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Assessment of Complementary Alternative Medicine (CAM) therapies being utilized by cancer patients at the end of life and communication of CAM usage between patients and physicians

By

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Prevention Science

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Assessment of Complementary Alternative Medicine (CAM) Therapies Being Utilized by Cancer Patients at the end of life and Communication of CAM Usage Between Patients and Physicians

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An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

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Abstract

Assessment of Complementary and Alternative Medicine (CAM) therapies being utilized by cancer patients at the end of life and communication of CAM usage between patients and physicians.

By

Carolina M. Lecours

Dying patients experience a heavy symptom burden. Cancer patients, especially those with advanced disease, may be more likely to face extremely frightening and less manageable circumstances than patients with other chronic or life-limiting diseases. In cancer patients, pain is one of the most feared and burdensome symptoms. Not only do patients with cancer commonly report fears of a prolonged death consumed by uncontrolled pain, they often fear the process of dying more than death itself. Quality of life (QOL) issues are particularly relevant for terminally ill cancer patients receiving palliative care.

Side effects from chemotherapy or radiation therapy can cause an array of traumatic side effects, such as fatigue, sleep disturbance, anxiety, depression, nausea and vomiting. Not finding adequate relief from these side effects with traditional medicine, cancer patients are seeking the aid of Complementary and Alternative Medicine (CAM). CAM is defined as “a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.”

Despite the emergent literature supporting the efficacy of specific CAM modalities for managing side effects and symptoms associated with cancer treatments, the exact nature of CAM usage in chronically ill cancer patients (e.g., the characteristics of patients who use CAM, and who don’t, what type of CAM is used, and whether they inform their physician) is not well documented. Although the study of CAM use among the general population is relatively wide-spread, less attention has been given to the study of CAM use among patients receiving palliative care. This is a grant proposal that will assess CAM therapies being utilized by end-stage cancer patients receiving palliative care and communication about CAM usage between the patients and physicians.

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Chapter I: Introduction

Dying patients experience a heavy symptom burden (Pan, Morrison, Ness, Fugh-Berman, & Leipzig, 2000). Cancer patients, especially those with advanced disease, may be more likely to face extremely frightening and less manageable circumstances than patients with other chronic or life-limiting diseases. In cancer patients, pain is one of the most feared and burdensome symptoms (van den Beuken-van Everdingen, de Rijke, Kessels, Schouten, van Kleef, & Patijn, 2007). Not only do patients with cancer commonly report fears of a prolonged death consumed by uncontrolled pain, they often fear the process of dying more than death itself (McCarthy, Phillips, Zhong, Drews, & Lynn, 2000).

Quality of life (QOL) issues are particularly relevant for terminally ill cancer patients receiving palliative care. The aim of palliative care is to provide the best possible QOL both for people approaching the end of life and for their families and caregivers (World Health Organization, 2016). It is a holistic approach to care and support, and takes into account emotional, psychological and spiritual needs as well as physical needs (World Health Organization, 2016). Pain control is central to the concept of palliative care (World Health Organization, 2016).

Side effects from chemotherapy or radiation therapy can cause an array of traumatic side effects, such as fatigue, sleep disturbance, anxiety, depression, nausea and vomiting (Yates, Mustian, Morrow, Gillies, Padmanaban, Atkins, Issell, Kirshner, & Colman, 2005), which combined with pain has a detrimental effect on the QOL of end stage cancer patients. Not finding adequate relief from these side effects with traditional

medicine, cancer patients are seeking the aid of Complementary and Alternative Medicine (CAM).

Problem Statement

The exact nature of CAM usage among dying cancer patients, the impact of CAM on palliative care and patient/physician communication concerning CAM are not well understood.

Purpose Statement

The purpose of the proposed study will be to assess CAM therapies being utilized by end-stage cancer patients receiving palliative care and communication about CAM usage between patients and physicians.

Proposed Research Question or Project

The objectives of this study are:

1. To understand the rate and type of CAM use and non-use among chronically ill cancer patients receiving palliative care.
2. Identify overall patient characteristics of CAM users and non-users.
3. Assess communication of CAM usage between the patient and the patient's oncologist, primary care physician or palliative care team.

Significance Statement

Despite the emergent literature supporting the efficacy of specific CAM modalities for managing side effects and symptoms associated with cancer treatments, the exact nature of CAM usage in chronically ill cancer patients (e.g., the characteristics of patients who use CAM, and who don't, what types of CAM is used, and whether they inform their physician) is

not well documented. CAM may offer patients additional options to control side-effects and symptoms from cancer treatments. As cancer patients are seeking CAM more often than in the past, it is necessary to investigate communication of usage with patient's oncologist, primary care physician, or palliative care team. It is not known what type of effect CAM may have on end stage cancer patients receiving palliative care, thus there is a possibility its effects could be unsafe. The paucity of knowledge of the effects of CAM on these patients is challenging. Communication may facilitate the ability of patients to weigh the safety and efficacy of CAM, ensure avoidance of harmful interactions with their conventional cancer treatments, and determine where and when they can most safely access CAM. It is important to understand the nature of CAM usage among dying cancer patients, and the impact it may have on palliative care.

Definition of Terms

Complementary and Alternative Medicine: Encompasses "a group of diverse medical and healthcare systems, practices and products that are not presently considered to be a part of conventional medicine" (National Center for Complementary and Integrative Health, 2016). Within this context, "complementary" describes therapies used in conjunction with conventional medicine, while "alternative" refers to therapies that replace conventional care (Leis & Millard, 2007).

Complementary Therapy: A selected therapeutic method, product or treatment by a practitioner used in combination with conventional mainstream medicine as a health service for patients (National Center for Complementary and Integrative Health, 2016).

Alternative Therapy: If a non-mainstream practice is used in place of conventional medicine, it is considered alternative (National Center for Complementary and Integrative Health, 2016).

Hospice: Hospice offers medical care toward a different goal: maintaining or improving QOL for someone whose illness, disease, or condition is unlikely to be cured (Hospice Foundation of America, 2017). Hospice care focuses on symptom management, which enables the patient to maintain dignity and QOL (Batchelor, 2010). Hospice care is offered both inpatient care at a facility or in a patient's home or other location.

Palliative Care: The aim of palliative care is to provide the best possible QOL both for people approaching the end of life and for their families and caregivers (World Health Organization, 2016). It is a holistic approach to care and support, and takes into account emotional, psychological and spiritual needs as well as physical needs (World Health Organization, 2016). Pain control is central to the concept of palliative care (World Health Organization, 2016).

Chronically ill: Chronic illnesses are characterized by fluctuations in trajectory, uncertainty in prognoses, extended disease timelines and stress (Effiong, 2012). Chronically ill individuals live with the affliction that accompanies chronic disease (Effiong, 2012).

End of life: There is no exact definition of end of life; however, the evidence supports the following components: (1) the presence of a chronic disease(s) or symptoms or functional impairments that persist but may also fluctuate; and (2) the symptoms or impairments resulting from the underlying irreversible disease require formal or informal care and can lead to death (National Institutes of Health, 2004).

Chapter II: Review of the Literature

The following section is a review of the literature. This section discusses cancer statistics and types of cancer treatments available, including palliative care. Research of cancer patients who are using CAM at the end of life is also included, as well as what types of CAM have shown to be effective and more popular among patients with different cancer diagnoses. Reasons for CAM usage and non-usage by cancer patients, and why these patients are utilizing it or not, and the reasons why are examined. In addition, primary sources of information on CAM are discussed, as well as which socioeconomic groups have been found to use CAM more often. Finally, the role of CAM for patients who are receiving palliative care is examined and the challenges the research has found in this area.

After a widespread search of the literature regarding CAM and cancer patients, the information presented provides a robust body of evidence that shows the important role CAM can play in conjunction with the treatment of terminally ill cancer patients. The literature was chosen based on the works of authors who have considerable experience in the study of CAM and oncology, and have conducted research that has yielded valuable knowledge to the field. Though the study of CAM in relation to palliative care has not been extensively researched, it is an area that is beginning to gain attention as researchers are beginning to consider the potential benefits it could have on the QOL of dying cancer patients.

About 1,688,780 new cancer cases are expected to be diagnosed in the United States 2017 (American Cancer Society, 2017). In addition, 600,920 Americans are expected to die of cancer in 2017, which translates to about 1,650 people per day (American Cancer Society, 2017). Cancer continues to be the number one diagnosis for hospice patients

(Running, Shreffler-Grant, & Andrews, 2008). There are many types of cancer treatments which vary depending on the type of cancer patients have. Most patients have a combination of treatments such as surgery with chemotherapy and/or radiation therapy. In addition, patients may have immunotherapy, targeted therapy, or hormone therapy. Palliative care is given to improve the QOL of patients with life-threatening diseases such as cancer; the goal is not to cure the disease.

The baby boom generation (those born between 1946-1964) has shown greater interest in CAM than previous age groups, and the post-baby boom cohort, Generation X, has been even more receptive (Lafferty, Tyree, Devlin, Andersen, & Diehr, 2008). These factors indicate a greater demand for CAM as well as an increased openness to trying it.

Although the study of CAM use among the general population is relatively wide-spread, less attention has been given to the study of CAM use among patients receiving palliative care (Hlubocky, Ratain, Wen, & Daughterty, 2006). Little is known about the use of and attitudes toward CAM in patients receiving palliative care (Muecke, Paul, Conrad, Stoll, Muenstedt, Micke, Prott, Buentzel, & Huebner, 2015). In addition, Muecke et al (2015) found that palliative care professionals as well as patients are highly interested in CAM, yet communication on CAM in the palliative care setting is scarce. An important means to improve this communication might be improving knowledge of healthcare professionals about the evidence of CAM methods in which palliative care patients are mostly interested (Muecke et al., 2015).

The prevalence of the use of CAM among patients with advanced cancer ranges from 7% to 73% (Correa-Velez, Clavarino, & Eastwood, 2005). The use of CAM in palliative care aims at “providing comfort to and increasing the QOL of patients who otherwise

may despair" (Correa-Velez, et al., 2005). Few studies, however have examined this issue in detail from the subjective experience of patients with advanced cancer (Correa-Velez, et al., 2005). There is no well-defined theoretical framework of CAM in palliative cancer care (Ernst, 2001). Recurring themes can, however, be identified (Ernst, 2001). These relate to the holistic nature of CAM, to individualized, patient-centered, treatment plans, to the absence of serious adverse effects, to the emphasis on improving the health of cancer patients instead of treating the disease alone, and to recognition of the importance of the mind-body connection (Ernst, 2001). Critics of CAM are keen to point out that these themes are by no means unique to CAM but are hallmarks of any palliative and supportive care of high quality (Ernst, 2001).

Researchers in Australia surveyed cancer patients at the end of their life regarding their use of complementary therapies and found that 48% of them had used some form of complementary therapy over the course of their illness (Running et al., 2008). They found that those who used CAM had decreased anxiety and pain, greater satisfaction with conventional medicine and a greater sense of control over treatment decisions as compared to those who did not use conventional medicine (Running et al., 2008). Pan, Morrison, Ness, Fugh-Berman, & Leipzig (2000) found that relaxation techniques such as breathing and acupuncture may improve intractable pain in dying patients. They identified that massage aids with pain relief, as well as acupuncture for cancer-related pain and dyspnea (Ness et al., 2000). In addition, Smith et al (2002) compared the outcomes of therapeutic massage for hospitalized cancer patients and reported a positive outcome for the study. It was also observed that therapeutic massage helped to alleviate pain, distress, as well as improving sleep patterns (Adams & Jewell, 2007). A study that looked into how cancer patients adjust to illness when treated with and without CAM in addition to conventional treatments found that patients treated by

complementary therapy with conventional therapy fared better psychologically as compared to those treated with only conventional therapy (Adams & Jewell, 2007).

Research by Balneaves, Weeks, & Seely (2008) found that CAM use is higher in breast and prostate cancer populations than in populations with other cancer diagnoses. Herbals and antioxidant supplements are among the most frequently used CAM approaches with use reported to be upwards of 50% in some cancer populations (Richardson, Masse, Nanny, & Sanders, 2004). Richardson et al (2004) found that given the widespread use of these products and data suggesting possible drug-herb-vitamin interaction, concerns of the oncology community are relevant. These concerns are magnified by studies that report 19-42% of cancer patients do not disclose CAM use to their oncologist (Richardson et al., 2004). Patients may currently practice therapeutic activities, as well as nutritional supplementation but may not know the collective practice by the name of CAM, thus not reporting usage to their physicians. The high use and limited disclosure of CAM communicates something about the needs and desires of patients in the conventional medical setting, but it also provides a “novel opportunity” for oncologists to communicate with and better understand the needs of their patients (Richardson et al., 2004). They also found that “consistent with the literature, cancer patients in this study who use CAM are not uneducated or desperate but rather are more educated and in higher income brackets than nonusers.” In addition, “they want hope and many seek spiritual support and other options after diagnosis, not necessarily because these will provide a cure but in hopes of improving survival, QOL, symptoms, or side effects related to conventional cancer treatment” (Richardson et al., 2004).

Primary sources of information on CAM are family members and friends, less frequently magazines and books and rarely physicians and the oncologist (Eschiti, 2007). Most

patients do not even inform their oncologists about the CAM methods they use (Conrad, Muenstedt, Micke, Prott, Muecke, & Huebner, 2014). They also found that 40% of patients did not discuss their use of other therapies with their physicians, suggesting a need for improved communication in this regard (Conrad et al., 2014). Unfortunately, medical doctors, particularly oncologists, are not taught about CAM in medical school and rarely receive any training in this area as part of residency, so meeting the needs of patients in this arena may be very challenging (Yates, et al., 2005). In addition they found that the most frequent CAM modalities discussed with at least one physician were diets, massage, and herbal medicine, respectively (Yates, et al., 2005). Disclosure of CAM use has been found to be higher among white non-Hispanics compared with minorities, and disclosure was higher for provider-based CAM (Arthur, Belliard, Hardin, Knecht, Chen, & Montgomery, 2012). Richardson et al (2004) found that physicians initiated discussions about CAM sometimes (25%) and often/very often (20%); however they reported that in most cases (91.7%), patients sometimes or often/very often initiated these discussions. In addition, Chao, Wade, & Kroneenberg (2008) found that patients may more willingly disclose use of provider-based CAM (e.g. chiropractic or acupuncture) relative to self-care CAM (e.g. vitamins and herbal medicine) if the former is perceived as more legitimate. Balneaves et al (2008) found that an individual's understanding of what constitutes appropriate treatment and how it can best be achieved are derived not only from personal experience, but also from social interaction and interface with cultural products-most notably the mass media. Information about CAM is increasingly available and accessible through media sources, which lend visibility and perceived legitimacy to this group of therapies and practices (Balneaves et al., 2008).

Although it is documented that CAM use is highest among those of higher socioeconomic status (SES) and younger, educated, female cancer patients (Arthur et al., 2012), many of these studies were not entirely representative of minority groups (Arthur et al., 2012). Minorities face multiple barriers to receiving adequate healthcare-including cost, communication, insurance and suboptimal sources of care (e.g. hospital emergency room) which may result in medical encounters that do not facilitate disclosure of CAM use (Chao et al., 2008). One study found that Asian Americans who disclosed CAM use with a healthcare provider rated their quality of healthcare higher than those that did not discuss CAM use (Chao et al., 2008). Healthcare factors that may limit opportunity to disclose CAM use include number and length of medical encounters, continuity of care and medical charting conventions (Chao et al., 2008). A remaining question is whether disparities in access to quality conventional care contribute to racial/ethnic differences in CAM disclosure (Chao et al., 2008).

Patients with advanced cancer experience a complex web of problems, all of which interact (Higginson & Evans, 2010). These include profound symptoms, which, unless alleviated, result in greater suffering for the person with cancer and his/her family, and emotional, social, and spiritual consequences associated with cancer, disability, and facing the end of life, for patients, their families, and those close to them (Higginson & Evans, 2010). Palliative care seeks to alleviate these problems and to enable patients to live well for as long as possible, to die with comfort and dignity, and to support the family (Higginson & Evans, 2010).

CAM in oncology is a particularly sensitive issue since side effects and interactions with CAM can induce adverse events (Conrad et al., 2014). Markman (2002) found that although many CAM approaches are quite safe, both minor and major toxicities have

been documented, including emesis, hypersensitivity reactions, cardiovascular events, neurologic dysfunction, hepatic and renal failure, and the development of malignant disease. As most oncologists are not informed on their patients using CAM, they will not be able to consider side effects and interactions with CAM substances as reason for adverse effects they diagnose in their patients (Conrad et al., 2014). Adverse effects may go unnoticed as in oncology most drugs have a broad spectrum of side effects on different organs (Conrad et al., 2014). Zeller, Muenstedt, Schweder, Senf, Ruckhaeberie, Serve, & Huebmer (2013) were the first to publish data estimating the number of patients in danger of interaction and loss of therapeutic efficacy caused by CAM based on an analysis of individual treatment data. At least one-third of all patients on active cancer therapy run the risk of suffering from interactions (Zeller et al., 2013). Of those choosing CAM products, three quarters are in danger of interactions, and this number is independent of whether the patient is receiving chemotherapy, endocrine therapy or antibodies (Zeller et al., 2013).

Whereas we have some data on interactions of CAM and chemotherapy, only few data are available on interaction of CAM and drugs used in palliative care (Conrad et al., 2014). In order to prevent these interactions, communication between patients and physicians is imperative. There are several reasons why patients do not inform their physicians. Mostly they do not think he or she might be competent or interested in this field (Conrad et al., 2014). Others are afraid of being told to stop CAM or even have tried to talk about CAM, but did not get a respectful answer (Conrad et al., 2014).

Although CAM use has become common within cancer care, it remains controversial. Many CAM practices originate within philosophical traditions that deviate from Western medicine, leading some individuals to view them skeptically (Weeks, Balneaves,

Paterson, & Verhoef, 2014). Furthermore, the body of research evidence for most CAM therapies tends to be smaller and often of lower quality than the evidence for conventional medical therapies (Weeks et al., 2014). Existing CAM research evidence is also often difficult to find, synthesize, and share with appropriate knowledge users (Weeks et al., 2014). Finally, the potential for interactions with conventional cancer therapies is another common concern (Weeks et al., 2014). A decisive element in patient-physician communication on CAM thus is the attitude of physicians (and other professionals) toward CAM and their knowledge regarding the different methods (Weeks et al., 2014).

Choice of cancer therapy at the end of life is becoming increasingly complex due to more options for therapy, high expectations from therapy, less toxic treatments and better supportive care (Kondo, Shimazu, Morizane, Hosoi, Okusaka, & Ueno, 2014). Supportive care is dedicated towards issues around treatment management and post-treatment issues, whereas palliative care focuses on issues frequent at end of life (Kondo et al., 2014). Consequences of these choices may have an enormous impact on patients and families and societal healthcare costs (Kondo et al., 2014). Although less aggressive care, especially palliative care, at the end of life is associated with better QOL near death, patients with cancer are receiving increasingly aggressive cancer care at the end of life (Kondo et al., 2014).

Wide variances in reported prevalence of CAM may be attributable both to the differences in populations sampled and definitions of CAM used (Ernst, Filshie, & Hardy, 2003). CAM modalities encompass multiple and not always concordant meanings of the body and illness/health and have a range of legitimacy accorded by medical practitioners, oncologists, and researchers alike (Ernst et al., 2003). Accordingly, some

have noted that it is of questionable validity to treat all CAM as if equivalent (Ernst et al., 2003).

Elliott, Kealey, & Oliver (2008) examined patient perceptions of both CAM users and non-users. In this study, “CAM users and non-users presented many different expectations and judgments of CAM and CAM users.” Both groups appeared to consider that any benefits to be obtained from CAM required a belief in their efficacy although non-users claimed not to have this belief (Elliot et al., 2008). CAM users valued CAM for perceived physical, psychological, philosophical, and social gains (Elliott et al., 2008). For some, decisions regarding CAM use were influenced by the positive or negative appraisal of others (Elliott et al., 2008). Although CAM uptake is often deemed to reflect a Western societal emphasis on individual responsibility for health, this research supports the findings of others that decisions about treatment-including both conventional and alternative treatments-are influenced by family members (Elliott et al., 2008).

If effective at improving dying patients’ QOL, CAM therapies may serve as useful alternatives or adjuncts in the care of terminally ill patients (Pan, et al. 2000). If CAM treatments are shown to help improve patients’ QOL in the end of life setting, the integration of CAM providers and services into palliative care teams may become an important “means to a better end.” Continued research will assist in integrating the best therapies of both fields to advance comfort and to ease suffering in dying cancer patients.

Chapter III: Methodology

Review of Funding Agencies

This section describes multiple sources of funding that support CAM, cancer, and palliative care research. Each agency offers unique research opportunities in their respective fields. The funding source chosen best matches the topic, scope, and budget of the proposed research.

The National Center for Complementary and Integrative Health (NCCIH), formerly the National Center for Complementary and Alternative Medicine (NCCAM) funds scientific research on complementary and integrative health, as well as training of researchers (nccih.org, 2016). The NCCIH is a part of the National Institutes of Health (NIH). The mission of the NCCIH is to define, through rigorous scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and health care (nccih.org, 2016). One of the goals of the NCCIH is to advance the science and practice of symptom management, which encompasses the investigation of using CAM treatments for terminally ill cancer patients receiving palliative care (nccih.org, 2016). The area of CAM and its relationship to cancer therefore falls under the umbrella of what the NCCIH typically funds, which is research to help answer important scientific and public health questions about complementary health approaches (nccih.org, 2016).

The American Cancer Society (ACS) supports QOL and survivorship research to lessen the negative effects of cancer and its treatment and to improve the lives of cancer survivors and their families (cancer.org, 2016). These efforts include relieving cancer pain, managing side effects of cancer treatment, and funding studies of cancer survivors (cancer.org, 2016). In addition, The ACS also funds research focusing on relieving and

preventing the suffering of patients by addressing the physical, emotional, spiritual, and social concerns that arise with advanced illness (cancer.org, 2016).

The National Palliative Care Research Center (NPCRC) funds palliative care research initiatives to create an evidence base to improve care for seriously ill patients and their families (National Palliative Care Research Center, 2016). In partnership with the Center to Advance Palliative Care, the NPCRC will rapidly translate these findings into clinical practice (npcrc.org, 2016).

NCCIH is the federal government's lead agency for scientific research on diverse medical and health systems, practices, and products that are not generally part of conventional medicine (nccih.org, 2016). For this reason, it was chosen as the funding agency for the proposed program. NCCIH offers a large variety of funding opportunities unique to CAM, making the available options the most suited to fit the researcher's needs. A distinct trend toward the integration of CAM therapies with the practice of conventional medicine is occurring. RFA-AT-01-002 or *Complementary/Alternative Medicine at the End of Life for Cancer and/or HIV/AIDS* was chosen as it presents a unique opportunity to research CAM at the end of life, which is an area that has not been extensively studied.

Description of Grant Announcement

The requirements of RFA-AT-01-002 are described in the following paragraphs. The next section is taken directly from the RFA, which can also be found in Appendix E. This proposal is in response to RFA-01-002 and seeks funding under the NIH R21 award mechanism. This type of grant was selected because it is intended to encourage exploratory/developmental research by providing support for the early and conceptual

stages of project development. The research has the potential to lead in advances in health research. In addition, the proposed research will not require a long timeframe and has limited preliminary data, thus making an R21 grant the best choice.

The NCCIH invites research grant applications to generate scientific knowledge on CAM therapies that will lead to improved care for individuals at the end of life. The intent of this initiative is to generate research that has the potential to improve the quality of life for individuals with cancer and/or HIV/AIDS who are at the end of life.

For the purposes of this request for application (RFA), CAM is defined as healthcare practices that are not an integral part of conventional medicine. CAM practices can be grouped into five major domains: (1) alternative medical systems, (2) mind-body interventions, (3) biologically-based treatments, (4) manipulative and body-based methods, and (5) energy therapies.

Eligible applicants include domestic and foreign, for-profit and non-profit organizations, public and private such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply.

The primary objective of this research initiative is to identify and evaluate CAM interventions for patients with advanced, terminal disease. Possible patient outcomes would include:

1) *Managing or reducing the symptoms associated with the conditions of end stage disease for cancer or HIV/AIDS,*
2) *Preventing or reducing side effects of medications such as anti-retrovirals, steroids, and chemotherapy/radiotherapy, and*

3) *Enhancing the psychosocial, social, and spiritual well-being and QOL at the end of life.*

This initiative will focus on the potential role of a spectrum of CAM approaches for patients with life-threatening illness due to cancer and HIV/AIDS. Applicants should focus on evaluating CAM therapies alone or in combination with other conventional treatment modalities. Integrated programs, holistic regimens, or diverse approaches with CAM interventions including, but not limited to, aromatherapy, music therapy, spirituality, massage and physical approaches, acupuncture, innovative psychosocial support interventions, botanicals (ie, drug-like therapies of single herbs or complex herbal formulas), vitamins and/or minerals, special dietary approaches, or energy approaches (ie Reiki, therapeutic touch) are appropriate for investigation.

The research must be oriented toward the most critically needed areas of CAM research, and toward collaborative activities that address new innovative possibilities in CAM research. The applicant should document that linkage to the relevant CAM communities exist and that certified or licensed CAM practitioners will provide appropriate input for the research. Ideally, the project would include conventional and CAM practitioners working as an interdisciplinary team.

This proposal is appropriate to NCCIH, as it is the federal government's lead agency for scientific research on diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine. NCCIH focuses on complementary health interventions used frequently by the American public. NCCIH strongly encourages attention to a range of endpoints meaningful to improved health, well-being, and quality of life. Though many cancer patients are using CAM, there have

been few studies researching how it can play a role in the QOL of end-stage patients. An investigation of the impact of CAM modalities in improving QOL is an area that is unique, and NCCIH is the most suitable given its existing research portfolio.

Review Criteria

RFA-AT-01-002 requires the applicant to develop a sound research plan approach that includes Significance, Approach, Innovation, Investigators and Environment. The following sections describe how the proposal is responsive to these criteria.

A. Significance

Physicians should know what patients are using in order to accurately monitor treatment outcomes, assess signs of adverse effects or drug-herb-vitamin interactions, and guide patients in the decision making process (Richardson et al., 2004). There are potential dangers for cancer patients receiving palliative care that are using CAM. The lack of knowledge regarding the effects CAM may have on these patients can be extremely dangerous. There is very limited data available on the interaction of CAM and drugs in palliative care. These issues need to be explored, as CAM may cause adverse effects if used in conjunction with certain drugs. There is a need for quality research on the relationship between CAM use and end stage cancer patients receiving palliative care.

B. Approach

The proposed research will be a descriptive, cross-sectional study to assess CAM modalities that end-stage cancer patients have adopted as well as how or if they are communicating with their oncologists about it. The conceptual framework, design, methods and analyses for this study were chosen as the

most appropriate to the aims of the study. Potential problem areas have been recognized and addressed as effectively as possible given the population are very sick patients. In addition, plans for dissemination and implementation of findings within and outside of the investigator's organization have been identified.

C. Innovation

This project aims to study end stage cancer patients receiving palliative care who are also using CAM. The focus on end stage cancer patients receiving palliative care is highly innovative. Though the use of CAM by cancer patients has been researched a great deal, the use of CAM by patients receiving palliative care has not been examined nearly as often. The specific aims assist in locating, analyzing, evaluating and making effective use of CAM research in scientific literature, and will provide guidance for practitioners, policy makers and academic researchers. The concepts and approaches of this project go beyond the traditional and strive to prove that CAM research is necessary to assess effective ways for oncologists and palliative care teams to gather information about CAM usage by cancer patients at the end of life and discern ways these therapies may enhance or interfere with traditional treatments

Investigators

The investigator's experience in research since 2009 makes her well suited for the role of Principal Investigator for this study. Though this will be her first time as Principal Investigator of a study, she has worked on multiple studies which have provided the skills necessary to oversee the research. Her past experience includes working with Emory University's Clinical Neuroscience Research Unit (ECNRU) on an NIH funded project, R01MH056120, *Neural Circuits in Women with Abuse and Post-Traumatic*

*Stress Disorde*r, in which she was a key contributor to the progress made throughout the study. Her specific role on the project was to work directly with the Principal Investigator, J. Douglas Bremner on activities such as IRB submission, data collection, adherence to applicable federal and institutional regulations, grant and budget preparation, and ensuring that the project was carried out according to the research protocol. She was successful in accruing the number of participants needed in order to achieve target accrual, and was effective in retention of those participants. The investigator's ability to motivate other staff members and continued passion for the research process proved to be invaluable to the progress made over the duration of the study. The investigator is an industrious, efficient researcher who provided professional and quality research by her attention to detail and her ability to contribute novel and innovative solutions to the research team. Dr. Bremner is a well-known Professor of Psychiatry and Radiology at Emory University and is Director of the ECNRU. He is also Director of Mental Health Research at the Atlanta Veteran's Association Medical Center in Decatur, Georgia. Dr. Bremner's work includes numerous publications such as *Posttraumatic Stress Disorder: A state-of-the science review* (2006); *Stress and brain atrophy. Current Drug Targets-Central Nervous System and Neurological Disorders* (2006); and *The enduring effects of childhood abuse and related experiences in childhood: A convergence of evidence from neurobiology and epidemiology* (2006).

In addition, the investigator also collaborated with Dr. Bremner and Dr. Viola Vaccarino, an internationally recognized expert in PTSD and cardiovascular epidemiology, on another NIH funded study, *Mechanisms of Depression in Cardiovascular Disease*. Her role included recruiting, consenting, administering and implementing a mental stress challenge during a PET scan.

In 2013, the investigator joined the Winship CTO, which provided vast experience in the area of cancer research and in addition, generated her interest in cancer research. She spent two years working as a Clinical Research Coordinator (CRC), with a focus on NIH funded Cooperative Group trials. In 2014, she joined the Clinical Trials Office Quality Management Office. This role provided extensive knowledge on Investigator Initiated clinical trials, in addition to Cooperative Group and Pharma clinical trials. Working in quality management secured a solid foundation for maintaining adequate and accurate research subject records to reflect adherence to protocol specific requirements, promptly reporting protocol deviations and adverse events to the IRB, adherence to standard operating procedures, prospectively obtaining and documenting informed consent in accordance with the current IRB-approved informed consent documents, and ensuring that the conduct of research studies adhered to Good Clinical Practice (GCP). During her years at the Winship CTO working as a CRC, the investigator achieved above and beyond the required 90% data reporting compliance and timeliness for ECOG-ACRIN, one of the largest clinical cancer research organizations in the United States, which conducts clinical trials in all types of adult cancers. This achievement was paramount for the organization, as it is vital that research coordinators and PIs participating in these trials are compliant in data reporting. In addition, she was able to make strides in the reporting of long-term follow-up data. Most research protocols specify follow-up until death, which presents challenges as many patients are not easily found in order to conduct the required long-term follow-up data forms and questionnaires. Many patients move to other cities and others may pass away. The investigator was able to increase the percentage of long-term follow-up data reporting by finding innovative techniques to track these patients or their families, allowing physicians to learn more about the long-term effects of cancer treatment and help them reduce problems related to treatment and improve patient QOL. The investigator presented on numerous occasions at in-house seminars with physicians, Winship leadership, and

other medical staff. Presentations included describing new and revised standard operating procedures, discussion of upcoming new ECOG-ACRIN protocols that may have been of interest to Winship, as well as preparation for audits among other cancer-related topics.

Working with long-term follow-up data also generated an interest in the QOL cancer patients. As a CAM user in her personal life, a connection grew between CAM and the QOL of terminally ill cancer patients. The investigator sought out a PI who conducts CAM research at Winship, Rebecca Pentz, PhD. Dr. Pentz has published several papers, including *Participants' perceptions of the use of natural compounds in chemoprevention trials and the influence of complementary and alternative medicine use on chemoprevention trial accrual, retention and post-trial behaviors.* The investigator initiated several meetings with Dr. Pentz, to discuss her studies and seek guidance on conducting this type of research. Dr. Pentz became a mentor, thus inspiring the investigator to pursue CAM research of end stage cancer patients.

Institutional Environment

The grant proposal is responsive to the Institutional Environment as Emory University is exceptionally well qualified to carry out the proposed research. Emory is one of the nation's leading research universities, building on a unique combination of campus-based resources and global partnerships. Winship Cancer Institute of Emory University has demonstrated that its outstanding research programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. As a result, Winship has earned the prestigious comprehensive cancer designation from the National Cancer Institute (NCI), placing it in the top one percent of all cancer centers in the United States and making it

the first and only one in the state of Georgia. Winship's comprehensive designation was awarded after a rigorous evaluation process conducted by the NCI that included submission of a written grant and a site visit conducted by more than two dozen scientists from peer institutions. Various first authors and senior authors from Winship have published 130 studies in major medical and scientific journals as of January 2017.

All of Winship's medical professionals are affiliated with Emory Healthcare, Georgia's largest healthcare system. Their nurses, navigators, social workers, technicians and support staff are all part of the comprehensive cancer care team. The Winship CTO facilitates the conduct of high-quality clinical research involving cancer patients by providing a central comprehensive management service. Winship CTO is staffed by highly trained professional research personnel specializing in areas of clinical coordination, data management, specimen processing and regulatory management. Winship CTO provides a supportive environment to conduct clinical trials in a cost-effective and efficient manner while ensuring compliance with Winship clinical trials SOPs, Good Clinical Practice (GCP), Emory IRB, U.S. Food and Drug Administration (FDA), other regulatory agencies and external sponsors.

Winship CTO manages the overall process of subject screening, consent, registration, data entry and regulatory document submission and management for clinical research studies involving cancer patients. In addition, Winship CTO is the central clearinghouse for the initiation and registration of clinical protocols involving cancer patients.

Winship's Supportive Oncology Outpatient Clinic delivers state of the art supportive oncology with a focus on integrative medicine for patients along the spectrum of cancer care. Their team strives to reduce the physical and emotional suffering through

comprehensive pain and symptom management and supportive counseling. The Supportive Oncology Outpatient Clinic delivers services that cover the full spectrum of cancer care from diagnosis to survivorship. Whatever stage of treatment patients are in, recovery or survivorship, the support care team designs an integrated program with the primary goal of improving QOL. These teams draw from wide-ranging resources in supportive oncology, integrative oncology, pain management and palliative care. This clinic helps patients to manage pain; manage symptoms such a nausea, difficulty breathing, loss of appetite, fatigue, and depression; provides counseling in making difficult medical decisions; provides emotional and spiritual support; coordinates home care referrals; assists with advanced care planning regarding future care and treatment; and provides resources, counseling, and referrals for evidence-based integrative oncology community resources.

The facilities and other resources available to the PI at Winship include everything needed to undertake and complete the proposed research project successfully. The intellectual environment is rich with other investigators who are doing work that is complementary to what is proposed in this grant application. This facility provides a scientific environment that is strongly supportive of the proposed research and, therefore, success of the project. In addition, Emory/Winship is close in proximity to and has established long-term relationships with the Centers for Disease Control and Prevention (CDC), as well as with the American Cancer Society (ACS). This is a vibrant research community and collaborative environment.

Methodology of the Grant Review Process

The reviewers were sent a copy of the proposal via email. The proposal included the following sections: Specific Aims, Research Strategy, Investigators, Institutional Environment, Recruitment and Retention of Subjects, Protection of Human Subjects, and Appendices. The proposal was distributed individually to each reviewer, along with an electronic copy of the RFA, instructions for the review process, a review evaluation scoring sheet, and a conflict of interest form, which are included in Appendices F, G and H. The reviewers were given two weeks to complete the review process. They were instructed to use the external review evaluation scoring sheet to evaluate each section for strengths, weaknesses, and recommendations. Each evaluation criterion had a total number of points: Significance: 25; Innovation: 20; Approach: 30; Investigators: 15; Environment: 10. There was a section for "additional review criteria," which included recruitment and retention of subjects; protection of human subjects; and inclusion of women and minorities. This section was not graded, only comments were encouraged, if applicable.

The information was returned via email by each of the reviewers, and a thank you email expressing gratitude for their time and feedback was sent back to each reviewer. Feedback and comments including strengths and weaknesses were given careful review, and themes were identified. All comments were copied and pasted into a new Microsoft Word document. Priority was given to editing the most challenging aspects first, as those would take longer to resolve. Consideration was given to each comment, and the proposal was edited to resolve reviewer's feedback on weaknesses. Responses to all comments were recorded. If there was lack of agreement by the author on specific reviewer comments, that information was noted along with justification for not making any changes. One of the reviewers additionally had comments via track changes in the

grant proposal itself. Those comments were also included in the list of weaknesses needing attention and were resolved in the same manner as above.

After all comments were received and revisions were made, chapter 4 was completed. Chapter 4 consisted of a list of all comments and how they were addressed. Finally, the first draft of chapter 5 was completed. This chapter is to be the final version of the proposal. Chapter 5 was sent out the thesis committee for review and upon completion of all remaining edits, the final version has been added to the thesis.

Description of Grant Reviewers

Johanna M. Hinman, MPH, MCHES, is the Associate Director of Education in the Department of Surgery at Emory University. Her prior experience includes working with the Emory Prevention Research Center in the Rollins School of Public Health, where she was responsible for the administration of the core PRC grant. She also teaches a research design and grant preparation class in the Emory Executive Master of Public Health program, which serves as a huge asset for grant review, and serves as Chair of the thesis committee.

Donna Knutson, PhD, is the Deputy Director for the National Center for Environmental Health, Agency for Toxic Substances and Disease Registry at CDC. Her previous experience includes acting as the Fund Manager for the Working Capital Fund at CDC. She has a 25 + year career with CDC, and her vast experience in many areas of public health will be extremely useful in the review process. Dr. Knutson serves as Field Advisor on the thesis committee.

Laurie Johnson, MPH is currently Deputy Director for the Division of Emergency and Environmental Health Services, National Center for Environmental Health, Agency for Toxic Substances and Disease Registry at CDC. She has a 20+ year career with CDC, and has developed many requests for proposals and has conducted scoring panels to review and rank the applicants.

Pamela Protzel-Berman, PhD, received her doctorate from Emory University, and currently serves as the Associate Director for Policy for the National Center for Environmental Health, Agency for Toxic Substances and Disease Registry at CDC. She has had substantial congressional experience in both the U.S. House and Senate and has worked in government relations for a public health organization.

Dana Ray, BFA, MPH Candidate, 2017 is the Assistant Director of Research Projects at Emory's Winship Cancer Institute. She has extensive grant writing experience in the field of cancer research, and has worked on Winship's P30 CCSG grant, U10 NCTN, the American Cancer Society Institutional Research Grants in addition to other smaller pilot project grants. She also has experience with the NIH and the Department of Defense (DoD).

Protection of Human Subjects

Emory University is the owner of all institutional data. In order to maintain HIPAA compliance, the data will be completely de-identified and therefore the need of authorization from the individual is waived (please see attached list of 18 identifiers in Appendix C). HIPAA covers a variety of issues including the Privacy Rule concerning patients' Protected Health Information (PHI) and the Security Rule governing patients' electronic PHI (ePHI). The Emory Office of Compliance will provide consultation and

training for compliance with HIPAA, and will serve as a point of contact for the research team.

Human Subject's Involvement, Characteristics, and Design

This is an investigator-initiated study; all research activities must be reviewed and approved by the Emory University Institutional Review Board (IRB). We are seeking limited review, as this is a non-therapeutic/non-invasive trial. If our protocol qualifies for a limited review, we will likely fall under the IRB review category of "expedited" or "exempt" (behavioral, QOL, etc.). These submissions will be sent to the Winship Clinical Trials Research Committee (CTRC) for protocol review. An application with the CTRC will be entered, which is designed to be a tool for the investigator(s) to ensure that before the approval process begins, the many facets surrounding the initiation of a study are carefully thought through, understood and agreed upon by all of those individuals involved. The form is designed in such a way that a completed form will provide the Winship regulatory department with all of the information needed for IRB submission, and application can be made to the IRB immediately following CTRC approval. All genders and racial/ethnic groups will be eligible for this study. Please see the Approach section of the grant proposal for inclusion and exclusion criteria.

Human Subject's Materials Collected

A study questionnaire will query participants on basic demographic information and which CAM modalities they utilize and whether or not these are discussed with either their oncologist or primary care physician. If patients do not utilize CAM, they will be questioned on their reasons for not using it.

A unique study ID will be assigned to each study participant. The research does not involve blood/tissue storage or banking. A review by a Data Safety Monitoring Board (DSMB) is not required, since it is not a treatment study or a clinical trial. Even though it is not a clinical trial, the study will be managed by the Winship Clinical Trials Office, and records will be stored in a secure area to ensure that the data is limited to authorized users. The investigator must receive training in the structure and definitions of institutional data as well as relevant policies prior to accessing data, and will be the only data user. Filing cabinets/areas will remain locked and placed in secured/locked rooms. Electronic data will be saved on a device that has the appropriate security safeguards and unique identification of authorized users, password protection, encryption, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss or theft. External hard drives will be used to back up data. All of these devices will have encryption solutions.

Recruitment and Informing Subjects of Study or Program

Once the participant has signed the informed consent and HIPAA forms, agreeing to participate, the investigator will review the study in detail and go over any risks involved as well as answer any questions and address any concerns the participant may have. The investigator will document the informed consent process by filling out an informed consent documentation form, which is to be signed, dated and kept in the patient record (see Appendix A: informed consent form and Appendix B: informed consent documentation form).

The informed consent document will explain to participants the purpose of the study. In addition, it will also inform them that they will be given a questionnaire to fill out

regarding their CAM usage, which will take 30-40 minutes to complete (see Appendix D: Study Questionnaire). They will be informed of who owns their study information, and how their health information will be stored and shared with other researchers. It will be explained that there will be no cost to them for participating. In addition, the informed consent document explains that they do not have to participate in the study, that it is entirely their choice. If they decide to join this study, they can change their mind later and withdraw from the research study. All efforts will be made to retain participants, by assisting them in any way possible, answering their questions in a timely manner, and communicating relevant information as it becomes available. The researchers will be sensitive to the fact that they are very ill, therefore very weak and at times not available in a timely manner. The researchers also have the right to stop their participation in the study without their consent for any reason; especially if they believe it is in their best interest. The informed consent document will let them know that taking part in a study is separate from medical care. The decision to join or not join in the research will not affect their status as a patient at Winship. The informed consent document will describe the study risks and procedures.

Potential Risks to Human Subjects

The questionnaire does not involve any specific risks or discomfort beyond those of a standard clinical questionnaire situation such as feeling upset at a review of their medical treatments or personal information, as well as boredom or fatigue. Some of the questions may make the participant uncomfortable. However, if they do not wish to answer any particular question, they are not required to do so; their participation is voluntary. It is possible that the researchers will learn something new during the proposed study about the risks of being in it. If this happens, they will tell the participant about it. The participant can decide if they want to continue to be in the study or not.

Benefits of the Research or Program to Human Subjects and Society

If a participant agrees to take part in the research study, there may or may not be direct medical benefit to them. It is possible that the researchers will learn something new during the proposed study about the risks of participating in the study. If this happens, they will tell the participant about it. The participant can decide if they want to continue to be in the study or not. The researchers hope that the information learned from this research study will benefit other patients with end-stage cancer in the future by learning how CAM therapies may or may not affect the body and subjects QOL. The results obtained from this study may widen CAM treatment options during palliative care, which could be beneficial to some patients.

Inclusion of Women and Minorities

All genders and racial/ethnic groups will be eligible for this study.

Chapter IV-Incorporation of Reviewer Comments

Thank you for agreeing to participate in the *Assessment of Complementary Alternative Medicine Therapies Being Utilized by Cancer Patients at the End of Life and Communication of CAM Usage Between Patients and Physicians* review. Your written review is critical as your comments provide substance as to the project and its strengths and weaknesses with respect to each evaluation criteria.

Reviewer 1 comments

Comment 1: The proposal should more clearly delineate the potential dangers posed by lack of knowledge of the intersection between CAM and palliative care.

Response to comment 1: An additional paragraph was added to the Significance section, "*There are potential dangers for cancer patients receiving palliative care that are using CAM. The lack of knowledge regarding the effects CAM may have on these patients may be extremely dangerous. There is very limited data available on the interaction of CAM and drugs in palliative care. These issues need to be explored, as CAM may cause adverse effects if used in conjunction with certain drugs. There is a need for quality research on the relationship between CAM use and end stage cancer patients receiving palliative care."*

Comment 2: The proposal is not entirely clear on the specific lack of knowledge of palliative care. It cites the increasing body of literature on CAM use generally but is not specific on where the line is drawn to describe palliative care. Clarify the distinction between standard cancer treatment and palliative care so as to make more clear what the particular knowledge gap is to strengthen the argument for the proposed project.

Response to comment 2: A few lines were added to first few lines of the Innovation section to make the distinction between standard cancer treatment and palliative care, *"There are many types of cancer treatments which vary depending on the type of cancer patients have. Most patients have a combination of treatments such as surgery with chemotherapy and/or radiation therapy. In addition, patients may have immunotherapy, targeted therapy, or hormone therapy. Palliative care is given to improve the QOL of patients with life-threatening diseases such as cancer, the goal is not to cure the disease. Little is known about the use of and attitudes toward CAM in patients receiving palliative care."*

Comment 3: There is a lack of clear description of the conceptual framework.

Response to comment 3**:** A detailed description of the conceptual framework section has been added in the first few paragraphs of the Approach. It includes two figures to help understand the concepts easier.

Comment 4: The investigator describes background and experience well, but it would strengthen the proposal to include some particular interest in the subject matter. Is there a mentor who can be identified as an advocate/advisor for this project, specifically to this topic/content area?

Response to comment 4: A section was added to the last paragraph in the Investigators section describing the investigator's interest in the use of CAM by end stage cancer patients, as well as the identification of a mentor in the early stages of the proposed research. Please see "*In addition to the investigator's interest in cancer research, working with long-term follow-up data produced an interest in cancer patient's QOL. As a*

user of CAM in her personal life, a connection grew between CAM and the QOL of terminally ill cancer patients. The investigator sought out a PI who conducts CAM research at Winship, Rebecca Pentz, PhD. Dr. Pentz has published several papers, including Participants' perceptions of the use of natural compounds in chemoprevention trials and the influence of complementary and alternative medicine use on chemoprevention trial accrual, retention and post-trial behaviors. The investigator initiated several meetings with Dr. Pentz, to discuss her studies and seek guidance on conducting this type of research. Dr. Pentz became a mentor, thus inspiring the investigator to pursue CAM research of end stage cancer patients."

Comment 5: Overall, the proposal is well written but possibly some redundancies that could be reduced to make room for more detail on: 1) Specific dangers posed by the lack of literature on CAM in palliative care; 2) The conceptual framework underlying the project and the types of statistics that may be generated (it will be a small sample size so need to acknowledge these will be descriptive statistics only); 3) Clarification of whether or not the questionnaire can be done as a verbal interview with the PI if such accommodation is needed by a particular patient.

Response to comment 5: 1) an additional paragraph including a citation was added to the Significance section, "*Physicians should know what patients are using in order to accurately monitor treatment outcomes, assess signs of adverse effects or drug-herb-vitamin interactions, and guide patients in the decision making process (Richardson et al., 2004). In summary, there are potential dangers for cancer patients receiving palliative care that are using CAM. The lack of knowledge regarding the effects CAM may have on these patients can be extremely dangerous. There is very limited data available on the interaction of CAM and drugs in palliative care. These issues need to be*

explored, as CAM may cause adverse effects if used in conjunction with certain drugs. There is a need for quality research on the relationship between CAM use and end stage cancer patients receiving palliative care." 2) a detailed description of the conceptual framework section has been added in the first few paragraphs of the Approach. It includes two figures to help understand the concepts easier; the proposed research will be qualitative; therefore descriptive, open coding will be used. This section has also been re-written to include the data analysis plan 3) the investigator will conduct a verbal interview in order to accommodate these participants so they are able to remain in the study, "*If a particular participant is not able to fill out the questionnaire by hand, the PI will conduct a verbal interview in order allow them to participate in the study."*

Reviewer 2 comments

Comment 1: The recognition that patients may currently practice therapeutic activities, as well as nutritional supplementation but do not know the collective practice by the name of complementary and alternative medicine is not discussed. The qualitative study does not attempt to measure the quality of life changes between CAM users and non-users, but to characterize and describe the practices of the patient. A quantitative measure of QOL would strengthen the significance of the paper.

Response to comment 1: To address the first part of this comment, a line was added to the Significance section, "*Patients may currently practice therapeutic activities, as well as nutritional supplementation but may not know the collective practice by the name of CAM, thus not reporting usage to their physicians."*

To address the second part of the comment, a quantitative measure of QOL to strengthen the significance of the paper was also added in the Approach section,

"*Though QOL itself is not the main focus of the study, and it is related to CAM use. Data will be collected to find out if participants feel that their use of CAM enhanced their QOL via the Assessment of Quality of life at the End of Life (AQEL) questionnaire. The AQEL was developed to assess health-related QOL in palliative care patients. A study by Henoch, Axelsson, & Bergman (2010) found evidence for the validity of the AQEL and its feasibility in patients with cancer in palliative care. It covers physical, psychological, social, existential and global aspects of QOL".*

Comment 2: There are a few sentences that are awkwardly structured (the first under "significance, for example), and inconsistencies in the sentence structure under the aims of the study. The second and third aim need to begin with "To" as the first aim does. Link the "significance" portion to better follow the "aims" with citations that address rates and types of CAM, known patient characteristics, and communication between patient and care provider.

Responses to comment 2: The first sentence under the Significance section has been removed and replaced with other cancer statistics from different sources, "*About 1,688,780 new cancer cases are expected to be diagnosed in 2017 (American Cancer Society, 2017). In addition, 600,920 Americans are expected to die of cancer in 2017, which translates to about 1,650 people per day (American Cancer Society, 2017). Cancer continues to be the number one diagnosis for hospice patients (Running, Shreffler-Grant, & Andrews, 2008)."*

The Aims have been revised as per suggestions above, and now include "*to identify*" and "*to assess*."

A few lines and a figure were added to the Significance section including rates and types of CAM and known patient characteristics, "*Figure 1 presents the ten most common types of CAM among adults in 2012. Initial research has suggested that adult CAM users may have an increased use of healthy lifestyle behaviors and a strong focus on overall wellness (Karlik, Ladas, Ndao, Cheng, Bao & Kelly, 2014). Analyses of data from the National Health Interview Study (NHIS) data, 2002 and 2007, found that healthy adult CAM users were more likely to use exercise and less likely to be obese than adults who did not use CAM (Karlik et al., 2014). Associations of CAM with exercise, higher vegetable intake, lower fat or lipid intake, and smoking cessation or decreased smoking have been reported in adult populations (Karlik et al., 2014).*

In addition, a few paragraphs were added to the Significance section regarding statistics of CAM usage by end stage cancer patients and CAM disclosure to oncologists. Please refer to citations of research done in Australia by Running et al 2008), Pan et al (2000), Smith et al (2002), Adams & Jewell (2007), and Richardson et al (2004).

Comment 3: There are a few statements that could have used citations to back up statements. For instance, a citation would strengthen the statement that there are "not too many studies that have evaluated why these patients are not using CAM", which would lend credibility to the innovative aim of looking at those who choose not to use CAM. If there is a "divide that exists between CAM and Western medicine", a citation would make the statement stronger, and support the innovative nature of the work.

Response to comment 3: The Innovation section has been revised. The statements mentioned in the comment above have been deleted and replaced, and proper citations have been added.

Comment 4: I would expect more information on how the groups will be sorted to compare the means (e.g., by use or non-use of CAM? Those that discussed with providers and those that didn't?). A stronger discussion about the variables to be analyzed would make the application stronger. Specificity pertaining to the data being gathered and analyzed should be found here, as well as how the data and analysis used will help inform the research questions being asked. For instance, which of the questions outlined in the approach would assist to understand the rate and type of CAM use and non-use? Those questions could be lumped together in one section for ease of understanding and clarity. Overall patient characteristics would be defined by which data? Are these simply descriptive statistics? And finally, grouping the questions and data needed to address the communication aspects between patient and provider could make the section stronger. Recruitment and retention of subjects is found in the Institution section, and perhaps it should be moved to approach, as well as protection of human subjects and IRB. This section could be made stronger by describing why the ANOVA will be used, where correlations will be run and for what outcome. Describe the specific data points that will be used to get to the "aims", and cite additional studies that indicate why an ANOVA should be used in this case. This section is crucial for publication and distribution to the field as outlined in the distribution plan. Patient protection should be mentioned here, and how personally identifiable information (PII) will be protected.

Responses to comment 4: The proposed research will be qualitative; therefore descriptive, open coding will be used. This section has been re-written and added to the data analysis section.

Recruitment and retention, and Protection of Human Subjects and IRB are actually not found in the Institution section. These topics stand alone and are listed as per the NIH format and RFA guidelines. How PHI will be protected is described the Protection of Human Subject section of the application.

Comment 5: Links to data analysis and reporting not present in the description of past activities of the investigator. Also, a short reference to publications or presentations in this field are absent. Add more robust description of previous published work, or link to work done and reported by teams in former positions.

Response to comment 5: Examples of publications by Dr. J. Douglas Bremner, who the investigator worked with in the past have been added to the Investigators section, "*Dr. Bremner's work includes numerous publications such as Posttraumatic Stress Disorder: A state-of-the science review* (2006); *Stress and brain atrophy. Current Drug Targets-Central Nervous System and Neurological Disorders* (2006); *and The enduring effects of childhood abuse and related experiences in childhood: A convergence of evidence from neurobiology and epidemiology* (2006). As the investigator has not had any publications yet, a section was added regarding presentations she has given in the field of cancer, "*During her time at Winship CTO, the investigator presented on numerous occasions at in-house seminars with physicians, Winship leadership, and other medical staff. Presentations included describing new and revised standard operating procedures, discussion of upcoming new ECOG-ACRIN protocols that may have been of interest to Winship, as well as preparation for audits among other cancer-related topics."*

Comment 6: I think some mention of recruitment and retention, protection of human subjects and IRB should also be found under the “Approach” section to assure the investigator has thought of these items and it is clear to the reviewer.

Response to comment 6: In the Approach section, a line was added to reflect there is a plan for recruitment and retention, protection of human subjects, and IRB*, “Please see sections below that provide detailed description of the plan for recruitment and retention of subjects and protection of human subjects. All research activities will be reviewed and approved the Emory University Institutional Review Board (IRB).”*

Reviewer 3 comments

Comment 1: Although the applicant acknowledges that “the use of CAM by cancer patients has been researched a great deal”, there is minimal information about the positive effects of CAM on chronically ill cancer patients. The applicant should’ve provided strong background information about the positive effects of CAM on chronically ill cancer patients, which would’ve been helpful in promoting the need for this study.

Response to comment 1: A few paragraphs were added to the Significance section regarding statistics of CAM usage by end stage cancer patients and CAM disclosure to oncologists. Please refer to citations of research done in Australia by Running et al 2008), Pan et al (2000), Smith et al (2002), Adams & Jewell (2007), and Richardson et al (2004).

Comment 2: The applicant’s plan to disseminate to more traditional medical/clinical journals and communities is unclear. Consider including dissemination of findings to traditional medical/clinical communities.

Response to comment 2: A few lines have been added in a paragraph under data analysis regarding including dissemination of findings to also include the Journal of Clinical Oncology, as well as the American Society of Clinical Oncology, which are considered to be a more traditional medical journal and medical association.

Reviewer 4 comments

Comment 1: The applicant could better describe the types of data that will be used in the analyses. There may be some challenges recruiting subjects given the focus on end-stage cancer patients. The scope of the study may be overly ambitious, including both questions about use of CAM and patient-physician communication.

Response to comment 1: The proposed research will be qualitative; therefore descriptive, open coding will be used. This section has been re-written and added to the data analysis section.

Comment 2: Could more clearly define palliative care and what inclusion criteria the researchers will use.

Response to comment 2: The definition of palliative care was provided in the introduction, *"Palliative care is an approach that improves the QOL of patients and their families facing the 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 (World Health Organization, 2016). "*

Inclusion criteria are discussed in detail in the Approach section.

Comment 3: It may be challenging to recruit in the proposed population due to the late stage of the illness. Consider expanding to those cancer patients in late stage, but not yet in palliative care.

Response to comment 3**:** In the Approach section, inclusion criteria was added for "patients with a life expectancy of at least 3 to 6 months".

Reviewer 5 comments

Comment 1: Typically a specific aims section is just a couple of sentences that articulate each aim. This section is then repeated in more detail later in the research strategy.

Response to comment 1: The aims were listed as suggested in just a few sentences and detail on each aim is discussed later in the Approach section.

Comment 2: This sentence is confusing, "*By 2020, in North America, the number of people who die annually of cancer is projected to increase by 51% to just under 1 million".* Not sure if you're saying it will increase by 1 million each year?

Response to comment 2: The changes have been made by deleting this sentence and replacing it with updated cancer statistics, "*About 1,688,780 new cancer cases are expected to be diagnosed in 2017 (American Cancer Society, 2017). In addition, 600,920 Americans are expected to die of cancer in 2017, which translates to about 1,650 people per day (American Cancer Society, 2017). Cancer continues to be the number one diagnosis for hospice patients (Running, Shreffler-Grant, & Andrews, 2008)."*

Comment 3: I think this could be elaborated on a lot more, with a correlation to the beneficial effects experienced by those who use these therapies who don't have cancer (This comment is in relation to a line in the Significance section, "*CAM includes various therapies such as natural products, deep breathing, yoga, Tai Chi, or Qi Gong, chiropractic or osteopathic manipulation, meditation, massage, special diets, homeopathy, progressive relaxation and guided imagery").*

Response to comment 3**:** Additional data that describes the benefits of CAM use for those who do not have cancer was added to the Significance section, "*Initial research has suggested that adult CAM users may have an increased use of healthy lifestyle behaviors and a strong focus on overall wellness (Karlik, Ladas, Ndao, Cheng, Bao, & Kelly, 2014). Analyses of data from the National Health Interview Study (NHIS) data, 2002 and 2007, found that healthy adult CAM users were more likely to use exercise and less likely to be obese than adults who did not use CAM (Karlik et al., 2014). Associations of CAM with exercise, higher vegetable intake, lower fat or lipid intake, and smoking cessation or decreased smoking have been reported in adult populations (Karlik et al., 2014)."*

Comment 4: Ditto – elaborate on this more. How efficacious are these therapies? (This comment is in relation to a line in the Significance section, "*despite the emergent literature supporting the efficacy of specific CAM modalities for managing side effects and symptoms associated with cancer treatments").*

Response to comment 4: Additional data on the efficacy of CAM therapies was added to the Significance section, please refer to citations of research done in Australia by

Running et al 2008), Pan et al (2000), Smith et al (2002), Adams & Jewell (2007), and Richardson et al (2004).

Comment 5: Any specific cancers? (This question was derived from the statement “CAM has been widely used over the past decades by patients with cancer.”)

Response to comment 5: A citation was added stating that Balneaves et al (2008) “*found that CAM use is higher in breast and prostate cancer populations than in populations with other cancer diagnoses.”*

Comment 6: Are you saying that the oncologists aren’t meeting the needs of their patients, which drives the patient to explore and seek out other therapies? This could also be related to a mistrust of doctors, or that some patients seek out alternative treatments because they don’t have money or insurance to cover these medical expenses.

Response to comment 6: This comment addresses a line that reads “*The high use and limited disclosure of CAM communicates something about the needs and desires of patients in the conventional medical setting, but it also provides a “novel opportunity” for oncologists to communicate with and better understand the needs of their patients*.” The comment was addressed by adding a few citations from a research study to reinforce the reasons that cancer patients use CAM. There was no evidence found upon researching CAM for this project that CAM usage is related to a mistrust of doctors or that patients seek out CAM because of financial reasons or lack of insurance.

Comment 7: What divide? This is a broad statement that needs more clarification and references (refers to a sentence that read "*There is currently a divide that exists between CAM and Western medicine, which limits the types of CAM available for palliative care*").

Response to comment 7: This line has been deleted as that section was re-written.

Comment 8: You may wish to consider specific types of cancer. Also, you may wish to study patients whose life expectancies are greater than 3 or 6 months. Your intent is not to study patients entering hospice (who are truly at end of life [EOL]).

Response to comment 8: The proposed research will not focus on any specific types of cancer. After conducting a thorough literature review, it was found that the majority of similar studies did not focus on any specific types of cancer. Inclusion criteria were revised to include patients with life expectancies of at least 3 to 6 months.

Comment 9: How will you introduce the study to the patient?

Response to comment 9: Clarification has been provided on introduction of the study to the patient by adding "*as the investigator spent three years working in research at Emory's Winship Cancer Institute Clinical Trials Office (Winship CTO), she has an existing relationship with both medical and radiation oncologists on the team. In addition, relationships were made with nurse practitioners, physician assistants, nurses, and clinical research coordinators who work directly with patients. This will facilitate communication to alert the PI when there is a prospective patient who may meet inclusion criteria."* This modification can be found in the Approach section.

Comment 10: I would think this would be ineligibility criteria.

Response to comment 10: This comment refers to the line in the Approach section, "*it is possible in many cases that the patient will not return to clinic and will not be able to participate in the study depending on the progression of their disease."* The sentence has been edited to say *"If a patient is not able to return to the clinic to participate in the study due to disease progression, he/she will be considered ineligible and excluded from the study."*

Comment 11: Don't understand this. Other reasons? What other reasons? You will definitely need to elaborate on this a lot more to the IRB for sure.

Response to comment 11: This comment refers to a line in the Approach section where inclusion criteria is discussed. *"Participants not able to complete the questionnaire (30-40 minutes) because of his/her illness, drugs or other reasons will be excluded*." The sentence was deleted after deciding it didn't read well.

Comment 12: Need to define "past". Past year, since they have been ill, all their life?

Response to comment 12: This comment is in reference to what type of CAM participants used in the past, and is found in the Approach section. The sentence was amended to say that *"participants will be queried about what type of CAM they use or have used since diagnosis of their illness and how often they have used it",* and the word "past" has been deleted.

Comment 13: You might consider introducing a validated QOL study instrument here to assess QOL status. See https://clinicaltrials.gov/ct2/show/NCT01904838.

Response to comment 13: A quantitative measure of QOL to strengthen the significance of the paper was also added in the Approach section.

Comment 14: How will you achieve this goal?

Response to comment 14: This comment refers to a line in the Approach section, *"Information will be collected in order to find out how their oncologist or palliative care team responded after learning they use or have used CAM while receiving treatment for cancer."* The sentence has been re-worded as follow to address the comment, as "*Information will be collected via questionnaire in order to find out how their oncologist or palliative care team responded after learning they use or have used CAM while receiving treatment for cancer."*

Comment 15: Actually there are validated study instruments that are routinely used in palliative care to assess these symptoms.

Response to comment 15: This comment refers to a line in the Approach section which read "*the techniques used to measure subjective experiences like pain, fatigue, the ability to perform daily activities, and mood state have experienced significant advances, but still remain a challenge."* In response to the comment, a line was added to clarify that even though this is a challenge, with the use of the AQEL will assist in obtaining these measures.

Comment 16: Not sure what you mean by this.

Response to comment 16: This comment refers to the data analysis section. The statement has been edited to read "*analysis of the data will be used to report on the significance of the investigation of CAM usage of end-stage cancer patients and to suggest recommendations for future CAM research*". The unclear words "*in previous and current research"* have been deleted.

Comment 17: This statement is a re-write of your specific aims.

Response to comment 17: This comment is in reference to a section in the Approach where the aims were stated again, making it redundant. The sentences were deleted as the aims have already been discussed in detail in another section.

Comment 18: This is a new specific aim.

Response to comment 18: This comment refers to the Specific Aims. The statement "*In addition, the investigator will identify and synthesize a set of criteria for evaluating the viability of potential CAM and cancer research studies, so that future researchers can build on the successes and avoid the pitfalls of past investigations"* has been deleted, as the investigator does not wish to add a new specific aim.

Comment 19: Do you intend to follow up with all the treating physicians? If so, this too could be considered a sub-aim of the above new specific aim.

Response to comment 19: This comment is in reference to a line in the Approach section "*reports will be mailed, followed by a phone or in-person conference with the investigator to discuss findings".* The investigator does intend to follow-up with all the treating physicians. This will be done as described above. As stated in response to comment 18, the investigator does not wish to add a new specific aim, thus the comment regarding a sub-aim will be disregarded. The investigator views follow up with physicians as part of the dissemination plan.

Comment 20: How do you plan to do this? You might expand this research out to rural communities to get a larger population, as your findings are limited to Winship only, and as such, may not be entirely generalizable enough to make a recommendation yet.

Response to comment 20: This comment is in reference to "*the investigator will brief the American Public Health Association with recommendations for prioritizing future research",* in the Approach. In response to the first question, the investigator will brief the American Public Health Association by participating in an oral session at a future meeting. This will provide an opportunity to present study findings in a formal setting. In response the second comment, as the work is meant to be exploratory and introductory work, the NIH R21 award mechanism was chosen. The work may be further expanded in a future application for funding in order to work with a larger sample in a longer period of time, which allows findings to be generalizable to the community. A section was added to the introduction describing the reasons for choosing the R21.

Comment 21: Provide grant number if possible.

Response to comment 21: This comment is in reference to the Investigators section, in reference to the study the investigator worked on in 2009, "*Neural Circuits in Women with Abuse and Post-traumatic Stress Disorder").* The grant number was provided.

Comment 22: I did not see if any other researchers had done similar work, or if there is research that has been conducted but on normal participants (and not cancer patients).

Response to comment 22: This comment refers to the Innovation section. Citations have been added to the Significance section, which refer to several studies that researched CAM and its effects on dying patients. Please see Running et al (2008), Pan et al (2000), and Adams & Jewell (2007). Information on research done on patients who do not have cancer was not included, as this study focuses on patients with cancer.

Comment 23: A lot of the text doesn't speak to the project innovation, it continues to provide background and significance to the study. Several statements are broad and could be further clarified and referenced.

Response to comment 23: This comment refers to the Innovation section, which has been revised as per recommendations; the sentences that were more relevant to the background have been deleted. In addition, the statements that were broad and needed further clarification were also deleted.

Comment 24: Did not see alternative tactics, but this may not be feasible given the study population are very ill cancer patients.

Response to comment 24: Alternative tactics are not feasible in this study population.

Comment 25: Consider eligibility criteria to include cancer patients who are not approaching end of life {>3 or 6 months to live}.

Response to comment 25: In the Approach section, inclusion criteria was added for "patients with a life expectancy of at least 3 to 6 months".

Comment 26: This is your opportunity to justify why you need grant funds. It is not a bad thing to talk about your successes in fulfilling job duties for another supervisor or PI. Think of this as a way to convince the reviewer that they want to hire you, and then write it out (this comment refers to the Investigators section).

Response to comment 26: Additions were made to the Investigators section, including lines on successes achieved while working at the Emory University's Clinical Neuroscience Research Unit. In addition, a few sentences were added to describe successes at Winship CTO.

Comment 27: It would be nice to see examples of CAM presented as a table to back up the information presented in the proposal.

Response to comment 27: This section refers to "other relevant comments." Figure 1 has been added describing the 10 most common types of CAM among adults in 2012.

Summary of Grant Review Process

The review process shed light on several areas of the application that needed to be strengthened. There were several significant issues that required major editing of the application. The Innovation section was revised as it contained many citations which

truly belonged in the background section. This section was the most challenging section to write. As it was written originally, it was not clear why the proposed research is innovative. Though the Innovation is shorter than it was originally, the points presented are more succinct to strengthen the application.

All reviewer comments relating to Institutional Environment and Investigators were addressed. These sections did not need to be included in the final proposal, but they were left as reviewers had commented on them, therefore they needed to remain. These two sections have been moved to the end of the proposal, as they are not part of the project plan specifically.

The original statistical analysis plan was lacking detail and justification for choosing ANOVA, and ways the data would be gathered and analyzed. As this is a qualitative study, a decision was made to only include qualitative data, and to use open coding. This was a more reasonable plan, as the study is descriptive and the sample size is very small.

Another theme found in the review process was the need for a validated QOL instrument in order to strengthen the significance of the paper. The AQEL instrument was added in order to assess the QOL of study participants. This instrument was developed to assess QOL solely on palliative care patients. Including the use of the AQEL provides more validity to the proposed research.

In addition, a lack of a clear conceptual framework was identified. This was addressed by providing a revised CAM framework based on the Behavioral Model of Health Services Use. Using this model allows the proposed revised CAM model to be based on

theory that has been used extensively over several decades, thus providing an alternative categorization of CAM therapies to facilitate further research.

After thoroughly going through each of the reviewer's comments, significant aspects were addressed, and then attention was given to more minor issues. Examining problematic areas brought up by the reviewers and making the corresponding changes was extremely helpful in strengthening the proposal, as it provided a better written proposal with aspects that would be taken into consideration in a real-world setting. Changes in sentence structure and other grammatical areas also helped to develop the proposal even further to provide more precise writing, thus making the application more effective in conveying stated goals. Finally, a few changes were made to the literature review in chapter 2, with the addition of several new citations in order to keep it consistent with additions to the final proposal. The methodology section of chapter 3 was also edited to be consistent with changes made to the final proposal, allowing the content to be consistent throughout the entire thesis.

Chapter V: Final Version of Grant Proposal

Dying patients experience a heavy symptom burden (Pan, Morrison, Ness, Fugh-Berman, & Leipzig, 2000). Cancer patients, especially those with advanced disease, may be more likely to face extremely frightening and less manageable circumstances than patients with other chronic or life-limiting diseases (van den Beuken-van Everdingen, de Rijke, Kessels, Schouten, van Kleef, & Patijn, 2007). In cancer patients, pain is one of the most feared and burdensome symptoms (van den Beuken-van Everdingen et al., 2007). Not only do patients with cancer commonly report fears of a prolonged death consumed by uncontrolled pain, they often fear the process of dying more than death itself (McCarthy, Phillips, Zhong, Drews, & Lynn, 2000). Quality of life (QOL) issues are particularly relevant for terminally ill cancer patients receiving palliative care. Palliative care is an approach that improves the QOL of patients and their families facing the problems 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 (World Health Organization, 2016).

Side effects from chemotherapy or radiation therapy can cause an array of traumatic side effects, such as fatigue, sleep disturbance, anxiety, depression, nausea and vomiting (Yates, Mustian, Morrow, Gillies, Padmanaban, Atkins, Issell, Kirshner, & Colman, 2005). Not finding adequate relief from these side effects with traditional medicine, cancer patients are seeking the aid of Complementary and Alternative Medicine (CAM). CAM is defined as “a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine” (National Center for Complementary and Integrative Health, 2015). The exact

nature of CAM usage among dying cancer patients, the impact of CAM on palliative care and patient/physician communication concerning CAM is not well understood.

This proposal is in response to RFA-01-002 and seeks funding under the NIH R21 award mechanism. This type of grant was selected because it is intended to encourage exploratory/developmental research by providing support for the early and conceptual stages of project development. The research has the potential to lead in advances in health research. In addition, the proposed research will not require a long timeframe and has limited preliminary data, thus making an R21 grant the best choice. There are three specific aims of the proposed study.

Aim 1: To understand the rate and type of CAM use and non-use among chronically ill cancer patients receiving palliative care.

Aim 2: To identify overall patient characteristics of CAM users and non-users.

Aim 3: To assess communication of CAM usage between the patient and the patient's oncologist, primary care physician or palliative care team.

Specific Aim 1: To understand the rate and type of CAM use and non-use among chronically ill cancer patients receiving palliative care.

The study of CAM in relation to palliative care has not been extensively researched, so it is an area that needs to start gaining attention in order for researchers to begin to consider the potential benefits it could have on the QOL of dying cancer patients. It is important to understand what types of CAM these patients are seeking, as well as the reasons for use. Understanding the rate and type of CAM use among this population will provide valuable information to the field as it continues to evolve. The findings of the proposed study may also be useful for chronically ill cancer patients in the future who may consider CAM. By gaining overall knowledge of what type of CAM this population is using and how often, it will provide valuable data on what types of CAM therapies or products may or may not be beneficial to them.

Specific Aim 2: Identify overall patient characteristics of CAM users and non-users.

There is a paucity of research studies that examine patient perceptions to both CAM and CAM users. It is important to determine who is using CAM before trying to develop theories to explain the growing popularity of CAM use among cancer patients. CAM users and non-users may have significant and important differences that may impact CAM use in the population identified as particularly likely to benefit from CAM. Finding these potential differences will assist in understanding if patient's perceptions regarding CAM use might limit the uptake of potentially useful CAM therapies. In addition, the research may identify socio-economic, gender, and ethnic groups, also known as "under-represented minorities" (URM) suffering from end-stage cancer that may or may not be using CAM. This information could be valuable in order for the field to be cognizant of who may be using CAM and can provide opportunities for patient education.

Specific Aim 3: Assess communication of CAM usage between the patient and the patient's oncologist, primary care physician or palliative care team.

CAM is often used alongside conventional medical care, yet many patients don't disclose CAM use to their physicians. Serious adverse events are possible due to CAM usage, so it is vital that patient's teams are aware of exactly what they are using and how often. It is also important to understand the reasons patients do not often disclose CAM usage. The findings of the proposed study will be useful to gain that knowledge, and may assist in creating awareness to these issues. There are future opportunities to incorporate usage of CAM into patient medical questionnaires or other ways of discovering if patients are using any CAM therapies or products. Insufficient disclosure of CAM to conventional providers represents a serious challenge in medical encounter communications.

Research Strategy

A. Significance

About 1,688,780 new cancer cases are expected to be diagnosed in 2017 (American Cancer Society, 2017). In addition, 600,920 Americans are expected to die of cancer in 2017, which translates to about 1,650 people per day (American Cancer Society, 2017). Cancer continues to be the number one diagnosis for hospice patients (Running, Shreffler-Grant, & Andrews, 2008). The baby boom generation (those born between 1946-1964) has shown greater interest in CAM than previous age groups, and the post-baby boom cohort, Generation X, has been even more receptive (Lafferty, Tyree, Devlin, Andersen, & Diehr, 2008). These factors indicate a greater demand for CAM as well as an increased openness to trying it.

If effective at improving dying patients' QOL, CAM therapies may serve as useful alternatives or adjuncts in the care of terminally ill patients (Pan, et al. 2000). If CAM treatments are shown to help improve patients' QOL in the end of life setting, the integration of CAM providers and services into palliative care teams may become an important "means to a better end." Continued research will assist in integrating the best therapies of both fields to advance comfort and to ease suffering in dying cancer patients.

Researchers in Australia surveyed cancer patients at the end of their life regarding their use of complementary therapies and found that 48% of them had used some form of complementary therapy over the course of their illness (Running et al., 2008). They found that those who used CAM had decreased anxiety and pain, greater satisfaction with conventional medicine and a greater sense of control over treatment decisions as compared to those who did not use conventional medicine (Running et al., 2008). Pan et

al (2000) found that relaxation techniques such as breathing and acupuncture may improve intractable pain in dying patients. In addition, they identified that massage aids with pain relief, as well as acupuncture for cancer-related pain and dyspnea. Smith et al (2002) compared the outcomes of therapeutic massage for hospitalized cancer patients and reported a positive outcome for the study. It was also observed that therapeutic massage helped to alleviate pain, distress, as well as improving sleep patterns (Adams & Jewell, 2007). A study that looked into how cancer patients adjust to illness when treated with and without CAM in addition to conventional treatments found that patients treated by complementary therapy with conventional therapy fared better psychologically as compared to those treated with only conventional therapy (Adams & Jewell, 2007). Despite the emergent literature supporting the efficacy of specific CAM modalities for managing side effects and symptoms associated with cancer treatments, the exact nature of CAM usage in chronically ill cancer patients (e.g., the characteristics of patients who use CAM, and who don't, what types of CAM is used, and whether they inform their physician) is not well documented. Although the study of CAM use among the general population is relatively wide-spread, less attention has been given to the study of CAM use among patients receiving palliative care (Hlubocky, Ratain, Wen & Daughterty, 2006).

Research by Balneaves, Weeks, & Seely (2008) found that CAM use is higher in breast and prostate cancer populations than in populations with other cancer diagnoses. Herbals and antioxidant supplements are among the most frequently used CAM approaches with use reported to be upwards of 50% in some cancer populations (Richardson, Masse, Nanny, & Sanders, 2004). Richardson et al (2004) found that given the widespread use of these products and data suggesting possible drug-herb-vitamin interaction, concerns of the oncology community are relevant. These concerns are magnified by studies that report 19-42% of cancer patients do not disclose CAM use to

their oncologist (Richardson et al., 2004). Patients may currently practice therapeutic activities, as well as nutritional supplementation but may not know the collective practice by the name of CAM, thus not reporting usage to their physicians. The high use and limited disclosure of CAM communicates something about the needs and desires of patients in the conventional medical setting, but it also provides a “novel opportunity” for oncologists to communicate with and better understand the needs of their patients (Richardson et al., 2004). They found that “consistent with the literature, cancer patients in this study who use CAM are not uneducated or desperate but rather are more educated and in higher income brackets than nonusers.” In addition, “they want hope and many seek spiritual support and other options after diagnosis, not necessarily because these will provide a cure but in hopes of improving survival, QOL, symptoms, or side effects related to conventional cancer treatment” (Richardson et al., 2004).

CAM in oncology is a particularly sensitive issue since side effects and interactions with CAM can induce adverse events (Conrad, Muenstedt, Micke, Prott, Muecke, & Huebner, 2014). Markman (2002) found that although many CAM approaches are quite safe, both minor and major toxicities have been documented, including emesis, hypersensitivity reactions, cardiovascular events, neurologic dysfunction, hepatic and renal failure, and the development of malignant disease. As most oncologists are not informed on their patients using CAM, they will not be able to consider side effects and interactions with CAM substances as reason for adverse effects they diagnose in their patients (Conrad et al., 2014). Adverse effects may go unnoticed as in oncology most drugs have a broad spectrum of side effects on different organs (Conrad et al., 2014). Zeller, Muenstedt, Schweder, Senf, Ruckhaeberie, Serve, & Huebmer (2013) were the first to publish data estimating the number of patients in danger of interaction and loss of therapeutic efficacy caused by CAM based on an analysis of individual treatment data. At least one-third of

all patients on active cancer therapy run the risk of suffering from interactions (Zeller et al., 2013). Of those choosing CAM products, three quarters are in danger of interactions, and this number is independent of whether the patient is receiving chemotherapy, endocrine therapy or antibodies (Zeller et al., 2013).

Physicians should know what patients are using in order to accurately monitor treatment outcomes, assess signs of adverse effects or drug-herb-vitamin interactions, and guide patients in the decision making process (Richardson et al., 2004). In summary, there are potential dangers for cancer patients receiving palliative care that are using CAM. The lack of knowledge regarding the effects CAM may have on these patients can be extremely dangerous. There is very limited data available on the interaction of CAM and drugs in palliative care. These issues need to be explored, as CAM may cause adverse effects if used in conjunction with certain drugs. There is a need for quality research on the relationship between CAM use and end stage cancer patients receiving palliative care.

If the proposed study is successful, there will be an increased understanding of the frequency and distribution of CAM use and non-use among chronically ill cancer patients receiving palliative care. In addition, the field will have a better grasp of the overall characteristics of CAM users and non-users. Finally, additional data on the communication of CAM between patients' and their oncologists, primary care physicians or palliative care teams will contribute to the knowledge base. This study may provide a significant contribution to the field and change the way that CAM is viewed in more traditional medical settings. If it is proven that CAM can be beneficial to this population of patients, this information will be useful to advance knowledge of less traditional therapies that can potentially improve a dying cancer patient's QOL. Likewise, if CAM therapies for

these patients are shown to decrease QOL, that is also a significant finding with meaningful implications.

B. Innovation

There are many types of cancer treatments which vary depending on the type of cancer patients have. Most patients have a combination of treatments such as surgery with chemotherapy and/or radiation therapy. In addition, patients may have immunotherapy, targeted therapy, or hormone therapy. Palliative care is given to improve the QOL of patients with life-threatening diseases such as cancer; the goal is not to cure the disease. Little is known about the use of and attitudes toward CAM in patients receiving palliative care (Muecke, Paul, Conrad, Stoll, Muenstedt, Micke, Prott, Buentzel, & Huebner, 2015). In addition, Muecke et al (2015) found that palliative care professionals as well as patients are highly interested in CAM, yet communication on CAM in the palliative care setting is scarce. An important means to improve this communication might be improving knowledge of healthcare professionals about the evidence of CAM methods in which palliative care patients are mostly interested (Muecke et al., 2015).

This project aims to study end stage cancer patients receiving palliative care who are also using CAM. The focus on end stage cancer patients receiving palliative care is highly innovative; though the use of CAM by cancer patients has been researched a great deal, the use of CAM by patients receiving palliative care has not been examined nearly as often. The specific aims assist in locating, analyzing, evaluating and making effective use of CAM research in scientific literature, and will provide guidance for practitioners, policy makers and academic researchers.

The proposed research seeks to fill a gap by satisfying those who would like to seek alternatives from traditional medicine. The concepts and approaches of the proposed project go beyond the traditional. The project strives to prove that CAM research is necessary to assess effective ways for oncologists and palliative care teams to gather information about CAM usage by cancer patients at the end of life. It is vital to understand ways these therapies may enhance or interfere with traditional treatments.

In addition, focusing on the individual within the socio-economic and cultural context of their life (holism) also adds to the project's innovation. CAM has an innovative potential to enable and support end-stage cancer patients as they navigate their last weeks or months of life. This potential demonstrates a need to integrate CAM into mainstream healthcare systems and palliative care facilities to be accessed and used in conjunction with conventional care for people who are terminally ill.

C. Approach

The proposed categorization of CAM services, products and practices can easily be integrated with the Behavioral Model of Health Services Use (Figure 1), which has been used extensively over the past three decades to guide research examining factors that predict utilization of, and access to, conventional health services (Fouladbakhsh & Stommel, 2007). The Behavioral Model of Health Services Use is a multi-level model that incorporates both individual and contextual determinants of health services use (Babitsch, Gohl, & von Lengerke, 2012).

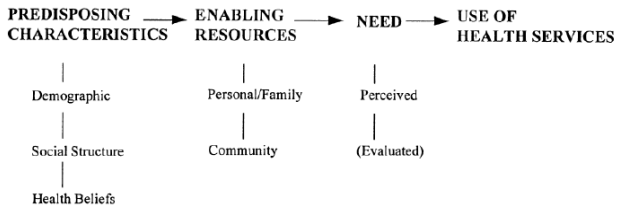

Figure 1. The Behavioral Model of Health Services Use

Adapted from: Andersen, R.M. (1995) Revisiting the Behavioral Model and Access to Medical Care: Does it Matter*? Journal of Health and Science Behavior, 36* (1), 1-10.

The application of the Behavioral Model to CAM use has been limited in the literature, and has primarily been applied to the CAM categories defined by NCCIH (Fouladbakhsh & Stommel, 2007). CAM includes various therapies such as natural products, deep breathing, yoga, Tai Chi, or Qi Gong, chiropractic or osteopathic manipulation, meditation, massage, special diets, homeopathy, progressive relaxation and guided imagery (National Center for Complementary and Integrative Health, 2017). Figure 2 presents the ten most common types of CAM among adults in 2012. Initial research has suggested that adult CAM users may have an increased use of healthy lifestyle behaviors and a strong focus on overall wellness (Karlik, Ladas, Ndao, Cheng, Bao & Kelly, 2014). Analyses of data from the National Health Interview Study (NHIS) data, 2002 and 2007, found that healthy adult CAM users were more likely to exercise and less likely to be obese than adults who did not use CAM (Karlik et al., 2014). Associations of CAM with exercise, higher vegetable intake, lower fat or lipid intake, and smoking cessation or decreased smoking have been reported in adult populations (Karlik et al., 2014).

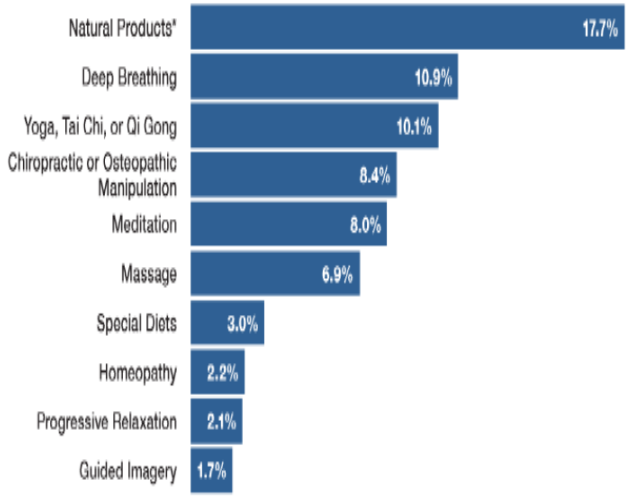

Figure 2. 10 Most Common Complementary Health Approaches Among Adults-2012

Image retrieved from: https://nccih.nih.gov/health/integrative-health#types

Most CAM approaches fall into one or two subgroups-natural products or mind and body practices (National Center for Complementary and Integrative Health 2017). Often lacking is a comparison of the concurrent use of conventional health care and CAM, and factors that influence these choices (Fouladbakhsh & Stommel, 2007). Fouladbakhsh & Stommel (2007) proposed an alternative categorization of CAM therapies to facilitate further research with the goal of promoting consistency and comparability across studies, thus the CAM Healthcare Model was developed.

The revised CAM Model (Figure 3) 1) used the major constructs of the Behavioral Model as factors influencing utilization of CAM and allows for examination of concurrent use with conventional health services, 2) added potential empirical indicators specific to CAM, and 3) modified the Behavioral model so self-directed CAM health practice and product use is included as well as provider-directed CAM use (Fouladbakhsh & Stommel, 2007).

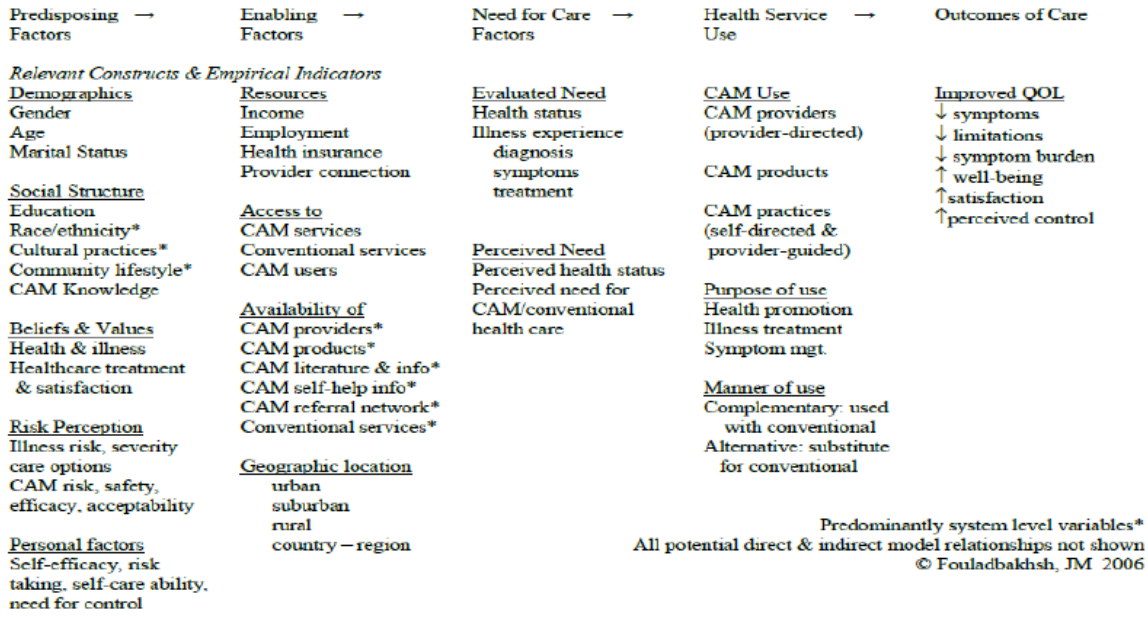

Figure 3. The CAM Healthcare Model

Adapted from: from: Fouladbakshs, J.M., & Stommel, M. (2007). Using the Behavioral Model for Complementary and Alternative Medicine: The CAM Healthcare Model. *Journal of Complementary and Alternative Medicine, 4*(1), 1-21.

The investigator has selected a descriptive cross-sectional study to assess CAM modalities that end-stage cancer patients have adopted as well as how or if they are communicating with their oncologists or palliative care team about it. The study population will be patients seen at Winship Cancer Institute who have been diagnosed with end-stage cancer of various types and are receiving or will begin to receive palliative care. As the investigator spent three years working in research at Emory's Winship Cancer Institute Clinical Trials Office (Winship CTO), she has an existing relationship with both medical and radiation oncologists on the team. In addition, relationships were made with nurse practitioners, physician assistants, nurses, and clinical research coordinators who work directly with patients. This will facilitate communication to alert the PI when there is a prospective patient who may meet inclusion criteria. If the patient expresses interest at an oncology appointment, the PI will

meet the potential participant and present the study schema, informed consent and HIPAA form. The informed consent and HIPAA form may be taken home and brought back on the next visit if the potential participant would like to take some extra time to read it or share it with family. After the informed consent and HIPAA are signed, when the participant returns to the clinic, he/she will then be given a questionnaire with demographic and CAM usage questions. Participants enrolling in the study must be (1) >18 years of age; (2) have advanced, end-stage cancer of any type, and receiving or will begin to receive palliative care at a the Emory Palliative Care Center in Atlanta, GA; (3) cancer patients with a life expectancy of at least 3 to 6 months; (4) need to be able to read and understand the study questionnaire; (5) provide written informed consent of participant; (6) need to be able to read and understand English. If a particular participant is not able to fill out the questionnaire by hand, the PI will conduct a verbal interview in order allow the individual to participate in the study. If a patient is not able to return to the clinic to participate in the study due to disease progression, he/she will be considered ineligible and excluded from the study. The expected duration of the study is 12 months; the target enrollment is 60 participants with a plan to accrue 5 participants per month. Target enrollment is based on the number of patients Winship CTO recruits monthly, which is an average of 60 patients per month. Please see sections below that provide detailed description of the plan for recruitment and retention of subjects and protection of human subjects. All research activities will be reviewed and approved the Emory University Institutional Review Board (IRB).

Emory University is the owner of all institutional data. In order to maintain HIPAA compliance, the data will be completely de-identified and therefore the need of authorization from the individual is waived (please see attached list of 18 identifiers in Appendix C). HIPAA covers a variety of issues including the Privacy Rule concerning

patients' Protected Health Information (PHI) and the Security Rule governing patients' electronic PHI (ePHI). The Emory Office of Compliance will provide consultation and training for compliance with HIPAA, and will serve as a point of contact for the research team.

Information will collected via questionnaire (see Appendix D), including the following issues. Participants will be queried about what type of CAM they use or have used since diagnosis of their illness and how often they have used it. The reasons why they chose a particular type of CAM will be explored as well. If participants do not or have never used CAM, they will be asked the reason(s) why. Though QOL itself is not the main focus of the study, it is related to CAM use. Data will be collected to find out if participants feel that their use of CAM enhanced their QOL via the Assessment of Quality of life at the End of Life (AQEL) questionnaire, which can be found in Appendix I. The AQEL was developed to assess health-related QOL in palliative care patients. A study by Henoch, Axelsson, & Bergman (2010) found evidence for the validity of the AQEL and its feasibility in patients with cancer in palliative care. It covers physical, psychological, social, existential and global aspects of QOL. Additionally, the ECOG Scale of Performance Status will be used to describe patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. A copy of the ECOG Scale of Performance Status is found in Appendix J. Participants will be asked if they believe the use of CAM is or has been effective at alleviating or controlling side-effects from different cancer therapies. The study will investigate the reasons participants started using CAM in order to identify overall characteristics of users and non-users. In addition, participants will be asked if they obtained information about the safety of CAM before they started it and what they expect to gain by using it. Participants will be asked if they have discussed their CAM use with their medical teams. The questionnaire will

include items about how their oncologist or palliative care team responded after learning they use or have used CAM while receiving treatment for cancer. If participants respond that they have not mentioned their CAM use with their medical teams, the reason(s) will be documented as well. The study will also query patients to find out if their physicians or other medical professionals involved in their care have asked them about CAM use.

The conceptual framework, design, methods and analyses for this study were chosen as the most appropriate to the aims of the study, though some challenges must be acknowledged due to the nature of this study population. In evaluating CAM therapies, study end points may be difficult to measure in a standardized way. Techniques used to measure subjective experiences like pain, fatigue, the ability to perform daily activities, and mood state have experienced significant advances, though still remain a challenge. The use of the AQEL questionnaire provides validated instrument that will assist in obtaining these measures. A potential problem area of the proposed research is that patients may not be willing or able to answer questions regarding their QOL as their death approaches. In addition, many participants may withdraw from the study due to family request, disease progression, and development of cognitive impairment.

Data Analysis

CAM use will be defined as broadly as possible and will follow the definition of the NCCIH. If patients identify their practice or use of a CAM product in association with treating their side effects from cancer and/or conventional cancer treatment, it will be listed as CAM use.

Data will be reviewed by the investigator and analyzed in detail using descriptive, open coding. These codes will then be grouped to form themes. Similarities and differences between the themes will be examined across participants and CAM therapies. The

results will be integrated into a conceptual model that will summarize participant's use of CAM into categories. Following the grounded theory approach, no prior hypotheses will be set about patients' perceptions, attitudes, beliefs, or practices. Analysis of the data will be used to report on the significance of the investigation of CAM usage of end-stage cancer patients to suggest recommendations for future CAM research.

The analysis and results of this study will be submitted to the *Journal of Complementary and Alternative Medicine,* the leading scholarly publication in the field, as well as other scholarly journals such as the *Journal of Clinical Oncology*. The criteria for evaluating CAM use by end-stage cancer patients will be disseminated to the oncology and CAM research communities in the form of a report published by the investigator. Reports will be mailed, followed by a phone or in-person conference with the investigator to discuss findings, and participants will be encouraged to comment on them. In addition, the investigator will submit the findings of the study as an abstract for the Integrative Medicine & Health Conference in 2018. In order to disseminate findings to traditional medical and clinical communities, the investigator will also submit findings to the American Society of Clinical Oncology 2018 annual meeting. Finally, the investigator will brief the American Public Health Association with recommendations for prioritizing future research. This will be done by participating in oral sessions at these meetings, which will provide an opportunity to present study findings in a formal setting.

Investigators

The investigator's experience in research since 2009 makes her well suited for the role of Principal Investigator for this study. Though this will be her first time as Principal Investigator of a study, she has worked on multiple studies which have provided the skills necessary to oversee the research. Her past experience includes working with Emory University's Clinical Neuroscience Research Unit (ECNRU) on an NIH funded project, R01MH056120, *Neural Circuits in Women with Abuse and Post-Traumatic Stress Disorde*r, in which she was a key contributor to the progress made throughout the study. Her specific role on the project was to work directly with the Principal Investigator, J. Douglas Bremner on activities such as IRB submission, data collection, adherence to applicable federal and institutional regulations, grant and budget preparation, and ensuring that the project was carried out according to the research protocol. She was successful in accruing the number of participants needed in order to achieve target accrual, and was effective in retention of those participants. The investigator's ability to motivate other staff members and continued passion for the research process proved to be invaluable to the progress made over the duration of the study. The investigator is an industrious, efficient researcher who provided professional and quality research by her attention to detail and her ability to contribute novel and innovative solutions to the research team. Dr. Bremner is a well-known Professor of Psychiatry and Radiology at Emory University and is Director of the ECNRU. He is also Director of Mental Health Research at the Atlanta Veteran's Association Medical Center in Decatur, Georgia. Dr. Bremner's work includes numerous publications such as *Posttraumatic Stress Disorder: A state-of-the science review* (2006); *Stress and brain atrophy. Current Drug Targets-Central Nervous System and Neurological Disorders* (2006); and *The enduring effects of childhood abuse and related experiences in childhood: A convergence of evidence from neurobiology and epidemiology* (2006).

In addition, the investigator also collaborated with Dr. Bremner and Dr. Viola Vaccarino, an internationally recognized expert in PTSD and cardiovascular epidemiology on another NIH funded study, *Mechanisms of Depression in Cardiovascular Disease*. Her role included recruiting, consenting, administering and implementing a mental stress challenge during a PET scan.

In 2013, the investigator joined the Winship CTO, which provided vast experience in the area of cancer research and in addition, generated her interest in cancer research. She spent two years working as a Clinical Research Coordinator (CRC), with a focus on NIH funded Cooperative Group trials. In 2014, she joined the Clinical Trials Office Quality Management Office. This role provided extensive knowledge on Investigator Initiated Clinical trials, in addition to Cooperative Group and Pharma clinical trials. Working in quality management secured a solid foundation for maintaining adequate and accurate research subject records to reflect adherence to protocol specific requirements, reporting promptly protocol deviations and adverse events to the IRB, adherence to standard operating procedures, obtaining prospectively and documenting informed consent in accordance with the current IRB-approved informed consent documents, and ensuring that the conduct of research studies adhered to Good Clinical Practice (GCP). During her years at the Winship CTO working as a CRC, the investigator achieved above and beyond the required 90% data reporting compliance and timeliness for ECOG-ACRIN, one of the largest clinical cancer research organizations in the United States, which conducts clinical trials in all types of adult cancers. This achievement was paramount for the organization, as it is vital that research coordinators and PIs participating in these trials are compliant in data reporting. In addition, the PI was able to gain strides in the reporting of long-term follow-up data. Most research protocols specify follow-up until death, which presents challenges as many patients are not easily found in order to

conduct the required long-term follow-up data forms and questionnaires. Many patients move to other cities and others may pass away. The investigator was able to increase the percentage of long-term follow-up data reporting by finding innovative techniques to track these patients or their families, allowing physicians to learn more about the long-term effects of cancer treatment and help them reduce problems related to treatment and improve patient QOL. The investigator presented on numerous occasions at in-house seminars with physicians, Winship leadership, and other medical staff. Presentations included describing new and revised standard operating procedures, discussion of upcoming new ECOG-ACRIN protocols that may have been of interest to Winship, as well as preparation for audits among other cancer-related topics.

The investigator's interest in cancer research, working with long-term follow-up data produced an interest in cancer patient's QOL. As a user of CAM in her personal life, a connection grew between CAM and the QOL of terminally ill cancer patients. The investigator sought out a PI who conducts CAM research at Winship, Rebecca Pentz, PhD. Dr. Pentz has published several papers, including *Participants' perceptions of the use of natural compounds in chemoprevention trials and the influence of complementary and alternative medicine use on chemoprevention trial accrual, retention and post-trial behaviors.* The investigator initiated several meetings with Dr. Pentz, to discuss her studies and seek guidance on conducting this type of research. Dr. Pentz became a mentor, thus inspiring the investigator to pursue CAM research of end stage cancer patients.

Institutional Environment

Emory University is one of the nation's leading research universities, building on a unique combination of campus-based resources and global partnerships. Winship Cancer Institute of Emory University has demonstrated that its outstanding research programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. As a result, Winship has earned the prestigious comprehensive cancer designation from the National Cancer Institute (NCI), placing it in the top one percent of all cancer centers in the United States and making it the first and only one in the state of Georgia. Winship's comprehensive designation was awarded after a rigorous evaluation process conducted by the NCI that included submission of a written grant and a site visit conducted by more than two dozen scientists from peer institutions. Various first authors and senior authors from Winship have published 130 studies in major medical and scientific journals as of January 2017.

All of Winship's medical professionals are affiliated with Emory Healthcare, Georgia's largest healthcare system. Their nurses, navigators, social workers, technicians and support staff are all part of the comprehensive cancer care team. The Winship CTO facilitates the conduct of high-quality clinical research involving cancer patients by providing a central comprehensive management service. Winship CTO is staffed by highly trained professional research personnel specializing in areas of clinical coordination, data management, specimen processing and regulatory management. Winship CTO provides a supportive environment to conduct clinical trials in a cost-effective and efficient manner while ensuring compliance with Winship clinical trials SOPs, Good Clinical Practice (GCP), Emory IRB, U.S. Food and Drug Administration (FDA), other regulatory agencies and external sponsors.

Winship CTO manages the overall process of subject screening, consent, registration, data entry and regulatory document submission and management for clinical research studies involving cancer patients. In addition, Winship CTO is the central clearinghouse for the initiation and registration of clinical protocols involving cancer patients.

Winship's Supportive Oncology Outpatient Clinic delivers state of the art supportive oncology with a focus on integrative medicine for patients along the spectrum of cancer care. Their team strives to reduce the physical and emotional suffering through comprehensive pain and symptom management and supportive counseling. The Supportive Oncology Outpatient Clinic delivers services that cover the full spectrum of cancer care from diagnosis to survivorship. Whatever stage of treatment patients are in, recovery or survivorship, the support care team designs an integrated program with the primary goal of improving QOL. These teams draw from wide-ranging resources in supportive oncology, integrative oncology, pain management and palliative care. This clinic helps patients to manage pain; manage symptoms such a nausea, difficulty breathing, loss of appetite, fatigue, and depression; provides counseling in making difficult medical decisions; provides emotional and spiritual support; coordinates home care referrals; assists with advanced care planning regarding future care and treatment; and provides resources, counseling, and referrals for evidence-based integrative oncology community resources.

The facilities and other resources available to the PI at Winship include everything needed to undertake and complete the proposed research project successfully. The intellectual environment is rich with other investigators who are doing work that is complementary to what is proposed in this grant application. This facility provides a scientific environment that is strongly supportive of the proposed research and,

therefore, success of the project. In addition, Emory/Winship is close in proximity to and has established long-term relationships with the Centers for Disease Control and Prevention (CDC), as well as with the American Cancer Society (ACS). This is a vibrant research community and collaborative environment to have access to.

Literature Cited

Adams, M., & Jewell, A.P. (2007). The use of complementary and alternative medicine by cancer patients. *International Seminars in Surgical Oncology,* 4:10. doi: 10.1186/1477-7800-4-10.

American Cancer Society (2016). Survivorship and Quality of Life Research. Retrieved April 5, 2016.from http://www.cancer.org/research/survivaltreatmentresearch/index

American Cancer Society (2017). Cancer facts and figures. Retrieved February 16, 2017 from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf

Arthur, K., Belliard, J.C., Hardin, S.B., Knecht, K., Chen, C.S., & Montgomery, S. (2012). Practices, attitudes, and beliefs associated with complementary and alternative medicine (CAM) use among cancer patients. *Integrative Cancer Therapies, 1,* 1(3), 232-242. doi: 10.1177/153473541I1433832.

Babitsch, B., Gohl, D., & von Lengerke, T. (2012). Re-visiting Andersen's Behavioral Model of Health Services Use: a systematic review of systematic of studies from 1998-2011. *GMS Psycho-Social Medicine, 9:* Doc11. doi: 10.3205/psm000089

Balneaves, L.G., Weeks, L., & Seely, D. (2008). Patient decision-making about complementary and alternative medicine in cancer management: context and process. *Integrative Oncology,* 15. doi: 10.1002/j.2048-7940.2010.tb00032.x

Batchelor, N.H. (2010). Palliative care or hospice care? Understanding the similarities and differences. *Rehabilitation Nursing, 35*(2), 60-64.

Chao, M.T., Wade, C., & Kronenberg, F. (2008). Disclosure of complementary and alternative medicine to conventional medical providers: variation by race/ethnicity

and type of CAM. *Journal of the National Medical Association, 100(11),* 1341-1349.

Conrad, A.C., Muenstedt, K., Micke, O., Prott, F.J., Muecke, R., & Huebner, J. (2014). Attitudes of members of the German society for palliative medicine toward complementary and alternative medicine for cancer patients. *Journal of Cancer Research in Clinical Oncology, 140,* 1229-1237. doi: 10.1007/s00432-014-1656-9.

Correa-Velez, I., Clavarino, A., Barnett, A.G., & Eastwood, A. (2003). Use of complementary and alternative medicine and quality of life: changes at the end of life. *Palliative Medicine, 17,* 695-703. doi: 10.1191/0269216303pm834oa

Davis, E.L., Oh, B., Butow, P.N., Mullan, B. A., & Clarke, S. (2012). Cancer patient disclosure and patient-doctor communication of complementary and alternative medicine use: a systematic review. *The Oncologist,* 17, 1475-1481.doi:10.1634/theoncologist.2012-0223.

Effiong, A. (2012). Palliative care for the management of chronic illness: a systematic review study protocol. *BMJ Open, 2,* 1-6. doi: 10.1136/bmjopen-2012-000899.

Elliott, J.A., Kealey, C.P., & Oliver, I.N. (2008). Using complementary and alternative medicine: the perceptions of palliative patients with cancer. *Journal of Palliative Medicine, 11(1).* doi:10.1089/jpm.2007.0102.

Ernst, E. (2001). Complementary Therapies in Palliative Cancer Care. *American Cancer Society, 91,* 2181-2185.

Ernst, E., Filshie, J., & Hardy, J. (2003). Evidence-based complementary medicine for palliative cancer care: Does it make sense? *Journal of Palliative Medicine, 17,* 704-707. doi: 10.1191/0269216303pm816oa

Eschiti, V.S. (2007). Lesson from comparison of CAM use by women with female-specific cancers to others: it's time to focus on interaction risks with CAM

therapies. *Integrative Cancer Therapies, 6(4),* 313-344. doi: 10.1177/1534735407309257.

Fouladbakhsh, J.M., Stommel, M., Given, B.A., & Given, C.W. (2005). Predictors of use of complementary and alternative therapies among patients with cancer. *Oncology Nursing Forum, 32* (6), 1115-1122. doi:10.1188/05.ONF.1115-1122.

Fouladbakhsh, J.M. & Stommel, M. (2007). Using the Behavioral Model for Complementary and Alternative Medicine: The CAM Healthcare Model. *Journal of Complementary and Integrative Medicine, 4*(1). Article 11. doi: 10.2202/1553-3840.1035.

Henoch, I., Axelsson, B., & Bergman, B. (2010). The assessment of quality of life at the end of life (AQEL) questionnaire: a brief but comprehensive instrument for use in patients with cancer in palliative care. *Quality Life Research Journal,* 19, 739-750. doi: 10.1007/s11136-010-9623-7.

Higginson, I.J. & Constantini, M. (2008). Dying with cancer, living well with advanced cancer. *European Journal of Cancer,* 44:1414-1424. doi: 10.1016/j.ejca.2008.02.024.

Higginson, I.J., & Evans, C.J. (2010). What is the evidence that palliative care teams improve outcomes for cancer patients and their families? *The Cancer Journal, 16(5),* 423-435. doi: 10.1097/PPO.0b013e3181f684e5.

Hlubocky, F.J., Ratain, M.J., Wen, M., & Daugherty, C.K. (2006). Complementary and alternative medicine among advanced cancer patients enrolled in Phase I trials: a study of prognosis, quality of life, and preferences for decision making. *Journal of Clinical Oncology,* 25 (5). doi: 10.1200/JCO.2005.03.9800.

Hospice Foundation of America (2017). What is hospice? Retrieved February 24, 2017 from https://hospicefoundation.org/End-of-Life-Support-and-Resources/Coping-with-Terminal-Illness/Hospice-Services

Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., & Forman, D. (2011). Global Cancer Statistics. *CA: A Cancer Journal for Clinicians,* 61, 69-90.

Kondo, S., Shimazu, T., Morizane, C., Hosoi, H., Okusaka, T., & Ueno, H. (2014). A retrospective analysis of factors associated with selection of end-of-life care and actual place of death for patients with cancer. *BMJ Open, 4,* doi: 10.1136/bmjopen-2013-004352. doi: 10.1136/bmjopen-2013-004352.

Lafferty, M.D., Tyree, P.T., Devlin, S.M., Andersen, M.R., & Diehr, P.K. (2008). Complementary and alternative medicine provider use and expenditures by cancer treatment phase. *The American Journal of Managed Care, 14*(5), 326-334.

Leis, A., & Millard, J. (2007). Complementary and alternative medicine (CAM) and supportive care in cancer: a synopsis of research perspectives and contributions by an interdisciplinary team. *Support Care Cancer, 15,* 900-912. doi: 10.1007/s00520-007-0303-2.

Lengacher, C.A., Bennett, M.P., Kip, K.E., Gonzalez, L., Jacobsen, P., & Cox, C.E. (2006). Relief of symptoms, side effects and psychological distress through use of complementary and alternative medicine in women with breast cancer. *Oncology Nursing Forum, 33*(1), 97-104. doi: 10.1188/06.ONF.97-104.

Markman, M. (2002). Safety issues in using complementary and alternative medicine. *Journal of Clinical Oncology*, 20, 39-41.

McCarthy, E.P., Phillips, R.S., Zhong, Z., Drews, R.E., & Lynn, J. (2000). Dying with cancer patients' function, symptoms, and care preferences as death approaches. *Journal of American Geriatric Society, 48,* 110-121. doi: 10.1111/1.1532-5415.2000.tb03120.x.

McLeroy, K.R., Bibeau, D., Steckler, A., & Glanz, K. (1988). An ecological perspective on health promotion programs. *Health Education Quarterly, 14(5)*, 351-377.

Micke, O., Bruns, F., Glatzel, M., Schonekaes, K., Micke, P., Mucke, R., & Buntzel, J. (2009). Predictive factors for the use of complementary and alternative medicine (CAM) in radiation oncology. *European Journal of Integrated Medicine, 1,* 22-30.

Molassiotis, A., Fernandez-Ortega, P., Pud, D., Ozden, G., Scott, J.A., Panteli, V., . . . Patiraki, E. (2005). Use of complementary and alternative medicine in cancer patients: a european survey. *Annals of Oncology, 16,* 655-663. doi: 10.1093/annonc/mdi110.

Muecke, R., Paul, M., Conrad, C., Stoll, C., Muedstedt, K., Micke, O., . . . Huebner, J. (2015). Complementary and alternative medicine in palliative care: a comparison of data from surveys among patients and professionals. *Integrative Care Therapies*, 1-7 doi: 10.1177/1534735415596423.

National Cancer Institute (2016). NCI Dictionary of Cancer Terms. Retrieved April 1, 2016 from http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=269448.

National Center for Complementary and Integrative Health (2012). CAM Basics. Retrieved February 12, 2015 from https://nccih.gov/sites/nccam/nih.gov/files/d347_05-25-2012.pdf.

National Center for Complementary and Integrative Health (2016). Complementary, Alternative, or Integrative health: What's in a name? Retrieved December 6, 2016 from https://nccih.nih.gov/health/integrative health.

National Center for Complementary and Integrative Health (2016). NCCIH Facts-at-a-Glance and Mission. Retrieved April 5, 2016 from https://nccih.nih.gov/about/ataglance.

National Center for Complementary and Integrative Health (2016). NCCIH's Funding Priorities and Focus. Retrieved March 26, 2016 from https://nccih.nih.gov/about.

National Institutes of Health. Annual report to the nation on the status of cancer, 1975-2011. Retrieved January 29, 2016 from http://www.cancer.gov/research/progress/annual-report-nation.

National Institutes of Health (2004). National Institutes of Health State-of-the-Science Conference Statement on Improving End-of-Life Care. Retrieved December 6, 2016 from https://consensus.nih.gov/2004/2004endoflifecaresos024html.htm.

National Palliative Care Research Center (2016). Mission. Retrieved April 5, 2016 from http://www.npcrc.org/content/37/Mission.aspx.

Pan, X.P., Morrison, R.S., Ness, J., Fugh-Berman, A., & Leipzig, R.M. (2000). Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life: A systematic review. *Journal of Pain and Symptom Management, 20(5),* 374-387. doi: 10.1016/S0885-3924(00)00190-1.

Pew Research Center (2015). Pew Research Center demographic questions web or mail mode. Retrieved May 11, 2017 from http://www.pewresearch.org/files/2015/03/Demographic-Questions-Web-and-Mail-English-3-20-2015.pdf.

Richardson, M.A., Masse, L.C., Nanny, K., & Sanders, C. (2004). Discrepant views of oncologists and cancer patients on complementary/alternative medicine. *Support Care Cancer,* 12:797-804. doi: 10.1007./s00520-004-0677-3.

Running, A., Shreffler-Grant, J., & Andrews, W. (2008). A survey of hospices use of complementary therapy. *Journal of Palliative Care*. 10(5), 304-312. doi: 10.1097/01.NJH.0000319177.25294.e.5.

Schleicher, S.M., Wood, N.M., Lee, S., & Feeley, T.W. (2016). How the affordable care act has affected cancer research in the United States: Has value for cancer patients improved? *Oncology,* 30(5), 468-471.

Smith, M.C., Kemp, J., Hemphill, L., & Vojir, C.P. (2002). Outcomes of therapeutic massage for hospitalized cancer patients. *Journal of Nursing Scholarship,* 34, 3: 257. doi: 10.1186/1477-7800-4-10.

van den Beuken-van Everdingen, M.H.J., de Rijke, J.M., Kessels, A.G., Schouten, H.C., van Kleef, M., & Patin, J. (2007). Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Annals of Oncology, 18,* 1437-1449. doi: 10.1093/annonc/mdm056.

Weeks, L., Balneaves, L.G., Paterson, C. & Verhoef, M. (2014). Decision-making about complementary and alternative medicine by cancer patients: integrative literature review. *Open Medicine, 8(2).*

World Health Organization, 2016. WHO definition of palliative care. Retrieved December 5, 2016 from http://www.who.int/cancer/palliative/definition/en/.

Yates, J.S., Mustian, K.M., Morrow, G.R., Gillies, L.J., Padmanaban, D.Atkins, . . . Colman, L.K. (2005). Prevalence of complementary and alternative medicine use in cancer patients during treatment, *Support Care Cancer, 13,* 806-811.doi: 10.1007/s00520-004-0770-7.

Zeller T, Muenstedt K, Stoll C, Schweder J, Senf B, Ruckhaeberle E, . . . Huebner J. (2013) Potential interactions of complementary and alternative medicine with cancer therapy in outpatients with gynecological cancer in a comprehensive cancer center. *Journal of Cancer Research in Clinical Oncology, 139*:357–365. doi: 10.1007/s00432-012-1336-

Appendix A

Informed Consent Form

Emory University
Consent to be a Research Subject

Title:

Principal Investigator:

Funding Source:

If you are the legal guardian of a child who is being asked to participate, the term "you" used in this consent refers to your child

Introduction
You are being asked to be in a research study. This form is designed to tell you everything you need to think about before you decide to consent (agree) to be in the study or not to be in the study. **It is entirely your choice. If you decide to take part, you can change your mind later on and withdraw from the research study. You can skip any questions that you do not wish to answer.**

Before making your decision:
- Please carefully read this form or have it read to you
- Please ask questions about anything that is not clear

You can take a copy of this consent form, to keep. Feel free to take your time thinking about whether you would like to participate. By signing this form you will not give up any legal rights.

Study Overview
The purpose of this study is to...

Procedures

Risks and Discomforts

New Information
It is possible that the researchers will learn something new during the study about the risks of being in it. If this happens, they will tell you about it. Then you can decide if you want to continue to be in this study or not. You may be asked to sign a new consent form that includes the new information if you decide to stay in the study.

Benefits
This study is not designed to benefit you directly. Y This study is designed to learn more about.... The study results may be used to help others in the future.

Compensation
You will not be offered payment for being in this study.

OR SOMETHING LIKE

You will get $____ for each completed study visit. If you do not finish the study, you will be paid for the visits you have completed. You will receive $____ total, if you complete all study visits. You may be asked to fill out a tax form, including your Social Security or Taxpayer Identification Number, in order to be reimbursed, depending on the amount and method of payment. Some payment methods involve mail coming to your house, which may be seen by others in your household. You can decline payment if you are concerned about confidentiality, or you can talk to the study team to see if there are other payment options.

Other Options Outside this Study

If you decide not to enter this study, there is care available to you outside of this research. [List the major standard care options and/or possibility of other studies] We will discuss these with you. You do not have to be in this study to be treated for [condition] OR to get [list services].

Confidentiality

Certain offices and people other than the researchers may look at study records. Government agencies and Emory employees overseeing proper study conduct may look at your study records. These offices include [the Office for Human Research Protections, the funder(s), the Emory Institutional Review Board, the Emory Office of Research Compliance]. Study funders may also look at your study records. Emory will keep any research records we create private to the extent we are required to do so by law. A study number rather than your name will be used on study records wherever possible. Your name and other facts that might point to you will not appear when we present this study or publish its results.

Study records can be opened by court order. They may also be produced in response to a subpoena or a request for production of documents.

We will do everything we can to keep others from learning about your participation in the research. To further help protect your privacy, the investigators have obtained a Confidentiality Certificate.

What the Certificate of Confidentiality protects:
The National Institutes of Health has given this study a Certificate of Confidentiality. Emory would rely on it to not give out study information that identifies you. For example, if Emory received a subpoena for study records that identify you, we would say no. The Certificate gives Emory legal backup to say no. It covers information about you that could harm your image or finances. It also covers information about you that could harm your chances at a job or getting insurance.

What the Certificate of Confidentiality does not protect:
The Certificate does not prevent you or someone other than you from making disclosing your information. The Certificate also does not prevent Emory from releasing information about you:

- Information to state public health offices about certain infectious diseases
- Information to law officials if child abuse has taken place
- Information Emory gives to prevent immediate harm to you or others
- Information Emory gives to the study sponsor as part of the research

Authorization to Use and Disclose Protected Health Information

The privacy of your health information is important to us. We call your health information that identifies you, your "protected health information" or "PHI." To protect your PHI, we will follow federal and state privacy laws, including the Health Insurance Portability and Accountability Act and regulations (HIPAA). We refer to all of these laws as the "Privacy

Rules." Here we let you know how we will use and disclose your PHI for the main study and for any optional studies in which you may choose to participate.

PHI that Will be Used/Disclosed:
The PHI that we will use or share for the main research study includes:

- Medical information about you including your medical history and present/past medications.
- Results of exams, procedures and tests you have before and during the study.
- Laboratory test results.

Purposes for Which Your PHI Will be Used/Disclosed:
We will use and share your PHI for the conduct and oversight of the research study. We will use and share your PHI to provide you with study related treatment and for payment for such treatment. We will also use and share your PHI to conduct normal business operations. We may share your PHI with other people and places that help us conduct or carry out the study, such as laboratories, data management centers, data monitors, contract research organizations, Institutional Review Boards (IRBs) and other study sites. If you leave the study, we may use your PHI to determine your health, vital status or contact information. We will use and disclose your PHI for the administration and payment of any costs relating to subject injury from the study. [ADD ANY PURPOSES FOR WHICH PHI WILL BE USED/DISCLOSED]

Use and Disclosure of Your Information That is Required by Law:
We will use and disclose your PHI when we are required to do so by law. This includes laws that require us to report child abuse or abuse of elderly or disabled adults. We will also comply with legal requests or orders that require us to disclose your PHI. These include subpoenas or court orders.

Authorization to Use PHI is Required to Participate:
By signing this form, you give us permission to use and share your PHI as described in this document. You do not have to sign this form to authorize the use and disclosure of your PHI. If you do not sign this form, then you may not participate in the research study or receive research-related treatment. You may still receive non-research related treatment.

People Who will Use/Disclose Your PHI:
The following people and groups will use and disclose your PHI in connection with the research study:

- The Principal Investigator and the research staff will use and disclose your PHI to conduct the study and give you study related treatment.
- Emory may use and disclose your PHI to get payment for study related treatment and to run normal business operations.
- The Principal Investigator and research staff will share your PHI with other people and groups to help conduct the study or to provide oversight for the study.
- _____ is the Sponsor of the study. The Sponsor may use and disclose your PHI to make sure the research is done correctly and to collect and analyze the results of the research. The Sponsor may disclose your PHI to other people and groups like study monitors to help conduct the study or to provide oversight for the study.
- The research team and the Sponsor may use and disclose your PHI, including disclosure to insurance carriers to administer payment for subject injury.
- [ADD ANY OTHERS].
- The following people and groups will use your PHI to make sure the research is done correctly and safely:
    - Emory offices that are part of the Human Research Participant Protection Program and those that are involved in study administration and billing. These include the Emory IRB, the Emory Research and Healthcare Compliance Offices, and the Emory Office for Clinical Research.

- Government agencies that regulate the research including: [Office for Human Research Protections; Food and Drug Administration; Veterans Administration].
- Public health agencies.
- Research monitors and reviewer.
- Accreditation agencies.
- [ADD ANY OTHERS].

Expiration of Your Authorization
Your PHI will be used until this research study ends.

Revoking Your Authorization
If you sign this form, at any time later you may revoke (take back) your permission to use your information. If you want to do this, you must contact the study team at:

At that point, the researchers would not collect any more of your PHI. But they may use or disclose the information you already gave them so they can follow the law, protect your safety, or make sure that the study was done properly and the data is correct. If you revoke your authorization you will not be able to stay in the main study.

Other Items You Should Know about Your Privacy
Not all people and entities are covered by the Privacy Rules. HIPAA only applies to health care providers, health care payers, and health care clearinghouses. If we disclose your information to people who are not covered by the Privacy Rules, including HIPAA, then your information won't be protected by the Privacy Rules. People who do not have to follow the Privacy rules can use or disclose your information with others without your permission if they are allowed to do so by the laws that cover them. The Sponsor, and people and companies working with the Sponsor on this study are not covered by the Privacy Rules. They will only use and disclose your information as described in this Consent and Authorization.

To maintain the integrity of this research study, you generally will not have access to your PHI related to this research until the study is complete. When the study ends, and at your request, you generally will have access to your PHI that we maintain in a designated record set. A designated record set is data that includes medical information or billing records that your health care providers use to make decisions about you. If it is necessary for your health care, your health information will be provided to your doctor.

We may remove identifying information from your PHI. Once we do this, the remaining information will not be subject to the Privacy Rules. Information without identifiers may be used or disclosed with other people or organizations for purposes besides this study.

Voluntary Participation and Withdrawal from the Study
You have the right to leave a study at any time without penalty. You may refuse to do any procedures you do not feel comfortable with, or answer any questions that you do not wish to answer.

The researchers and funder also have the right to stop your participation in this study without your consent if:

- They believe it is in your best interest;
- You were to object to any future changes that may be made in the study plan;
- [reasons specific to this study – delete if none]
- or for any other reason.

Contact Information
Contact [researcher contact person] at [tel numbers]:

Consent & Authorization

Please, print your name and sign below if you agree to be in this study. By signing this consent form, you will not give up any of your legal rights. We will give you a copy of the signed consent, to keep.

_____

Name of Subject

_____ _____

Signature of Subject Date Time

_____ _____

Signature of Person Conducting Informed Consent Discussion Date Time

_____ _____

Signature of Legally Authorized Representative Date Time

_____

Authority of Legally Authorized Representative or Relationship to Subject

Appendix B

Informed Consent Documentation

Use of Complementary Alternative Medicine (CAM) among Patients with End Stage Cancer Study

Subject ID: _____

Visit Date: _____

I have reviewed with _____the opportunity to participate in the. Use of Complementary Alternative Medicine (CAM) among Patients with End Stage Cancer Study.

I have also reviewed with the subject, in detail, the risks and benefits associated with this protocol. I have provided the subject the opportunity to ask questions and have answered questions regarding the study.

The subject verbalized understanding of the study and all study related visits and procedures. The patient signed and received a copy of the Informed Consent form on _____ _____ .

No study procedures were performed prior to obtaining informed consent.

Investigator conducting consent (print name):_____

Investigator conducting consent (signature): _____

Date: _____

Appendix C

HIPAA IDENTIFIERS

De-identified personal health information (PHI) does not fall under the HIPAA rule. Therefore you can waive authorization for its use and disclosure.

To de-identify PHI these 18 identifiers must be removed:

1. Names
2. Geographic subdivisions smaller than a state, including street address, city, county, precinct, zip code and their equivalent geocodes, except for the initial 3 digits of the zip code if, according to the current policy available from the Bureau of the Census
    - The geographic unit formed by combining all zip codes with the same 3 initial digits contains more than 20,000 people; AND
    - The initial 3 digits of the zip code for all geographic units containing 20,000 or fewer people is changed to 000.
3. Dates (except year) directly related to an individual (e.g., DOB, discharge date, date of death) and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
4. Telephone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security Number
8. Medical Record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic or code

Limited Data Sets

A “Limited Data Set” is a set of data that is not fully de-identified. You do not need authorization from the patient, nor do you need to seek a waiver, however you must have a “data use agreement” with Winship that describes the permitted uses and disclosures of the information received, and prohibits re-identifying or using this information to contact individuals. This plan must be reviewed by the IRB.

Of the 18 identifiers listed above, the following MAY be used in a Limited Data Set

1. Dates

2. Geographic information (not street address)
3. Other unique identifying numbers characteristics, or codes that are not

expressly excluded (The other 15 identifiers must be removed.)

Limited Data Sets

A "Limited Data Set" is a set of data that is not fully de-identified. You do not need authorization from the patient, nor do you need to seek a waiver, however you must have a "data use agreement" with Winship that describes the permitted uses and disclosures of the information received, and prohibits re-identifying or using this information to contact individuals. This plan must be reviewed by the IRB.

Of the 18 identifiers listed above, the following MAY be used in a Limited Data Set

4. Dates
5. Geographic information (not street address)
6. Other unique identifying numbers characteristics, or codes that are not expressly excluded (The other 15 identifiers must be removed.)

Appendix D

CAM Questionnaire

- Are you male or female or other?
  1. Male
  2. Female
  3. Other
- What is your age?
  _____ Years
- What is the highest level of school you have completed or the highest degree you have received?
  1. High school incomplete or less
  2. High school graduate or GED (includes technical/vocational training that doesn't count towards college credit)
  3. Some college (some community college, associate's degree)
  4. Four year college/bachelor's degree
  5. Some postgraduate or professional schooling, no postgraduate degree
  6. Postgraduate or professional degree, including master's, doctorate, medical or law degree
- Are you of Hispanic, Latino, or Spanish origin, such as Mexican, Puerto Rican, or Cuban?
  1. Yes
  2. No
- Which of the following describes your race? (You can select as many as apply)
  1. White
  2. Black or African-American
  3. Asian or Asian-American
  4. Native American/American Indian/Alaska Native
  5. Native Hawaiian/Other Pacific Islanders
  6. Some other race, specify: _____
- Which of the following best describes you?
  1. Married
  2. Living with a partner
  3. Divorced
  4. Separated
  5. Widowed
  6. Never been married
     (Pew Research Center, 2015)
- Please indicate all treatments that you have received.
  _____ Surgery
  _____ Chemotherapy
  _____ Hormonal therapy
  _____ Radiation
  _____ Palliative care
  _____ No treatment received
  _____ Others

  The following section primarily involves questions relating to Complementary and Alternative Medicine (CAM). CAM is defined as "a group of diverse medical and health care systems, practices, and products that are not generally

considered part of conventional medicine (National Center for Complementary and Integrative Health, 2015). CAM includes various therapies such as natural products, deep breathing, yoga, Tai Chi, or Qi Gong, chiropractic or osteopathic manipulation, meditation, massage, special diets, homeopathy, progressive relaxation and guided imagery.

- Have you ever used complementary and alternative medicine (CAM)?
  If you have not used CAM, please indicate the reason(s) why, and you may stop the questionnaire here
- When did you start CAM?
- Are you using CAM now?
- What kind of CAM do (did) you use?
  _____ Natural Products
  _____ Deep Breathing
  _____ Yoga, Tai Chi, or Qi Gong
  _____ Chiropractic or Osteopathic Manipulation
  _____ Meditation
  _____ Massage
  _____ Special Diets
  _____ Homeopathy
  _____ Progressive Relaxation
  _____ Guided Imagery

  ****These are the 10 most common CAM approaches among adults***

- Why did you start using CAM?
- Did you obtain enough information about the safety of CAM before you started it?
- What did (do) you expect by using CAM?
- Has CAM enhanced your quality of life? If so, explain.
- Has CAM been an effective aid in controlling side-effects from chemotherapy or radiation therapy?
- Did your doctor or other medical professional ask about CAM use?
- Have you discussed CAM use with your doctor?
  If 'yes', how did your doctor respond?
  If 'no', why didn't you mention it to your doctor?
- Have you ever used CAM products with anticancer drugs at the same time?

Appendix E

RFA-AT-01-002

COMPLEMENTARY/ALTERNATIVE MEDICINE (CAM) AT THE END OF LIFE FOR CANCER AND/OR HIV/AIDS

Release Date: January 16, 2001

RFA: RFA-AT-01-002

National Center for Complementary and Alternative Medicine
(http://nccam.nih.gov)
National Cancer Institute
(http://www.nci.nih.gov/)
National Institute of Allergy and Infectious Disease
(http://www.niaid.nih.gov/default.htm)
National Institute of Mental Health
(http://www.nimh.nih.gov/)
National Institute of Nursing Research
(http://www.ninr.nih.gov/)

Letter of Intent Receipt Date: February 26, 2001
Application Receipt Date: April 12, 2001

THIS RFA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS RFA

PURPOSE

The National Center for Complementary and Alternative Medicine (NCCAM) invites research grant applications to generate scientific knowledge on complementary and alternative medicine (CAM) therapies that will lead to improved care for individuals at the end of life. The intent of this initiative is to generate research that has the potential to improve the quality of life for individuals with cancer and/or HIV/AIDS who are at the end of life.

For the purposes of this request for application (RFA), CAM is defined as healthcare practices that are not an integral part of conventional medicine. Currently, CAM practices may be grouped into five major domains: (1) alternative medical systems, (2) mind-body interventions, (3) biologically-based treatments, (4) manipulative and body-based methods, and (5) energy therapies. A classification of CAM approaches may be found on the NCCAM website at: (http://nccam.nih.gov/health/whatiscam/)

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA entitled CAM Therapies at the End of Life for Cancer and/or HIV/AIDS is related to the priority areas of cancer and HIV/AIDS. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Proposed foreign grants must have the potential to advance knowledge that will benefit the United States and must propose opportunities for unusual talent resources, populations, or

environmental conditions that are not readily available in the United States. See POLICIES GOVERNING FOREIGN INSTITUTIONS AND INTERNATIONAL ORGANIZATIONS (PHS GPS 9505) for further guidelines for foreign applications (https://grants.nih.gov/grants/policy/gps/app4.htm). Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply.

MECHANISMS OF SUPPORT

This RFA will use the National Institutes of Health (NIH) R01 and NCCAM's R21 award mechanism. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this RFA may not exceed 2 years for the R21 or 4 years for the R01. This RFA is a one-time solicitation, and the anticipated award date is September, 2001.

R01 Applications. R01 awards will vary in size and duration reflecting the nature and scope of the research proposed. Future unsolicited competing continuation applications will compete with all investigator-initiated applications and be reviewed according to customary peer review.

R21 Applications. The objective of the exploratory/developmental mechanism (R21) is to encourage applications from individuals who are interested in testing innovative or conceptually creative ideas that are scientifically sound and may advance treatment options at the end of life with CAM approaches. Another objective is to encourage initial development that is necessary to provide a basis for future research project applications.

Exploratory/developmental studies are not intended for large-scale undertakings or to support or supplement ongoing research. Instead, investigators are encouraged to explore the feasibility of an innovative research question or approach that may not yet be sufficiently justified through existing research to compete as a standard research project grant (e.g., R01), and to develop a research basis for a subsequent application through other mechanisms. These grants are non-renewable, and the continuation of projects developed under the R21 program will be through the traditional unsolicited (R01) grant programs.

FUNDS AVAILABLE

The Institutes and Centers (ICs) intend to commit approximately $2.25 million (up to $1 million allocated for AIDS) for this activity in FY01 to fund new competitive grants in response to this RFA. The total cost over 4 years for this initiative is estimated at $9 million (up to $4 million allocated for AIDS). An applicant may request a project period of up to 2 years and a budget for total costs of up to $200,000 per year for the R21 or a project period of up to 4 years and a budget for total costs of up to $500,000 per year for the RO1. Because the nature and scope of the research proposed may vary, it is anticipated that the size of each award will also vary.
NINR is specifically interested in applications investigating holistic approaches that use mind/body interventions in persons with HIV/AIDS who are at the end of life. Although the financial plans of The Institutes and Centers (ICs) provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. The earliest anticipated award date will be September 1, 2001.

RESEARCH OBJECTIVES

Background:

The goal of palliative care is to provide for unmet physical, psychosocial, and spiritual needs of terminally ill patients and their families.1 The most important concerns expressed by hospice patients are the existential, spiritual, familial, physical, and emotional aspects of illness; however, these concerns are rarely the focus of care at the end of life.2 If cure is not an option, maintaining quality of life and controlling symptoms may be more appropriate than potentially distressing treatments that offer limited, temporary improvement at the cost of physical and emotional suffering. Social and cultural forces are demanding that conventional medicine offer a more holistic approach3 that conveys empathy and compassion to the sick and dying4and assists individuals sustain dignity and well-being in their final days.5 Therefore, treatment options for individual who are dying should be expanded and their emotional, social, cultural, and spiritual needs addressed.

At a 1997 meeting on symptoms of terminal illness that was sponsored by six NIH Institutes and the former Office of Alternative Medicine, palliative care was described as "…care that takes place in a context where …cure is no longer possible and disease modification provides diminishing returns."6 Symptoms are complex and include physical (fatigue and pain) and psychological distress, and subjective measures should expand beyond absence of pain or functional status to include spiritual states, peacefulness, or sense of life completion. The report from that workshop is available at http://www.ninr.nih.gov/end-of-life.htm. A subsequent Program Announcement was published in December, 1997, PA-98-019 entitled "Management of Symptoms at the End of Life" (https://grants.nih.gov/grants/guide/pa-files/PA-98-019.html). Currently, NCCAM cosponsors a Program Announcement entitled "Quality of Life for individuals at the End of Life" (https://grants.nih.gov/grants/guide/pa-files/PA-00-127.html). Many of the objectives for research from that program announcement are subsumed within this focused request for applications.

Public awareness of the limitations of end of life care and interest in improving treatment at the end of life is growing. In October, 1999, a Congressional hearing entitled "Improving Care at the End of Life with Complementary Medicine reviewed use of these modalites. In September, 2000, a television documentary entitled "On Our Own Terms- Moyers on Dying in America" and a Time cover story "Dying on our Own Terms" focused our nation on these issues. 7,8 In November, 2000, a newly formed End of Life Research Interest Group at the National Institute's of Health and the primary Institutes that comprise the group (National Institute of Nursing Research, National Cancer Institute, National Institute on Aging, and NCCAM) sponsored an open forum entitled "The End of Our Lives: Guiding the Research Agenda". The panelist and participants discussed the need for research, including exploration of ethnic disparities in end of life care. Therefore, this initiative responds to the public demand to increase programs for and research on the end-of-life care, including CAM interventions. This initiative will focus specifically on clinical studies of CAM modalities for related to cancer and/or HIV/AIDS because CAM is widely used by these patients with advanced disease and should be evaluated.

Cancer brings fear and hope9 along with 10therapeutic interventions with toxicities and sometimes limitations to control or cure disease. These factors may be driving the search by patients for alternatives.11 Although CAM is used at various stages along the disease continuum, patients with cancer report using CAM by 4 to 6 months after diagnosis when ongoing treatment outcomes may be uncertain;12,13 after a diagnosis with a poor prognosis,14 with recurrence or disease progression14-16, or at the advanced stages of disease.15-18

In studies conducted in different countries of patients with terminal cancer,

Research applications should be hypothesis-driven and include developmental pilot studies or phase I - II clinical trials aimed at expanding the therapeutic and palliative care options beyond technologic and conventional pharmacologic treatments with CAM approaches. Studies might include patients who refuse to participate in conventional Phase I trials, who are ineligible for protocols of conventional therapy, or who have no further treatment options but wish and warrant further treatment.

The applicant institution must document their experience and capacity to recruit and retain study participants; provide a description of the population currently available for the proposed protocol; describe the procedures for screening this population to identify eligible individuals, for recruiting these individuals into the trial; and describe proposed mechanisms for monitoring accrual performance and criteria for continued participation by each participating institution.

The project should provide new knowledge that can be generalized beyond the program being studied, including methodological issues that constrain research into the care of the dying. It is expected that some of this work will lead to definitive Phase III trials in which the efficacy of the CAM interventions could be proven. However, Phase III studies (defined below), surveys, health services research, epidemiologic, and basic science studies will not be accepted for this RFA.

For the purpose of this RFA, a Phase III trial is defined as a broadly based prospective investigation usually involving a substantial number of human subjects either at a single site or at multiple sites. The primary objective of such trials is to evaluate an experimental intervention in comparison with a standard or control intervention, or to compare two or more existing treatments. In Phase III trials, the primary endpoint is usually a significant change in some clinical outcome. The definition includes interventions given for disease prevention, prophylaxis, diagnosis, or therapy.

2. Linkages to the CAM community:

The applicant should document that linkages to the relevant CAM communities exist and that certified or licensed CAM practitioners will provide appropriate input for the research. Ideally, the project would include conventional and CAM practitioners working as an interdisciplinary team.

3. Monitoring Plan and Data Safety and Monitoring Board:

Research components involving Phase I and II clinical trials must include provisions for assessment of patient eligibility and status, rigorous data management, quality assurance, and auditing procedures. In addition, it is NIH policy that all clinical trials require data and safety monitoring, with the method and degree of monitoring being commensurate with the risks (NIH Policy for Data Safety and Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: https://grants.nih.gov/grants/guide/notice-files/not98-084.html).

NCCAM requires that all masked clinical trials, regardless of size, establish an independent data and safety monitoring board (DSMB). Funds should be budgeted for these activities. They should not duplicate internal review and monitoring systems that are already in place at the institution.

4. Adverse Events Reporting:

All studies should have a structured adverse event determination, monitoring

and reporting system, including standardized forms and protocols for referring and/or treating subjects experiencing adverse events. The proposed schedule for reporting adverse events to the DSMB, the NCCAM Program Officer and/or the FDA should be described.

5. Product Characterization and Dose:

Quality control of the source material for dietary supplements should be addressed and if possible, from one batch. Capsule formulation should be justified (ie, tablet, powder, soft gel capsule), and product specification for the identity, purity, strength, and dissolution of each product discussed. The batch should be well-characterized in terms of plant species identification (ie, mass spec, HPLC, or chemical fingerprinting), processing (good harvesting and manufacturing practices), and bioactivity markers. If several batches are used, procedures to minimize lot-to-lot variability should be described. The purity of plant products should be documented with testing of heavy metals, pesticide, other plant(s) contaminants. Authentication and characterization of the material will assure reproducibility for future trials.

Dosing must be carefully considered. If the dosage is not established but based on traditional use, a citation(s) from a well-recognized, accessible source to support the proposed dosage should be referenced. If the dosage deviates from traditional use, this decision should be justified. The potential for or known drug-herb-vitamin interactions should be discussed, and a thorough literature review of the traditional contraindication for the plant and/or the major components described, including the risks for vulnerable populations.

6. Investigational New Drug (or Device) applications (INDs):

It is the sole responsibility of the applicant to obtain all necessary clearances from the Food and Drug Administration as required. It is expected that applicants will have started the IND process, if required, well before submission of the application. In addition, applicants are strongly encouraged to consult their local Institutional Review Boards (IRBs) concerning IND status and the IRB approval process.

7. Institutional Support:

Applicants are encouraged to make use of ongoing research efforts where feasible. The institution should demonstrate a strong commitment to the stability and success of the project. The application must provide a plan that addresses how the institutional commitment will be established and sustained, how it will maintain accountability for promoting scientific progress, and how the research effort will be given a high priority within the institution relative to other research efforts. The institution should demonstrate commitment to the scientific value of the proposed research be in the form of commitments to recruit scientific talent, provision of discretionary resources to the applicant, assignment of clinical and research space, or other ways to be proposed by the applicant.

Applicants from institutions that have a General Clinical Research Center (GCRC) for conducting the proposed research may wish to identify these programs as a resource for use or for ongoing clinical trials. Furthermore, Hospice Programs and/or National Cancer Institute (NCI) designated Community Clinical Oncology Programs (CCOP) would be appropriate sources of cooperation for identifying and recruiting the study population as well as administering the intervention and data collection. A letter of agreement from the GCRC or CCOP Principal Investigator and/or the Hospice program director or Principal

requested for each year. This is not a Form page.

Under Personnel, list all project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of all personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Applicants are strongly encouraged to request the same number of modules for each year of funding. Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at https://grants.nih.gov/grants/funding/modular/modular.htm.

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

(b) Mailing Procedures
The RFA label available in the PHS 398 (rev. 4/98) application form must be affixed to the bottom of the face page of the application. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title, and number, must be typed on Line 2 of the face page of the application form and the YES box must be marked. The sample RFA label available at: https://grants.nih.gov/grants/funding/phs398/label-bk.pdf has been modified to allow for this change. Please note this is in pdf format.

Submit a signed, original of the application, including the Checklist, and four (4) signed photocopies of the application in one package to:

CENTER FOR SCIENTIFIC REVIEW (formerly Division of Research Grants)
NATIONAL INSTITUTES OF HEALTH

6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, send one (1) additional copy of the application to:

Chief, Review Branch
National Center for Complementary and Alternative Medicine
National Institutes of Health
6707 Democracy Boulevard, Suite 106
Bethesda, MD 20892-5475

It is important to send this copy at the same time that the original and four copies are sent to the Center for Scientific Review (CSR).

Applications must be received by April 12, 2001. If an application is received after that date, it will be returned to the applicant without review. The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed, but such applications must include an introduction addressing the previous critique.

REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCCAM. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NCCAM in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and may undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed, assigned a priority score, and receive a second level review by the NCCAM National Advisory Council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

In addition to the criteria list below, the initial review group will examine: the appropriateness of proposed project budget and duration; the adequacy of plans to include subjects of both genders, minorities (and their subgroups), and children as appropriate for the scientific goals of the research, and plans for the recruitment and retention of subjects; the provisions for the protection of human and animal subjects; and the safety of the research

research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

SCHEDULE

Letter of Intent Receipt Date:	February 26, 2001
Application Receipt Date:	April 12, 2001
Council Review:	August, 2001
Earliest Anticipated Start Date:	September, 2001

AWARD CRITERIA

Applications will compete for available funds with all other recommended applications submitted in response to this RFA. The following will be considered in making funding decisions:

o The quality of the proposed project as determined by peer review;

o Availability of funds; and

o The research priorities of the NCCAM.

INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding specific PROGRAMMATIC ISSUES to:

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Direct Inquiries regarding REVIEW ISSUES to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No.

93.213 and 93.361. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

REFERENCES

1. Seely JF, Mount BM. Palliative medicine and modern technology. Canadian Medical Association Journal. 1999;161(9):1120-1121.
2. Greisinger AJ, Lorimor RJ, Aday LA, Winn RJ, Baile WF. Terminally ill cancer patients: Their most important concerns. Cancer Practice. 1997;5(3):147-154.
3. Eskinazi DP. Factors that shape alternative medicine. (editorial). JAMA. 1998;280:1621-1623.
4. Dossey L; Reinventing Medicine. New York: Harper Collins Publisher; 1999.
5. Justice B; A Different Kind of Health: Finding Well-Being Despite Illness. Houston: Peak Press; 1998.
6. National Institutes of Health. Symptoms in Terminal Illness: A Research Workshop. Rockville, Maryland: htt://www.nih.gov/ninr/end-of-life.htm; 1997.
7. Committee on Government Reform Hearing. Improving Care at the End of Life With Complementary Medicine. Washington, DC: U.S. Government Printing Office; 1999.
8. Cloud J. Society: A kinder, gentler death. Time. 2000:61-74.
9. Hoey J. The arrogance of science and the pitfalls of hope. Canadian Medical Association Journal. 1998;159:803-804.
10. Durant JR. Alternative medicine: an attractive nuisance. Journal of Clinical Oncology. 1998;16:1-2.
11. Tannock IF, Warr DG. Unconventional therapies for cancer: a refuge from the rules of evidence? Canadian Medical Association Journal. 1998;159:801-802.
12. Risberg T, Lund E, Wist E, et al. The use of non-proven therapy among patients treated in Norwegian oncological departments: a cross-sectional national multicenter study. European Journal of Cancer. 1995;31A:1785-1789.
13. Verhoef MJ, Hagen N, Pelletier G, Forsyth P. Alternative therapy use in neurologic diseases. Neurology. 1999;52:617-622.
14. Sawyer MG, Gannoni AF, Toogood IR, Antoniou G, Rice M. The use of alternative therapies by children with cancer. Medical Journal of Australia. 1994;160:320-322.
15. Sollner W, Zingg-Schir M, Rumpold G, Fritsch P. Attitude toward alternative therapy, compliance with standard treatment, and need for emotional support in patients with melanoma. Archives of Dermatology. 1997;133:316-321.
16. Lerner IJ, Kennedy BJ. The prevalence of questionable methods of cancer treatment in the United States. CA A Cancer Journal for Clinicians. 1992;42:181-191.
17. Grothey A, Duppe J, Hasenburg A, Voigtmann R. Use of alternative medicine in oncology. Deutsche Medizinische Wochenschrift. 1998;123(31-32):923-929.

Appendix F

Instructions for Review Process

The function of this review is to impartially evaluate the merit of the enclosed application against the criteria published in the Request for Application (RFA). The review group serves to make recommendations to the student Principal Investigator, regarding the quality of the application against the criteria published in RFA-AT-01-002. These criteria are also listed on the review form you will complete.

Please provide a score for each criterion and comment on strengths and weaknesses of each. If you have any general comments, note them under “Other Relevant Comments” section on the review form. Also note whether the applicant has addressed any Additional Review Criteria (Recruitment and Retention of Subjects, Protection of Human Subjects and Inclusion of Women and Minorities) that may be included in the announcement. **Comments on Additional Review Criteria are appropriate and welcome but please do not give scores for these items.**

Appendix G

Grant Proposal Thesis

Emory Executive Masters in Public Health Program

Student Investigator: Carolina Lecours

EXTERNAL REVIEW EVALUATION SCORING SHEET

RFA-AT-01-002

Evaluation Criteria Score:

		POSSIBLE POINTS
A.	Significance	25
B.	Innovation	20
C.	Approach	30
D.	Investigators	15
E.	Environment	10
F.	Additional Review Criteria	N/A

Value totaling 100 points

FINAL SUMMARY OF CRITERION SCORES

Criteria	Score
A. Significance	
B. Innovation	
C. Approach	
D. Investigators	
E. Environment	
F. Additional Review Criteria *(Recruitment and Retention of Subjects; Protection of Human Subjects; Inclusion of Women and Minorities)*	N/A

Strengths:

Weaknesses:

Recommendations:

Recommendation: (Mark one) **Approve** _____ **Disapprove**_____

Reviewer Name_____**Date**_____

EVALUATION CRITERIA AND QUALITATIVE RATING TABLE

O=Outstanding
VG=Very Good
G=Good
F=Fair
P=Poor
U=Unsatisfactory

A. *SIGNIFICANCE (25 POINTS)*

a. This study addresses an important problem.
b. The application described how scientific knowledge will be advanced if the aims are achieved.
c. The application demonstrates the degree to which the research will improve our understanding of how we can narrow the gap between what is known and what is currently used as end of life treatments.

21-25	16-20	9-15	5-8	2-4	0-1
O	VG	G	F	P	U

Recommended Score: _____

Strengths:

Weaknesses:

Recommendations:

B. *INNOVATION (20 POINTS)*

a. The project employs novel concepts, approaches or methods.
b. The aims are original and innovative.

17-20	13-16	9-12	5-8	2-4	0-1
O	VG	G	F	P	U

Recommended Score: _____

Strengths:

Weaknesses:

Recommendations:

C. *APPROACH (30 POINTS)*

a. The conceptual framework, design, methods and analyses are adequately developed, well integrated, and appropriate to the aims of the project.
b. The applicant acknowledges potential problem areas and considers alternative tactics.
c. There is a robust plan for dissemination and implementation of findings within and outside the grantee's organization.

25-30	19-24	12-18	7-11	3-6	0-2
O	VG	G	F	P	U

D. *INVESTIGATORS (15 POINTS)*

a. The Principal Investigator is appropriately trained and well suited to carry out this work.
b. The work proposed is appropriate to the experience level of the Principal Investigator.

11-15	8-10	6-7	4-5	2-3	0-1
O	VG	G	F	P	U

Recommended Score: _____

Strengths:

Weaknesses:

Recommendations:

E. *ENVIRONMENT (10 POINTS)*

a. The scientific environment in which the work will be done contributes to the probability of success of the project.
b. The facilities are adequate to perform the proposed research, including clinical facilities and data management systems, when needed.

9-10		**7-8**	**5-6**	**3-4**	**1-2**	**0-1**
O		**VG**	**G**	**F**	**P**	**U**

Recommended Score: _____

Strengths:

Weaknesses:

Recommendations:

F. *ADDITIONAL REVIEW CRITERIA (NOT SCORED)*

a. Recruitment and Retention of Subjects
b. Protection of Human Subjects
c. Inclusion of Women and Minorities

Strengths:

Weaknesses:

Recommendations:

G. *OTHER RELEVANT COMMENTS*:

Appendix H

Conflict of Interest Form

PRE-REVIEW CERTIFICATION FORM REGARDING CONFLICT OF INTEREST, CONFIDENTIALITY, AND NON-DISCLOSURE OR REVIEWERS OF GRANT APPLICATIONS

Name [Last, First] _____

(Please print)

Other Employers (if applicable): _____

Funding Opportunity Number: **RFA-AT-01-002**

Date(s) of review:

Check only one (and provide any comments or explanations on reverse side):

☐ I have read the attached "Conflict of Interest, Confidentiality, and Non-Disclosure Rules and Information for Reviewers…" and have examined the list of applications/proposals to be reviewed, and hereby certify that, based on the information provided to me, **I do not have a conflict of interest in any of them.**

OR

☐ **For grant application reviews only:** I have read the attached "Conflict of Interest, Confidentiality, and Non-Disclosure Rules and Information for Reviewers…" and examined the list of applications to be reviewed and hereby certify that, based on the information provided, **I have a conflict of interest in the specific applications listed below** and hereby recuse myself from their review.

☐ **For contract proposal reviews only:** I have read the attached "Conflict of Interest, Confidentiality, and Non-Disclosure Rules and Information for Reviewers…" and examined the list of proposals to be reviewed and hereby certify that, based on the information provided, **I have a conflict of interest in the specific proposals listed below** and hereby recuse myself from their review. (Requires a waiver to participate in review meeting.)

I fully understand the confidential nature of the review process and agree: (1) to destroy or return all materials related to it; (2) not to discuss the materials associated with the review, my evaluation, or the review meeting with any other individual except as authorized by the Scientific Review Administrator (SRA) or other designated official; (3) not to disclose procurement information prior to the award of a contract; and (4) to refer all inquiries concerning the review to the SRA or other designated official.

Signature: _____ Date: _____

I am in conflict with the following applications/proposals (identify applications by number and identify proposals by name of offer)

CONFLICT OF INTEREST, CONFIDENTIALITY, AND NON-DISCLOSURE RULES AND INFORMATION FOR REVIEWERS OF GRANT APPLICATIONS OR R&D CONTRACT PROPOSALS

A conflict of interest in scientific peer review exists when a reviewer has an interest in an application or a proposal that is likely to bias his or her review of it. A reviewer who has a real conflict of interest with an application or proposal may not participate in its review. Appearance of a conflict of interest should be avoided whenever possible but, if it is established that there is no real conflict of interest and the government official managing the review (i.e., the Scientific Review Administrator [SRA] or equivalent) determines that the integrity of the process would not be impaired, the individual in question may participate in the review.

As it is reviewers themselves who are most familiar with their own situation, it is their personal responsibility: (1) to bring to the attention of the SRA any conflict of interest situations that my pertain, whether real or apparent, and (2) on the pre-meeting and post-meeting Conflict of Interest Certification Forms associated with this information sheet to (a) identify any applications where they have a conflict of interest and (b) certify both that they will not be and have not been involved in the review of any application where their participation constitutes a conflict of interest and that they will not disclose any matters related to the review proceedings. Federal employees should be aware that federal conflict of interest statutes carry criminal penalties for violation.

The following guidance, derived from 42 CFR Part 52h and federal conflict of interest statutes, will assist you in determining whether you are faced with a real or an apparent conflict of interest. The guidance is not all-inclusive, due to the nature of the conflict of interest subject matter. Therefore, you should consult the SRA in charge when there is any question about your participation in a review.

BASES FOR CONFLICTS OF INTEREST

There are several bases for a real conflict of interest, employment, financial benefit, personal, or professional. If applicable, any one may serve to disqualify a reviewer from participating in the review of an application proposal.

EMPLOYMENT: Officers or employees of the U.S. government may not participate in the review of a specific grant application or contract project for which they have had or are expected to have any other responsibility or involvement in their role as an officer or employee of the United States. Reviewers who are Federal employees will also have a conflict of interest with organizations for which they conduct outside activities, with organizations they serve as officers, directors, trustees, or partner and with organizations for which they are seeking employment

FINANCIAL BENEFIT: Reviewers who are Federal employees will have a conflict of interest if they have an outside activity with an organization (even if that activity is unrelated to the application), if they serve as officers, directors, trustees, or partner in an organization, if they are seeking employment with an organization, and if they (their spouse and their minor children) own, in aggregate, more than $5,000 in stocks in a publicly traded company.

RELATIVES OR ASSOCIATES: Reviewers who are Federal employees will have a conflict of interest if their spouse submits an application or proposal. The impartiality of reviewers who are Federal employees will be questioned if a member of their household (other than their spouse, a close personal relative, a colleague with whom they have a business or other contractual relationship (e.g., co-author), the employer of their spouse, parent, or dependent child, or their former non-Federal employer) submits an application or proposal within the past year.

STANDING REVIEW GROUP MEMBERSHIP: When a scientific review group meets regularly, a relationship among the individual members exists; therefore, the group as a whole may not be objective about evaluating the work of one of its members. In such a case, the member's application or proposal will be reviewed by another review group to insure that an objective review is obtained.

REQUEST FOR APPLICATIONS (RFA) OR REQUEST FOR PROPOSALS (RFP): Persons serving as the principal investigator or as one of the key personnel or as a consultant on an application submitted in response to an RFA or on a proposal in response to an RFP are generally considered to have a conflict of interest with all of the applications or proposals submitted in response to the RFA or RFP.

Conflict of Interest, Confidentiality, and Non-Disclosure Information: For Federal Employees

However, if no other reviewer is available with the expertise necessary to ensure a competent review, a waiver may be granted by the agency head or his/her designee that will permit an individual to review only those applications or proposals with which he/she has no conflict but not those with which he/she has a conflict of interest. No contract may be awarded to an individual who has served as a reviewer of the proposals submitted in response to the RFP nor to that person's spouse or any organization in which the individual has a financial interest at the time of review. No contract may be awarded to a Federal employee or to an organization owned or controlled by one of more Federal employees. Reviewers who are Federal employees may not participate in the review of a proposal in which they have a conflict of interest.

MULTI-SITE OR MULTI-COMPONENT PROJECT: Persons serving as either the principal investigator, as one of the key personnel, or as a consultant on one component of a multi-site or multi-component project have a conflict of interest with all of the applications or proposals connected with the same project; and, they may have a conflict of interest with other applications or proposals submitted by the principal investigator, other key personnel or consultants of the same project.

LONGSTANDING DISAGREEMENTS: the impartiality of Federal reviewers may be questioned where the reviewer has longstanding scientific or personal differences with an applicant.

APPEARANCE OF CONFLICT OF INTEREST: Where the impartiality of a Federal reviewer may be questioned, the government official in charge of the review will authorize the reviewer's participation and document: (1) that there is no real conflict of interest; and (2) that, at the time of the review, no practical alternative exists for obtaining the necessary scientific advice if the reviewer with the apparent conflict were to be excluded from the review.

CONFIDENTIALITY AND NON-DISCLOSURE OF MATERIALS AND PROCEEDINGS

The applications and proposals and associated materials made available to reviewers, as well as the discussions that take place during the review meetings, are strictly confidential and must not be disclosed to or discussed with anyone who has not been officially designated to participate in the review process. Disclosure of procurement information prior to the award of a contract is prohibited by the Procurement Integrity Act. Reviewers must certify that they will maintain the confidentiality of the review and not disclose this information to any other individual except as authorized by the official in charge of the review.

Appendix I

Assessment of Quality of Life at the End of Life Questionnaire (AQEL)

Nr:_____

AQEL 20 – Quality of Life form

Before you fill in this form we ask your to consider how things have been *the last week*. How have you felt? What has been bothering? What has been good?

Sometimes things are better, sometimes worse. Try to weigh together how things have been and circle the figure between 1 and 10 on the scale which best corresponds with the last week. Do not ponder too long, just circle the figure which spontaneously seems to agree to your state. Only circle one figure at each question.

Last week:

1. Approximately how many hours per day (8 a.m. to 8 p.m.) have you been lying down?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
One hour at most — 10 hours or more

2. How much help have you needed with dressing and hygiene?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
No help at all — Help with everything

3. How has your body strength been?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
None — As healthy persons of the same age

4. How much pain have you had during the last week?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Pain free — Worst possible pain

5. How much nausea have you had during the last week?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
None — Worst possible nausea

6. Have you had any trouble with your bowel movements?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
None — Worst possible

7. Have you felt breathlessness?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
None — Worst possible

8. Have you been able to do what you would like to do last week?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not at all — Yes, completely

9. How has your memory been for things happening lately?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Have had great difficulty in remembering — No problems in remembering

10. Have you felt worried?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not worried at all — Very worried

11. Have you had difficulty sleeping?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
None at al — Very difficult

12. How has your ability to concentrate been?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Very bad — Very good

13. Have you felt depressed/low in mood?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not at all — Very depressed/Low in mood

14. How much of your worries have you shared with any member of your family?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Nothing — Everything

15. Have your friends regarded you as usual?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not at all — Completely as usual

16. Has your day felt meaningful?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not at all — Completely

17. Has anything made you happy last week?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Nothing — A lot

18. How easy/hard has it been to get hold of medical staff who know you when it has been needed?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Very easy — Very hard

19. Have you received the medical care you have needed?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Not at all — Completely

20. How has your quality of life been the last week?

1 ------ 2 ------ 3 ------ 4 ------ 5 ------ 6 ------ 7 ------ 8 ------ 9 ------ 10
Very poor — Best possible

21. Has anything especially pleasant or unpleasant happened during the last week? In your family? Among your friends? With your disease? Write a couple of lines to explain

_____
_____
_____
_____
_____

AQEL Axelsson & Sjödén, 1999

References

1. WHO. (2002). National Cancer Control Programmes. Policies and behavioural guidelines. http://www.who.int/cancer/media/en/408.pdf. Accessed January 29 2009.
2. Haas, B. (1999). A multidisciplinary concept analysis of quality of life. *Western Journal of Nursing Research, 21*, 728–742.

Appendix J

ECOG Scale of Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead