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Project Title: Trajectories of Serious Illness: Patients and Caregivers

Abstract: *DESCRIPTION (provided by applicant): Dying patients confront complex and unique challenges that threaten their physical, psychosocial and spiritual integrity. Despite recent interventions to improve palliative care, little is known about how dying patients and their families progress along the continuum from serious illness to death, and the most effective strategies for integrating curative and palliative care. The purpose of this research is to follow patients with three representative advanced chronic illnesses - metastatic cancer, NYHA Class IV congestive heart failure, and chronic obstructive pulmonary disease with hypercapnea - and their caregivers prospectively in order to describe multiple dimensions of the end-of-life experience. The specific aims of this proposal are to: 1. Describe patients' trajectories of physical symptoms, functional status, emotional function, quality of life, preparation for death, spirituality, and awareness of dying. 2. Describe caregivers' trajectories of anticipatory grief, caregiver burden and awareness of dying. 3. Examine the relationships between these trajectories (e.g., patient spirituality and functional status). 4. Determine the extent to which these trajectories are modified by patient and caregiver characteristics (e.g., ethnicity, disease type, coping style) and health services utilization (e.g., emergency department visits, hospitalizations, hospice enrollment). 5. Assess, in post-death interviews, timing of caregivers' realizations that the patient was dying, and locate disease time points along pre-death patient and caregiver trajectories. Two hundred forty patients and their primary caregivers living within a circumscribed geographic region will be enrolled. Key domains as listed in the specific aims will be assessed monthly until death, or for up to two years. Longitudinal variables will be analyzed using generalized growth mixture models and linear mixed effects models, and four hypotheses tested. The results from these analyses will be used to develop clinical profiles of patient and caregiver subgroups, identifying times of heightened need and potential targets for intervention. Knowledge of domain-specific trajectory patterns, such as abrupt versus progressive functional decline, and interactions between domains, such as physical symptoms, mood and awareness of dying, will illuminate our understanding of how seriously ill patients and their caregivers experience the transition from serious illness to death, and guide efforts to improve care of the dying.*

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A. SPECIFIC AIMS

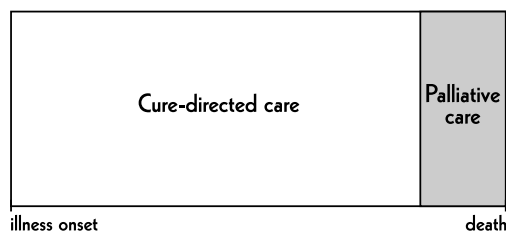
Dying patients confront complex and unique challenges that threaten their physical, psychosocial and spiritual integrity. Many patients die prolonged and painful deaths, receiving unwanted, expensive, and invasive care.¹ Patients' suffering at the end of life can be profound, yet health care providers are too frequently ill-equipped to respond to this suffering.²⁻⁷ Furthermore, underlying decision making in seriously ill patients is a culture that tends to promote two discrete options at the end of life – patients may choose to fight or choose to die.⁸

There was a full code in progress. I walked in the room and could see this person had no hair and one breast was missing. And I said, "Wait a minute, why are we flogging this person?" They said the husband wasn't ready for her to go. And I think he needed to see what "do everything you can" meant. Unfortunately, the patient was the one that suffered. – Nurse⁹

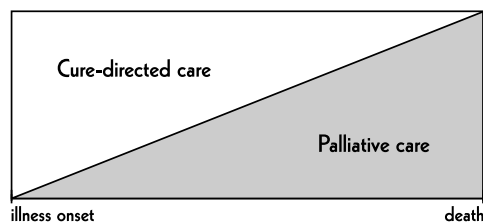
Health care providers struggle daily with vexing clinical scenarios like the one described by this nurse. In the absence of forethought and clear communication, a patient with advanced metastatic disease is brought to the emergency department for a full, yet unsuccessful, resuscitation attempt. Family members have not been properly informed about the disease course, and health care professionals provide care they perceive as futile. Unfortunately, accounts like this occur thousands of times a year, not only for cancer patients, but also among those suffering from illnesses rarely viewed as terminal, such as advanced congestive heart failure or chronic obstructive pulmonary disease.¹⁰

Patients, families, and providers experience such unsatisfying care at the end of life because the dominant model is one that does not introduce palliation until all perceived curative options are exhausted. This is reinforced by U.S. health care policy, embodied in the Medicare hospice benefit, that reflects a dichotomous approach to care. When physicians estimate that patients have six months or less to live, and patients and their families wish to receive hospice services, curative therapies cease, and palliative care begins (Model A).

Model A: Usual Care



Model B: Integrated Care



The two therapeutic approaches in Model A are discrete, and the transition from curative to palliative care usually is abrupt. This model of end-of-life care applies best to cancer diagnoses or illness trajectories marked by predictable progressive decline. Yet, even for such patients, and certainly for many others, their actual illness experience rarely includes a transition this sudden.

An alternate paradigm, more consistent with patient and family needs, is an integrated approach marked over time by reductions in cure-directed care and increases in palliative care (Model B). For example, the patient with advanced congestive heart failure may receive spiritual support early on when ACE inhibitors are introduced. The patient dying of non-small cell lung cancer may choose both the comfort of hospice while continuing chemotherapy. In such a flexible system, cure-directed care and palliation are not perceived to have competing goals. Rather, patients, families and providers are encouraged to recognize early the expected disease course, and treatments are applied based on patients' needs and individual preferences. Nurses and physicians can offer such integrated care only if provided an evidence-based understanding of patients' and families' experiences along the continuum from serious illness to death.

Despite considerable attention focused recently on the needs of dying patients, little is known about these experiences. For example, is preparation for the end of life related to awareness of dying, coping style or relationship with providers? Are treatment choices primarily the result of person factors such as emotional functioning or contextual factors such as social support or caregiver stress? Unfortunately, we have very little empirical evidence to inform our understanding of how patients and their families approach this crucial time. What we currently know is mostly from hospital-focused studies such as SUPPORT, small qualitative studies with selected populations, or retrospective proxy accounts of the dying process. Community based longitudinal studies of dying patients, identified early in their disease, and followed across multiple encounters do not exist.

The purpose of this research is to follow closely dying patients and their caregivers prospectively as they traverse the course of serious illness to death, and to describe multidimensional trajectories of experience. Key domains including functional status, mood, spirituality, awareness of dying and caregiver burden, will be assessed at regular intervals until death or for up to two years. Repeated measures of multiple domains will permit construction of empirically-derived trajectories that characterize the dying process. Knowledge of domain-specific trajectory patterns, such as abrupt versus progressive functional decline, and interactions between domains, such as physical symptoms, mood and awareness of dying, will illuminate our understanding of how seriously ill patients and their caregivers experience the transition from chronic illness to death. Trajectory patterns and slopes will uncover periods of heightened need among dying patients and their families, and identify opportunities for clinical efforts to improve care at the end of life.

Therefore, we propose *to identify patients with three representative advanced chronic illnesses – metastatic cancer, NYHA Class IV congestive heart failure, and chronic obstructive pulmonary disease with hypercapnea – and to study them through the end of their lives* with the following specific aims:

A.1 Primary Aims

- Describe patients' trajectories of physical symptoms, functional status, emotional function, quality of life, preparation for death, spirituality and awareness of dying.
- Describe caregivers' trajectories of anticipatory grief, caregiver burden and awareness of dying.
- Examine the relationships between these trajectories (e.g., patient spirituality and functional status; patient and caregiver awareness of dying).
- Determine the extent to which these trajectories are modified by patient and caregiver characteristics (e.g., gender, ethnicity, SES, disease type, coping style) and health services utilization (e.g., emergency department visits, hospitalization, hospice enrollment).

A.2 Secondary Aims

- Assess, in post-death interviews, timing of the caregivers' realizations that the patient was dying, and locate these time points along pre-death patient and caregiver trajectories.

B. BACKGROUND AND SIGNIFICANCE

B.1 The Challenge Of Dying Well In America: The Need For Palliative Care

Despite major advances in treatment, the majority of patients with cancer, advanced congestive heart failure (CHF) or chronic obstructive pulmonary disease (COPD) eventually die from their illness. In fact, between 40%-70% of these patients die within 5 years of diagnosis.¹¹⁻¹⁴ Many recent studies have documented that too many die in pain and without their needs met.^{1,2,15} As a result, public and private organizations have made improving end-of-life care a national concern. For example, the American Association of Colleges of Nursing, the American Medical Association, the American College of Physicians, the Nursing Leadership Consortium on End-of-Life Care, the National Institute of Nursing Research, the Institute of Medicine and the Veterans Health Administration have each outlined goals for improved care of the dying, and the Robert Wood Johnson Foundation has devoted millions of dollars to public education through The Last Acts initiative.^{2,16-21}

The success of these efforts is dependent upon greater and earlier access to palliative care. Palliative care is "comprehensive, interdisciplinary care, focusing primarily on promoting quality of life for patients living with a terminal illness and for their families. Such care includes assuring physical comfort, psychosocial and spiritual support, and provision of coordinated services across various sites of care."²² Awareness of the need for such care has recently brought significant changes, including the introduction of pain as a fifth vital sign in many health care facilities, and increasing availability of palliative care services through hospice and inpatient teams. *Nevertheless, many of the patients who could benefit still do not receive palliative approaches to care.*²

B.2 Who Should Receive Palliative Care?

The observation that the majority of patients with diseases such as advanced cancer, CHF or COPD eventually die from their illness implies that they all should receive palliative care. Yet, in practice, the point at which palliative care becomes the primary goal is elusive. Afraid of forgoing cure-directed treatments too early, clinicians struggle to identify the patients that are deemed "sick enough" to receive palliative care.²³ Although advance care planning, good communication and aggressive symptom control can be introduced even while a patient is still hoping for cure, optimal

palliation may require the cessation of treatments that cause disproportionate suffering. We can prognosticate mortality slightly more accurately the closer one gets to death. Yet, we can rarely say with certainty whether a particular individual is likely to live another day, week, month or three months and, therefore, cannot predict with sufficient precision whether and how much continued cure-directed treatment will increase lifespan. Palliative care tends to be introduced later, rather than earlier, reflecting a bias towards the preservation of life over the alleviation of suffering. Most efforts to improve care for patients at the end of life have tried to identify a defined population of dying patients and then to give them a new set of unique services, such as hospice. Unfortunately, this is contradictory with a philosophy that palliative and disease oriented care are complementary. ***Identification of patients as “dying,” or “not dying,” reinforces the dichotomous approach to care and abrupt transitions from illness to death.***

B.3 Dying Patients And Their Clinicians: The Struggle With Treatment Decisions

Even after palliative care has been introduced, seriously ill patients and their health care providers face a daily struggle to achieve balance between cure-directed treatments and those designed to relieve suffering. For example, they wonder whether to undergo another round of chemotherapy for metastatic malignancy, whether to attempt cardiopulmonary resuscitation for the person with class IV heart failure, or when and when not to intubate the patient with advanced COPD.

The struggle is fueled, in part, by nurses' and physicians' training that treatment directed towards cure and treatment directed towards palliation have competing goals. This implies that palliative care cannot be introduced until we have stopped curing. Given medicine's seemingly unlimited armamentarium of treatment options, attempts to cure can continue indefinitely. Furthermore, most clinicians (and patients) only know how to articulate hope in the context of curative medicine. Without a conceptual framework or language that allows hope to be part of palliation when death is expected, clinicians have trouble introducing palliative care.²⁴⁻²⁶

When the introduction to palliative care is delayed, the ultimate transition from illness to death risks being abrupt and conflict laden.^{27,28} Patients may have less time to accomplish life completion goals, and patients and family members have less opportunity to accommodate to the impending loss. This may result in more anxiety and depression at the end of life and more difficult bereavement.²⁹ ***Tensions between goals to cure and goals to palliate impede clinicians' abilities to address the full range of patients' and families' needs at the end of life.***

B.4 End-Of-Life Trajectories: Keys To Addressing Multidimensional Needs Of Patients And Families

As patients move through a serious illness and eventually die, a number of transitions occur. These may be changes in function, as they become more dependent on others for completing activities of daily living, or psychological transitions, as they come to experience the repercussions of their loss. Transitions are embedded in trajectories and give them distinctive shape and meaning.³⁰ Characterizing the progression of multiple dimensions of patients' and caregivers' experiences from serious illness to dying, be they gradual or abrupt, is the focus of this proposal.

In fact, we know very little about how patients accommodate to serious illness, how they construct meaning and hope during this time, and when they come to see themselves as dying. We do not know whether, for most patients, a single major transition point occurs, whether they follow a gradual trajectory of change, or whether an identifiable transition even exists. As described above, the dichotomous approach to curative versus palliative care presumes such a transition, or perhaps reinforces it. Do patients harbor the same biases about cure versus palliation held by health care providers? Without a good understanding of how patients move from being told they have a life threatening illness to dying, our practice in this arena is not evidence-based. Understanding more about how patients live through this experience at the end of life could provide many tangible benefits to clinicians attempting to provide nursing and medical care. Clinicians would have a better sense of periods of heightened need and what interventions would improve or undermine physical, emotional or spiritual health.

Furthermore, current health policy, as embodied in the hospice Medicare benefit, reflects the dichotomous approach to care at the end of life and results in referrals to hospice late in the course of disease.³¹ Payment of psychosocial and instrumental support services only begins when a physician declares a patient is dying, and hospice advocates argue that benefit could be maximized with earlier enrollment. ***Knowledge of how patients progress from serious illness to death, at what points they experience the most rapid declines and exhibit the greatest needs would inform clinicians and policy makers deciding when to introduce services, and how to optimally integrate care.***

B.5 Conceptualizing The End Of Life: Theories Of Death And Dying

As we seek to conceptualize the progression from serious illness to death, we draw upon decades of theoretical and empirical work. In-depth inquiry of death and dying first appeared in the medical, nursing and social sciences literature in

the 1960s. Two seminal qualitative accounts were published in the late 1960s following hospice founder Cicely Saunders' critique of modern medicine's inadequate attention to the needs of dying patients.³² She argued that the advances in biomedical technology to sustain life had outpaced medicine's ethical understanding and clinical care of patients at the end of life. Following her commentary, clinicians such as Kubler-Ross, nurse scientists such as Benoliel, and social scientists like Glaser and Strauss published rich *qualitative* descriptions of *inductively* derived theories of death and dying.³³⁻³⁵

This early research gave rise to three broad areas of theoretical emphasis regarding the end of life: stage theories, process theories and task theories. These perspectives are not mutually exclusive. Rather, they characterize an evolution in thinking about death and dying over recent decades, a chronology in which new theories have built upon the strengths of previous work and, where that work was limited, extended it's theoretical reach.

B.5.1 Stage Theories

Perhaps best known during the 1960s and still quite popular today among formal care providers, Kubler-Ross proposed five stages of psychological response to dying: denial, anger, bargaining, depression, and acceptance.³⁴ The theory was embraced by many in the medical community, perhaps because of its "single common pathway" approach, but has been criticized for an exclusive focus on defense mechanisms, orderly sequencing, and omission of the multifaceted elements of dying, particularly those of the physical and spiritual realms. More recent stage theories measure a dying person's progress by resolution of particular emotions versus movement through changes in emotion. For example, Buckman recently proposed a three-stage model based on the trajectory of dying: initial (facing the threat), chronic (being ill), and final (acceptance).³⁶ This model suggests a range of emotions possible within each stage. Despite apparent improvements over the Kubler-Ross stage theory, Buckman also espouses a mechanistic, purely psychological approach.³⁷

B.5.2 Process Theories

A second generation of theories responded to concerns surrounding a "single common pathway" approach by developing more fluid, process-oriented conceptualizations of the end of life. Emerging from a tradition of grounded theory, Glaser and Strauss became participant observers in hospital settings and described four "contexts of awareness" surrounding the dying experience: closed awareness, suspicion awareness, mutual pretense awareness, and open awareness.³³ Their conceptualization reflected an era during which patients often were not directly informed of terminal diagnoses and poor prognoses. Subsequently, they hypothesized that dying trajectories varied across individuals by two important elements, time and shape.³⁸

Building on these contextual and temporal conceptualizations, Pattison theorized a specific living-dying interval: a period of time between an individual's realization that death will occur, and the actual event of death.³⁹ This interval has three phases: acute crisis phase, chronic living-dying phase, and terminal phase during which the process of coping with grief and reaching acceptance is observed. In the 1980s, Benoliel offered a conceptual framework for nurses to use when working with families during the transition to terminal illness that builds upon knowledge about individuals undergoing change. She highlighted the concept of "safe conduct," that is, assisting dying patients and their families toward the achievement of their personal goals, as a guide for the creation of nursing services designed to offer personalized care at times of maximum family need.³⁵ More recently, Copp's "readiness to die theory" focuses on the dynamic nature of the nurse-dying patient relationship, termed "encountering," and the dying person's state of physical deterioration and personal acceptance of death.³⁷ The theory's four modes: person ready/body not ready; person ready/body ready; person not ready/body ready; and person not ready/body not ready, are hypothesized to determine, in part, the trajectory and quality of dying.

Pattison's theory of the living-dying interval and Copp's "readiness to die theory" are predominately clinical psychological models. Pattison's work stems from a psychodynamic and humanistic framework and Cobb's theory emerges from nurses' interpretations of patients' cues. However both models de-emphasize physical and social aspects of dying. Process theories work well when the trajectory of dying is fairly predictable (e.g. linear decline in many end-stage cancers) but offer less utility when prognosis is uncertain (e.g., COPD, CHF).

B.5.3 Task Theories

A third generation of research hypothesizes that the "work" of grieving is essential for adjustment to the dying process and bereavement and, as a result, identifies the concept of "tasks" at the end of life. Kalish suggested that "tasks of a dying person," such as coping and action, depend upon perceived distance from death.⁴⁰ That is, persons facing impending death respond differently compared to persons not facing imminent death. Subsequently,

Corr specified four domains in which task work occurred: physical, psychological, social, and spiritual.⁴¹ Of note, Corr's model includes all participants in the dying process: friends, family, formal providers, and the dying person.

B.5.4 Application Of Theory To The Proposed Work

No theory of dying emerges as a gold standard. However, each conceptualization shares several common features: dying is multi-dimensional, its dimensions are interdependent, and change occurs over time. Unfortunately, despite a rich theoretical tradition few of the aforementioned conceptualizations have been tested empirically. To do so requires longitudinal data, prospectively gathered, with the goal of capturing multiple dimensions of the dying process as experienced by patients and families. To date very few such studies exist.

Similarly, no single theory of death and dying guides all aspects of the proposed work. Key aspects of process and task theories make important contributions to understanding the transition from serious illness to death, and data from the proposed work will inform evaluation of existing theories. For example, task theories are particularly applicable because they address the individual concerns of dying patients, and how knowledge of these concerns moves caregivers and formal providers to improve the quality of dying. Our inclusion of caregivers' perspectives on the dying experience is central to Corr's task-based approach and also important to Copp's readiness to die theory.^{41, 42} Three theorists, Corr, Copp and Kalish urge attention to the transcendent meanings among dying persons, reflected in the proposed plan to capture trajectories of spirituality.⁴⁰⁻⁴² As another example, the longitudinal design of the proposed study draws from Glaser and Strauss' groundbreaking work on the shape, form and duration of dying, which Copp, Teno, and George recently suggested be extended to larger samples.^{38, 42-44}

[Although the preceding decades of study provide a rich theoretical context, there is to date, a relative lack of empirical evidence informing these theories. As a result, no obvious set of hypotheses exists to guide analyses. Still, end-of-life researchers face unanswered and fundamental clinical questions regarding how and when to intervene to reduce suffering and improve quality of life among dying patients and their families. These clinical uncertainties guide four hypotheses in the proposed research. These include: a) As death approaches, trajectories of functional decline will be significantly more pronounced among patients with cancer versus CHF and COPD; b) Awareness of dying and tasks of preparation for death will occur significantly earlier among patients with cancer versus patients with CHF and COPD; c) Psychosocial factors will be significantly less predictive of hospice referrals than functional status among patients in all disease groups; d) Despite changes in physical and emotional functioning, patients' trajectories of spirituality will remain relatively stable over time. Examining such hypotheses will have clear clinical significance, particularly if we learn that changes in trajectories for patients with CHF and COPD have identifiable features that would allow for earlier palliative care interventions. The formal testing of these hypotheses is described in section D.6.]

Below, we offer an overview of the seminal investigations of death and dying noting, where appropriate, the application of theory.

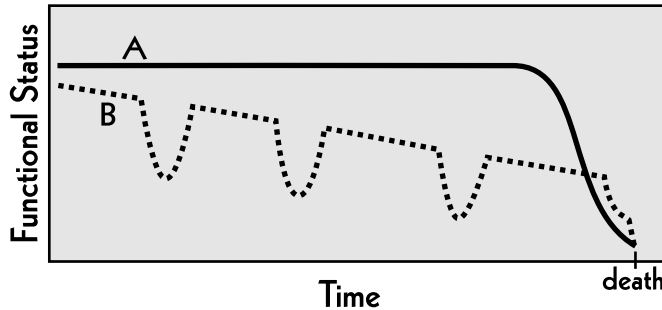
B.6 Quantitative Studies Of Death And Dying

Following the rich qualitative research of the 1960s, investigators initiated quantitative studies of patients at the end of life, most of which occurred in the nursing and medical sciences. These studies may be categorized according to three perspectives suggested by Bradley: the medical perspective, the health services perspective, and the patient perspective.⁴⁵

B.6.1 Dying: The Medical Perspective

The medical perspective defines dying as a period of time beginning with an increase in symptoms and decline in functional status. Terminal illness is defined according to physicians' prognosis of survival. The most prominent example from this perspective, and from dying research in general, was SUPPORT (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). This study followed 9,105 seriously ill hospitalized patients at five medical centers over four years, and amassed a wealth of information about their outcomes and preferences for treatment.⁴⁶ Among the primary findings were that patients often died after prolonged hospitalization in intensive care unit settings and experienced substantial pain; that models could be developed that provided better prognostic estimates than those made by physicians alone, yet still left considerable variability in their accuracy; that physicians often misunderstood patients' preferences, especially when patients did not want life-extending care; and that do-not-resuscitate orders were often written just before death.⁴⁷ SUPPORT described a landscape of hospital death in which mortality was only acknowledged or addressed in the last moments or days before death, and the transition from high technology life-extending care to palliation was late, abrupt or nonexistent.

SUPPORT also provided a window on the varying trajectories of dying for patients with cancer (see trajectory A below),⁴⁸ CHF⁴⁹ and COPD (see trajectory B).^{10, 50, 51} Patients with cancer experience significant functional decline at the end of life, patients with CHF experience good to excellent quality of life even shortly before death, and patients with COPD suffer substantial co-morbidity and symptoms in the year prior to death. One striking finding was the inability to prognosticate a patient's death very shortly before it happened. For example, on the day before death, patients with lung cancer had a median prognosis of 17% to live two months, and patients with CHF had a 60% likelihood of living 2 months on the day before death.¹⁰



trajectories. In addition, the primary focus was on patient preferences for treatment and decision-making, and SUPPORT did not offer data on awareness of dying, patient spirituality, preparation for death and similar constructs that embody the total patient experience at the end of life.

SUPPORT has proven a landmark study in the field of death and dying. However, several aspects of its design did not allow it to answer the questions asked in this proposal. SUPPORT only enrolled and followed hospitalized patients, thereby biasing its population to the sickest group of patients, enrolled late in the dying process, and requiring that the majority of data be collected from surrogates. Furthermore, patients or surrogates were interviewed only once after hospital discharge, and again after death, providing insufficient data points to describe

The trajectory data in SUPPORT was recently augmented by a mortality follow-back study by Teno.⁴³ They contacted next of kin for a systematic sample of 3,614 decedents and asked for a retrospective account of the decedents' functional status in the last year of life. They found that cancer patients experienced an increased rate of functional impairment as late as five months prior to death, while decedents from other diseases, such as COPD and CHF, had more disability for a greater period of time, but followed a more gradual slope of functional decline prior to death. The authors conclude that prospective, longitudinal, cohort studies are needed to better understand the experience of dying patients.

B.6.2 Dying: The Health Services Perspective

The most prominent example of the health services perspective may be the National Hospice Study, mandated by Congress in 1979 to examine the implications of a federally funded reimbursement program for hospice care.⁵² A total of 26 hospices were chosen to participate in a two-year demonstration project. The resulting quasi-experimental design compared quality of life and costs in hospice to conventional terminal care settings, and showed the typical hospice user as an educated, middle class male, with a caregiver, functionally impaired and diagnosed with cancer. Researchers also concluded that compared to conventional care, hospice used fewer diagnostic interventions and less aggressive therapy. By contrast, quality of life was not dissimilar between these settings, with the exception of pain and symptom management that was considered better in inpatient hospice facilities. Hospice patients were more likely to die at home and to have family satisfied members.

The National Hospice Study was a pioneering effort that provided an early understanding of hospice care. However, for several reasons, the study's health services perspective limited its generalizability. First, the median length of stay was only 35 days, so patients were identified very late in the dying trajectory. Second, quality of life measures specifically designed for the end of life were not available thereby restricting conclusions about the efficacy of hospice care.⁵³ Third, the findings pertain primarily to cancer patients. Fourth, the study is now 20 years old and both hospice and conventional care have changed significantly with the advent of managed care.

B.6.3 Dying: The Patient Perspective

A third definition of dying seeks to capture patients' subjective experiences. British researchers conducted some of the earliest and most significant work from this perspective. The National Care of the Dying Study examined records of all deaths in England over a one-year period.⁵⁴ Researchers interviewed surviving relatives to explore the causes, nature and quality of these deaths. The study was repeated in 1987 and spawned "Regional Care of the Dying" studies, one of the few examples of theory testing in a large nationally representative sample.⁵⁵

In this regional study, Seale studied a sub-set of relatives (n=3,696) of those who died in the National Care of the Dying sample.⁵⁶ Using retrospective proxy structured interviews with relatives or close friends they explored Glaser and Strauss' "awareness of dying" theory. Data suggest "open awareness" (both patient and caregiver knew

of impending death) was the most common context of awareness. “Full awareness,” marked both by knowledge of dying, and a value commitment towards openness was most associated with a diagnosis of cancer, not being mentally confused, having a respondent who knew them for some time, and higher social class. Those with full awareness were more likely to die at home. The authors hypothesized the high incidence of open awareness was associated with Anglo countries that value control over self-identity, and was an extension of a cultural value of individualism.⁵⁶ This work is one of the best unions of theory and quantitative design in end-of-life research. This large-scale, population-based study was able to describe deaths from a variety of causes and health care settings.

However, the study was limited by the use of retrospective proxy accounts of awareness of dying. In addition to recall bias, research suggests proxy respondents differ from patients in ability to rate patients’ levels of pain, quality of life and other subjective states.⁵⁷ This UK based study may have limited utility in the U.S. where both cultural values of death and dying and the organization of health care are markedly different.

Since SUPPORT, a number of U.S. investigators have conducted studies from the patient perspective. Several investigators have conducted focus groups with patients and those participating in their care to learn how they define quality at the end of life and to uncover their needs. Singer conducted focus groups with 126 patients that identified five important domains of quality end-of-life care: receiving adequate pain and symptom management, avoiding inappropriate prolongation of dying, achieving a sense of control, relieving burden, and strengthening relationships with loved ones.⁵⁸ Wenrich also used focus groups of 137 subjects to study patients and caregivers attitudes towards communication in end-of-life care.⁵⁹ Six areas were of central importance, including talking with patients in an honest and straightforward way, being willing to talk about dying, giving bad news in a sensitive way, listening to patients, encouraging questions from patients, and being sensitive to when patients are ready to talk about death. Described in more detail below, our investigative team has also used focus groups and surveys to study the attributes of quality at the end of life and to use these data to develop measurement tools.^{9, 60, 61}

Emanuel and colleagues conducted a large cross-sectional of 988 patients with terminal illness in six randomly selected US sites. They found that 50% reported moderate or severe pain, of which 29% was inadequately treated, 34.7% had substantial care needs, and that most patients relied completely on family members and friends for assistance.⁶²⁻⁶⁴ They correlated these and other findings with depressive symptoms, desire for hastened death and relationship with physicians. This large sample study explored several key domains at the end of the life, however, as a cross-sectional study provided no insights into the trajectories of these domains.

B.7 Methodological Limitations Of Current Research

The previously reviewed work, by no means exhaustive, illustrates the medical community’s intensified efforts to improve care of dying patients through empirical research. Despite significant contributions, end-of-life research remains limited methodologically, in several key ways:^{10, 43, 44} 1) Multiple definitions of dying, in the literature, confound comparisons between studies – patients in one study may be at a different stage of illness than in another study; 2) Most studies focus on a single disease – the dominant cancer model is less useful for other terminal illnesses; 3) Most research recruits patients from a single site and therefore introduces bias; 4) Sampling is usually the result of a convenience collection, rather than a randomized stratified representative design; 5) Convenience sampling limits understanding of variation between individuals in the dying process and, for example, we do not have good data on variation within ethnicities; 6) Studies have relied upon retrospective proxy accounts rather than the direct experience of patients; 7) Most research is cross-sectional - impeding understanding of the process of dying and the ways values, preferences, and behaviors vary over time.

The lack of longitudinal data may be the most important shortcoming of the current body of research in death and dying. Such data would be required to validate any of the theoretical understandings of death and dying. For example, we know little about how multiple dimensions of experience change over time and what influences change in patients’ perceptions. Many models of personal change have been primarily psychological and do not consider how social and cultural environment shapes the dying process. How are trajectories influenced by interaction with the health care system? Furthermore, how are multiple dimensions of quality of life linked and disparate?

In sum, we know little about the diverse pathways to death, how they differ between individuals, and how they change within individuals over time. We believe a dichotomous model of fighting disease or dying is inadequate, but are unsure how patients, particularly those without cancer, face the multitude of changes associated with dying. Yet, clinicians are faced with helping patients and families navigate this crucial time with little knowledge of the terrain. *An evidence-based understanding of the dying process is essential if clinicians, patients, and families are to work together effectively as partners toward a dignified final phase of patients’ lives.*

B.8 Trajectories Of Dying: What Has Been Done?

A scientific basis for understanding the dying process requires longitudinal studies that establish empirically-based trajectories of patients and families at the end of life. The concept of health trajectory creates a powerful image of physical, emotional, spiritual, and social functioning. of the individual moving through time.⁶⁵ Health trajectories reflect a blending of personal biography, physical constitution, social and cultural forces.^{30, 66-68} Their measurement requires at least three points of observation to capture nonlinear trends. To date only a few such studies exist, several capturing the patient perspective, others from a health services approach. All confront methodological challenges but contribute significantly by demonstrating the importance of documenting change over time.

From the patient perspective, studies most often examine changes in quality of life. For example, Morris studied a sample of cancer patients in 26 hospitals in the National Hospice Study and two palliative care units in Montreal.⁶⁹ Patients' quality of life was assessed from seven weeks to one week prior to death and included domains of awareness, social, emotional, and physical functioning, and pain.⁴⁵ Overall quality of life declined but a substantial minority showed quality of life stability; social functioning was the most stable. Similarly, Lawton created a longitudinal study of patients' experiences at the end of life using caregivers' retrospective accounts.⁷⁰ Three time points were recreated. Results showed that quality of life sub-domains varied in stability and slope. Overall quality of life declined linearly. However, one month before death 65% of the sample reported positive quality of life. Most recently, Bretscher conducted a longitudinal study of 16 patients admitted to the Mayo Clinic Hospice program.⁷¹ Patients were followed for the eight weeks prior to death displaying stability in overall quality of life with sub-domain variation. The physical distress scale varied most over time. All of these relied on retrospective data with the resultant shortcomings.

From a health services perspective, Lumney conducted a retrospective longitudinal study of cost of care in the last year of life for patients with severe chronic illness.⁵¹ Results showed that a cancer model of cost projections, on which hospice reimbursement is based, was not representative of patients with CHF, COPD, or chronic frailty. Similarly, Teno charted patterns of functional decline among persons with cancer and non-cancer terminal illness.⁴³ Results revealed different trajectory forms and gradients between diseases and hospice versus non-hospice use.

Each of these studies increases our understanding of the multiple pathways of dying that vary between patients according to diagnosis and within patients by multiple dimensions of quality of life. Most of these authors argue that more comprehensive large scale prospective studies of end-of-life trajectories are needed. ***The current understanding of dying patients' experiences, and their generalizability is limited by design features including single disease, single site, small sample size, and heavy reliance on retrospective proxy accounts.***

B.9 Trajectories Of Dying: What Is Needed?

To move forward in our knowledge of dying patients' experiences, we need improved data documenting patients as they progress through multiple transitions over the weeks and months that precede death. To this end, researchers must collect prospective, multi-disease, multi-site, patient- and caregiver-centered, longitudinal data on multiple dimensions of experience including physical, psychological, emotional, social, and spiritual functioning. Such research holds significant implications for theoretical advances, clinical practice, and health policy.

B.9.1 Dying Trajectories: Theoretical Significance

[The many theoretical conceptualizations of dying have contributed significantly to our understanding of what may be going on at the end of life. However, instead of advocating a single theory, and testing that framework, we wish to proceed in a way that is cognizant of the strengths and limitations of various theories, but permits us to concentrate on the experiences of patients and caregivers. The purpose of this study is to document, for the first time, the experience of patients and caregivers as they traverse the course from serious illness to death. However, once we have constructed trajectories and made comparisons of patient and caregiver groups, we intend to return to the theory base and evaluate the correspondence and divergence of findings with theory.]

The data collected in this study will inform our understanding of what theories offer the most utility and under what conditions. For example, an analysis of the extent to which emotional states, such as anxiety and depression, are associated with functional status may inform a discussion of Copp's Readiness To Die theory with its typology of person ready/body not ready, person not ready/body ready, etc. Furthermore, patient and family reports of preparing wills and making funeral arrangements, may be considered "tasks" of dying.⁶⁰ One may ask, to what extent these are associated with different diagnoses and illness courses? Are cancer patients, with a more predictable disease pattern, more likely to engage in such tasks than patients with advanced congestive heart failure who experiences more gradual decline marked by acute exacerbations followed by relatively quiescent periods?

[B.9.2 Dying Trajectories: Clinical Significance

Nurses and physicians require evidence-based knowledge of the dynamic nature of patient and caregiver experiences at the end of life. Trajectory data may show periods in the course of illness of heightened need, resilience, crisis, or increased receptivity. For example, if the data suggest predictable patterns in patient or caregiver awareness of prognosis, interventions may be more appropriately tailored and timed within the illness course. Moreover, such data will inform the nature and timing interventions from all members of the interdisciplinary palliative care team including chaplains, social workers, nurses and physicians. Perhaps most importantly, this research will provide the insights necessary to facilitate earlier and fuller integration of curative and palliative therapies.

B.9.3 Dying Trajectories: Health Policy Significance

Finally, knowledge of trajectories of function based on diagnosis category is crucial to an empirically based discussion regarding funding for end of life care. The six month rule for hospice reimbursement is a legislative artifact. Trajectory data would provide an evidence-based understanding of when hospice services would most appropriately meet patients' needs. Furthermore, the Medicare Hospice Benefit was based on a cancer model of functioning; results of this study will expand this model to include other serious life-limiting illnesses.]

B.9.4 Dying Trajectories: Implications For Understanding Diversity At The End Of Life

Research has shown that end-of-life experiences vary by ethnicity.⁷²⁻⁷⁷ For example, African-Americans are less likely to discuss advance care planning, more likely to desire and receive aggressive life-sustaining treatments, less likely to use hospice care, and may suffer from higher levels of pain at the end of life.^{75, 76, 78} What is less well known are the origins of these differences, and the contexts from which these differences arise. What is the relationship between ethnicity and awareness of dying, spiritual issues, trust of providers and location of care? The examination of trajectories by ethnicity will begin to answer some of these questions apparent in clinical settings. Fortunately, because of our location in Durham, North Carolina, our study population will be naturally enriched with at least 30% African-Americans.

C. PRELIMINARY STUDIES

C.1 An Experienced And Diverse Research Team

Our interdisciplinary research team of clinicians, social scientists, and health services researchers has produced a collective body of research that provides a broad foundation for the proposed work. Substantive areas of expertise include prognostication, provider-patient relationships, defining attributes quality of dying, measurement of quality of life at the end of life, caregiver well-being and burden, epidemiology of aging, conflict, location of death, and spirituality. Methodologically, the team brings extensive experience with large-scale population based studies, longitudinal, multi-disciplinary, patient and family-centered research, and qualitative and quantitative techniques. ***Members of this team have worked together for several years*** on a variety of projects to improve care at the end of life, and is skilled in each of the key components of the proposed research: 1) recruitment and retention of patients over time; 2) recruitment and retention of caregivers; 3) measuring quality of life at the end of life; and 4) conducting longitudinal analyses.

James A. Tulsky, MD is Associate Professor of Medicine, Associate Director of the Institute on Care at the End of Life, and Director of the Program on the Medical Encounter and Palliative Care at Duke University and the Durham VA Medical Center. He has supervised large, funded research projects on a range of issues from quality of dying to the quality of communication at the end-of-life. He is also a practicing internist and palliative care physician who is an authority on communications teaching interventions for physicians. Dr. Tulsky was a Robert Wood Johnson Clinical Scholar at the University of California, San Francisco (UCSF), where he received training in clinical epidemiology and medical ethics. He was awarded the 1994 Sergei S. Zlinkoff Junior Faculty Award for outstanding scientific presentation by the Society of General Internal Medicine. Dr. Tulsky is a member of the editorial board of the Journal of Palliative Medicine, the National Coordinating Committee of the VA Hospice and Palliative Care Initiative, and was a member of the American College of Physicians' Task Force on End-of-Life Care. Dr. Tulsky was a Project on Death in America Faculty Scholar, a Robert Wood Johnson Generalist Physician Faculty Scholar, and the recipient of a VA Health Services Research Career Development Award. He was recently awarded the Presidential Early Career Award for Scientists and Engineers (PECASE) by the White House Office on Science and Technology Policy.

Karen E. Steinhauser, PhD is Assistant Research Professor of Medicine, and Senior Fellow, Center for the Study of Aging and Human Development at Duke University, and Health Scientist at the Center for Health Services Research in

Primary Care, VA Medical Center, Durham. Dr. Steinhauser received her doctoral training in sociology at Duke where she specialized in the study of medical sociology and aging. Her dissertation examined the organizational evolution of hospice care. Particular attention centered on the influence of public funding, via Medicare, on a private sector volunteer organization. She completed post-doctoral training in Health Services Research at the Durham VA Medical Center, focusing her research on identifying what patients, families and health care providers value at the end of life. The qualitative and quantitative results of that work served as the foundation for a clinical instrument to assess the quality of dying. Dr. Steinhauser is Co-Principal Investigator of the study to validate that instrument. She is also Principal Investigator of a study to develop a twenty-year longitudinal database of hospice care in North Carolina.

Elizabeth C. Clipp, RN, PhD is Professor of Nursing and Associate Research Professor of Medicine at Duke University. She also is Senior Fellow in the Duke Aging Center, Division Leader for Psychosocial Oncology in the Duke Comprehensive Cancer Center, Core Faculty at the Duke Institute on Care at the End of Life, and Associate Director for Research at the Geriatric Research Education and Clinical Center (GRECC) at the Durham VA Medical Center. She received undergraduate and master's degrees in Nursing from the University of Maryland, a PhD in Developmental Psychology from Cornell University, and post-doctoral training in Aging Research at Duke. Dr. Clipp's research contributions fall into three primary areas: a) trajectories of health and illness across the life course, b) informal caregiving in chronic disease contexts, especially cancer and dementia, and c) quality of life at the end of life. Since 1998 she has lead the *National Longitudinal Caregiving Study (NLCS)* which examines informal cost and quality of life effects among a national sample of 2300 caregivers to older individuals with chronic illness. Dr. Clipp also is Principal Investigator of the newly funded NIH/NINR Nursing Research Exploratory Center supporting nurse-initiated studies focused on the theme of "*Trajectories of Aging and Care*" (TRAC Center). Dr. Clipp is a Fellow of the Gerontological Society of America (GSA) and Nurse Scientist with the Oncology Nursing Committee (ONC), Cancer and Leukemia Group B (CALGB).

Judith C. Hays, RN, PhD is Associate Research Professor of Geriatric Psychiatry and Gerontological Nursing, Senior Fellow in the Center for the Study of Aging and Human Development, and Center Scientist in the Templeton Foundation for the Study of Religion and Health at Duke University. She received an undergraduate degree in Nursing from Emory University, a Master's degree in Community Health Nursing at Yale School of Nursing, and a PhD in Chronic Disease Epidemiology and Aging at the Yale School of Medicine. In 1992 she completed a post-doctoral fellowship in Aging Research at Duke. Dr. Hays has published extensively over the past 15 years on the psychosocial care of the dying patient and family, on the natural history of grief, and on affective disorders, living arrangements, and religion in late life. Dr. Hays brings to this project expertise in longitudinal epidemiological methods and analysis, having taught research in nursing, medical and graduate schools over the past decade, and has co-authored a textbook on research methods in psychiatry. She is currently completing a Mentored Research Development Award (K01) in longitudinal methodology and changes in living arrangements, and also brings broad experience of data management of population-based studies and of scale development.

Maren Olsen, PhD is a Biostatistician in the Center for Health Services Research in Primary Care, VA Medical Center, Durham and an Assistant Research Professor in the Department of Biostatistics and Bioinformatics at Duke University. Dr. Olsen received an undergraduate degree in Mathematical Sciences from Johns Hopkins University and a PhD in Statistics from Pennsylvania State University in 1999. Her primary area of expertise is the use of random-effects models in the analysis of longitudinal data. Her dissertation research focused on the development of a two-part random-effects model for semi-continuous longitudinal data. In this work, she developed stand-alone software which implements a maximum-likelihood procedure to estimate parameters and standard errors of this two-part model. Dr. Olsen also has considerable expertise in principled methods for incomplete, multivariate data. She is currently a co-investigator on several VA HSR&D investigations, including a longitudinal study with Dr. Tulsky (PI) that examines the degree to which interactive voice response improves patient-centered outcomes.

Robert M. Arnold, MD is the Leo H. Crip Chair in Patient Care, Professor of Medicine and Chief, Section of Palliative Care and Medical Ethics at the University of Pittsburgh Medical Center. Dr. Arnold has conducted research on physician-patient communication at the end of life, and developed courses to train physicians in these skills, with a particular emphasis on the affective experience of the physician. He was a Project of Death in America Faculty Scholar, is a past President of the American Society of Bioethics and Humanities, and was Program Director of the 2000 Annual Meeting of the American Academy of Hospice and Palliative Medicine.

Nicholas A. Christakis, MD, PhD, MPH, a consultant investigator on this project, is a Professor of Medical Sociology in the Department of Health Care Policy at Harvard Medical School and an attending physician in the Palliative Medicine service at Massachusetts General Hospital. He is one of very few Ph.D.-level physician-sociologists in the country, and is nationally recognized for work on end-of-life care. His background includes training in advanced

quantitative and epidemiological methods and over ten years of experience working with raw Medicare claims data. He has also conducted *de novo* surveys, case-control studies, and cohort studies pertaining to end-of-life care, particularly on the topic of prognostication, and is the author of a well-known book on the role of prognosis in medicine. He is a member of the SNEM-3 Study Section of NIA.

These investigators have been working together for many years and have a proven record of close and effective collaboration. Together and separately, members of the team have conducted the following studies that create the background for the current proposal.

C.2 Conflict During Withdrawal Of Life Sustaining Treatment

Dr. Tulsky and colleagues identified 102 consecutive adult patients in six Duke intensive care units who were being considered for withdrawal or withholding of life-sustaining treatments, to determine the incidence and nature of interpersonal conflicts that arise in this setting.^{27, 28} Immediately after death or transfer from the ICU, they conducted semi-structured interviews with two nurses and two physicians for each patient (n=406), and asked about disagreements during life-sustaining treatment decision-making. Eighteen months later, they also interviewed the deceased patients' family members. At least one health care provider in 78% of cases described a situation coded as conflict. Non-white ethnicity and length of stay predicted disagreement ($p=0.004$ and $p<0.001$, respectively). Conflict occurred between the staff and family members in 48% of the cases, among staff members in 48% and among family members in 24%. 46% of family members perceived conflict during their loved one's ICU stay; the vast majority was between themselves and the medical staff and involved communication. ***This study demonstrated that conflict is more prevalent in the setting of intensive care decision-making than previously demonstrated, and the difficulties experienced by families and professional caregivers when the goals of care change abruptly at the end of an illness and just prior to death.***

C.3 Provider-Patient Communication At The End Of Life

Dr. Tulsky and colleagues have extensively studied provider-patient communication regarding decision-making at the end of life. They have analyzed audio-taped encounters using quantitative and qualitative methods, and have examined patient and provider satisfaction with the discussions. First, they audio-taped conversations between thirty one medical residents and hospitalized patients about the decision to withhold cardiopulmonary resuscitation (CPR),⁷⁹ and found that physicians often did not provide sufficient information to allow patients to make an informed decision. The potential outcomes of treatment were rarely discussed and quantitative probabilities of survival were never shared with patients. Only 10% of physicians in this study asked patients about their values or goals for care. A related survey of 115 resident physicians identified inadequate provider education as a contributing factor. 33% had never been observed by a more experienced physician while discussing do-not-resuscitate decisions. Because they rarely observed others or were themselves observed, they had little opportunity to learn differently.

Drs. Tulsky and Arnold collaborated on a study of fifty-six audio-taped discussions about advance directives between attending physicians and their outpatients at five sites, in two cities.^{80, 81} They found that physicians focused advance directive discussions on scenarios that were of only limited value to future decision-making. In post-visit surveys, many patients demonstrated poor understanding of key concepts relevant to decisions about life-sustaining treatments.⁸¹ Even after discussing advance directives, physicians' predictions of patients' wishes for treatment were no better than chance. They followed this study by observing discussions about advance directives conducted by physicians nationally recognized for their expertise in medical ethics and communication.⁸² Experts were less verbally dominant, gave less information and asked fewer questions about biomedical issues than non-expert physicians, but tended toward more psychosocial discussion and engaged in more partnership building with their patients. Thus, these experts employed specific communication skills that could be identified and taught to all clinicians.

They have responded to these findings by designing interventions to improve communication between providers and patients at the end of life. Dr. Tulsky and Dr. Arnold currently are funded by a National Cancer Institute R25 grant to train oncology fellows in communication at the end of life, and to evaluate the intervention in a pre-post design. ***This body of work has recognized significant shortcomings in provider-patient communication at the end of life, and identified a key factor that impairs the ability of patients to accommodate to serious illness and face death.***

C.4 Prognosis

Christakis and colleagues published a study of all 184,843 Medicare patients newly admitted to hospices in 1993, a cohort representing 10-15% of all elderly decedents in the U.S.⁸³ They examined this cohort, identified by linking Medicare claims, Census, and Area Resource File data at the individual level, to identify socioeconomic and market factors associated with the timing of hospice use. They reported median hospice stay among Medicare recipients was 36

days, with 15.6% dying within 7 days.³¹ He has also authored a book based on his own extensive research on the attitudes of physicians toward prognosis and a thorough review of the relevant medical and sociological literature.⁸⁴ The book considers the relative absence of prognosis from modern medical thought. Although implicit in nearly all diagnostic and therapeutic decisions, prognosis per se is neglected, avoided, and even despised. The book examines data showing physicians convey an optimistic bias when discussing prognoses with each other and when sharing them with patients and families. They are likely to overestimate survival and future quality of life. *The failure to formulate or communicate a prognosis, or mistakes in either, can affect the care that patients get near the end of life in numerous ways.*

C.5 Location Of Death

A series of case-control studies conducted by Dr. Hays described where hospice patients were cared for during the last six weeks of their lives and examined antecedents of place of death.^{85, 86} She found that during the last days of life, patients who used both home hospice care and inpatient hospice care had more pain, nausea, vomiting and other symptoms than patients who used only home hospice care. Further, family caregivers of patients who used both sites of care reported more anxiety and fatigue than caregivers of patients who stayed at home. Thus, unstable clinical and psychosocial factors were associated with relocation in the days prior to death. A separate cross-sectional prevalence study examined cause of place of death among 219 subjects in a North Carolina continuing-care retirement community (CCRC) characterized by a low rate of hospital deaths.⁸⁷ Death-related planning played a part in the decision of 40% of independent-living residents to move to the CCRC. A majority of residents reported a clear preference for place of death, and a majority of these preferred to die on the CCRC campus. *These studies demonstrate the relationship between clinical and psychosocial factors and practical concerns such as housing at the end of life.*

C.6 Spiritual History

Studies of religion and spirituality have been limited by lack of an historical perspective on personal behaviors and feelings. Hays conducted this study to develop an instrument to measure spiritual life histories.⁸⁸ In Phase 1, semi-structured interview probes were based on the extant literature of three disciplines: (1) socio-epidemiologic studies of religiousness, (2) studies of 'turnings' or significant periods of loss or growth of faith over the life span, and (3) psychiatric studies of life events and difficulties, their stimuli, severity, duration, effects, and implications. In Phase 2, closed-ended items were coded, and open-ended comments were grouped into conceptual categories, scaled, and factor analyzed in an independent sub-sample of 150 elders. Principal components analysis suggested four factors with favorable psychometrics: God Helped, Lifetime Religious Social Support, Family History of Religiousness, Cost of Religiousness. Health-impaired subjects reported a history of seeking/receiving divine aid (God Helped). Regardless of current attendance, subjects who reported higher Lifetime Religious Social Support received more instrumental social support. Healthy behaviors were associated with both God Helped and Lifetime Religious Social Support. Cost of Religiousness predicted depressive symptoms and impaired social support. Family History of Religiousness was unrelated to late life health. *This instrument will be used to assess the baseline spiritual histories of the study cohort.*

C.7 Quality Of Life At The End Of Life

Drs. Tulsky, Steinhauser, Clipp, and Christakis have collaborated over the last four years on research to identify what patients, family members and health care providers consider important at the end of life, with the ultimate goal of creating a measure specifically designed to assess the quality of life of patients at the end of life. In the initial phase of study, they convened focus groups and conducted in-depth interviews with participants in end of life care (physicians, nurses, social workers, chaplains, hospice volunteers, patients and recently bereaved family members) and asked them to define the attributes of the quality of dying.⁶⁰ Participants identified over 70 attributes of a "good death" which were collapsed into six broad themes: pain and symptom management, clear decision making, preparation for death, completion, contributing to others and affirmation of the whole person. In addition to these domains, participants also emphasized the very individual nature of definitions of a "good death." The results suggested that although biomedical care is critical, it is only a point of departure to total end of life care that includes psychosocial and spiritual concerns.

Attributes generated qualitatively were then translated into survey items and distributed to nationally representative samples of patients, families, physicians, and other health care providers.⁶¹ Sample participants (n=1,462; 78% response) rated the importance of 44 attributes of quality of dying on a 5-point scale. Twenty-six items were rated as important across all four groups, including pain and symptom management, preparation for death, achieving a sense of completion and being treated as a whole person. Eight items received strong importance ratings from patients but less from physicians (p<.001), including being mentally aware, having funeral arrangements planned, not being a burden, helping others and coming to peace with God. Ten items had broad variation within as well as among the four groups, including

decisions about life-sustaining treatment, dying at home and talking about the meaning of death. Participants ranked freedom from pain most important, and dying at home least important among nine major attributes.

These results were used to develop a new multi-dimensional instrument to assess the quality of life at the end of life (QUAL-E). The first stage of validation was just completed with 200 ambulatory patients with advanced serious illness (85% response rate), including cancer, CHF, and COPD. The initial instrument contained fifty-four items measured on a 5-point scale covering six domains. We assessed psychometric properties using factor analysis. Factor analysis yielded a final instrument with 25 items in five distinct domains (overall Cronbach alpha = 0.83). The first factor (6 items; alpha=0.84) measured a sense of completion, particularly through contributions to others. The second factor (7 items; alpha=0.77) measured relationships with the health care system. The third factor (6 items; alpha=0.77) measured anticipatory concerns. The fourth factor (4 items; alpha=0.77) measured symptom severity, and the final factor (2 items; alpha=0.60) measured social support. Results suggested the new instrument is acceptable to a seriously ill population and exhibits excellent psychometric properties. The factors related to completion and anticipatory concerns represent particularly new contributions to quality of life measurement. ***This work highlights that dying is a multidimensional construct, there is no such thing as one good death, and that patients follow and desire different trajectories at the end of life. In addition to resulting in a new measure of quality of life at the end of life, these studies have demonstrated the research team's ability to capture such data from extremely compromised patients and stressed family members.***

C.8 The Health Consequences Of Providing Informal Care For Chronically Ill Individuals

Dr. Clipp's caregiving research has focused for two decades on chronic illness trajectories in the context of the family. Her studies of dementia caregivers demonstrated that institutional placement resulted from caregiver characteristics and stress rather than patient functioning or disease severity;⁸⁹ that the neediest caregivers often receive the least social support;⁹⁰ that caregivers' use of psychotropic drugs is significantly higher than among non-caregivers, reflecting levels observed in institutionalized populations,⁹¹ and etiologies of caregivers' physical and emotional health problems are multi-factorial.⁹² She subsequently conducted clinical studies of patients with cancer and their spouse caregivers, and with AIDS patients and their spouses or partners to test the generalizability of earlier findings on dementia within other disease contexts.⁹³⁻⁹⁶ Dr. Clipp also added caregiver outcomes to designs of industry-sponsored trials and demonstrated significant caregiver benefit.⁹⁷⁻⁹⁹

This foundation resulted in The National Longitudinal Caregiving Study (NLCS), the largest longitudinal study to date of informal dementia caregivers, that follows more than 2,300 community-dwelling caregivers with four yearly surveys. In this work Dr. Clipp is examining multiple aspects of the caregiving career including physical and mental health effects of caregiving, health services use, informal caregiving costs, and predictors of institutionalization.¹⁰⁰⁻¹⁰² Currently, she is comparing the NLCS caregivers to other caregiving samples to examine selection effects and social class distinctions, and non-caregiver elderly to better understand the burden of caregiving task and time demands. Also, and of particular relevance to the proposed work, Dr. Clipp currently is modeling unique aspects of caring informally for demented family members who also are dying. ***The experience of caregivers both influences and is markedly influenced by trajectories of the seriously ill loved ones for whom they care.***

C.9 Trajectories Across The Life Course

Research team members have studied health across the life course and the psychosocial conditions that variously foster or impair health. Much of this experience has come through the Duke/EPESE, a 10-year prospective cohort study that described the health and psychosocial trajectories of 4,162 elders over age 64 in central North Carolina.¹⁰³ The two primary missions of the Duke/EPESE were examination of the health status of African-American vs. Caucasian, and rural vs. urban elders. Assessment included recent stressful life events, incident medical diagnoses, functional and cognitive status, depressed mood, sensory problems, health behaviors, global health ratings, social support, and health service utilization.

Dr. Hays served as a member of the Duke/EPESE Steering Committee, and supervised recruitment of over 1000 subjects who remained in the study through the 7th annual interview for the most invasive procedures of the Duke/EPESE program (blood collections in the home setting), and developed an archived blood tissue bank and corresponding electronic data base of clinical blood test results. Study investigators have published multiple papers using longitudinal Duke/EPESE data.^{66, 88, 104-112} This research has focused on developmental and temporal health processes, including changes over time in depression, social support, grief, living arrangements, religious behaviors and religious beliefs.

In addition to work with the EPESE sample, Dr. Clipp has demonstrated, using large longitudinal data sets, that earlier war experiences continue to affect physical and emotional health in later life.^{30, 113-119} She has also integrated medical and social science approaches to the clinical care of older veterans,¹²⁰ yielding multidimensional findings on

trajectories of health, function and behaviors in a large community-based regional sample. *These studies demonstrate our ability to use large scale, epidemiologic, longitudinal designs to map health trajectories over decades.*

D. RESEARCH DESIGN AND METHODS

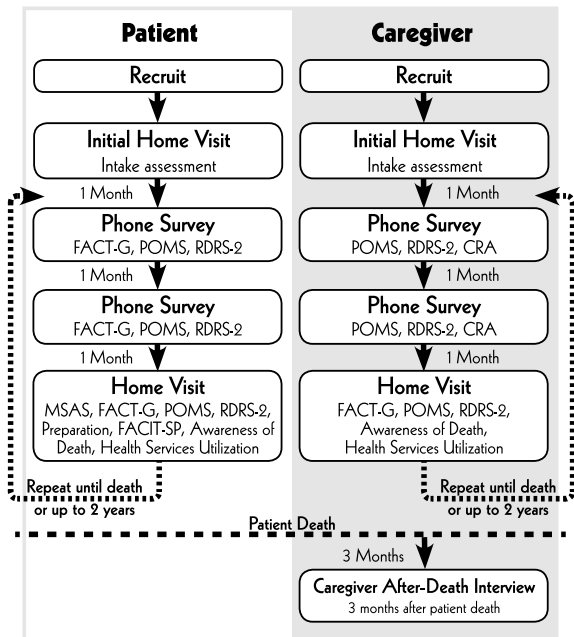
D.1 Overall Study Design

We will enroll seriously ill patients and follow them prospectively until death, or the end of the data collection period, whichever comes first. Patients still alive at the end of the data collection period will have been followed for at least two years. In addition, we will also enroll the primary informal caregiver identified by each patient, and follow them until three months after the patient's death. In monthly interviews of both patients and caregivers, we will measure the domains of interest to the study. These interviews will vary between in-home interviews every three months, that include all measures of interest, and short monthly telephone interviews during the two intervening months, that include only four primary outcome measures (RDRS-2, POMS, FACT-G, and CRA, see below). Three months after patients' deaths, we will interview their surviving caregivers to record their retrospective assessment of the patient's illness and death, as well as to assess their own adjustment to the loss.

D.2 Subjects

[Our objective is to study a population of patients with common, advanced chronic illnesses, that is sufficiently large and representative to draw valid conclusions about the relevant trajectories. The ideal population would be patients with a wide variety of illnesses that die one year after enrollment. We aim to study a human process, rather than a specific disease process, and therefore seek greater breadth in patient selection. However, since we expect disease type to influence trajectory, we have chosen to limit the number of illnesses studied. We have elected to study three categories of advanced chronic disease, Stage IV (metastatic) cancer, New York Heart Association (NYHA) Class IV congestive heart failure (CHF), and chronic obstructive pulmonary disease (COPD) with hypercapnea. These three categories represent the most common causes of death from chronic disease in Durham County that do not primarily impair cognitive function and disrupt the patients' ability to report on their experiences (as with cerebrovascular disease). Patients with these diseases are usually aware of the serious nature of their illnesses, and their deaths are generally not unexpected. Furthermore, patients with these diagnoses and disease severity (as measured by the stage of cancer, NYHA class of CHF and hypercapnea in COPD) have an approximate 50% one year survival, providing sufficient time for enrollment and capture of multiple data points along their illness trajectories, yet allowing follow-up through death for the majority of subjects.^{121, 122} These diseases represent trajectories with varying levels of certainty regarding illness course and functional decline. In fact, these different trajectories are most often cited and compared to each other with regard to the creation and funding of appropriate health services (see Section B.6.1). We will recruit 80 patients and their caregivers from each of the three groups, for a total of 240 patients and 240 caregivers (see Section D.7 below, Power and Sample Size Considerations).

Within the cancer category, we have selected four representative malignancies (female breast, colo-rectal, lung, and prostate), and will recruit patients with known metastatic disease (Stage IV). We chose these malignancies because they are the four cancers with the highest mortality rates,¹²³ they allow an equal sampling of men and women, and they provide a broad age range of patients. For analytic purposes, ***we will treat all four malignancies as a single group.*** We make this decision for both theoretical and practical reasons. First, among Stage IV cancer patients, with respect to the trajectories we are studying, we do not expect significant differences by disease type in the last 6-12 months of life.⁴³ Clinically, at this point in the illness, patients with all four malignancies tend to experience similar symptoms of fatigue, pain and discomfort from distant metastases. While specific symptoms may vary (e.g., prostate cancer is more likely to metastasize to bone whereas colorectal cancer is more likely to spread to the liver), we anticipate the resulting patient experiences to be more similar than different. Their overall prognoses and rates of decline are fairly comparable, and we expect most of the trajectories we are measuring to be more similar among cancer patients, than between cancer and non-cancer patients.^{124, 125} Second, from a policy and health services perspective, guidelines created by organizations such as the National Hospice and Palliative Care Organization also treat different advanced malignancies as one group. Finally, from a practical perspective, categorizing Stage IV malignancy as one group enhances patient recruitment and likelihood of



achieving the necessary sample size for the study. With the exception of lung cancer, there are not enough patients in our population with any other single malignancy to meet the sample size requirements within the two-year time frame. We will look at different trajectories between cancer types, although small numbers may limit generalizability (see D.6.1).]

The ideal population would also be geographically based, inclusive of all patients with the targeted illnesses. Given the limitations of information technology, one cannot identify such a population of patients in a geographically defined sample prospectively and rapidly enough to enroll them prior to death. However, patients can be identified using hospital databases. Therefore, we have chosen to access all eligible patients with the targeted conditions that live within a 30 mile radius of Durham, North Carolina, and who can be identified via databases at the three Durham hospitals – Duke University Hospital, Durham Regional Hospital and the Durham VA Medical Center. These three hospitals serve different populations. Duke University Hospital is a tertiary referral center for the Southeastern United States, yet has a commitment to serving the health care needs of Durham and maintains a network of primary care practices, including an indigent care clinic. Durham Regional Hospital is the former county hospital, now owned by the Duke University Health System, and functions as Durham’s primary community hospital. The Durham VA Medical Center serves the area’s veteran population.

D.2.1 Patient Ascertainment

[D.2.1.1 **Cancer** –We will identify patients with Stage IV breast, colon, lung or prostate cancer using the Duke Tumor registry (which includes patients from Duke University and Durham Regional Hospitals), and the VA VISTA patient database.]

The Duke Tumor Registry has a 4-6 month lag time between final staging and data entry. Therefore, for Duke and Durham Regional patients we will use a rapid ascertainment process whereby we will identify, on a weekly basis, all patients seen in the inpatient or outpatient setting with one of the relative ICD-9 codes for breast, colo-rectal, lung and prostate cancer (162.X,174.X, 153.X, 154.X, and 185.X), and with a home zip code within the defined 30 mile radius (27215, 27216, 27217, 27231, 27243, 27253, 27258, 27278, 27502, 27503, 27509, 27510, 27511, 27513, 27514, 27515, 27516, 27522, 27529, 27540, 27541, 27559, 27560, 27562, 27565, 27572, 27573, 27581, 27583, 27587, 27588, 27599, 27601, 27603, 27604, 27605, 27606, 27607, 27608, 27609, 27610, 27611, 27612, 27613, 27614, 27615, 27695, 27701, 27702, 27703, 27704, 27705, 27707, 27708, 27710, 27712, 27713, 27715). We will then manually scan the computerized medical records of identified patients to detect which patients have Stage IV disease.

To ascertain VA patients, we will use the FILEMAN program to query the hospital VISTA database (computerized medical record) accessing the same ICD-9 codes and zip codes. We will then manually scan the computerized medical records of identified patients to detect which patients have Stage IV disease.

D.2.1.2 **Congestive Heart Failure** – no common mandated registry exists for CHF as it does for cancer, so ascertainment requires a different approach. However, Duke University does maintain a comprehensive database for congestive heart failure created to identify patients for their congestive heart failure clinics and research protocols. The database includes all patients referred to the CHF clinic from any location. Because Durham Regional Hospital is part of the Duke University Health System, many patients with CHF are referred to the Duke CHF Clinic and are entered into the database. In addition, patients are routinely added by the CHF clinic nurses who review echocardiogram reports at both hospitals and identify all patients with low ejection fractions. The database is up to date, and can be easily queried for patients with NYHA Class IV disease (symptoms at rest), who live in the area demarcated by the zip codes above. To further improve the likelihood of identifying all patients who are seen at these two hospitals, the study will fund part of a CHF nurse’s salary to review the emergency department logs of Duke University and Durham Regional Hospitals to identify all patients with emergency department visits for CHF.

To ascertain VA patients with CHF, we will use a similar method as described above, querying the VISTA database for the appropriate ICD-9 (425.0, 425.4, 428.X, 429.X) and zip codes. This will be followed by manual scan of computerized medical records to detect patients who have met the threshold for NYHA Class IV disease (i.e., symptoms at rest) at any time in the course of their illness.

D.2.1.3 **Chronic Obstructive Pulmonary Disease** – as with CHF, there are no mandated registries for COPD. However, hypercapnea (i.e., elevated arterial blood pCO₂) is an excellent predictor of mortality in COPD, and we can use pCO₂ to identify eligible patients.^{14, 122} At Duke University and Durham Regional Hospitals, the section of Pathology Informatics can provide a list of patients that live in the designated zip code areas, have had a pCO₂>50 at any time, and a COPD ICD-9 code (490.X-496.X). In addition, to further increase the probability that

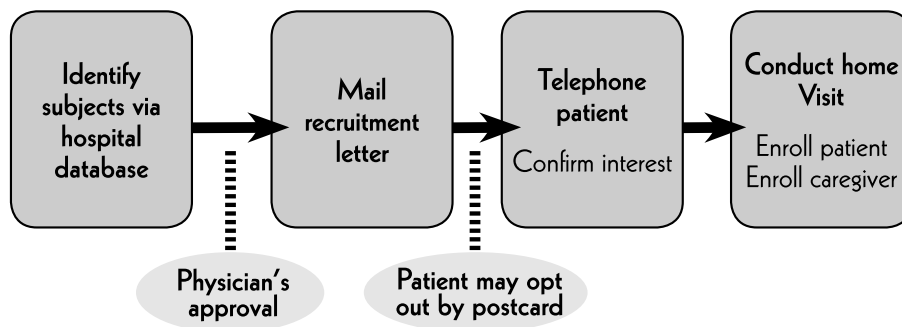
we identify patients that meet our prognostic requirements, we will include those with at least one emergency department visit or hospital admission in the past year. Patients selected in this manner will not require manual record review. At the VA, we will use the FILEMAN program to identify an identical set of patients.

D.2.2 Caregiver Ascertainment

For every patient enrolled in the study, we will also seek to enroll their primary caregiver. We will ask the patient to identify the person who spends the most time with them, the person who provides most of their day-to-day care, assistance, and support. We have used this identification in past caregiver research to identify the person most aware of their needs and concerns.^{90, 102} In those cases where caregivers cannot be identified, or refuse to participate, we will still seek to enroll and follow the patients.

D.2.3 Subject Recruitment And Retention

[Although patients will be identified in the separate ways described above, they will all be recruited through the same mechanism. After informing and obtaining approval from patients' physicians (a requirement of the Duke University IRB), we will send a letter to the patients explaining the study and offering them the opportunity to participate. At this time, they may send in a self-addressed, stamped postcard requesting not to be contacted further (opt out). If we do not receive the postcard, we will follow-up this mailing with a phone call to the patients further explaining the study and requesting their participation. If the patient agrees to participate, we will arrange a home visit by our interviewer, and send the patient a copy of the informed consent form to review prior to the intake interview. Patients will be asked to identify the person who provides the patient the most day-to-day support. We will then request that this individual, the patient's caregiver, be present at this visit, if possible, to consider enrollment as well. At this home visit, the patient will be enrolled in the study and complete the intake interview. If the caregiver is present, we will attempt to enroll that person as well and complete their intake interview. If the caregiver is not present, we will ask the patient for their caregiver's (or closest confidant's) contact information, and we will repeat the process of a phone call and in-home visit with that person. Of course, the patient or caregiver may also choose at this time not to participate in the study. Exclusion criteria include: non-English speaking, no telephone, inability to speak, and cognitive impairment. All subjects will complete the Short Portable Mental Status Questionnaire (SPMSQ) during the consent process and we will exclude those with a score less than 8/10.¹²⁶]



To enhance recruitment and retention of subjects we will offer compensation and several incentives. First, patients and caregivers will each be compensated \$20 for every completed interview, whether in-person or by phone. We trust this amount represents fair remuneration for their time without being coercive. Second, the patients' physicians will be notified prior to contacting the patients to approve the

patient's participation. This will allow us to include the physician's name when recruiting patients for the study, and to establish a personal connection. We will encourage subjects to feel like participants in the research process by sending them periodic updates on the study progress and providing framed certificates for study participation. We have observed that this gesture of recognition enhances subjects' sense of contribution. Finally, our research program has extensive experience interviewing patients with serious chronic illness and those near death, as well as their caregivers, and our interviewers are skilled at maintaining a relationship which, although not therapeutic, offers sensitivity and care for the patients and caregivers at a vulnerable time. Furthermore, we recognize the value of the interviewer-subject relationship in study recruitment and retention. Such a relationship decreases interview burden and, in our past experience, has created strong bonds that make us welcome in the home.²⁸

D.3 Measurements

As stated in the Specific Aims, we will describe patients' trajectories of physical symptoms, functional status, emotional function, quality of life, preparation for death, spirituality, and awareness of dying. We will also describe caregivers' trajectories of anticipatory grief, burden and awareness of dying, as well as their after death assessments of their awareness of when the patient was dying within the context of their illness trajectory. Finally, we are interested in the role of a variety of covariates on these trajectories, including patient and caregiver demographic and personality

characteristics as well as health services utilization. To assess these domains, we will use the following measures, the majority of which are recommended in the Toolkit of Instruments to Measure End-of-Life Care.¹²⁷ Unless discussed otherwise below, the instruments' psychometric properties are highly acceptable, details of which can be found in the corresponding references and the Toolkit website.

D.3.1 Patient Longitudinal Measures

D.3.1.1 Physical Symptoms – the Memorial Symptom Assessment Scale (MSAS) is a 32-item multidimensional scale developed to measure the prevalence, characteristics and distress of common symptoms, including pain, in seriously ill patients.¹²⁸ Internal consistency and validity are high, and the questionnaire has been acceptable to patients (administration time 6 minutes).

D.3.1.2 Functional Status – the Rapid Disability Rating Scale-2 (RDRS-2) is an 18-item scale that measures mobility and activities of daily living, mental capacity, continence, medications and confinement to bed.¹²⁹ It has good reliability and validity and is sensitive to change over time (administration time 2 minutes).

D.3.1.3 Emotional Function – the Brief Profile of Mood States (POMS) measures psychological distress, and has been used extensively in this population with excellent validity and reliability (administration time < 2 minutes).¹³⁰ We will use a modified 12-item form that reflects what was used in the SUPPORT study, yet eliminates two items that are duplicated on the FACT-G (i.e., sad, hopeless).

D.3.1.4 Quality of Life – the FACT-G is a 27-item questionnaire that measures four domains of quality of life (physical well-being, functional well-being, social/family well-being, and emotional well-being).^{131, 132} Although other quality of life measures have been developed for specific use in the terminally ill population, we believe this remains the most broadly used, well validated and reliable tool available (administration time 4 minutes). In addition, we will add two single-item measures of perceived health and overall quality of life that have been shown to correlate extremely well with other covariates.

D.3.1.5 Preparation for Death – There are two components to preparation – instrumental (e.g., wills, funeral arrangements) and cognitive-emotional. We have chosen to measure instrumental preparation retrospectively in the after-death interview so as to not influence patients' behaviors. Cognitive-emotional preparation for death will be measured using five items on preparation from the QUAL-E, a new instrument designed to measure quality of life at the end of life.¹³³ The items measure, on a 5-point scale, the patient's fears of death and concerns about the future (administration time 1 minute).

D.3.1.6 Spirituality – the FACIT-SP is a 12-item scale that complements the FACT-G and asks about spiritual well-being.¹³⁴ It has been validated in patients with cancer and HIV, exhibits good reliability and consistency. In addition, we will obtain a more in-depth baseline assessment using the Spiritual History Scale (SHS-4; see below) to use as a covariate (administration time < 2 minutes).

D.3.1.7 Awareness of Dying – Chappell has created a measure to assess this construct that includes four items.¹³⁵ Only validated in a small population, the measure has considerable intuitive appeal. We will use one of these items, a visual analog scale that asks the patient to mark where they currently are on a ten-centimeter line with anchors of "birth" and "death." The distance from the patient's mark to the end of the line (death) will be the metric for awareness of dying (i.e., shorter distance = greater awareness). In addition, we will ask the patient to provide a quantitative estimate in years, months or days of their own life expectancy (administration time < 1 minute).

D.3.2 Caregiver Longitudinal Measures

D.3.2.1 Patient Functional Status – the caregiver, in addition to the patient, will be asked to complete the Rapid Disability Rating Scale-2 (RDRS-2) and report the patient's functional status. This will be done for several reasons. First, when patients become too ill to complete the measure, we will still be able to receive this proxy account of their function. Second, this will allow an assessment of the accuracy of proxy report of functional status in these seriously ill patients. The RDRS-2 was actually designed to be completed by health care providers, so it is not inappropriate to use it for third party assessment in this way (administration time 2 minutes).

D.3.2.2 Anticipatory Grief – the Anticipatory Grief Scale (AGS) is a 27-item instrument that was designed to assess the bereavement experience of spouses of dementia patients.¹³⁶ However, in the Toolkit of Instruments to Measure End-of-Life care, Teno recommends using this for anticipatory bereavement by converting the word "dementia" to the patient's primary illness. In this study, dementia will be replaced by cancer, heart

failure or chronic lung disease, as appropriate. The instrument is reliable, valid, sufficiently short, and well tolerated (administration time 7 minutes).

D.3.2.3 **Burden** – the Caregiver Reaction Assessment (CRA) is 24-item multidimensional instrument designed to measure a caregiver’s reactions to caregiving for family members with a variety of chronic illnesses.¹³⁷ It measures caregiver esteem, family support, impact on finances, impact on schedule and impact on health. It is valid and well tolerated (administration time 6 minutes). In addition, we will ask a single item “Overall, how much do you wish family and friends would help you more with your responsibilities?” which we have found to be a very powerful predictor of caregiver well-being.⁹⁰

[D.3.2.4 **Emotional Function** – as described above in D.3.1.3, the Brief Profile of Mood States (POMS) measures psychological distress. In contrast to patients, caregivers do not complete the FACT-G, therefore we will administer the complete POMS to caregivers, including the two questions assessing depression.]

D.3.2.5 **Awareness of Dying** – the Chappell instrument will be used with the caregiver as well, with the language slightly altered to reflect that the questions about survival refer to the patient, not the caregiver.

D.3.3 After-Death Interview Measures

The after death interview will take place in the caregiver’s home 3 months after the patient’s death. We will use Teno’s After-Death Bereaved Family Member Interview.¹³⁸ This is a comprehensive interview schedule that covers all major domains of quality of life and quality of care, and has been validated substantively in three populations of patients (nursing home, hospice and hospital). The interview covers 2 domains, advance care planning and satisfaction, which we purposely do not assess in our pre-death interviews so as not to create intervention effects. Three different forms of the instrument exist that are worded slightly differently for the appropriate site of death. We will delete those aspects of the survey (e.g., demographics), that are covered elsewhere. In addition, we will ask at this time about when the patient completed, if ever, several tasks indicating an instrumental readiness for death including advance directive, estate will and funeral arrangements. Finally, we will ask the caregiver at what point in time they came to know the patient was dying. We will ask them to be as specific as possible with the date (administration time 25 minutes).

D.3.4 Covariates

The following variables will be assessed during the initial intake interview with the patient and caregiver. In addition, one of them, the Primary Care Assessment Survey, will also be asked during the three month interviews.

D.3.4.1 **Demographics** – these include age, gender, ethnicity, education, income and religious affiliation.

D.3.4.2 **Clinical Status** – this will include patient disease type, time from first diagnosis, and weight (which will be measured by the interviewer using a portable scale brought to the home for this purpose).

D.3.4.3 **Personality Characteristics**

D.3.4.3.1 **Coping** – the Mini-MAC is a valid, short version of the Mental Adjustment to Cancer scale that allows a rapid assessment of coping style in cancer patients.¹³⁹ This scale taps into four coping responses labeled helpless-hopelessness, fighting spirit, fatalism, and anxious preoccupation. We have modified five words in this 29-item scale to reflect the patient’s disease (e.g., cancer vs. CHF) (administration time 7 minutes).

D.3.4.3.2 **Sense of Coherence** – we will use this construct to evaluate whether patients have meaning systems that allow them to make sense of what is happening. Antonovsky developed a valid, 29-item scale that has been used in multiple settings (administration time 7 minutes).¹⁴⁰

D.3.4.3.3 **Experience With Death And Dying** – reactions to illness and life transitions is influenced by previous experience. We will ask the age and cause of subjects’ parent’s deaths, and whether they had ever experienced a death personally in a close friend, family member or as a caregiver.

D.3.4.4 **Understanding of Prognosis** – we will assess patients’ understandings of their own prognosis and self-efficacy with open-ended questions: “What have you been told about your illness?” “Have you talked to your doctor about your prognosis?” and “What do you think your family knows about the status of your illness?”

D.3.4.5 **Relationship with Physicians** – we will use four scales (24-items) measuring relationship quality from the Primary Care Assessment Survey (PCAS).¹⁴¹⁻¹⁴³ These scales – communication, interpersonal treatment,

physician's knowledge of the patient and patient trust – have been shown to correlate well with outcomes of care such as adherence and satisfaction (administration time 5 minutes).

D.3.4.6 Participatory Decision Making – we will use a 3-item scale developed for the Medical Outcomes Study that asks patients to rate the decision-making style of their physician.¹⁴⁴ The items are valid and shown to correlate with demographic characteristics of patients and physicians, length of relationship and patient satisfaction (administration time < 1 minute).^{144, 145}

D.3.4.7 Social Support – social interaction, one domain of social support, is already measured in the FACT-G. In addition, we will measure household composition with a single item, and existence of a confidant, using 2 items from the Duke EPESE survey.¹⁴⁶ Finally, we will also measure instrumental support given using 13 items from the EPESE survey. Because patients and families value contributing to others at the end of life, we view this particular construct as essential (administration time 3 minutes).^{60, 61}

D.3.4.8 Spirituality – the Spiritual History Scale (SHS-4) is a valid measure of lifetime religious and spiritual experience that correlates with depressive symptoms and impaired social support.⁸⁸ We will use three of the four dimensions (17-items) (administration time 5 minutes).

D.3.4.9 Health Services Utilization – as mentioned earlier, we will measure completion of living wills and the presence of DNR orders retrospectively during the after-death interview. At baseline and each 3 month interview we will ask the patient and caregiver to report: bed days at home, emergency department visits, hospitalizations, admissions to intensive care, use of cardiopulmonary resuscitation, cessation of chemotherapy (in cancer patients), use of home health services (e.g., home health aids, nurses, physical therapy), and hospice referral. We will not ask about hospice referral directly so as to reduce patients' biases about prognoses. However, when patients answer positively about home health services, we will ascertain whether they have enrolled in hospice (administration time 5 minutes).

D.4 Respondent Burden

The total number of items for the patient intake interview will be 245 and should take approximately 60 minutes. [The total number of items for the caregiver intake interview will be 222 and should take approximately 57 minutes. The 3 month in-home patient interviews will comprise 108 items and take approximately 20 minutes to complete. The 3 month in-home caregiver interviews will comprise 88 items and take approximately 18 minutes to complete. The monthly patient phone interviews will include 57 items and take approximately 8 minutes to complete. The monthly caregiver phone interviews will include 56 items and take approximately 10 minutes to complete.] To each of these time estimates, it is realistic to increase them by as much as 50% for some patients. Nevertheless, aside from the intake interview, no interview should take longer than 30-40 minutes (aside from social time with the subject). The interview schedule has been designed carefully to minimize the burden to the subjects. The patient interview will begin with neutral topics, such as asking about the patient's family, in order to make the interview experience a pleasing one. Despite these precautions, some patients may not be able to complete some interviews due to fatigue or confusion. The most important measures will be asked first to preserve as much data as possible. Missing data will occur and will be managed as described in the Analysis section below.

D.5 Is The Study An Intervention?

Repeated questioning about the patients' attitudes towards the relevant outcomes could change their approach towards these outcomes. For example, asking about how someone is adjusting to their illness may prompt them to intervene to improve those aspects that are noted to be problematic. We offer three responses to this concern. First, all of these measures have been used to study similar populations and this problem has not been noted. This study may include more frequent contact with subjects than some other cohort studies looking at a variety of diseases, yet no evidence exists to suggest this would be a problem. Second, we will avoid the most problematic issues by asking about instrumental readiness for death (e.g., wills, funeral arrangements) of the caregiver after death. Finally, there is no way to design a study that obtains the depth of knowledge about patients that we seek here without asking such questions prospectively. To obtain such data these risks must be tolerated.

D.6 Analysis Plan

The study of patient and caregiver trajectories at the end-of-life presents several unique methodological challenges. The analysis plan reflects recent developments in statistical methods for longitudinal data that allow us to meet these complexities. For example, the methods are particularly adept at handling incomplete and unbalanced data. All observed data will be used, not just from participants with complete data. This moves beyond traditional methods (e.g. repeated

measures ANOVA) by allowing the analyst to model explicitly means and variances, both within subjects and between disease groups. As a result, these techniques provide rich information that will enable the study team to translate the statistical results into findings that are clinically relevant.

The four primary aims structure the analysis plan. There are seven primary patient-level variables: physical symptoms, functional status, emotional function, quality of life, preparation for death, spirituality, and awareness of dying. [There are four primary caregiver-level variables: anticipatory grief, burden, awareness of dying, and depression.] All of these are continuous, longitudinal outcomes. The majority will be collected every three months over the two-year post-enrollment period. A subset of the measures (POMS, FACT-G, CRA, and RDRS-2) will be assessed every month. In addition, the patient will be asked monthly two single-item questions concerning overall quality of life and perceived health. Other demographics and self-report measures will be used as predictors in the models. They will be collected either during the intake interview or during the post-death caregiver bereavement interview.

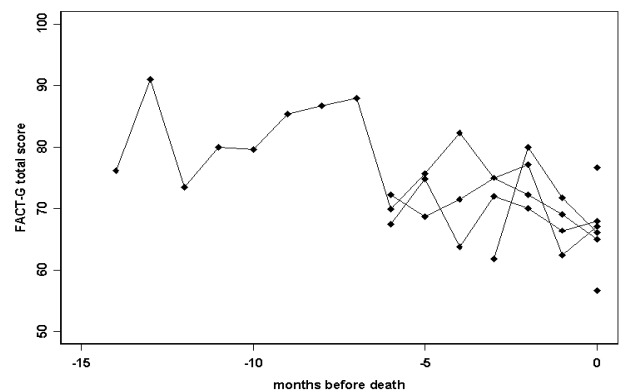
Descriptive statistics, including graphical displays, will be used to summarize all demographic and self-report measures. Descriptive statistics also will be calculated at each time point for the longitudinal variables. For continuous measures, means, standard deviations, percentiles, ranges, box plots and histograms will be generated. For categorical variables, frequencies and proportions will be generated. During this phase of the analysis, we will examine the statistical properties of the variables used in the analytic modeling. We are particularly interested in the distributional properties of our continuously measured dependent variables. If necessary, appropriate corrective measures will be taken (e.g. transformations to achieve normality). For the categorically measured variables, we will examine the distribution or “allocation” of responses within categories.

D.6.1 Primary Aims 1 and 2: Describing Patient and Caregiver Trajectories

The first goal of the descriptive analyses is to plot the trajectories of the patients’ observed values and caregivers’ observed values for each domain over time. In this study, the common time point of reference is “time of death.” As a result, time is characterized on the x-axis of the plots as the “number of months before death of patient,” and $time=0$ represents the last observed measurement before death. On patients for whom we have the last possible observation before death, $time=0$ will be within 1 month of death. The plots of these trajectories provide important descriptive information and guide the longitudinal model-building process. Below is a trajectory plot of observed QOL as measured by the FACT-G for six fictional patients. Notice that two patients have only one observation before death, while one patient was followed for 14 months. Most of the patients have a gentle, decreasing trend in QOL as they approach death, but there is some within-individual variability.

As a preliminary descriptive tool, the plots of individual trajectories permit the following assessments:

- ***Discern mean trends in each domain over time.*** For example, most patients and caregivers may exhibit a steady linear increase in awareness of dying over the study period. In contrast, patients’ spirituality may remain fairly constant over the study period.
- ***Determine degree of within-subject variability.*** Are the measurements at each time point relatively constant or are there spikes in the trajectories? Is there more within-subject variability at points in time further from death as compared to time closer to death?
- ***Determine degree of between-subject variability.*** We will see how much between-subject variability is exhibited at the “time 0” measurement. For example, is emotional function more similar immediately before death as compared to the heterogeneity one might expect one year before death? In addition, we will also examine how much between-subject variability there is over time. Do some patients exhibit a steady linear decline in functional status, while other patients show a stable trend followed by a sharp decline (indicative of a quadratic shape)?
- ***Examine subgroup differences (e.g. advanced CHF, COPD, cancer) with respect to mean trends and degree of variability.***
- ***Evaluate variation in intercepts and slopes of end-of-life trajectories between patients with relatively few assessments (shorter survival time) and patients with many assessments (longer survival time).***



The second goal of the descriptive analyses is to identify categories or classes of trajectories. Preliminary studies provide evidence for variation in expected patient trajectories. For example, Bretscher found stable quality of life trajectories while others have supported a dramatic quality of life decrease in the months before death.^{43, 71}

The general concept of defining groups or classes of individuals is popular in many applications of cross-sectional data analysis and includes such methods as cluster analysis, finite mixture analysis, and latent class analysis. Recent statistical advances extended this idea to longitudinal data using a class of methods called general growth mixture modeling (GGMM).¹⁴⁶ In conventional longitudinal data modeling, analysts generally think of explaining heterogeneity in trajectories with observed, predictor variables. With the GGMM approach, individuals' trajectories are instead thought of as emerging from unobserved or latent classes of trajectories.

The general approach of GGMM proceeds as follows. First, specify the general shape of the latent trajectory classes (e.g. quadratic or linear). These general shapes will have been observed in the trajectory plots. Second, determine the number of latent trajectory classes that best fit the observed data. In general, the Bayesian information criterion (BIC) statistic provides a quantitative benchmark for selecting the appropriate number of classes.¹⁴⁷ A low BIC value indicates a model that fits well. In addition, it also is important to include clinical judgment at this stage. If some of the trajectory classes are very similar in trend or only represent a small number of individuals, they may not be clinically useful and therefore can be eliminated. Finally, the exact shape of the trajectory and percentage of individuals corresponding to that trajectory are estimated for each trajectory class. As part of primary aims 1 and 2, GGMM will be used to define latent trajectory classes for the caregiver and patient longitudinal variables. The results from GGMM will be used to develop clinical profiles of patient and caregiver subgroups, identifying times of heightened need and potential targets for intervention. All GGMM analyses will be conducted using the software Mplus.¹⁴⁸

D.6.2 Primary Aim 4: Identifying Modifiers of Patient and Caregivers Trajectories

Because the analyses for primary aim 4 serve as foundation for primary aim 3 analyses, they will be discussed first. For each of the longitudinal variables, we will use the general and flexible class of linear mixed-effects models to derive expected change over time and to quantify between- and within-subject variability.¹⁴⁹ A linear mixed-effects model has several properties that make it an attractive analysis tool for longitudinal data. First, the model is subject specific; therefore each subject may have an unequal number of observations at unequally-spaced time intervals. Second, under this model each subject contributes the same amount of information to parameter estimation, but subjects with more observations will have more precise information.

The linear mixed model (LMM) for individual i at time point j is:

$$Y_{ij} = X_{ij}\beta + Z_{ij}b_i + e_{ij}$$

[In this model, Y_{ij} represents the observed outcome for individual i at time point j . Baseline and time-varying covariates are incorporated into the design matrix, X_{ij} . As described in primary aim 4, baseline covariates include gender, ethnicity, disease type, etc. The population-average parameters, β – also called “fixed effects” – quantify mean intercepts and slopes and are used to create population-level growth curves of responses over time. The magnitude of population-average parameter estimates determines the extent to which these trajectories are modified by patient and caregiver characteristics. Linear mixed-effects models will be used to examine the first two hypotheses specified in Section B.5.4.

The goal of the first hypothesis is to compare trajectories of functional decline for cancer versus non-cancer patients. The fixed-effects component of a LMM for this comparison can be constructed as follows:

$$Y_{ij} = \beta_0 + cancer*\beta_1 + time*\beta_2 + time^2*\beta_3 + cancer*time*\beta_4 + cancer*time^2*\beta_5$$

Assume that *time* is coded such that *time* = 0 represents the last possible observation before death, *time* = 1 represents 1 month before death, etc. In addition, assume that *cancer* is an indicator variable such that *cancer* = 0 for non-cancer patients and *cancer* = 1 for cancer patients. Fitted values for β_0 and β_1 quantify the expected intercepts for the cancer and non-cancer groups. Specifically, β_0 represents the expected functional status for non-cancer patients immediately before death; β_1 represents the change in expected functional status at *time* = 0 for cancer patients as compared to non-cancer patients. In this example, both linear and quadratic slope parameters are included to reflect a steeper decline in functional status as patients approach death. The estimates for β_2 and β_3 are used to construct the expected trajectory for non-cancer patients. Finally, estimates of β_4 and β_5 represent the differential change in linear and quadratic slope for cancer patients as compared to non-cancer patients and will be used to construct the expected functional status trajectory for cancer patients. Testing for fixed effects is similar to

testing parameters in a linear regression model. The hypothesis that cancer patients have a steeper quadratic decline in functional status as compared to non-cancer patients will be addressed by testing $H_0: \beta_5=0$ vs. $H_a: \beta_5 \neq 0$.

The second hypothesis states that awareness of dying and tasks of preparation for death will occur significantly earlier among patients with cancer versus patients with CHF and COPD. To examine this hypothesis, we will fit two different linear mixed-effects models; the outcome measure for the first model will be *awareness of dying*, and the outcome for the second model will be *preparation for death*. We anticipate that the expected trajectories for the two chronic illness groups will be quadratic. Therefore, both models will have the same fixed-effects form as the model specified for the first hypothesis. In each model, if the estimate for β_5 is positive and significantly different from zero, this will provide evidence that patients with cancer have earlier awareness of dying and tasks for preparation.

The remaining components of the LMM can be constructed to model explicitly subject-level variability. Z_i is the design matrix for the vector of random effects, b_i . The random effects, b_i , are assumed to be normally distributed with mean zero and variance equal to Ψ . In LMM, Z_i is often coded such that the random effects represent random, subject-level intercepts and slopes. Extending the example from above, let b_i be a column vector in which the first element represents a random intercept and the second element represents a random linear time component. The covariance matrix Ψ would then be a 2 x 2 matrix as follows:

$$\Psi = \begin{pmatrix} \Psi_{11} & \Psi_{12} \\ \Psi_{21} & \Psi_{22} \end{pmatrix}$$

where Ψ_{11} is the between-individual variance of the intercepts. In the context of the first hypothesis, the magnitude of this estimate quantifies how variable functional status is between patients at their last observation before death. In this example, Ψ_{22} is the between-individual variance of linear slopes. The magnitude of this estimate quantifies how variable the change in functional status is between patients. If most individuals have similar rates of change in functional status at the end of life, then the estimate for Ψ_{22} would be relatively small. Ψ_{12} is a covariance and provides insight into how individuals' intercepts and slopes may be related. If the estimate of this term is negative and significantly different from 0, this indicates that individuals with lower functional status at their last observation had greater rates of change in their functional status over the study time. In contrast, a positive covariance indicates that a higher functional status at the last observation is related to a steeper change over time. Testing of the variance components will be conducted as described in Verbeke and Molenberghs.¹⁵⁰

Within the class of LMM, there are numerous ways that the random-effects structure can be specified to reflect the structure of the observed data. For example, cancer patients and non-cancer patients may have different magnitudes of variability in functional status over time. Cancer patients may be more similar in their profiles while CHF patients are more variable. If this is the case, then the random effects would be parameterized to represent separate random slopes for cancer patients and non-cancer patients.]

Finally, the within-subject residual measurement error, e_{ij} , is assumed to be independent of the random effects and normally distributed with mean zero and variance $\sigma_e^2 V_i$. In many situations, V_i is simply an identity matrix, which assumes that time points within a subject have exchangeable errors. The structure of V_i can easily be modified to reflect other patterns of residual errors (e.g. first-order autoregressive).

All LMM analyses will be conducted with SAS procedure MIXED (SAS Version 8, Cary, NC) or the S-PLUS function *lme* (Insightful, Inc.), and model assumptions will be checked using diagnostic procedures described by Pinheiro and Bates and Verbeke and Molenberghs.^{150, 151}

D.6.3 Primary Aim 3: Examining Relationships Between Trajectories

Thus far, all proposed analyses have focused on understanding, explaining, and quantifying single longitudinal variables. The third primary aim of the study is to examine the relationships between trajectories. For example, what is the relationship between patients' spirituality and functional status over time? Or, what is the relationship between patients' awareness of dying and their caregivers' awareness of dying?

These types of questions can be investigated within the class of LMM. Both baseline (time-invariant) and time-varying covariates may be included in LMM. In the discussion above, the only time-varying predictor was *time*. Relationships between longitudinal variables can be investigated by incorporating one of the measures as a time-varying covariate while the other measure is the outcome. For example, the fixed-effects portion of the model may be specified as:

$$Y_{ij} = \beta_0 + \text{time} * \beta_1 + \text{time}^2 * \beta_2 + (\text{spirit}) \beta_3$$

where Y_{ij} is physical function for patient i at time j and *spirit* is the spirituality for patient i at time j . A positive estimate for β_3 would provide evidence that spirituality and functional status have a positive relationship. The magnitude of β_3 quantifies the expected change in physical function for a unit change in spirituality.

[While this approach is straightforward, it may not be optimal in all situations. For example, information will be discarded if either of the longitudinal measures has a missing observation where the other does not. In addition, it may be unnatural to regard one of the variables as a predictor and the other as an outcome. As another option, we plan to investigate relationships between variables using a multivariate linear mixed-effects model.¹⁵² The remaining two hypotheses from section B.5.4 will be examined using this analytic technique.

Multivariate linear mixed-effects models (MLMM) allow more than one response variable on the “left hand side” of the equation. So, instead of each patient having a vector of responses over time, each has a matrix of responses over time. The estimation algorithms that have been developed for this model allow for different patterns of incomplete data in the response variables.¹⁵² Similar to the univariate (single response variable) model, the population-average (or fixed effects) component of the multivariate model quantifies the means and slopes of each response over time. In fact, each of the responses may have a different set of predictor variables. The relationships among response variables are captured in the covariance matrix of the random effects. If both a random intercept and slope are included for both responses, then an unstructured covariance matrix would include estimates of how these quantities co-vary. For example, we could examine whether or not the intercepts for the two responses are related. The covariance of the slopes would indicate whether or not the change over time for each response is in the same direction (positive value) or opposite direction (negative value).

For the third hypothesis, the multivariate outcome will include both psychosocial factors and measures of functional status. The main predictor of interest will be whether or not each patient was referred to hospice; this predictor will be incorporated into the population-average component of the model. We hypothesize that patients who were referred to hospice will have a significantly different mean and slope for functional status as compared to patients who were not referred to hospice. In contrast, there will be no intercept and slope differences on psychosocial factors for patients referred to hospice as compared to those who were not.

The fourth proposed hypothesis explores the relationship between the trajectories for spirituality and physical and emotional functioning. This hypothesis will be examined using both the fixed effects and the random effects parts of the model. First, using the fixed effects, we will test whether or not spirituality remains stable over time (estimated average slope equals zero) while physical and emotional functioning change over time (estimated slopes not equal to zero). In addition, we will examine the covariance of the random effects for spirituality and the other outcomes. If these covariance terms are close to zero, this provides evidence that change over time in physical and emotional functioning is not related to change over time in spirituality.]

D.6.4 Additional Analytic Considerations

A subset of patients will not die during the 24-month post-enrollment period. Also, a subset of patients and caregivers will drop out of the study for reasons other than death. For these subjects, the longitudinal variables may not be assessed at the time points closer to death. We will make every attempt to determine their date of death if it occurs before study completion. The observed data from subjects in either of these scenarios will be included in the exploratory plots and the linear mixed models but will be incomplete for some time period before death.

In the proposed study, there also will be a subset of patients who die quickly after enrollment. Again, we plan to include any available information in the analysis. A distinct issue, however, is that their end-of-life trajectories (e.g., QOL 3 months before death) may look different than the end-of-life trajectories for patients who have been enrolled and followed for a longer period of time. Because we are making every attempt to enroll patients with stringent clinical benchmark criteria, the patients who die shortly after enrollment will likely have had a shorter duration of serious illness. In our analysis, duration of illness will be an important predictor variable and will enable us to explore its impact on end-of-life trajectories. For example, decline of physical functioning in the 3 months before death may be similar, regardless of illness duration. In contrast, patients with a shorter illness course may exhibit a different pattern of preparing for death as compared to patients with a longer illness course.

D.7 Power and Sample Size Considerations

The proposed study is not motivated by hypotheses, rather its goals are to empirically describe caregivers' and patients' end-of-life trajectories. Consequently, the sample size considerations are not hypothesis-driven. Rather, the goal is to enroll an appropriate number of subjects such that the study is feasible, while simultaneously insuring a sample size large enough to conduct analyses and estimate models as described in section D.6. As described in Section D.2.1, we will

enroll 80 patients per disease group for a total $n=240$ patients. Below we present power calculations for two different primary longitudinal variables: patients' quality of life (FACT-G) and caregiver burden (CRA).

The FACT-G will be measured monthly on all patients. Of interest will be to distinguish between quadratic, linear, and stable trends over time; the figure on the next page shows a graphical depiction of these trends. The following linear mixed model specifies the expected trends for the three groups.

$$Y_{ij} = \beta_0 + \text{group2} * \beta_1 + \text{group3} * \beta_2 + \text{group2} * \text{time} * \beta_3 + \text{group3} * \text{time} * \beta_4 + \text{group3} * \text{time}^2 * \beta_5 + b_i + e_{ij}$$

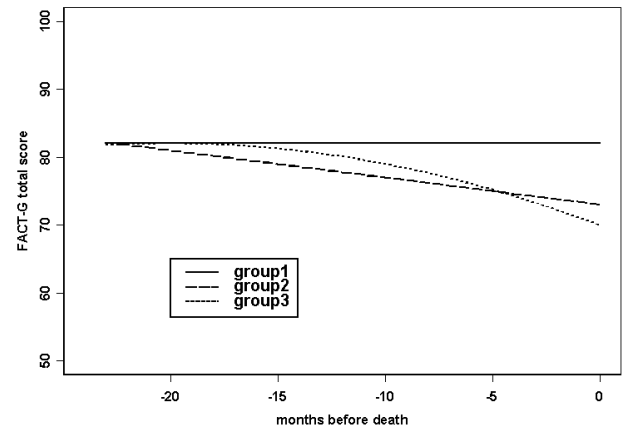
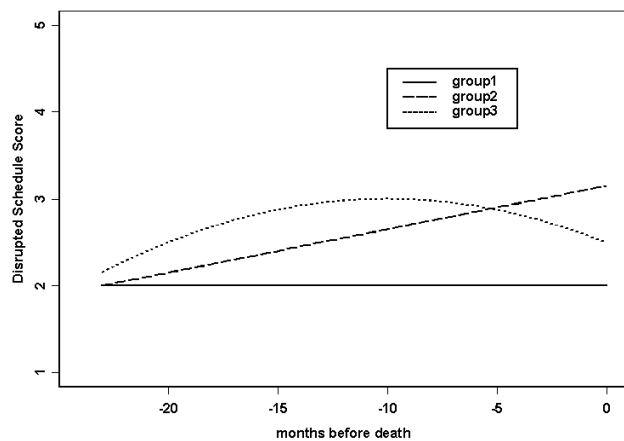
Group2 is a dummy coded variable that represents a group of patients with a linear trend; *group3* represents the group of patients with a quadratic trend. A test of whether or not *group3* has a quadratic vs. a linear trend is equivalent to the hypothesis $H_0: \beta_5=0$ and $H_a: \beta_5 \neq 0$. Similarly, a test of whether or not *group2* has a linear vs. a stable trend is equivalent to the hypothesis $H_0: \beta_3=0$ and $H_a: \beta_3 \neq 0$. For simplicity, b_i represents a random intercept and is normally distributed with mean zero and variance σ_b^2 . The random measurement error is also normally distributed with mean zero and variance σ_e^2 . A random intercept only model corresponds to an exchangeable correlation structure, where the correlation between repeated observations (ϕ) is the ratio of σ_b^2 and $\sigma_b^2 + \sigma_e^2$.

Because standard sample size formulas and software are not available for these types of tests, S-PLUS 2000 (Insightful, Inc.) was used to simulate data under the null and alternative linear mixed models. Data simulation provides the extra flexibility to incorporate expected rates of missing data directly into the power calculations. We estimate that 20% of the patients will not complete more than three interviews. Of the remaining patients, we estimate that 80% will die within the two-year post-enrollment period. The power estimates below take into account incomplete data for patients who die soon after enrollment, as well as for patients who are still alive at study completion. Sensible parameter estimates for the fixed effects ($\beta_0=82$; $\beta_1=-9$; $\beta_2=-12$; $\beta_3=-0.4$; $\beta_4=1.2$; $\beta_5=-0.03$) and variance components were derived from a recent longitudinal study that measured the FACT-G on hepatocellular carcinoma patients over a two-year period.¹⁵⁴

One hundred simulated data sets were generated under the alternative model and fit under both the null and alternative models.¹⁵⁵ Below are the empirical power estimates for a sample size of 240; patients were assumed to be equally divided between the three trajectory groups. For all estimates, the type-I error rate is 0.05.

Power Estimates for the FACT-G

Correlation	high ($\phi=0.75$)	medium ($\phi=0.5$)	low ($\phi=0.25$)	high ($\phi=0.75$)	medium ($\phi=0.5$)	low ($\phi=0.25$)
Type of Hypothesis	quadratic ($\beta_5=0$)	quadratic ($\beta_5=0$)	quadratic ($\beta_5=0$)	linear ($\beta_3=0$)	linear ($\beta_3=0$)	linear ($\beta_3=0$)
Power	90%	80%	60%	99%	99%	98%



The analytic goals for caregiver burden trajectories are similar to the patients' quality of life. The CRA contains five subscales that measure distinct dimensions of the caregiver experience. The exploratory power analyses focus on the "disrupted schedule" subscale. The mean of this subscale ranges from 1 to 5; a higher value indicates increased caregiver burden. Similar to the FACT-G, it will be important to have an adequate sample size to distinguish between quadratic, linear, and stable trends over time. As shown in the figure at left, *group1* has a stable disrupted schedule score. The caregivers in *group2* have a steadily increased disrupted schedule, indicating a constantly increasing caregiver burden. Finally, *group3* has a quadratic trend – burden increases as the patients move closer to death, but then burden begins to stabilize and then decline as patients near death. Perhaps patients of these caregivers have entered hospice, so the burden lessens closer to death.

Using the same linear mixed model as specified above, one hundred simulated data sets were generated under the alternative model and fit under both the null and alternative models. The same rates of missing data were taken into account during the simulation stage. Sensible parameter estimates for the fixed effects ($\beta_0=2.0$; $\beta_1=1.15$; $\beta_2=0.5$; $\beta_3=-0.05$; $\beta_4=0.1$; $\beta_5=-0.005$) and variance components were derived from a longitudinal study that measured the CRA on caregivers of colorectal cancer patients over a six-month period.¹⁵⁶ To account for the possibility that some patients may not have a caregiver, the empirical power estimates were derived for a sample size of 225. In the simulation, caregivers were assumed to be equally divided between the three trajectory groups. For all estimates, the type-I error rate is 0.05.

Power Estimates for the CRA

Correlation	high ($\phi=0.75$)	medium ($\phi=0.5$)	low ($\phi=0.25$)	high ($\phi=0.75$)	medium ($\phi=0.5$)	low ($\phi=0.25$)
Type of Hypothesis	quadratic ($\beta_5=0$)	quadratic ($\beta_5=0$)	quadratic ($\beta_5=0$)	linear ($\beta_3=0$)	linear ($\beta_3=0$)	linear ($\beta_3=0$)
Power	96%	95%	80%	99%	99%	98%

D.8 Data Management And Quality Control

A Steering Committee, chaired by the Principal Investigator (Dr. Tulsky) and comprised of all the Co-Investigators, will oversee the study. Dr. Steinhauser, as Project Director, will directly supervise the Project Manager and Interviewers, and respond to questions about day-to-day operational issues. This management team, structured with multiple checks and balances, will ensure quality control. Furthermore, the study will be housed in the Center for Health Services Research in Primary Care at the Durham VA, and will be guided by that unit's rigorous Standard Operating Procedure Manual. The data from all *in-person* interviews will be entered directly into survey forms on the Palm Pilot, a hand-held personal digital assistant (PDA). Survey forms will be created using "Satellite Forms," a software product by Puma Technology. Satellite Forms makes it possible to use the Palm Pilot as a hand-held CADI (computer-assisted data input) system. Data will be transferred daily from the Palm Pilot into a central Microsoft Access database. All interviewers will receive training in the use of the Palm Pilot. We have used this method of data entry in numerous studies with excellent results.¹⁵⁷ The *telephone interviews* will be entered directly into an Access database via computerized survey forms.

All general data management will be done in the Access database and then transferred to SAS for analysis at the completion of data collection. Microsoft Access is a flexible relational database that is SAS compatible and allows easy implementation of survey forms in a user-friendly environment. The Master's level statistician will develop the Access database, data entry forms, verification forms, and Palm pilot forms. Monthly reports detailing the accrual and frequency of demographics will be generated and study progress monitored. The Master's statistician will be responsible for monitoring data quality and integrity, ensuring a smooth transition of the data into SAS upon completion of the study. These procedures will make it possible to begin data analysis soon after the data collection phase is complete.

Methods for insuring subject confidentiality will be dictated by the Standard Operating Procedures. These procedures include not identifying any subject on any reports generated from the study. Computer files will be password protected. Files containing names and addresses will have separate passwords and be accessible only to personnel who need to contact subjects. The computer data will be backed up daily. Backed up data will be stored in a separate office in our unit in a locked cabinet. These measures are designed to protect against data loss and maintain patient confidentiality.

D.9 Timeline

The timetable below outlines the plan for piloting, recruitment, follow-up and analyses. We will follow surviving patients for a minimum of two years after recruitment; those enrolled early may be followed for up to three years.

Activities	Month											
	O	N	D	J	F	M	A	M	J	J	A	S
Year 1												
Hire and train staff	X	X										
Program database and Palms		X	X									
Pilot enrollment and survey				X	X	X						
Enroll patients							X	X	X	X	X	X
Monthly follow-up interviews								X	X	X	X	X
Year 2												
Enroll patients	X	X	X	X	X	X						
Monthly follow-up interviews	X	X	X	X	X	X	X	X	X	X	X	X
Year 3												
Monthly follow-up interviews	X	X	X	X	X	X	X	X	X	X	X	X
Year 4												
Follow-up interviews	X	X	X	X	X	X						
Continue after-death interviews							X	X	X	X	X	X
Year 5												
Analysis	X	X	X	X	X	X	X	X	X	X	X	X
Manuscript preparation							X	X	X	X	X	X

E. HUMAN SUBJECTS ISSUES

E.1 Protection Of Human Subjects

E.1.1 Consent Procedures

Patients will be asked to read and sign the study consent form prior to the first interview. The consent form will include sections detailing that: 1) the purpose of the study is to learn how patients experience serious illness and change with regard to their functional status and quality of life; 2) medical care will not be affected if they choose not to participate in the study; 3) patients will be responsible for the costs of their clinical care; and 4) they can discontinue participation in the study at any time. In addition, at the time of initial consent, we will ask subjects for permission to be contacted again in the future, after the study period has ended, and permission to check their Medicare claims files for health services utilization. These last two consents will be to make future studies with this population easier, however, subject refusal of these two items will not preclude participation in the rest of the study.

E.1.2 Potential Risks And Benefits:

The primary risk to the study subjects is that the interviews will precipitate a negative emotional response. If they have such a response they will be referred to their primary care provider and offered a mental health referral. In addition, patients and caregivers may find visits and calls from the interviewers to be intrusive, particularly when they become more ill. The primary benefit will be the payment of \$20 for each interview.

E.1.3 Data Collection

Data will be collected by trained research assistants in-person or over the phone. Data will be collected on Palm Pilots in person or via Computer Assisted Telephone Interview on the phone. The data will be downloaded into password protected electronic files. All participants will be assigned a code number that will be the sole identifier on all study data forms. The names, addresses, telephone numbers that correspond to study identifiers will be stored in a separate secured file. Access to this file will be limited to study personnel. The research assistant will sign a statement of confidentiality indicating that all participant information is not to be discussed outside of the research setting. Standard operating procedures for the Durham Center for Health Services Research for telephone surveys and data management emphasizing security procedures for maintaining patient confidentiality have been developed and used in many studies. The procedures will be adhered to in this study.

E.2 Inclusion Of Women

By targeting lung, breast, colon, and prostate cancers, as well as congestive heart failure and chronic obstructive lung disease we anticipate recruiting equal numbers of female and male patients. In Durham county, for the year 1996, women comprised 55% of the people who died with these diseases.¹⁵⁸ Surrounding counties reflect similar numbers.

E.3 Inclusion Of Minorities

In Durham county for the year 1996, African-Americans comprised 36% of people who died with the diseases we are studying.¹⁵⁸ We anticipate our sample to reflect similar numbers.

E.4 Inclusion Of Children

Children will not be included in this study. Palliative care for children is tremendously important, and understanding the trajectories they and their families follow prior to death is essential to understanding and improving their experience at the end of life. However, because of the complex developmental issues involved with children facing death, such a study would require different theoretical understandings, different or additional measures, and special expertise not present in our research team.

E.5 Data Safety Monitoring Plan

E.5.1 Potential Adverse Events

Potential adverse events (AE) for this project are all non-medical in nature. Patient participants may experience mild anxiety when answering survey questions about quality of life or awareness of dying. If patients have a more severe emotional reaction, we will refer them to their physician, and also have a list of mental health providers available for consultation.

E.5.2 Monitoring Safety Of Participants

There are several ongoing mechanisms for monitoring the occurrence of adverse events. The project manager oversees day-to-day monitoring of the study activities. This monitoring is facilitated by: (1) a toll-free number provided to participants upon entry into the study to report concerns related to study participation; (2) bi-weekly meetings with project staff and investigators to discuss study progress, reactions to the intervention, and any adverse events; and (3) direct supervision of the interviewers. To address patients' and physicians' psychological distress, the interviewers and project manager have a referral list of phone numbers for local mental health service organizations.

E.5.3 Plans For Assurance Compliance Regarding Adverse Event Reporting

The Principal Investigator is required to report adverse events to the Institutional Review Board (IRB) on an annual basis. Every research project conducted at Duke University Medical Center is required to have yearly departmental and IRB review. For any cancer-related projects such as this, the Cancer Protocol Committee also reviews and must approve the protocol and consent form on an annual basis. The VA Center for Health Services Research in Primary Care will also require compliance and will audit our data. Additionally, all adverse events are reported as part of the progress reports in the non-competitive and competitive renewals.

E.5.4 Plans For Assuring That Action Resulting In Suspension Of Trial Is Reported

The Principal Investigator is responsible for contacting the NIH grant program director in the event that any action resulting in temporary or permanent suspension of the study occurs. Because this study does not involve any investigational medication, the action would be limited to an IRB or investigator initiated suspension.

E.5.5 Plans For Assuring Data Accuracy And Protocol Compliance

To assure data accuracy, data entered by the trained interviewers is reviewed by the data manager on a bi-weekly basis. The data manager processes the database to search for errors and generate basic reports for dissemination at regular meetings. Protocol compliance is monitored at the weekly project staff meetings. In addition, investigators will meet weekly, and eventually monthly, with interviewers to train and ensure adherence to the intended protocol.

F. VERTEBRATE ANIMALS

None used

G. LITERATURE CITED

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