Russell, and Mitchell Max, "Pain Research—The Design of Clinical Trials." In *The Oxford Textbook of Clinical Medicine*. 3rd edition. Edited by Derek Doyle, Geoffrey Hanks, Nathan Cherny and Kenneth Calman, 144–53. New York: Oxford University Press, 2004.
- Reyna, Yolanda Zuriarrain, Michael I. Bennett, and Eduardo Bruera. "Ethical and Practical Issues in Designing and Conducting Clinical Trials in Palliative Care." In *Research Methods in Palliative Care*. Edited by Julia M. Addington-Hall, Eduardo Bruera, Irene J Higginson, and Sheila Payne, 27–41. New York: Oxford University Press, 2007.
- Scottish Partnership for Palliative Care. *A Beginner's Guide to Successful Palliative Care Research*. Edinburgh: Scottish Partnership for Palliative Care, 2011.
- ten Have, Henk. "Vulnerability as the Antidote to Neoliberalism in Bioethics." *Revista Redbioética* 1, no. 9 (2014): 87–92.

- ten Have, Henk, and Michèle Jean. *The UNESCO Universal Declaration on Bioethics and Human Rights: Background, Principles and Application*. Paris: UNESCO Publishing, 2009.
- U.S. Department of Health and Human Services. "Institutional Review Board Guidebook." http://www.hhs.gov/ohrp/archive/irb/irb_introduction.htm
- U.S. Department of Health and Human Services, "Institutional Review Board Guidebook. Chapter III, Basic IRB Review," http://www.hhs.gov/ohrp/archive/irb/irb_chapter3.htm
- U.S. Department of Health and Human Services, "Institutional Review Board Guidebook, Chapter VI, Special Classes of Subjects," http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm
- U.S. Food and Drug Administration. "Institutional Review Boards Frequently Asked Questions – Information Sheet." <http://www.fda.gov/RegulatoryInformation/Guidances/ucm126420.htm>

Zahtijeva li profiliranost istraživanja o palijativnoj skrbi različite etičke smjernice?

SAŽETAK

Palijativna skrb i skrb na kraju života doživljava promjene, postaje sve rasprostranjenija i poboljšava se za pacijente. Ipak, trenutno dostupna literatura iz tog područja navodi da su materijali o palijativnoj skrbi i skrbi na kraju života donekle ograničeni. Istraživanja o odlukama o liječenju, obiteljskoj skrbi i naputku za buduću zdravstvenu njegu u određenim okolnostima samo su neka od područja koja zahtijevaju velike istraživačke napore. Istraživanje o palijativnoj skrbi bitno je zbog stalnog pružanja učinkovitih tretmana onima koji pate u posljednjim fazama terminalne bolesti. Doista, cilj dobrog istraživanja palijativne skrbi ublažavanje je patnje i poboljšanje kvalitete života. Slično kao i u bilo kojem drugom području, programi palijativne skrbi moraju se razvijati na istraživačkoj osnovi, a njega pacijent će patiti ako nije potpomognuta znanstvenim istraživanjem. No, oni koji su protiv ove potrebe su oni koji ostaju pri mišljenju da su etički i praktični izazovi istraživanja palijativne skrbi jedinstveni i nepremostivi. Ova analiza razmatra jesu li različite etičke smjernice potrebne za istraživanje palijativne skrbi.

Ključne riječi: palijativna skrb; palijativna sedacija; ranjivost; skrb na kraju života; analiza rizika i koristi; sposobnost odlučivanja.