

TRAJECTORIES AND PATTERNS OF DELIRIUM AND VULNERABILITY  
IN OLDER CANCER PATIENTS IN THE HOSPITAL AND AT HOME  
NEAR THE END OF LIFE

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## ABSTRACT

STEWART MICHAEL BOND: Trajectories and Patterns of Delirium and Vulnerability in Older Adults with Cancer in the Hospital and at Home Near the End of Life  
(Under the direction of Virginia J. Neelon)

Patients with advanced cancer often develop delirium (acute confusion), the prevalence rising to 90% in the final weeks of life. Age, illness severity, comorbidity, and preexisting cognitive impairment increase the risk of delirium, but despite its prevalence, little is known about delirium in older cancer patients.

This three-phase study addresses the empirical gap in knowledge about delirium in older cancer patients. The first phase, a secondary analysis of data from studies of acute confusion in hospitalized elders, examined delirium and its etiology in 76 hospitalized older cancer patients, 10 of whom were near the end of life. The second phase comprised a pilot study of a home-based protocol to evaluate delirium in older adults with advanced cancer. The third phase was a descriptive, longitudinal, multiple case study of delirium and delirium vulnerability in seven older adults with advanced cancer near the end of life.

The findings clarify the role of delirium in older cancer patients. Delirium occurred in all seven with advanced cancer (the three patients who died had reversible and terminal episodes of delirium; the four who lived each had one reversible episode). Delirium also was common in the hospitalized older cancer patients: 43 of 76 (56%) were delirious at some point during hospitalization; 8 of 10 (80%) who were near the end of life became delirious. Delirium resolved in 13 of the 43 (30%) hospitalized patients, but in 30 (70%) delirium

symptoms persisted at discharge.

These older cancer patients were at risk for multiple etiologies of delirium: 90%, (including all near the end of life) had metabolic-nutritional risks, and hypoxic, orthostatic-dehydration, and metabolic-toxic risks were common. Five of the hospitalized patients and one of the seven with advanced cancer had chronic cognitive impairment (all became delirious).

Physical, behavioral, and physiological functioning in the older adults with advanced cancer declined before they became delirious. This decline in functioning may indicate diminishing reserve capacity, and suggests that early interventions aimed at specific etiologic risk factors may sustain reserve capacity and minimize delirium, thereby enhancing the quality of living and dying of older cancer patients, and minimizing distress for their caregivers.



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## LIST OF ABBREVIATIONS

APA	American Psychiatric Association
APACHE II	Acute Physiology and Chronic Health Evaluation II
BBL	Biobehavioral Laboratory
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CAM	Confusion Assessment Method
CCC	Caregiver Confusion Checklist
CNS	Central Nervous System
CR	Creatinine
CRS	Confusion Rating Scale
DOCS	Delirium Observational Checklist Scale
DSM	<i>Diagnostic and Statistical Manual of Mental Disorders</i>
FACT-G	Functional Assessment of Cancer Therapy-General
GDS	Geriatric Depression Scale
GI	Gastrointestinal
HIPAA	Health Insurance Portability Act and
IADL	Instrumental Activities of Daily Living
ICU	Intensive Care Unit
ID	Participant Identification Number
IOM	Institute of Medicine
IRB	Institutional Review Board

Lbs	Pounds
MDAS	Memorial Delirium Assessment Scale
MMSE	Mini-Mental State Examination
MSAS-SF	Memorial Symptom Assessment Scale – Short Form
NC	North Carolina
NEECHAM	NEECHAM Confusion Scale
NIH	National Institutes of Health
O <sub>2</sub>	Oxygen
OARS	Older Americans Resources and Services
PA	Phase Angle
PADL	Physical Activities of Daily Living
PCLN	Psychiatric Consultation Liaison Nurse
PHI	Protected Health Information
PPS	Palliative Performance Scale
PRN	As Needed
R	Reactance
RASS	Richmond Agitation-Sedation Scale
SRS	Sleep-Rest Subscale
SSS	Stanford Sleepiness Scale
UNC	University of North Carolina at Chapel Hill
Xc	Resistance

## CHAPTER ONE

### INTRODUCTION

People dying from cancer experience an array of distressing symptoms that greatly diminish their quality of living and dying. In recent years, there have been increasing demands and efforts to improve cancer care and to incorporate palliative care throughout the disease course particularly in the advanced stages and at the end of life (IOM, 1999; IOM 2001). Research and other quality improvement initiatives have focused on improving pain control and the management of symptoms such as fatigue and dyspnea. To date, however, little research has investigated the prevention and management of delirium, a common and troubling symptom in cancer patients at the end of life. There is a need to develop a better understanding of end-of-life delirium in cancer patients and to develop a rational, systematic, evidenced-based treatment approach based on this understanding.

#### *Background and Significance*

##### *Delirium in Advanced Cancer*

Cognitive impairment is a common and feared complication of terminal illness. Concerns about cognitive impairment negatively affect quality of life among terminally ill patients (Cohen et al., 2002). Steinhauser et al. (2000) found that the number one desire, endorsed by 92% of terminally patients, was to remain mentally aware. Cognitive impairment in patients with advanced cancer often occurs in the context of delirium, a pathophysiologic syndrome characterized by the rapid onset of impaired cognitive function,

altered attention, and disturbed psychomotor behavior. Delirium is the second most common neuropsychiatric disorder in cancer patients (Massie & Holland, 1987), occurring in 14-56% of hospitalized cancer patients (Flostein, Fetting, Lobo, Niaz, & Capozzoli, 1984; Levine, Silberfarb, & Lipowski, 1978; Tuma & DeAngelis, 2000). The incidence of delirium increases in this population with disease progression and approaching death. Up to 90% of patients with advanced cancer exhibit delirium in the final weeks of life (Bruera et al., 1992; Lawlor, Gagnon et al., 2000, Massie, Holland, & Glass, 1983, Minigawa, Uchitomi, Yamawaki, & Ishitani, 1996; Morita, Tei, Tsunoda, Inoue, & Chihara, 2001).

Delirium in patients with advanced cancer negatively affects quality of life and care (Breitbart, Bruera, Chochinov, & Lynch, 1995) and forecasts shortened survival (Caraceni et al., 2000; Lawlor, Gagnon et al., 2000; Metitieri, Bianchetti, & Trabucchi, 2000; Morita, Tsunoda, Inoue, & Chihara, 1999). Delirium is distressing for cancer patients, their family members, and professional caregivers (Brajtman, 2003; Brajtman, Higuchi, & McPherson, 2006; Breitbart, Gibson, & Tremblay, 2002; Gagnon et al., 2002; Hallberg, 1999; Hull, 1990; Morita, Hirai, Sakaguchi, Tsuneto, & Shima, 2004; Schofield, 1997). Patients experiencing delirium need more assistance with self-care activities and require close monitoring to prevent injury. Delirium impairs patient-family communication, hinders treatment decision-making, and interferes with the recognition and management of other physical and psychological symptoms (Bruera, Fainsinger, Miller, & Kuehn, 1992; Coyle, Breitbart & Weaver, 1994; Feldt, Ryden, & Miles, 1998; Miller, Moore et al., 1996; Miller, Neelon et al., 1996). Although many patients with advanced cancer desire to remain at home during their final days, delirium deters home care at the end of life (Fainsinger, Cemoissac, Cole, Mead-Wood, & Lee, 2000) and often contributes to the decision to hospitalize elderly cancer

patients or place them in other institutional settings (Berkman, Stolberg, Calhoun, Parker, & Stearns, 1983; Cintron et al., 2003; Evans, Cutson, Steinhauser, & Tulskey, 2006).

### *Older Cancer Patients: A Population at Risk for Delirium*

Currently, 60% of all cancers and 70% of cancer deaths occur in older adults (Yancik & Ries, 2000). Since older age (Andersson, Gustafson, & Hallberg, 2001; Duppils & Wikblad, 2000; Eden, Foreman, & Sisk, 1998; Schor et al., 1992; Williams, et al., 1985), advanced illness (Francis, Martin, & Kapoor, 1990; Inouye, Viscoli, Horwitz, Hurst, & Tinetti, 1993; Rockwood, 1989), comorbidity (Andersson et al.; Eden et al.; Pompei et al., 1994; Rahkonen et al., 2001), and pre-existing cognitive impairment (Duppils & Wikblad; Eden et al.; Fisher & Flowerdew, 1995; Francis, Martin, & Kapoor; Galanakis, Bickel, Gradinger, von Gumpfenberg, & Forstl, 2001; Inouye et al; Pompei et al; Rahkonen et al.; Rockwood; Schor et al.; Williams et al.) are significant risk factors for delirium, older cancer patients are more likely to develop delirium particularly at the end of life. However, research on delirium in older cancer patients is almost non-existent (Boyle, 2006). With the projected growth of the aging population and the associated increase in cancer in older adults (Yancik & Ries), cases of delirium are likely to increase, underscoring the need to better understand this clinical problem in older patients with advanced cancer.

### *Delirium in the Home Setting*

Delirium in patients with advanced cancer has been studied primarily in inpatient hospice and palliative care settings (Bruera et al., 1992; Caraceni et al., 2000; Gagnon, Allard, Masse, & DeSerres, 2000; Lawlor, Gagnon et al., 2000; Morita et al., 2001; Pereira,

Hanson, & Bruera, 1997; Stiefel, Fainsinger, & Bruera, 1992). While the prevalence of confusion has been examined retrospectively in home hospice patients (Nowels, 2002), delirium has not been studied prospectively in patients with advanced cancer cared for at home.

The early recognition and treatment of delirium in patients being cared for at home is critical and requires ongoing and prompt clinical assessment. Because of their ongoing presence and interaction with patients and their knowledge of baseline functioning, family caregivers may play a key role in monitoring for and detecting subtle cognitive and behavioral changes associated with the onset of delirium (Cassarett & Inouye, 2000; Irving, Fick, & Foreman, 2006). Family caregivers can notify clinicians as soon as the first signs of delirium occur, facilitating earlier and more rapid intervention that may prevent the development of more severe delirium.

There are few studies of delirium in patients being cared for at home and on the role of family caregivers in the detection of delirium. Research is needed to gain a better understanding of delirium in cancer patients cared for at home and to examine the role of family caregivers in the early identification of delirium symptoms. These are important gaps in current palliative care research and practice knowledge.

### *Delirium at the End of Life*

Prospective longitudinal studies of delirium in patients with advanced cancer, in general, have examined the prevalence and incidence of delirium; its etiology; its behavioral and psychomotor manifestations; and outcomes such as reversibility and survival (Bruera et al., 1992; Massie et al., 1983; Caraceni et al., 2000; Lawlor, Gagnon, Mancini, Pereira, &



Bruera, 1998; Lawlor, Gagnon et al., 2000; Morita et al., 1999; Morita et al., 2001; Power et al., 1993; Sarhill, Walsh, Nelson, LeGrand, & Davis, 2001; Tuma & DeAngelis, 2000; Zhukovsky et al., 1998). Yet, little is known about the nature of delirium and delirium vulnerability in older cancer patients at the end of life, and how they change over time. Anecdotal and other evidence suggests that delirium at the end of life is a dynamic condition characterized by much heterogeneity and change (Gagnon et al., 2000). The onset, manifestations, and course of delirium vary not only between individuals but also within an individual over time. Similarly, delirium vulnerability and patterns of risk also are likely to vary both within and between individuals over time.

There have been no studies of the natural course and progression of delirium in older cancer patients receiving palliative and end-of-life care in the home setting. In addition, investigators have not examined the relationships between baseline vulnerability and changes in delirium vulnerability at the end of life and the development of delirium. Longitudinal studies are needed to provide basic descriptive information about delirium in this population specifically focusing on individual variations in delirium at the end of life, patterns of change in delirium vulnerability during this period, the relationship between individual vulnerability and the development of delirium, and factors associated with delirium reversibility. Knowledge of the characteristics and course of delirium at the end of life will help to distinguish potentially reversible delirium from other irreversible patterns of delirium and cognitive decline associated with advanced cancer and dying.

The early identification of patients at risk and the identification and correction of underlying etiologic mechanisms are critical for preventing and managing delirium near the end of life. Recent studies of delirium in patients with advanced cancer show that correctable

etiologic factors can be identified with minimally burdensome diagnostic procedures (Lawlor, Gagnon et al., 2000; Morita et al., 2001). Furthermore, when etiologic factors are identified and treated, delirium near the end of life is reversible in up to 50% of cases (Bruera et al., 1992; Gagnon et al., 2000; Lawlor, Gagnon et al.; Morita et al.; Pereira et al., 1997). Delirium in cancer patients at the end of life too often is viewed as an inevitable, irreversible condition—a view which leads to symptomatic treatment with sedative medications rather than a search for correctable causes and attempts at reversal (Lawlor, Fainsinger, & Bruera, 2000). Clinicians are challenged by the inability to differentiate between delirium that is potentially reversible and other irreversible patterns of delirium and cognitive impairment. Currently, there is little phenomenological or pathophysiological data to guide clinicians in distinguishing between them (Rockwood & Lindesay, 2002).

This research examines delirium in older cancer patients approaching the end of life and begins to explore the relationships among factors influencing its development and reversibility. This research contributes important information to the understanding of and differentiation between irreversible patterns of delirium and cognitive impairment associated with advanced cancer and dying and pathologic patterns that are treatable and reversible. The ability to differentiate between these conditions will promote the use of more appropriate treatment strategies consistent with the goals of care and will enable clinicians to better educate and support patients and their family caregivers. The appropriate and effective management of delirium and other patterns of cognitive and functional decline at the end of life will enhance the quality of living and dying for older cancer patients and minimize distress for their caregivers.

### *Overview and Purpose of the Study*

The purpose of this study was to examine delirium in older cancer patients in order to develop a better understanding of the phenomenon in this population. The study involved three phases of investigation. In order to learn more about delirium in hospitalized older cancer patients and to develop a basis for studying delirium in older cancer patients at the end of life, the first phase consisted of secondary analyses of data from the Acute Confusion in Hospitalized Elders Studies (NR01339-05: Neelon & Champagne). The second phase was a pilot study to test the feasibility and burden associated with a protocol to study delirium in older cancer patients near the end of life. In the third phase, a longitudinal, multiple case study design was used to identify and describe the nature of delirium and to examine delirium vulnerability in older adults with advanced cancer near the end of life, during active palliative treatment and in the terminal period.

## CHAPTER TWO

### LITERATURE REVIEW

This literature review starts with an overview of delirium, presenting a historical perspective and the definition and pathophysiological basis of delirium and discussing issues associated with its diagnosis and measurement. The review contrasts delirium with other common disorders characterized by cognitive impairment in older adults—specifically dementia, depression, terminal decline, and terminal restlessness. Age-associated cognitive decline in older adults and cognitive impairment in cancer patients, in general, are discussed because both likely increase delirium risk in older cancer patients. The review examines the literature about cognitive changes at the end of life. It then focuses on delirium in the context of cancer in general, and in the context of advanced cancer in particular. The review concludes by presenting a framework for studying delirium and delirium vulnerability at the end of life. The specific aims and research questions for each phase of investigation are presented.

#### *Overview of Delirium*

##### *History of Delirium*

Lipowski (1990) provides an extensive historical review of delirium dating back to the first century AD. Even so, delirium, a common neuropsychiatric disorder in older adults, is poorly understood. Delirium remains underrecognized, underdiagnosed, undertreated, and

understudied in at risk populations (Breitbart et al., 1995). Clinical care and research on delirium have been impeded by the multiplicity of terms used to refer to the syndrome including acute confusion, acute confusional state, acute brain failure, acute brain syndrome, cerebral insufficiency, exogenous psychosis, ICU psychosis, metabolic encephalopathy, organic brain syndrome, post-pump psychosis, reversible dementia, toxic psychosis, and toxic delirium (Lipowski, 1990). The nursing literature typically uses the term acute confusion while the medical literature uses delirium. The two also are often used interchangeably. There is a need to establish consistency in language related to delirium.

### *Definition of Delirium*

Delirium is a neuropsychiatric syndrome that results from disturbances in central nervous system functioning. Delirium encompasses a broad spectrum of psychophysiological and behavioral manifestations. Delirium is characterized by the rapid onset of disordered cognitive function (thinking, perception, and memory), a disturbance of consciousness resulting from reticular activating system dysfunction (arousal and attention), and altered psychomotor behavior (hyperactivity or hypoactivity), which are often accompanied by adverse physiologic manifestations and autonomic nervous system instability (Lipowski, 1990; Neelon, 1990; Neelon & Champagne, 1992).

Strictly speaking, delirium is a psychiatric diagnosis defined by a specific set of criteria put forth in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The first two DSM editions defined pathophysiological disorders of the brain as organic brain disorders differentiating between acute and chronic disorders and between psychotic and non-psychotic disorders (Tucker, 1999). Diagnostic

criteria for delirium based on specific cognitive and behavioral symptoms were first included in DSM III (American Psychiatric Association [APA], 1980). In the initial version of DSM IV (APA, 1994) and in the current version, DSM IV-Text Revised (DSM IV-TR) (APA, 2000), the specific symptoms were deleted and the focus placed on the attentional and cognitive deficits seen in delirium. Sleep-wake cycle disturbances and altered psychomotor behavior, both common in delirium, are viewed as associated features. Table 2.1 presents the DSM IV-TR diagnostic criteria for delirium. With the exception of the DSM IV criteria, which have been subjected to limited validation testing, the diagnostic criteria for delirium have been based on consensus of expert opinion and clinical experience without systematic scientific evidence (Smith, Breitbart, & Platt, 1995).

Table 2.1. DSM IV-TR diagnostic criteria for delirium

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A.	Disturbance of consciousness with a reduced ability to focus, sustain, or shift attention
B.	A change in cognition <i>OR</i> the development of a perceptual disturbance
C.	Develops over a short period or time and tends to fluctuate over the course of the day
D.	Evidence that the disturbance is caused by the direct physiological consequence of a medical condition <i>OR</i> substance intoxication <i>OR</i> substance withdrawal <i>OR</i> medication side effect or toxin exposure <i>OR</i> multiple etiologies

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*Source.* APA, 2000

Delirium is characterized by alterations in consciousness involving both cognition and arousal. Trzepacz, Meagher, & Wise (2002) place delirium on a continuum of consciousness between alert and awake and stupor and coma. Similarly, Plum and Posner (1982) define delirium as a state of acutely altered consciousness that falls between clouding of consciousness and obtundation, stupor, and coma. Delirium often precedes stupor and coma, and it also is seen in individuals emerging from stupor and coma (Plum & Posner).

Patients experiencing delirium exhibit reduced levels of awareness, impaired attention spans, and fluctuating levels of alertness. They also may exhibit impaired orientation and memory, disorganized thinking, and distorted perceptions. The behavioral manifestations of delirium vary between hyperactivity, or agitation, and hypoactivity, or lethargy (Foreman, 1993; Lipowski, 1983; Lipowski, 1990; Neelon, 1990). They are easily distracted and have disturbed sleep-wake cycles. The manifestations of delirium develop abruptly over hours to days and fluctuate diurnally, often worsening at night (Foreman; Neelon). In general, delirium is defined as a transient condition that is potentially reversible, particularly with the early recognition and treatment of its underlying causes (Lipowski, 1990; Wolanin & Phillips, 1981).

Three clinical delirium subtypes have been identified: hyperactive or hyperalert, hypoactive or hypoalert, and mixed (Camus et al., 2000; Lipowski, 1990; Liptzin & Levkoff, 1992; Stagno, Gibson, & Breitbart, 2004). In the literature, the subtypes have been defined inconsistently with some authors focusing on the psychomotor behavior component (Meagher, O'Hanlon, O'Mahony, Casey, & Trzepacz, 2000; O'Keefe & Lavan, 1999), others on the arousal component (Ross, Peyser, Shapiro, & Folstein, 1991), and others on both (Lipowski; Liptzin & Levkoff). Hyperactive delirium is characterized by increased

psychomotor activity, sympathetic nervous system overactivity, increased alertness or hypervigilance, psychosis, and labile mood. In contrast, hypoactive delirium is exhibited as decreased psychomotor activity, withdrawal, apathy, lethargy or somnolence, and inattention. Psychotic features—delusions and perceptual disturbances—also are common in hypoactive delirium (Stagno et al.). In the mixed delirium subtype, symptoms associated with hyperactive and hypoactive delirium alternate in the same individual. The distinction between subtypes is important because the subtypes may have different etiologies and pathophysiology (Meagher, O’Hanlon, O’Mahony, Casey, & Trzepacz, 1998; O’Keefe, 1999; Ross et al.), may respond differently to treatment (Kobayashi, Takeuchi, Suzuki, & Yamaguchi, 1992; Liptzin & Levkoff), and may be associated with different outcomes (Liptzin & Levkoff; O’Keefe & Lavan, 1999).

#### *Pathophysiology of Delirium*

Engel and Romano (1959) characterized delirium as a “syndrome of cerebral insufficiency” representing a global failure of brain metabolism based on their finding of diffuse slowing of the electroencephalograph (EEG) in delirious patients that correlated with clinical severity and occurred regardless of the underlying medical condition or etiology. On the other hand, patients presented with appreciably different constellations of cognitive and behavioral symptoms. More recent reviews (Flacker & Lipsitz, 1999; Trzepacz, 1999; van der Mast, 1998), suggest that delirium results from dysfunction of multiple brain regions including cortical and subcortical areas and multiple interacting neurotransmitter systems rather than global metabolic failure of the brain. Electrophysiological, neuroimaging, and neurotransmitter studies (Gaudreau & Gagnon, 2005; Jacobson & Jerrier, 2000; Koponen,



1999; Reischies et al., 2005) support this new understanding of the neuropathogenesis of delirium.

Varying degrees of impairment occur in multiple domains of cognitive function including attention, arousal, orientation, memory, thought processing, language, perception, visuospatial and constructional abilities, and executive functioning (Trzepacz, Meagher, and Wise, 2002). Trzepacz (1994a) emphasizes the involvement of the right hemisphere and prefrontal cortex. Flacker & Lipsitz (1999) identify probable neurological mechanisms of delirium that result from the effects of multiple etiological factors and pathophysiological processes. For example, medications may affect cholinergic, dopaminergic, and serotonergic systems resulting in delirium. Other neurotransmitter systems, gamma-aminobutyric acid and glutamate, may also play a role in delirium. In addition, abnormal cortisol (Flacker & Lipsitz; van der Mast, 1998) and cytokine levels (Broadhurst & Wilson, 2001; Flacker & Lipsitz; van der Mast) have been identified as neurobiological factors involved in the pathogenesis of delirium.

The etiology of delirium in cancer patients is multifactorial. Older cancer patients are at increased risk for delirium because of age-related changes in the brain and other age-related physiological changes. Delirium in cancer patients is related to the direct and indirect effects of cancer (and cancer treatment) on the central nervous system (CNS) (Fann & Sullivan, 2003; Meyers, 2000). Delirium also may be caused by factors unrelated to the cancer such as prior stroke, pre-existing dementia, or other comorbid processes common in the elderly.

Primary and metastatic brain tumors can compress the brain and its blood vessels, obstructing the flow of blood and cerebral spinal fluid, thus causing delirium and other

neurological symptoms. Encephalopathy following therapeutic radiation of the brain can occur within hours of the first treatment, or be delayed by weeks, months or years after treatment (Keime-Guibert, Napolitano, & Delattre, 1998; Moretti, Torre, Antonello, & Cazzato, 2001). Biotherapies such as interleukin-2 and interferon- $\alpha$  can produce acute confusion or other disorders like depression and mania (Forman, 1994; Raison, Demetrashvili, Capuron, & Miller, 2005).

Metabolic encephalopathies are common in cancer patients, particularly those with primary or metastatic liver involvement, and those with underlying liver and renal dysfunction. Wernicke's encephalopathy (thiamine deficiency) is an often overlooked but reversible cause of delirium in malnourished cancer patients (Onishi et al, 2004; Turner, Alley, & Sharpless, 2005). Hypoxia, ischemia, infection, and electrolyte abnormalities (Morita et al., 2001; Tuma & DeAngelis, 2000), as well as paraneoplastic syndromes, resulting from tumor secretion of pro-inflammatory cytokines or antineuronal autoantibodies or other substances, can induce delirium in cancer patients (Kung, Mueller, Geda, & Krahn, 2002; Munshi et al., 2005; Young, 1998; Zeimer, 2000).

Medications used to treat cancer or to ameliorate symptoms can cause delirium. These include anticholinergics like diphenhydramine (Tune & Egeli, 1999), chemotherapeutic and biological agents (Lerner, Stoudemire, & Rosenstein, 1999; Young, 1998), opioids (Gaudreau, Gagnon, Harel, Roy, & Tremblay, 2005; Lawlor, 2002), corticosteroids (Gaudreau et al.; Jenkins & Bruera, 2000; Stiefel, Breitbart, & Holland, 1989), and non-opioid psychoactive medications including benzodiazepines, hypnotics, and antiemetics (Guadreau et al., Lawlor, Gagnon et al., 2000).

### *Measurement of Delirium*

Multiple designs and methods have been used to study and measure delirium. Retrospective methods have used medical record reviews to identify a documented diagnosis of delirium or to identify delirium based on documentation of delirium symptoms or diagnostic criteria. However, retrospective methods are imprecise (Johnson et al., 1992) and have significant limitations primarily because it is well documented that delirium is underrecognized and underreported by physicians and nurses (Inouye, Foreman, Mion, Katz, & Cooney, 2001; Neelon, Champagne, McConnell et al., 1992). Additionally, the evaluation and documentation of cognitive function and behaviors associated with delirium in clinical practice are not systematic or complete (Foreman, 1993). Prospective longitudinal designs using valid and reliable instruments to measure delirium are crucial to study and gain a better understanding of the phenomenon. Because delirium is characterized by alterations in cognition and behavior, the bedside assessment and observation of cognitive function and behavior are required for proper identification and measurement.

In addition to the gold standard – a clinical interview by a psychiatrist – more specific instruments and scales have been developed for screening, diagnosing, and monitoring delirium in research and clinical settings. These instruments have been extensively reviewed (Smith et al., 1995; Levkoff, Liptzin, Cleary, Reilly, & Evans, 1991; Rapp et al., 2000; Trzepacz, 1994b). Smith et al. (1995) separate these instruments into three main categories: cognitive impairment screening instruments such as the Mini-Mental Status Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), delirium diagnostic instruments such as the Confusion Assessment Method (CAM) (Inouye et al., 1990), and delirium numerical rating scales such as the Delirium Rating Scale (DRS) (Trzepacz, Baker, & Greenhouse, 1988), the Delirium

Rating Scale-Revised-98 (DRS-R-98) (Tzrepacz et al., 2001), the Memorial Delirium Assessment Scale (Breitbart et al., 1997) and the NEECHAM Confusion Scale (Neelon, Champagne, Carlson, & Funk, 1996). All of these instruments have established psychometric properties and have been used in research and in clinical practice to measure delirium and acute confusion.

Neelon et al. (1996) identify the characteristics of an ideal instrument for measuring delirium. It should cause low respondent burden, allow for rapid bedside assessment, and measure all aspects of the phenomenon. Furthermore, it should allow repeated measurement and monitoring of delirium over time.

The MMSE and other cognitive impairment screening instruments are measures of global cognitive function and are not specific for delirium because they exclude the evaluation of behavioral symptoms commonly seen in delirium. Therefore, some (Lawlor & Bruera, 2002; Inouye et al., 1990) have suggested that the use of cognitive screening instruments followed by a more in-depth delirium assessment using a delirium instrument is best.

As previously noted, a number of methods and instruments have been used to identify and diagnose delirium. Observational instruments that are minimally burdensome may be the most useful and most practical in the palliative care setting. Patients with advanced cancer near the end of life may not be able to complete instruments that require active participation. They may have the cognitive ability but lack the motor skills required to complete the test. Lawlor, Nekolaichuk et al. (2000) found that 20-30% of advanced cancer patients could not participate in the objective assessment components on the MDAS because of fatigue, dyspnea, and delirium. Similarly, in a retrospective review of the MMSE, Pereira et al.

(1997) found a number of missing items. The items most frequently missing were those that required writing and drawing.

Several observational instruments have been developed specifically to measure delirium in terminal cancer patients. The Bedside Confusion Scale (Stillman & Rybicki, 2000) is a screening tool that assesses level of alertness and attention. The Agitation Distress Scale and the Communication Capacity Scale (Morita, Tsunoda, Inoue, Chihara, & Oka, 2001) are observational rating scales that quantify agitation and ability to communicate in terminally ill patients with delirium. Although these scales were found to be reliable and valid in limited testing, they need further evaluation.

### *Subsyndromal Delirium*

The development and use of the DSM criteria has increased reliability in the diagnosis of delirium. However, these criteria are restrictive and do not identify patients with emerging or partial delirium syndromes. Subsyndromal delirium, the manifestation of delirium symptoms without meeting diagnostic criteria for the full syndrome may be a common phenomenon in patients with advanced cancer at the end of life. Subsyndromal presentations of delirium may indicate a change in the underlying medical condition or the development of a new undiagnosed medical condition (Caraceni & Grassi, 2003). The prompt recognition and treatment of subsyndromal delirium may promote symptom improvement and prevent the development of more severe delirium. Delirium must be more broadly understood as a spectrum of nonadaptive psychophysiological responses encompassing a range of cognitive and behavioral abnormalities ranging from mild to severe (Neelon & Champagne, 1992). Subsyndromal or preclinical delirium may represent the

milder range of the continuum, while delirium meeting diagnostic criteria represents the more severe extreme (Levkoff et al., 1996).

Lipowski (1990) describes a pre-delirious state in which patients exhibit one or more symptoms of delirium including difficulty with thinking and concentration, restlessness, anxiety, irritability, drowsiness, insomnia, hypersensitivity to environmental stimuli, nightmares, and transient perceptual disturbances. Similarly, Meagher & Trzepacz (1998) describe a prodromal phase characterized by disturbances in behavior, affect, and sleeping patterns. Subsyndromal manifestations of delirium have been minimally studied. Levkoff et al. (1992) found that a number of hospitalized medical-surgical patients may exhibit individual symptoms of delirium without meeting full diagnostic criteria. Patients with pre-delirium may or may not go on to develop diagnostic delirium. Currently there is no measure for subsyndromal delirium.

Delirium does, in fact, demonstrate a continuum of severity. Typically, delirium is often only recognized, diagnosed, and treated when severe symptoms such as disorientation, hallucinations, and agitation are present. While this prevents false-positives in diagnosis, it has significant implications—specifically the failure to recognize and diagnose, and therefore, the failure to treat mild delirium and hypoactive presentations of delirium. Symptoms of subsyndromal or mild delirium include fearful mood or anxiety, inattention, and distractibility; these symptoms are non-specific and may be difficult to distinguish from normal behavior. Mild delirium is most often missed, overlooked, or misdiagnosed, but may be the most treatable. Early treatment may prevent progression to moderate or severe delirium. Furthermore, subsyndromal delirium is not only common, but also clinically relevant because it increases the risk of further cognitive decline, functional dependence, and

increased mortality during and after hospitalization (Francis & Kapoor, 1992; Levkoff et al., 1992)

In clinical practice, delirium often is not recognized until a patient exhibits extreme cognitive and behavioral dysfunction (i.e., agitated confusion). It is likely that subsyndromal delirium or acute confusion can be identified before all of the diagnostic criteria for delirium are met. Clinicians often either fail to recognize subtle cognitive and behavioral changes associated with subsyndromal delirium or they see them as normal for the patient's condition. Acute confusion may precede delirium as an indication that something is not right. Early and prompt recognition and treatment of acute confusion may prevent more severe delirium from developing.

*Differentiating Patterns of Impaired Cognitive Functioning: Confusion, Dementia, Depression, Terminal Decline, and Terminal Restlessness*

Impaired cognitive functioning refers to problems in the brain's ability to acquire, process, store, and retrieve information (Lawlor, 2002). Cognitive impairment is common in older adults, and most likely results from structural and functional changes in the brain. Cognitive impairment is a defining feature in a number of psychiatric and clinical disorders including delirium, dementia, depression, terminal decline, and terminal restlessness. These syndromes are not mutually exclusive, as they frequently coexist. Since delirium is often misdiagnosed as dementia or depression there is a need to discuss the unique features that differentiate between these disorders. Additionally, dementia and depression are recognized risk factors for delirium. The defining features of delirium, dementia, and depression are presented in Table 2.2.

Table 2.2. Defining features of delirium, dementia, and depression

Feature	Delirium	Dementia	Depression
Onset	Acute, abrupt	Slow, progressive	Weeks to months
Course	Fluctuates, often diurnal	Stable	Stable or with situational fluctuation
Duration	Short or variable	Chronic	Variable
Consciousness	Clouded, decreased	Alert	Intact
Orientation	Often impaired particularly to place, time, and events	Often impaired	Intact
Attention	Reduced or vigilant	Usually normal	Variable
Memory	Impaired, variable	Impaired	Normal or impaired short-term
Affect	Mood lability	Mood lability	Consistent, flat, or blunted
Thinking	Disorganized, fragmented	Abstraction and judgment impaired	Intact but with hopelessness and helplessness
Speech	Incoherent, slow or rapid	Word finding difficulty	Normal or slowed
Sleep-wake cycle	Disturbed, cycle reversed	Fragmented	Fragmented, increased or decreased
Delusions	Common, often paranoid	Sometimes	Occasional in severe cases
Hallucinations	Visual and auditory common, tactile and olfactory possible	Uncommon	Rare except in severe cases

*Sources.* Insel & Badger, 2002; Kennedy, 2003; Lipowski, 1990



### *Confusion*

Confusion is a non-specific term often used to describe a state of cognitive impairment. There is much imprecision in the use of the term, clinically and in research reports. Clinicians often use the term “confused” indiscriminately to describe or label persons exhibiting cognitive impairment. Nurses often use the term confusion to describe a state of disorientation, while physicians emphasize memory component (Wolanin & Phillips, 1981).

### *Dementia*

Dementia, in contrast to delirium, is characterized by a progressive, usually gradual, decline in global cognitive function. The prevalence of dementia increases with age. Dementia affects up to 10% of older adults over 65 years of age and 50% of those over the age of 85 (Insel & Badger, 2002; Kennedy, 2003; Ritchie & Lovestone, 2002). Patients with dementia exhibit profound alterations in thinking and memory such that it interferes with normal daily function (Insel & Badger). The ability to learn and retain new information is significantly impaired. Executive functioning is also impaired. Typically, attention and alertness remain intact in dementia until late in the disease.

The cognitive changes associated with dementia are often accompanied by alterations in mood, behavior, and personality (Ritchie & Lovestone, 2002). These changes are similar to those that occur with delirium and depression contributing to the difficulty in differentiating between them. The presence of dementia is a significant risk factor for delirium so that clinicians should be aware of the potential for delirium superimposed on dementia.

### *Depression*

Rates of depression in community-dwelling older adults are low, but increase in hospitalized older persons, nursing home residents, and those who are chronically ill (Koenig & Blazer, 2003). The prevalence of depressive symptoms can average 20-30% (Insel & Badger, 2002). Older persons with depression experience prominent difficulties with memory and concentration. Depressed persons may also exhibit apathy and irritability. Older persons may be more likely to experience cognitive dysfunction when depressed. Patients with cognitive impairment also experience depression, suggesting that depression and cognitive impairment likely have interactive, reciprocal influences (Goy & Ganzini, 2003). Depression in older adults accompanied by cognitive impairment may herald the onset of dementia (Kennedy, 2003).

### *Terminal Drop and Terminal Decline*

Kleemeier (as cited in Siegler, 1975) introduced the terminal drop hypothesis when he reported a relationship between intellectual function and death. More specifically, Kleemeier (as cited in Berg, 1996) noted that individual differences in intellectual functioning in old age could be accounted for by a terminal drop or decline associated with the death of the individual rather than the chronological age of the individual. Two terms, terminal drop and terminal decline, have been used to describe observed decrements in cognitive functioning prior to death. Palmore & Cleveland (1976) differentiated between the two by noting that a curvilinear decline of intellectual functioning close to death is terminal drop, while a more gradual linear deterioration is terminal decline.

### *Terminal Restlessness*

Terminal restlessness is a common occurrence at the end of life. Terminal restlessness is characterized by agitation, fidgeting, involuntary muscle twitching or jerking, and moaning in the context of impaired consciousness (Back, 1992; Travis, Conway, Daly, & Larson, 2001). Terminal restlessness is disturbing for family caregivers (Brajtman, 2003; Morita et al., 2004) and professional caregivers (Brajtman, 2006). Several authors have discussed the need to differentiate between delirium and the terminal state (Neelon & Champagne, 1992) or between reversible delirium and delirium as a terminal event (Lindesay, Rockwood, & MacDonald, 2002).

### *Age-Related Cognitive Decline in Older Adults*

Age-related cognitive decline in older adults increases their baseline vulnerability for delirium. Therefore, this section discusses normal cognitive changes associated with aging and factors contributing to cognitive decline in older adults, specifically age-related central nervous system (CNS) changes and other physiological and health-related factors.

### *Normal Age-Related Cognitive Changes*

Baltes (1993) describes the trajectory of cognitive functioning across the lifespan. He notes that cognitive mechanics, or fluid intelligence, involve the speed and accuracy of processing, visual and motor memory, and other aspects of working memory, and that cognitive pragmatics, or crystallized intelligence, include reading and writing skills, language comprehension, and other learned skills and procedural knowledge. Typically, decrements in the cognitive mechanics begin in early adulthood and continue throughout life. On the other

hand, the cognitive pragmatics continue to develop across the lifespan and remain relatively stable into old age.

While there is an overall pattern of age-related decline, cognitive functioning in older adults is marked by significant individual differences. In a review of cognitive functioning in old age, Backman, Small, Wahlin, & Larsson (2000) demonstrate that demographic, cognitive, psychological, lifestyle, and biological factors influence cognitive performance in older adults and probably account for these individual differences in cognitive function. Many factors and age-related processes contribute to cognitive decline in older adults.

#### *Age-Related Central Nervous System (CNS) Changes*

Raz (2000) provides an extensive overview of neuroanatomical and neurophysiological changes associated with aging. Multiple global structural and biochemical changes have been observed in the aging brain. In the normal aging brain, the loss of neurons is limited to discrete areas and exhibits individual variability. More extensive neuronal loss occurs with age-associated neurological disorders such as Alzheimer's disease and Parkinson's disease (Timiras, 2003). While the question regarding an age-related reduction in the total number of neurons is widely debated, neurons undergo significant and pervasive structural changes, including the loss of dendrites and synapses (Raz, Timiras). There is a reduction in white matter resulting from changes in myelin and neuronal atrophy. Autopsy studies have revealed an overall decrease in brain weight and volume with aging. In addition, there is enlargement of the cerebral ventricles and the cerebral sulci. Functional neuroimaging studies have shown evidence of a reduction in cerebral blood flow and a reduction in glucose and oxygen metabolism (Raz). Multiple cognitive processes are affected

by age-related changes in neurological structures—including the hippocampus, amygdala, striatum, and prefrontal cortex—and changes in the levels and functioning of neurotransmitters (Raz, Timiras).

*Physiologic and Health-Related Factors Associated with Cognitive Decline in Older Adults*

A number of health-related factors associated with aging significantly affect cognitive function in older adults (Backman, Small, Whahlin, & Larsson, 2000). These health-related factors include systemic biological changes and factors such as nutrition, vitamin deficiency, hormonal changes, and medications. In addition, age-related decreases in organ functional capacity or reserve and the failure of regulatory mechanisms and homeostatic systems also cause systemic changes that impair cognitive functioning. Acute and chronic illnesses are increasingly common in older adults. Disease-specific factors associated with cardiovascular disease and hypertension (Brown, Baird, Shatz, & Bornstein, 1996; Madsen, Nielsen, & Christiansen, 2000), diabetes (Croxon & Jagger, 1995), lung disease (Rourke & Adams, 1996), and cancer (Meyers, Byrne, & Komaki, 1995) contribute to alterations in cognitive functioning in older adults. Hamerman et al. (1999) reported that inflammatory processes involving cytokines are associated with many acute and chronic conditions in older adults. These inflammatory processes have both local and systemic effects that result in additional health-related morbidity and chronicity. Cytokines have been associated with alterations in cognitive function and the role of cytokines in delirium has been proposed as discussed below (Broadhurst & Wilson, 2001; Flacker & Lipsitz, 1999; van der Mast, 1998).

### *Cognitive Impairment in Cancer Patients*

Studies of cognitive impairment and delirium in cancer patients have included patients with a wide range of ages. Few studies have examined cognitive alterations or delirium exclusively in older adults with cancer, nor have they described particular cognitive alterations that occur in older cancer patients with delirium. Studies have examined the frequency of psychiatric disorders, neuropsychiatric symptoms, and neurocognitive impairments in cancer patients at different stages of illness (Derogatis, 1983; Minagawa, Uchitomi, Yamawaki, & Ishitani, 1996; Portenoy, Krupp, & Kanner, 1986). Some studies have examined symptom prevalence, including cognitive symptoms in cancer patients (Grond et al; 1994; Portenoy et al, 1994). Studies also have focused on cognitive impairment in specific patient populations, small cell lung cancer patients (Myers, Byrne, & Komaki, 1995) and breast cancer patients (Cimprich, 1998; Schagen, 1999), and in association with different cancer treatments such as surgery (Cimprich) and adjuvant chemotherapy (Schagen) in breast cancer and cytokine therapies including interferon (Bender et al., 2000) and interleukin-2 (Rosenberg et al., 1989). An increasing number of studies have examined cognitive impairment or delirium in patients with advanced or terminal cancer (Bruera et al, 1992; Caraceni et al., 2000; Cobb et al., 2000; Donnelly & Walsh, 1995; Gagnon, Allard, Masse, & DeSerres, 2000; Lawlor et al., 2000; Massie, Holland, & Glass, 1983; Minagawa et al.; Morita, Tei, Tsunoda, Inoue, & Chihara, 2001; Pereira, Hanson, & Bruera, 1997; Sarhill et al., 2001; Stiefel, Fainsinger, & Breura, 1992; Wakefield & Johnson, 2001). Findings from these studies have shown that delirium and cognitive impairment are common in patients with advanced cancer and become more prominent closer to death.

Studies of cognitive impairment and delirium in cancer patients have used a variety of

methods making it difficult to summarize and compare results. However, multiple cognitive alterations are common in cancer patients and may be related to direct effects of the cancer, side effects of cancer treatment, or possibly unrelated processes. Alterations have been found in many domains of cognitive function including attention (Cimprich, 1998; Schagen, 1999), orientation and alertness (Rosenberg et al, 1989), mental flexibility and speed of information processing (Schagen), verbal memory (Myers et al, 1995), visual memory (Schagen), motor function (Myers et al; Schagen) and executive function (Myers et al.). Myers et al. found that similar cognitive alterations in small cell lung cancer patients were present before and after treatment suggesting that the disease itself may be a contributing factor. In her study evaluating attention in women following surgery for breast cancer, Cimprich found that older women had significant declines in attention regardless of the extent of surgery. Although only one study (Cimprich) evaluated a single aspect of cognitive function in older women, it is expected that cognitive alterations in older adults with cancer would be similar to cognitive alterations in other cancer patients but possibly even more pronounced and long-standing.

### *Cognitive Changes at the End of Life*

Cognitive impairment is one of the most common, and most feared, complications of terminal illness. Studies examining symptom prevalence in patients with advanced cancer receiving palliative and end of life care have reported a variety of cognitive symptoms including confusion (Brescia et al., 1990; Coyle, Adelhart, Foley, & Portenoy, 1990; Klinkenberg, Willems, van der Wal, & Deeg, 2004; McCarthy, Phillips, Zhong, Drews, & Lynn, 2000), impaired memory and concentration (Curtis, Krech, & Walsh, 1991), agitation (Elshamy & Whedon, 1997), drowsiness (Fansinger et al., 1991), altered level of

consciousness (Fainsinger et al., Lichter & Hunt, 1990; Morita et al., 1998, Peruselli et al., 1999), sedation (Curtis et al.), hallucinations (Fountain, 2001), and other parapsychological phenomena such as visions (Barbato et al., 1999).

A pattern of diminishing level of consciousness is common in patients approaching the end of life. Studies of dying patients report that 50% or more were comatose or unconscious in the last hours of life, most of the others were drowsy, and only a small percentage of patients remained awake or alert (Fainsinger et al., 1991; Morita et al., 1998). Lichter and Hunt (1990) reported that 30% of 200 hospice patients were conscious until death. The timing of loss of consciousness was examined in the other patients: 38% became unconscious from 0-12 hours prior to death, 24% became unconscious from 12-24 hours prior to death, 7% became unconscious 24-48 hours prior to death, and 1% were unconscious 48 hours or more prior to death. However, the level of consciousness is not described further. Interestingly, Turner et al. (1996) found that 60% of patients maintained cognitive function and were able to speak lucidly at a moderate to good level in the last 3 days of life according to physician and nurse ratings.

Fainsinger et al. (1991) found that average visual analogue scale scores (0-100) for drowsiness increased from  $51 \pm 28$  on Day 6 prior to death to  $85 \pm 45$  on the date of death. Additionally, a large percentage of patients experienced changes in their level of consciousness from the day of admission to the date of death. On the day of admission, 72% of patients were alert, 28% drowsy, and 0% unresponsive; whereas on the date of death, 2% were alert, 41% drowsy, and 57% unresponsive.

Klinkenberg et al. (2004) conducted after-death interviews with close relatives of 270 deceased older persons from a population-based sample of older persons in the Netherlands



to examine symptom burden in the last week of life. The sample included 167 (62%) and 103 women (38%) with a mean age of 80 years (range 59-91). Thirty five percent of the sample had cancer. The remainder had a variety of chronic disease diagnoses. At least 36% of patients experienced cognitive decline over the last three months of life. Patients with severe cognitive decline over the last three months of life were reported to have had higher levels of symptom burden than those with low or no decline in cognitive function. Relatives reported that 34% of patients were unable to make decisions in the last week of life. Relatives also reported that no communication was possible during the last week in 15% and that 4% of patients were unconscious throughout the last week.

McCarthy, Phillips, Zhong, Drews, and Lynn (2000) conducted a retrospective analysis of the last 6 months of life to describe the dying experience of lung and colon cancer patients enrolled in the SUPPORT project. Patients experienced functional decline and poorly controlled pain and confusion. Severe confusion was more common in lung cancer patients than in colon cancer patients during the 3-6 month period prior to death, but in the last 3 days of life the frequency of severe confusion was similar in both groups. Approximately 28% of patients in both groups experienced severe confusion during this period.

Brescia et al. (1990) retrospectively studied symptom prevalence in 1,103 advanced cancer patients admitted to a palliative care hospital. One third (33%) of the patients exhibited at least one episode of confusion or disorientation during the first 24 hours after admission. Confusion was greater in older patients; those over the age of 75 years were more likely to experience confusion.

Coyle et al. (1990) conducted a retrospective record review to identify the prevalence of symptoms volunteered by patients in the last 4 weeks of life. Symptoms had been elicited by daily telephone contacts between the team nurse and patient or family. Only the symptoms volunteered by patient or family informants were included. Cognitive impairment reported by 24% of informants was one of the most prevalent symptoms 4 weeks before death. One week prior to death 28% of informants reported mental haziness or confusion. The prevalence of sleepiness increased from 24% 4 weeks before death to 57% one week before death.

Morita et al (1998) prospectively studied the process of dying in 100 terminally ill cancer patients. The level of consciousness of patients was measured using a categorical scale: awake, drowsy, very drowsy, and coma. The level of consciousness diminished over the last week of life. One week prior to death 56% of patients were awake, 44% drowsy, and 0% comatose. In the last 24 hours, 26% were awake, 62% drowsy, and 12% comatose. In the final 6 hours of life, half of patients (50%) were comatose, 42% were drowsy, and 8% were awake.

Elshamy and Whedon (1997) conducted a secondary analysis of data obtained from a retrospective chart review to examine the frequency of dyspnea, pain, agitation, and confusion in hospitalized patients during the last 48 hours of life. The sample included patients with cancer, cardiovascular disease, respiratory disease, and other diagnoses. They found that nearly half of the patients (43%) were fully oriented within 2 days of death. Overall, 47% of the patients experienced agitation in the last 48 hours; 52% of cancer patients experienced agitation. Among all patients, 32% experienced confusion; 37% of

cancer patients experienced confusion. The frequency of agitation and confusion was similar in cancer and non-cancer patients.

In an Italian study, Peruselli et al. (1999) examined the place, circumstances, and quality of death in 401 patients admitted to home palliative care units. Following the patient's death the palliative care team completed the Support Team Assessment Schedule (STAS), an instrument designed to evaluate quality of care, quality of life, and team effectiveness and a quality of death questionnaire. They report that 34% of the patients were conscious until death. However, level of consciousness is not further defined and data were missing for 44 patients. They also found that 25% of the patients required pharmacological sedation for symptom management in the last 12 hours of life

The previously reviewed studies focused on cognitive impairment in the last weeks of life. Other studies have looked at symptom prevalence in cancer patients at the time of referral to palliative care services (Conill et al., 1997; Curtis, Krech, & Walsh, 1991; Jenkins, Schulz, Hanson, & Bruera, 2000). In these studies, patients were at various places in their disease trajectories and, in some cases, still receiving active cancer treatments.

Conill et al. (1997) compared the frequency of symptoms at the first palliative care evaluation to the frequency of symptoms during the last week of life in 176 patients with advanced cancer. Patients' self-reports of confusion more than doubled between the two assessments. At the initial assessment, 53 (30.1%) patients reported confusion compared to 120 (68.2%) patients at the second assessment during the last week of life.

Curtis et al. (1991) prospectively documented the presenting symptoms of 100 advanced cancer patients upon referral to a palliative care service. The total number of symptoms experienced ranged from 1 to 25 with a median of 6. Cognitive symptoms, present

in a small number of patients, included confusion in 11%, memory problems in 10%, and sedation in 7%.

Jenkins, Schulz, Hanson and Bruera (2000) retrospectively examined symptom profiles in cancer patients at the time of referral to a palliative care consult team in a tertiary hospital. Of the 95 patients, 36 were either newly diagnosed or diagnosed with a recurrence of a potentially cured cancer. Of the remaining 56 patients, 46 had a progressive terminal cancer, 5 had a potentially curable cancer, and 8 were thought to be in remission or potential remission. Almost half (44%) of the 91 patients assessed with the mini-mental status questionnaire (MMSQ) on the consult day exhibited cognitive impairment based on a score of less than 24/30 or less than 80% if they could only partially complete the test. An additional 10 of the 91 patients had evidence of delirium by DSM IV criteria despite a normal score on the MMSQ. Three patients who could not complete the MMSQ had cognitive impairment on the basis of clinical evaluation. Overall, 53 of the 95 (56%) patients referred for palliative care consultation had evidence of cognitive impairment. In this study, 18 of 19 patients (95%) who died during hospitalization had cognitive impairment.

The findings from these studies indicate that cognitive impairment frequently occurs in the last weeks of life as a pre-terminal event. Moreover, the findings also suggest that cognitive impairment in patients with advanced cancer may be a significant problem earlier in the illness trajectory.

### *Delirium in Cancer Patients*

Most studies of delirium in cancer patients, in general, have focused on estimating its prevalence and incidence in hospitalized patients. These studies indicate that delirium is a

significant problem in hospitalized cancer patients but the findings are not consistent. The reported rates of delirium in cancer patients vary widely from 8% (Derogatis et al., 1983) to 66% (Tuma & DeAngelis, 2000). Studies of delirium in cancer patients date back to 1978, utilize retrospective and prospective designs, and operationalize and measure delirium differently. A variety of terms are used to refer to delirium in these studies including cerebral dysfunction (Massie et al., 1979), organic mental disorders (Derogatis et al.), organic brain syndrome (Levine et al., 1978), acute encephalopathy (Tuma & DeAngelis, 1992), altered mental status (Tuma & DeAngelis, 2000), and cognitive impairment (Folstein et al., 1984). Most studies used DSM criteria to establish a diagnosis of delirium. However, different versions of the criteria were used including DSM II (Levine et al.); DSM III (Derogatis et al.); DSM III-R (Tuma & DeAngelis, 2000); and DSM IV (Fincannon, 1995). Studies using one version are not directly comparable to studies using another version. In most reports, the operationalization and application of DSM criteria are also not explicitly described. Folstein et al. (1984) used the MMSE to measure cognitive impairment in cancer patients.

Several studies have evaluated the frequency of delirium in cancer patients referred for psychiatric consultation (Fincannon, 1995; Levine, Silberfarb, & Lipowski, 1978; Massie, Gorzynski, Mastrovito, Theis, & Holland, 1979). Studies examining psychiatric consultation in cancer patients indicate that a small number of referrals are made for suspected delirium and that delirium is often misdiagnosed as depression. Fincannon (1995) reported that only 6% of 102 patients were referred to a psychiatric consultation liaison nurse (PCLN) for delirium, but in fact 14% were diagnosed by the PCLN as having delirium. Six patients (19%) referred for depression were diagnosed with delirium. In a retrospective review of 100

psychiatric referrals, Levine et al. (1978) noted that while only 21% of patients were referred for delirium (organic brain syndrome), 40% were diagnosed by the consulting psychiatrist as having delirium. Moreover, 26 patients with delirium had been misdiagnosed as having depression by the referring physician. These findings suggest that the actual incidence of delirium in cancer patients is probably underrepresented because of either failure to recognize symptoms or misdiagnosis.

Tuma & Deangelis (2000) examined the clinical findings, causes, and outcomes of altered mental status in 140 hospitalized cancer patients referred for neurology consultation. Thirty-four percent of patients had altered mental status on admission and 66% developed altered mental status during hospitalization. Patients exhibited a number of cognitive symptoms including lethargy and coma (61%), agitation (44%), disorientation (83%), and delusions and hallucinations (28%). A single cause of altered mental status was identified in 33% of patients, while multiple causes were identified in 67%. Altered mental status improved in 67% of patients but it was a poor prognostic factor overall—25% of patients died within 30 days and 44% died within 6 months.

Methodological issues and differences among studies of delirium in cancer patients make comparison across studies difficult. Studies have included heterogeneous samples with a wide age range, a variety of cancer diagnoses, and variable stages of disease. Few studies have examined delirium specifically in older cancer patients. In addition, few studies have prospectively examined delirium in the home setting. The frequency of measurement has varied across studies. The conceptualization and measurement of delirium also has varied across studies. Multiple instruments have been used to measure delirium. When diagnostic criteria have been used, investigators have operationalized them differently resulting in

imprecision and lack of standardization of measurement. Finally, delirium often has been diagnosed as a dichotomous outcome—present or absent—without regard to its level of severity.

### *Delirium in Patients with Advanced Cancer*

Over the past decade an increasing number of studies have examined delirium and cognitive impairment in patients with advanced cancer. Most of these studies included terminally ill cancer patients near the end of life and were conducted primarily in hospital and in inpatient palliative care settings. Studies can be divided into three groups: those examining confusion as a symptom at the end of life, those specifically addressing cognitive function or cognitive impairment (failure), and those examining delirium. Many different instruments were used to measure delirium and cognitive failure (Hjermstad, Loge, & Kaasa, 2004). Studies have focused on estimating the frequency of delirium (prevalence and incidence), identifying etiological factors, and evaluating outcomes of delirium (reversibility and symptom improvement).

#### *Frequency of Delirium in Patients with Advanced Cancer*

Massie et al. (1983) prospectively evaluated 19 cancer patients who were likely not to survive hospitalization. After an initial interview, assessments using a 58-item delirium rating scale were conducted three times a week. Six of the patients improved or were discharged. The 13 patients who died during hospitalization were monitored until death. Eleven of 13 patients (85%) developed delirium prior to death. The other two patients remained mentally clear until shortly before death.

Bruera, Chadwick, Weinlick, and MacDonald (1987) completed a retrospective case review to evaluate the frequency of delirium and severe sedation in 30 patients with metastatic cancer who were hospitalized for at least one week. All patients were assessed daily. Delirium was diagnosed clinically if a patient exhibited a confusional state with or without hallucinations or hyperactivity. Severe sedation was diagnosed if a patient was unable to converse because of diminished level of consciousness. Twenty-three of 30 patients (77%) developed impaired mental status. Sixteen had delirium and the remaining 7 exhibited severe sedation.

Several studies with retrospective and prospective designs have used serial MMSE measurements to examine the frequency and course of cognitive impairment in patients with advanced cancer. Bruera, Miller et al. (1992) prospectively evaluated cognitive function in 61 cancer patients admitted to an acute palliative care unit. In a retrospective study, Pereira et al. (1997) examined the frequency and clinical course of cognitive failure in 348 patients admitted to a palliative care unit over a 26-month period. Zhukovsky et al. (1998) found that 21% of cancer patients exhibited cognitive impairment ( $MMSE \leq 23$ ) at the time of referral to a palliative care service.

In a consecutive series, Minigawa et al. (1996) evaluated 93 terminally ill cancer patients within the first week of admission to determine the range of psychiatric diagnoses among them. They administered the MMSE followed by the Structured Clinical Interview (SCID) for the DSM-III-R. Overall, 54% of patients met DSM III-R criteria for a psychiatric disorder. Based on MMSE scores, 39 patients (42%) were cognitively impaired. Delirium was observed in 26 patients (28%), and was the most common psychiatric diagnosis. Ten patients (10.7%) were diagnosed with dementia.



In a retrospective review of 100 consecutive patients admitted to a palliative care unit, Fainsinger et al. (1991) used nursing and physician notes to determine the presence or absence of delirium. Thirty-nine patients experienced delirium. For reasons previously mentioned, the use of chart documentation to identify or evaluate delirium has significant limitations.

Two studies (Gagnon et al., 2000; Lawlor, Gagnon et al., 2000) used daily screening and ongoing symptom monitoring to detect delirium. When delirium symptoms were noted a more in-depth diagnostic assessment was performed.

Gagnon et al. (2000) conducted a prospective cohort study to determine delirium frequency and outcome in 89 cancer patients hospitalized for terminal care. The nursing staff screened patients for delirium symptoms three times a day using the Confusion Rating Scale (CRS). If a patient screened positive, a diagnostic assessment with the Confusion Assessment Method (CAM) was performed within 24 hours. The prevalence of delirium on admission was 13.3%, and the incidence during hospitalization was 32.8%. The CRS also was used to monitor delirium symptoms following delirium diagnosis.

Lawlor, Gagnon et al. (2000) studied the prevalence and incidence of delirium in 104 of 113 patients consecutively admitted to an acute inpatient palliative care unit at a university-affiliated teaching hospital. Screening with the MMSE was conducted on admission and twice weekly and anytime delirium was suspected. If patients were cognitively impaired based on the MMSE score, or if there was clinical evidence of delirium, then they underwent a semi-structured interview that operationalized DSM IV criteria for delirium. Patients meeting DSM IV criteria had an assessment of delirium severity using Memorial Delirium Assessment Scale (MDAS) and daily nursing assessments using the

Delirium Observational Checklist Scale (DOCS). Patients who remained delirious underwent an interview and MDAS testing every 72 hours until their delirium resolved or until their death. The prevalence of delirium on admission was 42%, and the incidence of delirium during hospitalization was 45%. Overall 71 patients experienced a total of 94 episodes of delirium. Terminal delirium occurred in 46 (88%) of the 52 patients who died during hospitalization.

It is difficult to compare studies examining the frequency of delirium in advanced cancer patients because they have numerous methodological differences. Studies have used retrospective and prospective as well as longitudinal and cross-sectional designs. Most studies included small heterogeneous samples with a variety of cancer diagnoses. The samples have been select cohorts as well in that they were primarily patients admitted to inpatient palliative care units and hospitals for severe symptomatology. Based on the information provided in the reports, no studies evaluated patients for or excluded patients with prior cognitive impairment. Patients were followed for relatively short periods of time. Different methods were used for case identification including screening on admission and on an ongoing basis, and clinical evaluation by physicians and nurses. The studies also used different measures and methods of cognitive assessment including the MMSE, the CAM, the MDAS, DSM IV criteria, and chart documentation. The frequency and timing of evaluations and the intensity of follow-up varied from daily to two or three times a day to three times a week. Since delirium is transient and symptoms fluctuate, episodes may have been missed with longer intervals between assessments.

### *Timing of Delirium Symptoms in Relation to Death*

Two studies examined the timing of delirium symptoms in relation to death. Bruera et al. (1987) detected symptoms of cognitive impairment an average of  $9 \pm 6$  days before death. In a subsequent study, Bruera et al. (1992) found that patients with advanced cancer developed cognitive failure an average of  $16 \pm 6$  days prior to death.

### *Subsyndromal Delirium in Advanced Cancer Patients*

Subsyndromal delirium may be common in patients with advanced cancer near the end of life. A few studies have underscored the problem of delirium symptoms in patients with advanced cancer by differentiating between the presence of delirium symptoms and the full syndrome. Gagnon et al. (2000) used the CRS to screen for delirium symptoms and to trigger a diagnostic assessment. The prevalence and incidence of delirium symptoms was higher than confirmed delirium. The prevalence of delirium symptoms was 20.2% whereas the prevalence of confirmed delirium was 13.3%. The incidence of delirium symptoms during hospitalization was 52.1% while the incidence of confirmed delirium was 32.8%.

Nowels et al. (2002) used nurses' report to estimate the prevalence of confusion in terminally ill cancer and non-cancer patients enrolled in hospice. Common manifestations of confusion included disorientation, impaired short-term memory, drowsiness, altered sleep-wake cycle, and easy distractability. For confused patients, nurses were asked a series of questions about the patients' cognition based on DSM IV criteria for delirium. According to the nurses' responses to these questions, 14% of the confused patients were likely to have delirium. Chang (2002) questions whether confusion in terminally ill patients could represent pre-delirium that might evolve into delirium or terminal restlessness.

### *Etiology of Delirium in Patients with Advanced Cancer*

Posner (1979) posited that neurologic complications of systemic cancer including delirium were caused by direct effects of the cancer on the CNS or by indirect effects of the cancer or its treatment. Neurologic complications in cancer patients may also be unrelated to cancer but associated with or result from other comorbid medical conditions. The etiologic mechanisms associated with the development of delirium are often multifactorial involving multiple physical (physiologic), psychological, and socio-environmental factors. In a recent study, Lawlor, Gagnon et al. (2000) identified a median of 3 precipitating factors per episode of delirium in 71 cancer patients in an acute palliative care unit. Similarly, Morita et al. (2001) identified a median of 2 precipitating factors per person. In both studies the number of identified factors ranged from 1-6.

The ability to identify specific etiologies of delirium in patients with advanced cancer has varied across studies depending on how potential etiologies were conceptualized and measured. In several studies, the etiologies of delirium could not be established in the majority of patients. Bruera et al (1987) were able to identify the cause of cognitive impairment in 21% of cases. In a subsequent prospective study, Bruera, Miller et al. (1992) could not identify a cause for cognitive impairment in 56% of cases. In a retrospective study of delirium requiring psychotropic drug treatment, Stiefel et al. (1992) were unable to identify a reason for delirium in 75% of cases. These studies did not incorporate a standardized or systematic approach or criteria for identifying etiologic factors.

Two studies using specific criteria for identifying delirium etiologies (Lawlor, Gagnon et al. 2000; Morita et al., 2001) identified etiologic factors in most cases. Morita et al. determined the cause of delirium in 93% of cases. Lawlor, Gagnon et al. identified

precipitating factors for the first episode of delirium in all patients (n = 71) who developed delirium.

Massie et al. (1983) established the cause of delirium in 9 of 11 patients who developed delirium. Delirium was caused by metabolic encephalopathy related to electrolyte imbalance, sepsis, drugs, or organ failure and direct effects of the cancer by structural invasion of the brain, or both. The cause of delirium in the other two patients could not be determined because no laboratory studies were allowed.

### *Delirium Subtypes in Advanced Cancer*

Delirium has been divided according to psychomotor behavior into three clinical subtypes: hyperactive, hypoactive, and mixed (Lipowski, 1983). Hyperactive delirium is characterized by increased psychomotor activity, sympathetic nervous system overactivity, increased alertness or hypervigilance, psychosis, and labile mood. In contrast, hypoactive delirium is exhibited as decreased psychomotor activity, withdrawal, apathy, lethargy or somnolence, and inattention. Symptoms of hyperactive and hypoactive forms of delirium alternate in the same individual when the mixed subtype of delirium is present

Lawlor et al. (1998) observed the mixed subtype in 167 (48%) of 350 delirium episodes, the hypoactive subtype in 166 (47%), and the hyperactive subtype in 11 (3%). The delirium subtype was non-classifiable in 6 (2%) episodes. Lawlor et al. also examined the subtypes associated with terminal delirium that occurred within 72 hours of death. Sixty five percent of patients exhibited the hypoactive subtype and 35% exhibited the mixed subtype. In a study of delirium in the last week of life, Steifel et al. (1992) reported that the majority of patients exhibited the hyperactive or mixed subtype.

### *Reversibility of Delirium in Advanced Cancer*

Delirium is conceptualized as a transient, potentially reversible condition caused by treatable underlying pathophysiologic disturbances. Lipowski (1990) identifies a number of factors that influence the reversibility of delirium including age; overall physical condition; baseline cognitive function; the appropriateness, effectiveness, and timeliness of treatment of underlying cause; and the management of delirium itself. The reversibility of delirium also depends on its underlying cause.

The reversibility of delirium in patients with advanced cancer at the end of life creates significant clinical and ethical dilemmas. Lawlor and Bruera (2002) suggest that all delirium should be considered potentially reversible unless signs of active dying, related to advanced end-stage organ failure, or inconsistent with goals of care. On the other hand, particularly in patients with advanced cancer at the end of life, not all of the pathophysiologic and etiologic factors associated with delirium will be reversible. Furthermore, it may not always be possible to alter the patient's baseline vulnerability or to remove or correct all precipitating factors. The primary treatment of delirium focuses on the identification and treatment of etiologic factors.

In the context of terminal illness, delirium is often treated symptomatically. Patients who are pleasantly confused and who exhibit hypoactive manifestations of delirium are often not treated. On the other hand, patients exhibiting agitation and restlessness are often sedated. The rapid sedation of patients with delirium without adequate assessment and management inhibits patient–family communication and possibly shortens survival.

An increasing number of studies provide empirical support for the potential reversibility of delirium in patients with advanced cancer even at the end of life (Lawlor,

Gagnon et al., 2000; Morita et al., Pereira et al., 1997) and that significant symptom improvement can occur in many cases even without specific intervention (Bruera, Miller et al., 1992; Gagnon et al., 2000). Bruera, Miller et al. found that delirium improved in 22 episodes (33%)—spontaneously in 10 episodes and as a result of treatment in 12 episodes. Similarly, Pereira et al. found that delirium improved in 29% of patients with advanced cancer prior to death or discharge from a palliative care unit. Gagnon et al. (2000) noted that delirium improved in 50% of cases. However, reversibility of repeated episodes was significantly less than reversibility of first episodes. Additionally, patients with delirium on admission were less likely to have symptom improvement. Lawlor, Gagnon et al. (2000) found that delirium reversal occurred in 49% of episodes in 71 patients. Treatment of delirium was based on clinical evaluation. Patients with signs of opioid toxicity had opioid reduction. Hypodermoclysis was used for dehydration. Oral or intravenous antibiotics were given for infection. Hypercalcemia was treated with bisphosphonates. The criteria used to determine delirium reversal or improvement are not always defined.

Lawlor, Gagnon et al. (2000) used univariate and multivariate Cox proportional hazards models to examine the association between etiologic factors and delirium reversibility. Opioids and other psychoactive medications were independently associated with delirium reversal. Dehydration was also significantly associated with delirium reversibility at the univariate level, but its association was not independent in the multivariate analysis. Hypoxic encephalopathy resulting from pulmonary cancer or respiratory infection and metabolic factors were associated with non-reversibility of delirium in the univariate analysis. In the multivariate analysis, only hypoxic encephalopathy was retained as a factor. Non-respiratory infection emerged as a significant independent factor associated with non-

reversibility of delirium in the multivariate analysis. Similarly, Morita, Tei et al. (2001) found that recovery often occurred in delirium associated with medications and hypercalcemia and that recovery was unlikely in delirium caused by hepatic failure, dehydration, hypoxia, and disseminated intravascular coagulation.

The identification of persons at risk for delirium will promote enhanced surveillance and monitoring of these persons and earlier implementation of prevention and intervention strategies. The prevention and management of delirium in older persons with advanced cancer will not only improve the quality of life for patients but may also extend their lives and improve the quality of dying.

### *Conceptual Framework*

Vulnerability-challenge or stress models have been used to understand and study the development of delirium in hospitalized older patients. Neelon & Champagne (1992) used an information-processing framework, a vulnerability model that incorporated reserve capacity and the threshold nature of vulnerability, and an environmental press model to understand and study the development of acute confusion in hospitalized elders and to develop an intervention framework. More recently, Inouye and Charpentier (1996) proposed and validated a vulnerability-stress model of delirium development in hospitalized elderly that involves the interrelationships between predisposing factors, or vulnerability factors, and precipitating factors, or acute insults associated with hospitalization. These models also emphasize the cumulative effects and interactions of vulnerability and challenge.

In the vulnerability-challenge model (Figure 2.1), delirium develops when an individual's threshold of vulnerability is exceeded. The threshold of vulnerability is related to



reserve capacity, or an individual's ability to respond to challenge. Johnson (1985) describes the decline in functional capacity or reserve capacity associated with aging. This decline in reserve capacity may occur over a number of years without lowering functional capacity below threshold. However, when reserve capacity is depleted or so diminished that homeostasis cannot be maintained, system failure occurs.

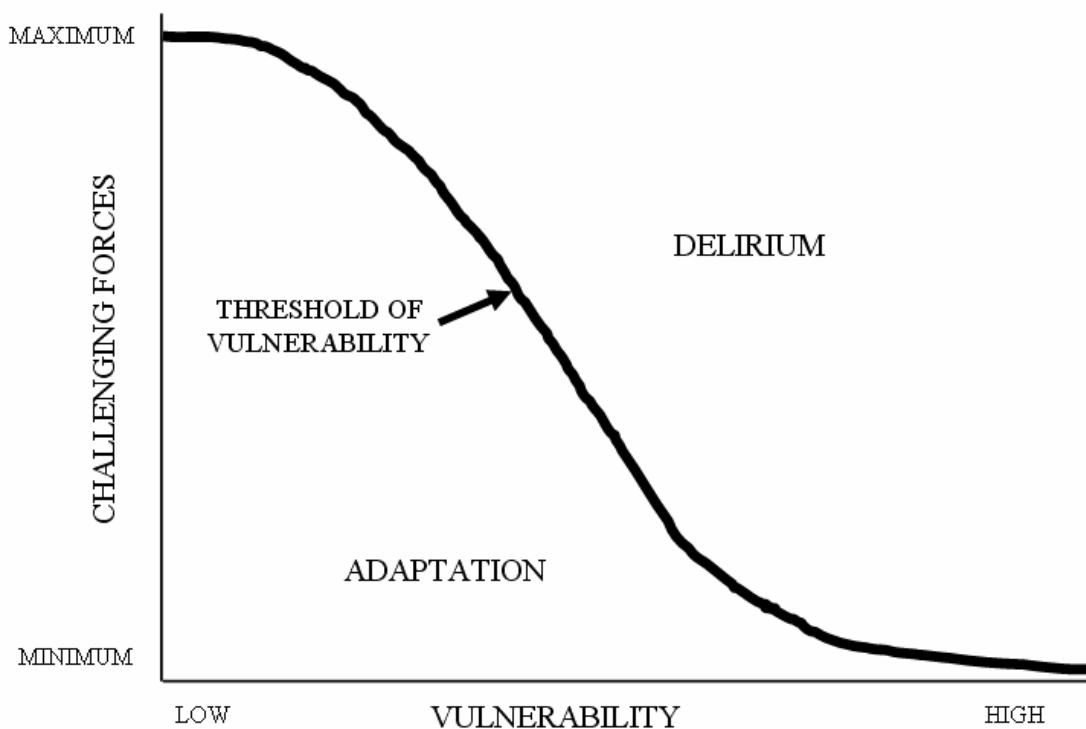


Figure 2.1. Vulnerability-challenge model of delirium development

From: "Vulnerability—a new view of schizophrenia" by J. Zubin and B. Spring, (1977), *Journal of Abnormal Psychology*, 86, p. 110. Copyright 1978 by the American Psychological Association. Adapted with permission.

The onset of delirium occurs when reserve capacity is so diminished that neurophysiologic systems are no longer able to respond adaptively to challenge. Therefore,

reserve capacity influences the development of delirium at different levels or degrees of vulnerability and challenge and provides an explanation for why individuals under similar circumstances may or may not develop delirium. In the vulnerability-challenge model, the level of challenge needed to cause delirium depends upon the vulnerability threshold, or reserve capacity of the individual. For example, an older person with preexisting cognitive impairment has a lower threshold because of diminished cognitive reserves. Therefore, this individual is more likely to develop delirium than a cognitively intact elder when faced with environmental, physiological, or psychosocial stressors.

Vulnerability-challenge models also emphasize that the risk for developing delirium is associated with interactions between and the cumulative effects of vulnerability and challenge. In two studies, Inouye et al. (1993) and Inouye and Charpentier (1996) proposed and validated a risk stratification model that supports the cumulative nature of delirium risk. The model predicted an increased likelihood of developing delirium as the number of predisposing and precipitating factors increased. Delirium risk was determined by adding one point for each predisposing or precipitating factor present. The risk groups were stratified into low-risk, intermediate-risk, and high-risk. No factors were present in the low risk group; one or two were present in the intermediate risk group; and more than three were present in the high-risk group. Development and validation cohorts in both studies showed a statistically significant and progressive increase in the delirium rate among each group from low-risk to high-risk.

Neelon & Champagne (1992) identified patterns of confusion development that were associated with diminished reserve capacity in three areas: cognitive reserve, physiological reserve, and biochemical reserve. These three categories will be used to examine changes in

delirium vulnerability and the relationship between changes in delirium vulnerability and the development of delirium at the end of life.

Reserve capacity also influences the outcome of delirium. Clearly, at some point in the dying trajectory, reserve capacity becomes totally depleted and challenges to neurophysiologic and other functional systems result in irreversible damage and complete system failure. At this point, treatment strategies should focus on managing the symptoms of delirium and comfort rather than on delirium reversal. On the other hand, if reserve capacity is sufficient enough, treatment strategies aimed at correcting the underlying mechanisms of delirium may result in delirium resolution.

Several authors (IOM, 1997; Lunney, Lynn, and Hogan, 2002; Teno, Wietzen, Fennell, & Mor, 2001) have described the typical dying trajectory of cancer patients. These patients live relatively well with their illness for a long period before the illness becomes overwhelming. At that point, patients enter a terminal phase characterized by a rapid decline in function and death usually within 6 weeks. It is hypothesized that delirium vulnerability increases significantly as cognitive, physiological, and biochemical reserves diminish during this terminal phase. The individual is less able to respond to the multiple challenges associated with progression of their disease and its treatment and, therefore, the individual is more likely to develop delirium during this period.

### *Specific Aims and Research Questions*

#### *Phase I: Delirium in Hospitalized Older Cancer Patients*

The first phase involves extensive secondary analyses of data from the Acute Confusion in Hospitalized Elders Studies (NR01339-05: Neelon & Champagne) to examine

delirium in a sample of hospitalized older cancer patients. The specific aims of the analyses were: 1) to characterize the nature and course of delirium in hospitalized older cancer patients; 2) to determine etiologic patterns based on key clinical markers; 3) to compare characteristics and etiologic patterns in patients with delirium and those without delirium; 4) to examine trajectories of delirium resolution; 5) to compare characteristics and etiologic patterns in patients with delirium that resolved prior to discharge and those who had persistent delirium; and 6) to identify delirium trajectories and etiologic patterns in a subset of patients who were near the end of life.

*Phase II: Development and Pilot Testing of a Protocol to Study Delirium in Older Adults with Advanced Cancer*

The second phase involves a pilot study to assess the feasibility of and the burden associated with a protocol to study delirium and cognitive decline in older cancer patients receiving palliative and end of life care. The primary aims of the pilot study are: 1) to test the feasibility of the protocol, first, in a laboratory and, then, in the home setting; 2) to determine the level of patient and caregiver burden associated with the protocol; 3) to evaluate and refine instruments and data collection procedures; and 4) to identify and resolve methodological issues related to recruitment, consent, measurement and retention that may be encountered in studying delirium and cognitive decline in older adults with advanced cancer being cared for at home. More specifically the pilot study will address the following research questions:

1. What minimally invasive instruments and methods can be used to measure cognitive, behavioral, functional, psychological, and physiological parameters associated with delirium in older patients with advanced cancer?

2. To what extent can family caregivers monitor for and identify signs of delirium in the home setting?
3. What issues and concerns do participants and family caregivers have with regard to the research process?

*Phase III: Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer Near the End of Life*

Findings from the first two phases of investigation—the secondary data analyses and pilot study—shaped the design of the final phase of this research. The purpose of the third phase of investigation was to develop a clearer understanding of the nature and course of delirium within the context of advancing illness and approaching death. A longitudinal, multiple case study approach, using quantitative and qualitative methods, was used to examine delirium in older cancer patients near the end of life, during active palliative treatment and in the terminal period. The primary aim of this phase is to identify and describe delirium and trajectories of delirium vulnerability. This aim was achieved by critically examining episodes of delirium when they occur and developing a comprehensive description of the characteristics and course of the delirium episodes. In addition, trajectories of delirium vulnerability and vulnerability factors (cognitive function, physical functioning, symptom prevalence and distress, depression, weight, etiologic pattern markers, and medication use and treatments) will be examined to evaluate how they change over time and in relationship to delirium episodes. A second aim is to examine similarities and differences in delirium in older cancer patients at the end of life and in hospitalized older cancer patients. A third aim is to identify issues associated with studying delirium in older cancer patients at the end of life. The following primary research questions will be addressed:

1. What is the nature and course of delirium in older adults with advanced cancer near the end of life?
2. How does delirium vulnerability change over time and in relationship to the development of delirium in older cancer patients at the end of life?
3. How is delirium in older cancer patients at the end of life similar to or different from delirium in hospitalized older cancer patients?
4. What issues are associated with studying delirium in older cancer patients at the end of life?

## CHAPTER THREE

### METHODS

This chapter provides an overview of the methods used in each of the three phases of investigation. The discussion of each phase presents a description of the design, the sample, the setting, the variables measured, and data analysis. The discussions of Phase II and Phase III also describe the recruitment and data collection procedures and protocols. The instruments used consistently throughout are described in the Variables and Instruments section in the discussion of Phase III unless otherwise noted.

#### *Phase I: Delirium in Hospitalized Older Cancer Patients*

In the first phase of investigation, a series of secondary data analyses were conducted to examine delirium in a sample of hospitalized older cancer patients. The specific aims of the first analysis were: 1) to determine the prevalence and incidence of delirium in the sample, 2) to examine the course of delirium, 3) to identify etiologic patterns, and 4) to compare characteristics and etiologic patterns in patients with and without delirium. The specific aims of the second analysis were: 1) to examine trajectories of delirium resolution, and 2) to compare characteristics and etiologic patterns in patients with delirium that resolved prior to discharge and those who had persistent delirium. The specific aims of the third analysis were: 1) to describe delirium trajectories, and 2) to identify etiologic patterns in a subset of the patients who were near the end of life.

### *Design*

The first phase of investigation consisted of secondary analyses of data collected in three studies of acute confusion in hospitalized older adults (Neelon & Champagne: NR01339-05). The first of the three studies identified factors associated with delirium and patterns of delirium development in a sample of 158 hospitalized older medical patients. Written informed consent to participate in the study was obtained either from the patient or a family surrogate. The second study determined the incidence of delirium in a sample of 168 hospitalized older medical patients. The third study tested pattern-specific interventions in 301 patients admitted to an intervention unit and a control unit. The second and third studies were conducted in conjunction with a program to incorporate regular cognitive and functional assessments into usual nursing care. All studies were approved by the Institutional Review Board.

### *Sample*

#### *Analysis 1: Incidence and Prevalence.*

The sample for the first analysis consisted of 76 hospitalized older cancer patients, who were a subset of the total sample of 627 patients enrolled in the three parent studies. Patients were admitted to general medical units in a university-affiliated teaching hospital in the Southeastern US. Patients were 65 years of age or older, had cancer as a primary or secondary admitting diagnosis, and were able to speak English. Patients admitted with a primary psychiatric diagnosis and those admitted for terminal care were excluded in the parent studies.



### *Analysis 2: Delirium Resolution.*

The sample for the second analysis included the 43 hospitalized older cancer patients from the sample of 76 who had delirium at some point—at admission, during hospitalization, or at discharge.

### *Analysis 3: Delirium Near the End of Life.*

The sample for the third analysis included 10 patients from the pattern-specific intervention study who, though not considered terminal at admission, died within 3 months of hospital discharge.

## *Variables and Instruments*

### *Delirium*

Delirium was measured with the NEECHAM Confusion Scale (NEECHAM) (Neelon, Champagne, Carlson, & Funk, 1996) on admission, at least daily during hospitalization, and at discharge. A NEECHAM score  $\leq 24$  on admission, during hospitalization, or at discharge indicated the presence of delirium.

The NEECHAM was developed for the rapid and unobtrusive bedside assessment of cognitive function and behavioral performance in order to detect the presence of disturbed information processing and early signs of delirium (acute confusion), to rate the severity of delirium, and to monitor its response to treatment. The NEECHAM is a nine-item scale organized into three subscales: processing, behavior, and physiologic control. The processing subscale assesses attentiveness and alertness, ability to follow complex commands, and memory and orientation. The behavior subscale assesses sensory-motor function and speech

including appearance and posture control, motor activity, and verbal responsiveness and behavior. The physiologic control subscale evaluates physiological and autonomic stability and includes vital signs (temperature, heart rate, respiratory rate, and blood pressure), oxygen saturation and use of supplemental oxygen, and urinary incontinence. The items on the processing and behavior subscales are scored based on the patient's response or behavior during the rater's interaction. Scoring of the physiologic stability items is based on the presence or absence of abnormal physiologic measurements. Item specific scores are summed to determine a score for each of the three subscales. These scores are then summed to obtain a total NEECHAM score that ranges from 0-30. Higher scores indicate better cognitive and behavioral function.

The NEECHAM has been used in research and in clinical practice to assess acute confusion in hospitalized elders and nursing home residents. In elderly hospitalized patients with acute illnesses, the alpha coefficient was 0.90, and inter-rater reliability was 0.91. Concurrent validity was established (Neelon et al., 1996) by correlating the NEECHAM to other measures of cognitive function and delirium including the MMSE ( $r = .87$ ) and the sum of DSM-III-R positive items (APA, 1987) ( $r = -.91$ ). The NEECHAM exhibited excellent sensitivity (0.95) and acceptable specificity (0.78) when compared with the DSM-III criteria for delirium, the MMSE, and nurses' report of mental status problem (Neelon, Champagen, McConnell, Carlson, & Funk, 1992).

NEECHAM scores distinguish four categories or levels of confusion (Neelon et al., 1996). A score greater than 27 indicates normal function or low risk for confusion or delirium. A score between 25 and 26 or greater than 26 with the presence of one of the following clinical risk markers—respiratory rate  $> 23$  breaths/minute, use of supplementary

oxygen, oxygen saturation < 91%, serum albumin < 3.0, or report of mental status change—is indicative of risk for delirium. A score between 20 and 24 indicates mild or early delirium. These patients most likely exhibit preclinical or subsyndromal delirium, that is, they have one or more delirium symptoms but do not meet DSM diagnostic criteria. A NEECHAM score less than 20 is indicative of moderate to severe confusion or delirium. Patients with NEECHAM scores < 20 usually satisfy DSM III and DSM III-R criteria for delirium. Neelon et al. (1992) found that 78% of patients with NEECHAM score < 20 met at least 6 of 8 DSM III criteria. In another analysis (Neelon et al., 1996), 96% of patients with a NEECHAM score < 20 on admission had diagnosable delirium by DSM III-R criteria.

#### *Patient Characteristics*

Patient characteristics including age, gender, ethnicity, severity of illness, and functional status were collected at the time of admission. Severity of illness was measured with the Acute Physiology and Chronic Health Evaluation (APACHE II) scale (Knaus et al, 1985). Scores on the APACHE II range from 0-30. An increasing score is associated with greater severity of illness. Functional status was measured by the Instrumental Activities of Daily Living (IADL) subscale of the Older Americans Resources Scale (OARS) (Fillenbaum et al., 1988). IADL scores range from 0-14. A lower score indicates greater functional impairment. These items were asked so as to measure performance within the month prior to hospitalization to eliminate the impact of the acute episode. Length of stay was measured in days from admission to discharge.

### *Clinical Risk Markers and Etiologic Patterns*

A number of clinical markers including laboratory tests were determined at admission in order to classify patients into etiologic patterns associated with the development of delirium. The five etiologic patterns were determined in prior analyses using likelihood ratios and cluster analysis, and include: metabolic-nutritional, hypoxic, metabolic-toxic, orthostatic-dehydration, and chronic cognitive impairment (Belyea Champagne, Ng'andu, & Neelon, 1992; Neelon, Champagne, Moore et al., 1992). Figure 3.1 shows the clinical risk markers associated with each pattern. In the present study, patients were classified as exhibiting the pattern if any one of the clinical risk markers was present except as noted for chronic cognitive impairment.

### *Data Analysis*

#### *Analysis 1: Incidence and Prevalence*

In the first analysis, descriptive statistics were used to examine patient characteristics, the prevalence and incidence of delirium, and etiologic patterns. The NEECHAM score on admission, the lowest NEECHAM score during hospitalization, and the NEECHAM score at discharge were used to examine the overall course of delirium during hospitalization. If a patient had a NEECHAM score less than 25 at any point during hospitalization, they were categorized as having delirium. Prevalent delirium was defined as the presence of delirium at the admission assessment, and incident delirium was defined as the development of delirium at any time during the entire hospital stay in patients who were free of delirium at the admission assessment. Chi-square and t-tests were used as appropriate to compare patient characteristics and etiologic patterns in patients with delirium and those without delirium.

#### *Metabolic-Nutritional*

- BMI <20
- Weight loss > 5 kg or 10%
- Albumin < 3.5 g/dl
- Lymphocyte count < 1000/cubic mm

#### *Hypoxic*

- On oxygen
- O<sub>2</sub> saturation < 91%
- Hemoglobin < 9.0 g/dl

#### *Metabolic-Toxic*

- Albumin < 3.0 g/dl
- Creatinine > 2.0 mg/dl
- Diagnosis of liver or renal failure

#### *Orthostatic-Dehydration*

- Diagnosis of dehydration
- Presence of orthostatic symptoms
- Blood Urea Nitrogen/Creatinine ratio > 20

#### *Chronic Cognitive Impairment*

- Report of mental status problems *and* inability to take meds without assistance
- Diagnosis of dementia

#### *Figure 3.1. Etiologic Patterns and Clinical Risk Markers*

Adapted with permission from: Neelon, V.J., & Champagne, M.T. *Acute Confusion in Hospitalized Elders: Patterns-Interventions*. Funded by NIH, National Center for Nursing Research, 1988-1993. (NR01339-05).

#### *Analysis 2: Delirium Resolution*

In the second analysis, descriptive statistics were used to examine patient characteristics and delirium resolution. Delirium resolution was defined as a change in NEECHAM score  $\leq 24$  either at admission or during hospitalization to a score  $\geq 25$  at discharge. A change in NEECHAM score  $\geq$  to 3 points is considered clinically meaningful.

Chi square, Fisher's exact, and t-tests were used to evaluate the differences in patient characteristics, etiologic patterns, and factors in patients with and without delirium resolution.

### *Analysis 3: Delirium Near the End of Life*

In the third analysis, descriptive statistics were used to summarize patient characteristics and to determine etiologic patterns. Plots of daily NEECHAM scores from admission to discharge were visually examined to describe delirium trajectories.

## *Phase II: Development and Pilot Testing of a Protocol to Study Delirium and Cognitive Decline in Older Adults with Advanced Cancer*

The second phase of investigation was a pilot study to assess the feasibility of and the burden associated with a protocol to study delirium and cognitive decline in older cancer patients receiving palliative and end of life care. The primary aims of the pilot study were: 1) to test the feasibility of the protocol, first, in a laboratory and, then, in the home setting; 2) to determine the level of patient and caregiver burden associated with the protocol; 3) to evaluate and refine instruments and data collection procedures; and 4) to identify and resolve methodological issues related to recruitment, consent, measurement and retention that may be encountered in studying delirium and cognitive decline in older adults with advanced cancer being cared for at home.

### *Design*

An exploratory longitudinal design was used to evaluate minimally invasive instruments and methods to measure cognitive, behavioral, functional, psychological, and

physiological parameters associated with delirium and cognitive decline in older patients with advanced cancer. Participants, patients and their family caregivers, were recruited from the medical oncology clinics at the North Carolina (NC) Cancer Hospital at the University of North Carolina at Chapel Hill (UNC), from a community-based cancer support group, and from UNC Hospice. After providing informed consent, participants participated in 4 data collection sessions, a baseline assessment that was done in the Biobehavioral Laboratory (BBL) at the UNC School of Nursing and in-home assessments that were done weekly for three weeks. Each day during the study, family caregivers completed the Caregiver Confusion Checklist in the morning and evening. If symptoms of confusion, or delirium, were noted, caregivers were asked to notify the investigator who would perform an in-depth delirium assessment within 12 hours. Feedback regarding the data collection procedure and any other issues and concerns related to participation in the study and the research process were elicited from participants at each assessment.

### *Sample*

Three older adults with advanced GI cancer who were at a stable state in their illness trajectory and their family caregivers were recruited from the medical oncology clinics at the NC Cancer Hospital at UNC Hospitals. All study participants were English speaking. Participants with advanced cancer were also 65 + years of age and undergoing palliative treatment. All patient participants possessed normal cognitive capacity at the time of enrollment as indicated by a Mini-Mental State Examination score of 24 points or greater.

### *Setting*

The study was conducted in the BBL at the UNC School of Nursing and in participants' homes. Initial testing was conducted in the BBL. The BBL in the School of Nursing at UNC is located on the ground floor and has direct access to public transportation. Parking was provided in the Bell Tower Parking Lot within walking distance to the School of Nursing. The monitoring area in the BBL consists of two independent sleep rooms, which are sound proofed and equipped with florescent lighting, phosphorescent lighting, temperature controls, and video cameras. For this study, one of the sleep rooms was set up to simulate a bedroom in a home environment and was used for data collection. After receiving permission from the participants, the investigator's mentor monitored the data collection sessions via video and provided feedback on the procedures.

### *Recruitment*

Research participants were recruited from medical oncology clinics at the NC Cancer Hospital at UNC Hospitals, from a cancer patient support group in the community, and from UNC Hospice.

#### *Recruitment from medical oncology clinics*

Medical oncologists working with thoracic and GI oncology patients were given information about the study. At the start of each clinic day the principal investigator reviewed the list of patients to be seen in the clinic that day. According to the limited waiver of HIPAA requested for this study, the principal investigator reviewed potential subjects' medical records as a screening method to determine eligibility. The information reviewed



included patient name, medical record number, patient's birthdate and/or age; patient's address; type of cancer; current treatment, and living situation. Information reviewed from the medical record will be used solely to identify potential subjects. None of the information reviewed by the principal investigator was documented in writing or communicated to any other persons; therefore there is a minimal risk to the privacy of the potential subjects and their rights and welfare will not be affected in any way by this review of their health information for eligibility screening.

Potential subjects were approached personally by the principal investigator and informed of the study during their clinic appointment after they were placed in a private patient examination room. All patients who met eligibility criteria and who expressed an interest in knowing more about the study were provided with a recruitment flyer. Patients who indicated a desire to participate in the study during this meeting were asked to complete the information section of the recruitment flyer so that the principal investigator could contact them at a later date to schedule informed consent and the initial data collection session. All other patients who met eligibility criteria were provided with a recruitment flyer and self-addressed stamped envelope. They were instructed to contact the principal investigator at a future time if they would like to participate in the study. The methods for contacting the principal investigator were reviewed. The principal investigator had no other contact with potential subjects unless they contacted him.

A limited waiver of HIPPA was requested to examine the patient list and medical records of patients in the UNC medical oncology clinic to prescreen for eligibility of potential subjects for the study. The specific protected health information that was reviewed included patient name, medical record number, patient birthdate and/or age; patient address;

type of cancer; current treatment, and psychosocial history to determine living situation. The information was used solely to identify potential subjects. None of the information was documented in writing or communicated to any other persons.

#### *Recruitment from community support groups*

The investigator talked with the leader of a community-based cancer support group for patients with advanced illness. Written information about the study was provided so that it could be distributed to support group members. In addition, the investigator was willing to attend a support group meeting to provide information about the study and to answer patient questions regarding study participation.

#### *Recruitment from UNC Hospice*

The investigator met with the staff of UNC Hospice to discuss the study. Hospice staff members were asked to identify potential patients who met the inclusion criteria and to provide these patients with a recruitment flyer. Patients interested in study participation were provided with five ways to contact the investigator: by calling the investigator's cell phone number, by calling the investigator's home phone number, by sending an email to the investigator, by completing the patient contact information on the flyer and sending it to the investigator in a self-addressed stamped envelope provided with the flyer, or by completing the patient contact information on the flyer and giving it to the hospice staff. The investigator planned to telephone persons who responded to the flyer to provide more detailed information about the study. For those interested in participating, the investigator would schedule a convenient time to meet with them and their family caregivers to obtain informed

consent. The meeting to obtain informed consent and baseline sociodemographic and cognitive data would take place in patients' homes prior to initiating data collection.

### *Human Subjects Considerations*

This study was approved by the Lineberger Comprehensive Cancer Center Oncology Protocol Review Committee and the Nursing Institutional Review Board at the University of North Carolina at Chapel Hill.

Minimally invasive instrumentation and observational techniques were used to decrease intrusiveness and discomfort. The investigator, a registered nurse with experience in cancer and palliative care nursing, performed all data collection. Participants were observed for signs and reports of fatigue. Participants were allowed to rest if needed during the data collection process. Data collection could be divided into several sessions if necessary. Participants and their family caregivers were allowed to refuse or to discontinue observations and measurements at any time if they became too burdensome.

The study and participation in the study were discussed in detail with prospective participants. Participants provided written consent to participate in the study. Confidentiality was maintained by assigning an identification number to each participant. All data instruments were coded with the participant ID number. No names appeared on data collection forms. The list of participants with matching identification numbers was kept in a locked drawer in the BBL in the School of Nursing. Additionally, all data collection forms were kept in a separate locked drawer in the BBL. In general, findings from this study will be presented in aggregate forms. Any report of finding using participant data as case exemplars will only use ID numbers or fictitious initials.

Participants received monetary compensation for their participation in this study. Patients and their family caregivers were given \$25 each at the completion of each data collection session. They each were paid a total of \$100.00 if they participated in the entire study.

### *Variables and Instruments*

Self-report and clinician-rated instruments were used to measure cognitive, behavioral, functional, psychological, and physiological parameters associated with delirium and cognitive decline.

#### *Cognitive Function*

Cognitive function was assessed using the Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and three cognitive items on the Symptom Scale. The MMSE, the most widely used measure of global cognitive function, was used to screen participants for pre-existing cognitive impairment at baseline and as a measure of cognitive function at subsequent evaluations. The MMSE will be described in more detail in the section on Phase III. The Symptom Scale developed by the investigator is described below.

Three items on the Symptom Scale were used to measure subject self-report of confusion and altered cognitive function. The Symptom Scale was developed by the investigator and is derived from the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) and the M.D. Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000). The cognitive symptoms included on this scale are difficulty in concentrating,

feeling confused or mixed up, and difficulty remembering things. Responses range from 1 = not at all to 3 = some to 5 = very much.

#### *Level of Consciousness*

Level of consciousness was measured using the Richmond Agitation-Sedation Scale (RASS) (Sessler et al., 2002). The RASS will be described in detail in the section on Phase III.

#### *Delirium*

Delirium was assessed using the NEECHAM Confusion Scale (NEECHAM) (Neelon et al., 1996), the Confusion Assessment Method (CAM) (Inouye et al., 1990), and the DSM IV criteria for delirium (American Psychiatric Association, 1994). Additionally, the Caregiver Confusion Checklist (CCC) was used by caregivers to identify early signs of confusion and delirium and to monitor delirium symptoms over time. The DSM IV criteria for delirium are considered the clinical standard for the diagnosis of delirium. The presence or absence of DSM IV criteria was documented. The NEECHAM was described in the section on Phase I. The other instruments (CAM and CCC) will be described in detail in the variables and measurement section on Phase III.

#### *Clinical Markers and Etiologic Patterns*

Etiologic patterns and associated clinical risk markers were described in the variables and measurement section on Phase I.

### *Symptom Prevalence and Distress*

Symptom prevalence and distress was determined in the pilot study using a Symptom Scale adapted by the investigator from the Memorial Symptom Assessment Scale (MSAS) (Portenoy et al., 1994) and the M.D. Anderson Symptom Inventory (MDASI) (Cleeland et al., 2000). The Symptom Scale includes 20 physical and psychological symptoms that are common in patients with advanced cancer. Examples of the items on the scale are pain, lack of energy, nausea, shortness of breath, constipation, lack of appetite, feeling sad, feeling worried, and feeling upset or distressed. Using a five-point scale with numerical and verbal descriptors ranging from 1 (not at all) to 5 (very much), participants will rate the degree of bother associated with each symptom in the previous 24 hours. Total scale scores range from 20-100. A high score indicates a high degree of symptom distress.

### *Physical Functioning*

Physical functioning was assessed using the Older American Resources and Services (OARS) Activities of Daily Living Scale (Fillenbaum, 1978) and the Palliative Performance Scale (PPS) (Anderson, Downing, Hill, Casoroso, & Lynch, 1996). These instruments are described in detail in the section on Phase III.

### *Depression*

Depression was measured using the short form of the Geriatric Depression Scale (GDS-15) (Sheikh & Yesavage, 1986). The GDS-15 is described more fully in the section on Phase III.

### *Comorbidity*

Comorbidity was measured using the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987). The Charlson Comorbidity Index is described in the section on Phase III.

### *Sleep Quality and Quantity*

Sleep quality and quantity were measured using the Stanford Sleepiness Scale (Hoddes et al., 1973) and the Sleep and Rest subscale from the Sickness Impact Profile (John Hopkins University, 1977). These instruments are discussed in the section on Phase III.

### *Physiological Variables*

Vital signs including heart rate, respiratory rate, temperature, blood pressure, and arterial oxyhemoglobin saturation were obtained by the investigator each time the NEECHAM was administered. Nutritional status was assessed by measuring height and weight and calculating body mass index. Phase angle was measured by bioelectrical impedance analysis.

### *Sociodemographic Data*

Sociodemographic data were collected using a questionnaire developed by the investigator. Participants were asked to report their gender, age, ethnicity, years of formal education, employment status, treatment history (current and prior chemotherapy, radiation, and/or hormonal therapy), smoking and alcohol history, prior history of confusion, self-reported health rating, and use of sensory aids (eyeglasses and hearing aids).

### *Caregiver Sociodemographic Data*

Caregivers completed a sociodemographic questionnaire developed by the investigator at the baseline assessment. Caregivers were asked to report their gender, age, ethnicity, years of formal education, marital status, employment status, relationship to the patient, and types of assistance provided to the patient.

### *Medication Profile*

A medication profile developed by the investigator and include all routine and pro re nata (PRN) medications (prescribed and over-the-counter) being taken by the participant. Participants were asked to show the investigator all current medications. Medication changes were assessed and documented at each weekly assessment.

### *Research Burden Assessment*

At the conclusion of each assessment, participants, patients and family caregivers, were asked to provide information about the level of burden associated with research participation and the data collection procedures. The semi-structured interview was audiotaped.

### *Data Collection Procedures*

The pilot study involved 4 data collection sessions, a baseline assessment that was done in the Biobehavioral Laboratory (BBL) at the UNC School of Nursing and in-home assessments that were done weekly for three weeks. Table 3.1 shows the data collection timeline for the study.



Family caregivers accompanied patient participants to the BBL. The investigator greeted participants in the parking lot and escorted them from the parking lot to the BBL. Written informed consent to participate in the study was completed before any measurements were made.

### *Baseline Assessment*

After providing informed consent, participants underwent a baseline assessment and interview in the BBL. The baseline assessment included measures of cognitive function and delirium; determination of functional status, comorbidity, symptom prevalence and distress, depression, sleep quality, and medication history; collection of demographic data; and measurement of physiological variables using minimally-invasive instrumentation and procedures. The time required for data collection and any problems associated with the data collection protocol were documented. After the data collection was completed, an audiotaped interview was conducted to evaluate the level of participant burden associated with the data collection protocol. The caregivers provided demographic information and were trained by the investigator to complete the Caregiver Confusion Checklist (CCC).

### *Weekly Assessments*

After baseline testing, participants participated in three weekly assessments and interviews in their homes. The weekly assessments included measures of cognitive function and delirium, functional status, symptom prevalence and distress, sleep quality, medication changes, and measurement of physiological variables. Additionally, during the three-week field-testing period, family caregivers completed the CCC, twice daily, in the morning and

evening. Caregivers were instructed to notify the investigator of a CCC score  $\geq 2$ , which indicated a probable episode of delirium. After being notified, the investigator would complete an in-depth delirium assessment within 12 hours. If delirium was verified, the caregiver would be asked about changes in medications, health status, sleep patterns, and symptoms or behavior or events that preceded the delirium. Feedback regarding the data collection procedure and any other issues and concerns related to participation in the study and the research process were elicited from participants and their family caregivers at each weekly assessment.

#### *Delirium Episode Assessment*

A delirium episode assessment was conducted by the investigator when the caregiver notified the investigator that the patient was exhibiting signs of delirium as evidenced by a score of 2 or more on the Caregiver Confusion Checklist or by a NEECHAM score  $\leq 24$  at the time of a scheduled assessment by the investigator. The delirium episode assessments included the completion of the MMSE and an unstructured interview with the patient for the completion of observational measures including the NEECHAM, CAM, DSM-IV criteria checklist, delirium motor patterns, the Richmond Agitation-Sedation Scale, and the Palliative Performance Scale. Physiologic data including vital signs, arterial oxyhemoglobin saturation, weight (if patient able to stand), and phase angle also were collected. In addition, the investigator conducted a semi-structured open-ended interview with caregivers to learn more about the symptoms or behaviors or events that preceded the delirium and to inquire about any changes in medications, patients' health status or overall condition, physical symptoms, and sleep patterns.

### *Data Analysis*

Quantitative data were analyzed using standard descriptive statistics and techniques for evaluating patterns, change and variability, and sequencing of events. Plots were used to characterize patterns and trends in the data. The feasibility and burden of the protocol was assessed quantitatively and qualitatively. Measures such as the length of time required to complete instrument, the number of rest periods needed, the number of questions about the instruments or the need for clarification, as well as the length of the complete evaluation were documented. Additionally, patient comments and feedback during the evaluation were documented. Patients and caregivers were interviewed at the end of each weekly assessment to identify components of the study that were difficult or uncomfortable. The interviews were audiotaped and the content of the interviews was examined to determine the level of burden associated with research participation and the data collection procedures.

Table 3.1. Phase II: Data Collection Timeline

Variables/Instruments	Informed Consent	Baseline Evaluation	Week 1 Evaluation	Week 2 Evaluation	Week 3 Evaluation	Delirium Episode
<b>Cognitive Function</b>						
Mini-Mental State Exam	X	X	X	X	X	X
<b>Level of Consciousness</b>						
Richmond Agitation-Sedation Scale		X	X	X	X	X
<b>Delirium Assessment</b>						
NEECHAM Confusion Scale		X	X	X	X	X
Confusion Assessment Method						X
DSM-IV Criteria						X
Delirium Etiologic Pattern Screen		X				X
Delirium Motoric Pattern Screen						
Caregiver Confusion Checklist		X (Daily)	X (Daily)	X (Daily)	X (Daily)	
<b>Symptom Prevalence/Distress</b>						
Symptom Scale		X	X	X	X	
<b>Functional Status</b>						
OARS		X	X	X	X	
Palliative Performance Scale		X	X	X	X	X
<b>Comorbidity</b>						
Charlson Comorbidity Index		X				
<b>Depression</b>						
Geriatric Depression Scale (Short Form)		X	X	X	X	
<b>Sleep Quality and Quantity</b>						
Stanford Sleepiness Scale		X	X	X	X	
Sleep and Rest Subscale (Sickness Impact Profile)		X	X	X	X	
<b>Physiological Variables</b>						
Temperature		X	X	X	X	X
Heart Rate		X	X	X	X	X
Respiratory Rate		X	X	X	X	X
Blood Pressure -- Orthostatics		X	X	X	X	X
Height		X				
Weight		X	X	X	X	
Oxygen Saturation		X	X	X	X	X
Phase Angle		X	X	X	X	
<b>Sociodemographic Data and History</b>						
Medication Profile/Update	X	X	X	X	X	X
<b>Research Burden Assessment</b>		X	X	X	X	
Caregiver Delirium Assessment						X

### *Phase III: Trajectories and Patterns of Delirium and Delirium Vulnerability in Older Adults with Advanced Cancer*

#### *Design*

A longitudinal, multiple case-study descriptive design using event analysis was used to examine key aspects of delirium in a small number of older cancer patients receiving palliative and end of life care. The longitudinal case-study design with repeated measures is appropriate for examining the dynamic nature of delirium at the end of life because it facilitates the intense study of phenomena and is particularly well-suited for studying the complexity and contextual nature of phenomena (Scholz & Tietje, 2002; Yin, 2003). The design also allows for the evaluation of change over time and the identification of patterns and trends within cases and between cases. Participants were followed from enrollment into the study for up to six months or until the patient's death or withdrawal from the study. At the end of six months, participants were given an option to end the study or continue for up to an additional six months.

Event analysis involves the development of a detailed description and analysis of a specific event that is important to an investigation (Kayser-Jones, 2002). It is useful when the aim is to achieve a comprehensive description and explanation of a phenomenon in a complex clinical situation or setting (Happ, Swigart, Tate, & Crighton, 2004). Event analysis results in more than a description and explanation of the event itself but rather integrates multiple aspects of the event including its precursors, its consequences, relationships between and among key variables, and how they are related to or influence the event (Happ et al.). In this study, the development of delirium at the end of life was the event examined. Quantitative and qualitative data from a variety of sources were used to develop a comprehensive description of the presentation, course, characteristics, and outcomes of

delirium episodes in older cancer patients receiving palliative and end of life care.

### *Sample*

A sample of 7 older adults with advanced cancer and their family caregivers were recruited from the medical oncology clinics at the NC Cancer Hospital at UNC Hospitals, a university-affiliated medical center. All study participants, cancer patients and caregivers, could speak, understand, and read English, and they lived within 50 miles of the university medical center. Participants with advanced cancer were also 65+ years of age; diagnosed with an advanced or recurrent non-hematologic malignancy (including but not limited to lung, GI tract, breast, genitourinary, head and neck, reproductive, or tumors of unknown primary); and undergoing palliative treatment (non-curative but may be life-prolonging) for either disease modification or symptom management. Caregiver participants were over 18 years of age, lived either with the patient or nearby, had at least daily contact with the patient, and assisted the patient with care as needed.

### *Setting*

The study was conducted across care settings. Data collection took place primarily in the participants' homes, but also in the hospital if participants were admitted during the study. The family caregiver was asked to notify the investigator if the patient was admitted to the hospital or to any other inpatient or institutional setting.

### *Recruitment*

Participants were recruited from medical oncology clinics at the NC Cancer Hospital

at UNC Hospitals and UNC Hospice. Medical oncologists working with solid tumor patients were provided with information about the study. The list of eligibility criteria and an abstract of the study protocol was given to each physician. Permission to approach their patients regarding participation in the study was elicited (Appendix A).

#### *Recruitment from medical oncology clinics*

The following method was used to recruit study participants from the medical oncology clinics. At the start of each clinic day the investigator reviewed the list of patients to be seen in the clinic that day. According to the limited waiver of HIPAA requested for this study, the investigator reviewed potential subjects' medical records as a screening method to determine eligibility. The information that was reviewed included the patient's name, medical record number, birthdate and/or age, address, type of cancer, current treatment, and living situation. Information reviewed from the medical record was used solely to identify potential participants. The information was documented on a potential participant information form. The information form was kept until the investigator contacted the potential participant as discussed below. The information form was discarded in a shredding bin after the investigator contacted the potential participant. There was a minimal risk to the privacy of the potential participants and their rights and welfare were not affected in any way by the review and documentation of their health information for eligibility screening.

Potential participants were approached personally by the investigator and informed of the study during their clinic appointment after they have been placed in a private patient examination room. All patients who met eligibility criteria and who expressed an interest in knowing more about the study were provided with a study brochure and recruitment flyer

(Appendix A). Patients indicating a desire to participate in the study during this meeting were asked to complete the information section of the recruitment flyer so that the investigator could contact them at a later date to schedule informed consent and the initial data collection session. All other patients who met eligibility criteria were provided with the study brochure and a recruitment flyer and self-addressed stamped envelope. They were instructed to contact the investigator at a future time if they would like to participate in the study. The methods for contacting the investigator were reviewed. Patients were informed that their family caregiver must also agree to participate in the study. The investigator did not have any other contact with potential participants unless they contacted him.

#### *Recruitment from UNC Hospice*

After being informed about the study, the administration and nursing staff of UNC Hospice agreed to assist with participant recruitment. The hospice nurses were asked to identify patients who met the inclusion criteria and to provide these patients and their family caregivers with a study brochure. The nurses, then, would determine whether the patient and family caregiver would like to learn more about the study from the investigator. If a patient and family caregiver expressed an interest in the study, the hospice nurse would obtain permission to provide the patient's name and telephone contact information to the investigator. If so, the investigator contacted the patient and/or family caregiver by phone to provide more information about the study and to elicit whether the patient and family caregiver would like to participate. If so, the investigator would schedule a home visit to obtain informed consent and to initiate data collection. The home visit would be scheduled at a time that was convenient for the patient and family caregiver.



### *Human Subjects Considerations*

This study was approved by the Lineberger Comprehensive Cancer Center Oncology Protocol Review Committee and the Nursing Institutional Review Board at the University of North Carolina at Chapel Hill (Appendix B).

The sample in this study, older persons with advanced cancer nearing the end of life, is a vulnerable population. Although there was minimal risk associated with the study, measures were taken to minimize any physical or psychological discomfort that participants may experience. Minimally-invasive instrumentation and observational techniques were used to decrease intrusiveness and discomfort. Still, participation in the study and frequent observation including audiotaping may increase feelings of vulnerability. Attachment to monitoring devices may restrict movement for short periods and contribute to minimal physical discomfort. Some participants may experience fatigue during the evaluation and interview process.

The investigator, a registered nurse with clinical experience in cancer and palliative care settings, performed all data collection. Participants were observed for signs and reports of fatigue and agitation. If fatigue or agitation occurred, participants were given the option of taking a rest period of 30-60 minutes or rescheduling the remaining data collection for another time. If possible, the data collection will be completed later the same day after a rest period or within the next 2 days. The subsequent data collection session will be done no less than 5 days and no longer than 7 days from the date of the last data collection session. Participants were also told that data collection could be scheduled in two sessions if desired. Participants and their family caregivers were allowed to refuse or to discontinue observations and measurements at any time if they become too burdensome.

If new symptoms developed or if changes in a participant's condition were noted by the investigator, the participant and/or family caregiver were instructed to follow-up with their care provider (MD, nurse practitioner, hospice nurse, etc) in the usual manner.

Participants received compensation for participation in the study. Patients and their family caregivers were each given their choice of either a gift card for gas or long-distance telephone calls (\$25 value) or \$25 in cash after the baseline visit and each month while enrolled in the study. If patients developed persistent cognitive impairment during the study, their family caregivers were allowed to select for them and to use the compensation at their discretion. If patients died, their family caregivers received a final compensation payment of choice, valued at \$50.

### *Informed Consent*

The investigator obtained informed consent from participants, patients and their family caregivers, upon enrollment in the study prior to the initiation of any data collection. During the informed consent process, prospective participants received a detailed verbal and written explanation describing the study, data collection procedures, potential benefits, potential risks, and a guarantee of confidentiality and data anonymity. Prospective participants were informed that their participation in the study was voluntary and that they could withdraw from the study at any time. They also were assured that refusal to participate in the study or withdrawal from the study would not affect the care or services they received from their medical provider. Prospective participants were given an opportunity to ask questions about the study. If they expressed a desire to participate in the study, patients and their family caregivers were asked to sign respective consent forms (Appendix C), which

they had read or had been read to them by the investigator. In addition, patients were asked to sign a HIPAA Authorization for Use of Protected Health Information (PHI) (Appendix C). The requested PHI included the patient's diagnosis, diagnosis date, current and previous treatment plan, past medical history to determine comorbid medical conditions, diagnostic tests to determine extent and current status of disease, progress notes to follow the progress of the disease and treatment, and laboratory values to monitor etiologic pattern markers for the delirium pattern screen. Participants were given a copy of the consent forms and the investigator kept the originals in a locked file drawer in the BBL in the School of Nursing.

### *Confidentiality*

Confidentiality was maintained by assigning an identification number to each participant. All data collection forms were coded with the participant identification number. No names appeared on data collection forms. Participant information with matching identification numbers was kept in a separate locked file drawer in the BBL. Additionally, all data collection forms, including diskettes and CDs were kept in a locked file drawer in the BBL. All computerized data was kept in password-protected files on the UNC School of Nursing network. Participants were assigned a fictitious alphabetical initial for the presentation of case data.

### *Variables and Instrumentation*

A variety of data collection methods and sources of evidence were used to examine episodes of delirium and changes in delirium vulnerability in older cancer patients during active palliative treatment and during the terminal period. Self-report and clinician-rated

instruments were used to measure cognitive, behavioral, functional, psychological, and physiological parameters associated with delirium. A copy of the instruments can be found in Appendix D. Observational methods aided the completion of clinician-rated instruments. Biobehavioral instrumentation was used to measure physiological variables. Open-ended semi-structured interviews and unstructured informal interviews with patients and family caregivers were conducted to better understand the development of delirium and critical aspects of delirium episodes. The medical record also was used to obtain information related to cancer diagnosis and treatment history, comorbid medical conditions, laboratory values, current treatment, and disease status. Detailed field notes were written following each encounter.

### *Cognitive Function*

Cognitive function was assessed using the Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and items from the adapted Memorial Symptom Assessment Scale – Short Form (MSAS-SF) (Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000) including those added by the investigator noted below.

#### *Mini-Mental State Examination*

The MMSE, the most widely used measure of global cognitive function, was used to screen participants for pre-existing cognitive impairment at baseline and as a measure of cognitive function at subsequent evaluations. The MMSE assesses several domains of cognitive function including: orientation, registration, attention, calculation, recall, language, and visual construction. Total scores range from 0-30. The recommended criterion score of

24 or less was used as an indicator of cognitive impairment. The MMSE has been used to measure cognitive function in advanced cancer patients receiving palliative and end of life care (Bruera et al., 1992; Pereira et al., 1997; Zhukovsky et al., 1998). Test-retest reliabilities for different time periods and different patient populations range from .83-.90 (Anthony, LeResche, Niaz, Korff, & Folstein, 1982). Concurrent validity, obtained by correlating the MMSE total score with the Wechsler Adult Intelligence Scale, they report an  $r = .78$  for verbal IQ and an  $r = .66$  for performance IQ (Folstein et al., 1975).

### *Self-Report of Cognitive Symptoms*

Two symptoms on the MSAS-SF, difficulty concentrating and feeling drowsy, and two symptoms added by the investigator, difficulty remembering and feeling confused, were used to measure participant self-report of confusion and altered cognitive function. The participant was asked to identify whether he/she had experienced any of the symptoms during the past week and if so how much it bothered him/her. Responses range from 1 = not at all to 3 = some to 5 = very much. Self-report of confusion or altered cognitive function may be indicative of prodromal delirium or diminished cognitive reserve and delirium risk. Bosisio et al (as cited in Caraceni and Grassi, 2003) found that although a group of patients reported no confusion while fulfilling diagnostic criteria for delirium, self-report of confusion correlated with Delirium Rating Scale and Memorial Delirium Assessment scores for delirium. Patients with severe symptoms were not able to answer the questionnaire.

## *Level of Consciousness*

### *Richmond Agitation-Sedation Scale*

Level of consciousness was measured using the Richmond Agitation-Sedation Scale (RASS) (Sessler et al., 2002). The RASS is a 10-point scale that measures four levels of agitation (+1 to +4), one level that denotes a calm and alert state (0), and five levels of sedation (-1 to -5). The RASS is an observer-rated scale that was developed to measure agitation and sedation in ICU patients. It uses three clearly defined steps and has discrete criteria for determining levels of sedation and agitation. Excellent inter-rater reliability ( $r = 0.922-0.983$ ) ( $\kappa = 0.64-0.82$ ) was demonstrated in a variety of ICU patients (Sessler et al., 2002). In initial validity testing, the RASS correlated highly with other agitation-sedation scales including a visual analogue scale anchored by “combative” and “unresponsive” ( $r = 0.84-0.98$ ), the Ramsay sedation scale ( $r = -0.78$ ) and the Sedation Agitation Scale ( $r = 0.78$ ) (Sessler et al., 2002). In further reliability and validity testing, Ely et al. (2003) demonstrated excellent inter-rater reliability (weighted  $\kappa = 0.91$ ) and construct validity using several methods including correlation with an attention screen examination ( $r = 0.78$ ), Glasgow Coma Scale scores ( $r = 0.91$ ), and bispectral electroencephalography ( $r = 0.63$ ). Furthermore the RASS showed significant differences between levels of consciousness ( $p < .001$ ) and correctly identified fluctuations within patients over time ( $p < .001$ ). Criterion validity of the RASS was evaluated by comparing the RASS to neuropsychiatric expert ratings of patients’ levels of consciousness as normal, delirium, stuporous, or comatose. Data demonstrated significant discrimination between each level of consciousness (all  $p < .001$ ). The following scores on the RASS corresponded with the following levels of consciousness: 0 = normal, -1 and -2 = delirium, -3 and -4 = stuporous, and -5 = comatose.

## *Delirium*

Delirium was assessed using the NEECHAM Confusion Scale (NEECHAM) (Neelon et al., 1996), the Confusion Assessment Method (CAM) (Inouye et al., 1990), and the DSM IV-TR criteria for delirium (APA, 2000). In addition, the Caregiver Confusion Checklist was used by family caregivers to monitor for early signs of delirium and to monitor delirium symptoms over time.

### *NEECHAM Confusion Scale*

The NEECHAM was completed at each assessment. It is described in detail in the section on Phase I. The total NEECHAM score was used in conjunction with the CAM to identify the presence of delirium and to measure delirium risk and severity. A total NEECHAM score  $\geq 27$  indicated low risk for delirium. A score between 25 and 26 or greater than 26 with the presence of an identified risk marker indicated risk for delirium. A score between 20 and 24 with a negative CAM was indicative of subsyndromal delirium. A score between 20 and 24 with a positive CAM indicated mild or early delirium. A total NEECHAM score less than 20 with a positive CAM was indicative of severe delirium.

The processing and behavior subscales of the NEECHAM were used as measures of cognitive function and reserve. The physiologic control subscale was used as a measure of physiologic reserve.

### *Confusion Assessment Method*

The Confusion Assessment Method (CAM) has been widely used as a diagnostic measure of delirium in studies involving older adults and in clinical practice. The CAM

consists of nine operationalized criteria from the DSM-III-R. Delirium is scored as present or absent using the CAM algorithm based on four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Inter-rater reliability using 19 paired observations ranged from 84-100% ( $\kappa = 0.56-1.0$ ). Concurrent validity was established by comparison with psychiatric assessments in two samples; sensitivity ranged from 94-100% and specificity from 90-95%. The CAM exhibited convergent agreement with four other mental status indexes including the MMSE ( $\kappa = .64$ ), story recall ( $\kappa = .59$ ), visual analogue scale for confusion ( $\kappa = .82$ ), and digit span test ( $\kappa = .66$ ). The CAM can be completed in 5-10 minutes.

#### *DSM IV-TR Criteria for Delirium*

The DSM IV-TR criteria developed by the American Psychiatric Association (2000) are considered the clinical standard for the diagnosis of delirium. The presence or absence of DSM IV-TR criteria was documented on a checklist developed by the investigator.

#### *Caregiver Confusion Checklist*

The Caregiver Confusion Checklist (CCC) was completed each morning and evening by the family caregiver. The CCC, adapted from the Confusion Rating Scale (CRS) by Williams (1985), asks caregivers to record the presence or absence of behaviors indicative of confusion (disorientation, inappropriate behavior, inappropriate communication, illusions/hallucinations, and altered alertness) using a two-item response scale (0 = not present and 1 = present). The responses are summed to obtain a total score. A CCC score of 2 or more indicated a positive screening and triggered a more in-depth delirium assessment by



the investigator. This low cut-off was used to maximize the sensitivity of the CCC as a screening instrument and result in an early diagnostic evaluation for delirium. Following a diagnostic confirmation of delirium, the CCC score was used to monitor symptom fluctuation over time and to determine whether symptom improvement and resolution occurs. A CCC score of 0 for at least 24 hours following a delirium diagnosis was used as an indicator of clinically significant symptom improvement.

The CRS was originally designed for use by nurses in hospitals and has not been previously used by family caregivers. Gagnon et al. (2000) used the CRS to screen for delirium in hospitalized terminally ill cancer patients. In the present study, the CCC was used to identify early signs of delirium and as an indicator for a more in-depth delirium assessment conducted by the investigator using the NEECHAM, the CAM, and DSM criteria. In addition the CCC was used as an ongoing monitor of delirium symptoms since the investigator was unable to conduct daily assessments.

### *Delirium Risk Markers and Etiologic Patterns*

#### *Delirium Pattern Screen*

Delirium risk markers and etiologic patterns were determined using a Delirium Pattern Screen developed by Neelon et al. (1992) to identify and describe patterns of delirium development at the time of hospital admission and to guide interventions. The etiologic patterns and delirium risk markers were described in the section on Phase I.

## *Symptom Prevalence and Distress*

### *Memorial Symptom Assessment Scale (Short Form)*

Symptom prevalence and distress was determined using an adapted version of the short form of the Memorial Symptom Assessment Scale (MSAS-SF) (Chang et al., 2000). The MSAS-SF is a patient-rated instrument that measures the distress associated with 26 physical symptoms and the frequency of 4 psychologic symptoms during the past week. A physical symptom subscale (PHYS), psychologic symptom subscale (PSYCH), and global distress index (GDI) can be derived from the MSAS-SF. The PHYS subscale comprises 12 prevalent symptoms including lack of energy, pain, lack of appetite, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight, loss, feeling bloated, and dizziness. The PSYCH subscale includes 6 prevalent psychologic symptoms (worrying, feeling sad, feeling nervous, difficulty sleeping, feeling irritable, and difficulty concentrating). The GDI subscale includes four psychologic symptoms (feeling sad, worrying, feeling irritable, and feeling nervous) and six physical symptoms (lack of energy, pain, lack of appetite, feeling drowsy, constipation, and dry mouth).

The MSAS-SF was validated in a sample of mostly elderly male cancer patients with advanced disease (Chang et al., 2000). The instrument was easy to administer and took less than 5 minutes to complete. Chronbach alpha coefficients for the MSAS-SF and its subscales ranged from 0.76 to 0.87. Test-retest correlation coefficients for the MSAS-SF subscales ranged from 0.86-0.94 at 1 day and 0.40 to 0.84 at 1 week. Criterion validity was evaluated by assessing the MSAS-SF subscales scores against the subscales of the FACT-G. Correlation coefficients were -0.74 for the PHYS and FACT-G physical well being subscale, -0.68 for the PSYCH and FACT-G emotional well-being subscale, and -0.70 for the GDI and

FACT-G summary of quality of life subscales scores. The MSAS-SF demonstrated convergent validity with performance status measured by the Karnofsky Performance Status, inpatient status, and extent of disease.

Five symptoms with a frequency of < 25% and that may be more often associated with active cancer treatment (changes in skin, mouth sores, problems with sexual interest or activity, hair loss, and “I don’t look like myself”) were eliminated from the adapted version used in this study. In addition, two cognitive symptoms (difficulty remember and feeling confused) were added to measure patient self-report of confusion. All symptoms in the three MSAS-SF subscales are included. Additionally, two spaces were added for patients to identify any other symptoms that they may have experienced during the past week.

### *Physical Functioning*

Physical functioning was assessed using the Older American Resources and Services Activities of Daily Living Scale (OARS) (Fillenbaum, 1978) and the Palliative Performance Scale (PPS) (Anderson, Downing, Hill, Casoroso, & Lynch, 1996).

#### *Older American Resources and Services (OARS) Activities of Daily Living Scale*

The OARS Activities of Daily Living Scale is comprised of two subscales addressing physical activities of daily living (PADL) and instrumental activities of daily living (IADL). The 7-item PADL subscale measures functional abilities with personal self-care activities (eating, dressing, grooming, walking, bathing, getting in and out of bed, and continence). The 7-item IADL subscale measures functional abilities with more complex tasks (using the telephone, walking long distances, taking medicine, shopping, arranging, transportation,

preparing a meal, and handling money). Both subscales ask subjects to grade their ability to independently complete each task, using response items that range from 0-2 points; a score of 0 indicates that the subject is completely unable to complete the task, a score of 1 indicates inability to complete a task without help by another, and a score of 2 indicates ability to complete the task without help. In community-dwelling older adults, studies have reported a Spearman rank-order correlation of .70 with the Katz and Barthel Index (Fillenbaum & Smyer, 1981). The IADL subscale of the OARS was used to measure functional status in a sample of hospitalized older cancer patients (Bond, Neelon, & Belyea, 2002). Functional status was more impaired in patients with delirium compared to those without delirium.

#### *Palliative Performance Scale (PPS)*

The PPS is a clinician-rated tool that was developed to measure functional performance and progressive functional decline in palliative care patients. Based on the Karnofsky Performance Scale (KPS), physical performance is divided into 11 categories, measured in 10% decremental levels from fully functional and healthy (100%) to dead (0%). Determination of the level of performance is based on five observable parameters: ability to ambulate, activity level and extent of disease, ability to perform self-care activities, food and fluid intake, and level of consciousness. The PPS correlated with length of survival in patients admitted to a palliative care unit (Anderson et al., 1996). Formal reliability and validity testing are currently being done by the scale developers.

## *Comorbidity*

### *Charlson Comorbidity Index*

Comorbidity was measured using the Charlson Comorbidity Index (Charlson, Pompei, Ales, & MacKenzie, 1987). The Charlson measures comorbidity associated with 19 medical conditions. Each condition is weighted 1-6 based on its relative risk of death. The total score on the Charlson ranges from 0-30 with a higher score indicating greater comorbidity. The Charlson can be adjusted for age by adding a point for each decade of age starting at 50 years. Interrater reliability was 0.74 by interclass coefficient in older cancer patients (Extermann et al., 1998). Test-retest reliability was 0.86 in the same population. The Charlson correlated highly with illness severity (log rank test  $\chi^2=148$ ) in an independent sample (Charlson et al., 1986).

## *Depression*

### *Geriatric Depression Scale (GDS-15)*

Depression was measured using the short form of the Geriatric Depression Scale (GDS-15) (Sheikh & Yesavage, 1986). The GDS-15 is a self-report measure of depression consisting of 15 yes/no questions. The total score on the GDS-15 ranges from 0 – 15; scores greater than 5 indicate probable depression. Chronbach's alpha for the GDS-15 was .81 in a sample of older depressed patients (Almeida & Almeida, 1999). Both long and short-forms of the GDS-15 were successful to differentiating depressed from non-depressed subjects with a high correlation ( $r=.84$ ,  $p<.001$ ) (Sheikh & Yesavage, 1986). The use of the cutoff point 4/5 for the GDS-15 produced sensitivity and specificity rates of 92.7% and 65.2% in comparison to the ICD-10 and 97.0% and 54.8%, respectively, when compared to the DSM-

IV diagnostic criteria for depression (Almeida & Almeida, 1999).

### *Sleep Quality and Quantity*

Sleep quality and quantity was measured using the Stanford Sleepiness Scale (Hoddes et al., 1973) and the Sleep and Rest subscale from the Sickness Impact Profile (John Hopkins University, 1977). In addition, patients were asked to provide information about the quantity and quality of their sleep during the previous week. Patients were asked to rate the overall quality of their sleep using a 4-point scale: 1=very good, 2=fairly good, 3=fairly bad, 4=very bad. Patients were also asked if they experienced any disturbed dreams that seemed real or caused awakening and if they have awakened during the night feeling confused or disoriented. Patients with delirium have reported unpleasant dreams and nightmares and waking experiences that merged with dreams (Lipowski, 1990).

### *Stanford Sleepiness Scale*

The Stanford Sleepiness Scale (SSS) was administered by the investigator at each scheduled weekly assessment. The SSS offers a series of phrases describing various states of arousal and sleepiness. The subject responds by selecting the set of adjectives that most closely corresponds to their current state of sleepiness or alertness. In studies of sleep deprivation (Babkoff et al., 1991) the SSS has been shown to be reliable with the Epworth Sleepiness Scale ( $r = .91$ ) and appears to track well over a course of a day in studies of sleep deprivation. The SSS however, has two noteworthy limitations: (1) it is not suitable for persons with a limited vocabulary and persons whose primary language is not English. In these situations, an analog scale is recommended—one end representing extreme sleepiness

and the other end alertness. The subject is asked to mark the scale to describe their state at the time of testing.

#### *Sickness Impact Profile – Sleep and Rest Subscale*

An adapted version of the Sleep and Rest subscale (SRS) from the Sickness Impact Profile was administered by the investigator at each scheduled weekly assessment. The SRS is a 7-item choice scale that asks the subject to select those responses that “describe you today and are related to your state of health”. The adapted version asks the subject to provide a yes or no response to each statement to describe his/her sleep and rest patterns over the past week. Each item is weighted with scores ranging from 4.9 to 10.4 points. By totaling the weighted item scores, the range of possible scores on the SRS is 0-49.9 points. In a sample of chronically ill adults (Pollard et al., 1976), the SRS has and test-retest reliability over 1 week ( $R=.69$ ,  $p<.01$ ). In a second study of hypothyroid patients (Bergener, et al., 1981), lower scores on the SRS correlated with lower T4 levels over repeated measures.

#### *Physiological Variables and Instruments*

Vital signs including temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation were obtained by the investigator each time the NEECHAM is administered.

#### *Vital Signs*

Heart rate was measured by auscultating the apical pulse while palpating the radial pulse for 1 minute. Regularity of the heartbeat was documented. Respiratory rate was

measured by counting the number of chest movements completed in 1 minute. Temperature, blood pressure, and arterial oxyhemoglobin saturation were measured using the Welch Allyn Vital Sign Monitor 300 Series (Welch Allyn, Beaverton, OR). Temperature was measured in degrees Celsius. Systolic and diastolic blood pressure was measured to the nearest 1mm HG in either the right or left arm of the subject. Arterial oxyhemoglobin saturation was measured by placing the pulse oximeter probe on the index finger.

#### *Nutritional Status (Height/Weight/Body Mass Index)*

Nutritional status was assessed by measuring height and weight and calculating body mass index. A stadiometer (Prospective Enterprise, Kalamazoo, MI) was used to measure height in inches to the nearest tenth. A digital scale (Scaletronix, Great Plains, NY) was used to measure body weight in pounds (lbs) to the nearest tenth. Height and weight were entered into the following equation to estimate the person's body mass index: [weight in lbs/height in inches X height in inches] X 703.

#### *Phase Angle*

Phase angle (PA), a measure of the electrical properties of tissues, was determined by bioelectric impedance analysis (BIA) using the Valhalla 1990B Bioimpedance Analyzer (Scientific Inc, San Diego, CA). BIA measurements include resistance in Ohms, reactance, and impedance. The Valhalla 1990B obtains these measures by delivering a safe low-level electrical alternating current of 500 $\mu$ A at a frequency of 50 kHz. This signal has been shown to be non-detectable and electrically safe (NIH, 1996). Reported manufacturer accuracy for resistance is 0.25% $\pm$ 1 Ohms with a detecting current range of 0-1023 Ohms.



PA is equal to the arc tangent of the  $X_c$  to  $R$  ratio ( $X_c$  = resistance and  $R$  = reactance). Toso et al. (2000) compared tissue electric properties in men with advanced lung cancer with healthy matched controls. The mean PA was 5.9 in healthy controls compared to 4.7 in patients with stage IIIB cancer and 4.4 in patients with stage IV lung cancer. Among lung cancer patients, those with a PA less than 4.5 had a significantly shorter survival. A low PA has also correlated with mortality in hemodialysis patients (Chertow et al, 1997; Di Iorio & Bellizzi, 2000; Maggiore et al, 1997). Although the biological meaning of PA is not fully understood, it may be a marker of physiological and cellular integrity.

#### *Sociodemographic Data*

Sociodemographic data were collected at the baseline assessment using a questionnaire developed by the investigator. Participants were asked to report their gender, age, ethnicity, years of formal education, disease status, treatment history (surgery and/or current and prior chemotherapy, radiation, hormonal therapy, and/or other biological therapies), smoking and alcohol history, and use of sensory aids (eyeglasses and hearing aids). The participant's cancer diagnosis, diagnosis date, extent of disease, and treatment history will also be confirmed by review of the medical record. These sociodemographic data were used to describe the characteristics of the participants.

#### *Caregiver Sociodemographic Data*

Caregivers completed a sociodemographic questionnaire developed by the investigator at the baseline assessment. Caregivers were asked to report their gender, age, ethnicity, years of formal education, marital status, employment status, relationship to the

patient, and types of assistance provided to the patient.

### *Medication Profile*

During the baseline assessment, participants were asked to show the investigator all of their current medications including routine and pro re nata (PRN) medications (prescribed and over-the-counter). The names of the medications, dosages, and reasons for taking the medications were documented on a medication profile developed by the investigator. Medication changes were documented at each weekly assessment.

### *Delirium Episode Caregiver Interview*

When delirium symptoms were identified either by the family caregiver or the investigator, the investigator conducted an informal interview with the family caregiver. The investigator attempted to determine when the patient first exhibited changes in his cognitive function or behavior, the temporal nature of the symptoms (whether they developed rapidly or gradually), the pattern of the symptoms (whether they have been fluctuating or consistent), the current state of symptoms (whether the patient is exhibiting the symptoms now), whether the patient's condition had changed in any other way (whether the patient has been experiencing any new physical symptoms or whether the patient has had a change in any ongoing symptoms), what medications the patient had taken in the past 24 hours and whether any new medications had been started or whether there had been any medications changes, and the caregiver's perception of what may have contributed to the change in the patient's condition.

### *Data Collection Procedures and Protocols*

Because participants were enrolled in the study for different lengths of time, the data collection period for each participant varied. Data were collected from the time of enrollment in the study for up to 6 months or until the participant's death. At the end of 6 months, participants were given the option to discontinue the study or to continue in the study for up to another 6 months. Data were collected at the baseline assessment, at scheduled weekly assessments, at delirium episode assessments, and at delirium episode follow-up assessments. Table 3.2 shows the data collection timeline for the study.

#### *Baseline Assessment*

After providing informed consent, participants underwent a baseline evaluation and interview. The baseline evaluation included collection of demographic data; measures of cognitive function and delirium; determination of functional status, comorbidity, symptom prevalence and distress, depression, sleep quality and quantity, and medication history; and measurement of physiological variables.

#### *Scheduled Weekly Assessments*

After baseline testing, participants underwent weekly evaluations in their homes. The weekly evaluations include measures of cognitive function and delirium, physical functioning, symptom prevalence and distress, depression, sleep quality and quantity, medication changes, and measurement of physiological variables.

### *Daily Monitor for Delirium Symptoms*

During the baseline assessment, family caregivers were provided with information about delirium and were instructed on completion of the Caregiver Confusion Checklist (CCC). Following this instruction, family caregivers were asked to complete the CCC twice daily in the morning and evening. Caregivers were instructed to contact the investigator, if the CCC score was  $\geq 2$ , indicating the presence of two or more signs of delirium. When contacted the investigator completed an in-home delirium episode assessment at the earliest possible convenience—within 1 to 2 hours.

### *Delirium Episode Assessments*

A delirium episode assessment was conducted by the investigator when the caregiver notified the investigator that the patient was exhibiting signs of delirium as evidenced by a score of 2 or more on the Caregiver Confusion Checklist or by a NEECHAM score  $\leq 24$  at the time of a scheduled assessment by the investigator. The delirium episode assessments included the completion of the MMSE and an unstructured interview with the patient for the completion of observational measures including the NEECHAM, CAM, DSM-IV criteria checklist, delirium behavior checklist, delirium motor patterns, the Richmond Agitation-Sedation Scale, and the Palliative Performance Scale. Physiologic data including vital signs, arterial oxyhemoglobin saturation, weight (if patient is able to stand), and phase angle also were collected. In addition, the investigator conducted an informal interview with caregivers to learn more about the symptoms or behaviors or events that preceded the delirium and to inquire about any changes in medications, patients' health status or overall condition, physical symptoms, or sleep patterns.

Table 3.2. Phase III Data Collection Timeline

	Baseline Evaluation	Weekly Evaluation	Delirium Episode Evaluation	Delirium Episode Follow-Up Evaluation
<b>Informed Consent</b>	X			
<b>Demographic Data and History</b>	X			
<b>Cognitive Function</b>				
Mini Mental State Exam	X	X	X	X
Self-Report of Confusion	X	X	X	X
<b>Level of Consciousness</b>				
Richmond Agitation-Sedation Scale	X	X	X	X
<b>Delirium Assessment</b>				
Delirium Etiologic Pattern Screen	X	X		
NEECHAM Confusion Scale	X	X	X	X
Confusion Assessment Method			X	X
DSM-IV Criteria for Delirium			X	X
Delirium Motor Pattern Screen			X	X
Delirium Behavior Checklist			X	X
Caregiver Confusion Checklist		X (Daily)		
<b>Symptom Prevalence/Distress</b>				
Memorial Symptom Assessment Scale	X	X		
<b>Physical Functioning</b>				
OARS	X	X		
Palliative Performance Scale	X	X	X	X
<b>Comorbidity</b>				
Charlson Comorbidity Index	X			
<b>Depression</b>				
Geriatric Depression Scale	X	X		
<b>Sleep Quality and Quantity</b>				
Sleep Questionnaire	X	X		
Stanford Sleepiness Scale	X	X		
Sleep and Rest Subscale	X	X		
<b>Physiological Variables</b>				
Temperature	X	X	X	X
Heart Rate	X	X	X	X
Respiratory Rate	X	X	X	X
Blood Pressure	X	X	X	X
Oxygen Saturation	X	X	X	X
Height	X			
Weight	X	X	X	X
Phase Angle	X	X	X	X
<b>Medication Profile/Update</b>	X	X	X	X
<b>Caregiver Delirium Interview</b>			X	
<b>Caregiver Delirium Follow-Up Interview</b>				X

### *Delirium Episode Follow-Up Assessments*

When possible, a delirium follow-up assessment was conducted on the day after a delirium episode assessment. The delirium episode follow-up assessment included the completion of the MMSE and an unstructured interview with the patient for the completion of observational measures including the NEECHAM, CAM, DSM-IV criteria checklist, delirium behavior checklist, delirium motor patterns, the Richmond Agitation-Sedation Scale, and the Palliative Performance Scale. Physiologic data also were collected. In addition, an informal interview was conducted with caregivers to determine the current status of delirium symptoms and the patient's overall condition, other symptoms, medication changes, and whether there has been any contact with the patient's primary provider. Family caregivers and patients, if able, and the investigator agreed upon the frequency and timing of further follow-up assessments. The following guidelines were used:

- 1) If the patient did not score positive for delirium by either the NEECHAM (score  $\leq$  24), or the CAM at a delirium episode assessment or at a delirium episode follow-up assessment, then the next assessment was done at the time of the next scheduled weekly assessment.
- 2) If the patient remained positive for delirium (NEECHAM score  $\leq$  24 and CAM +) at the delirium episode follow-up assessment and the scheduled weekly assessment was within 3 days of the follow-up assessment, then the next assessment was done at the time of the next scheduled weekly assessment.
- 3) If the patient remained positive for delirium (NEECHAM score  $\leq$  24 and CAM +) at the delirium episode follow-up assessment and the scheduled weekly assessment was more than 3 days from the follow-up assessment, then the

investigator made additional visits as agreed upon by the family caregiver and the investigator.

### *Data Analysis*

The primary aim of this phase of investigation was to describe the nature of delirium and delirium vulnerability in older adults with advanced cancer near the end of life. Data analysis used standard descriptive statistics and graphic techniques for evaluating patterns, change and variability, and sequencing of events.

Data analysis involved several different levels. First, analysis focused specifically on examining and describing episodes of delirium. Second, analysis focused on understanding delirium and delirium vulnerability factors among individuals and subgroups of individuals. Individual case studies were developed for each participant using the format in Figure 3.2.

Key variables were plotted over time for each participant to characterize individual patterns and trends in the data. The variable score or value was plotted on the y-axis and the number of days from enrollment to death or from enrollment to the end of the study in reverse chronological order was plotted on the x-axis. In addition, key events—treatments, hospitalizations, medications, falls, disease progression, and hospice referrals—occurring during the study were documented on the x-axis. The graphed data were visually inspected to examine and describe patterns of change over time and in relation to the development of delirium. Data also were displayed in tables and matrices for examination of individual cases and comparison across cases. Individual data were examined to understand and describe patterns and trends within subjects. Then, data were examined to identify similarities and differences between subjects.

The first research question addressed the nature and course of delirium in older cancer patients at the end of life. In order to answer this research question, key variables and data associated with delirium episodes—total NEECHAM score, NEECHAM subscale and item scores, cognitive functioning, level of consciousness, delirium behaviors, delirium motor patterns, physiological variables, and narrative data—were examined and used to develop a comprehensive description of delirium episodes. Delirium episodes in participants who died were examined for similarities and differences. Similarly, delirium episodes in participants who lived were examined for similarities and differences. Finally, reversible delirium episodes in participants who died were compared to reversible delirium episodes in participants who lived.

The second research question related to changes in delirium vulnerability at the end of life and the development of delirium. Measured variables—cognitive functioning, physical functioning, depression, symptom prevalence and distress, physiological functioning, etiologic pattern markers, and medication use and other treatment-related factors—were examined as unique markers of diminished reserves and increased vulnerability to the development of delirium. These variables were examined at baseline to classify participant's risk at entry into the study. Plots of the variables, as well as narrative data, were examined to evaluate how these markers and factors changed over time and in relation to the development of delirium.

The third research question asked, “How is delirium in older cancer patients at the end of life similar to or different from delirium in hospitalized older cancer patients?” In order to answer the third research question, findings related to delirium and etiologic pattern markers in the older cancer patients at the end of life in Phase III will be compared to



findings related to delirium and etiologic pattern markers in the hospitalized older cancer patients in Phase I.

The fourth research question addressed issues associated with conducting this research in older cancer patients near the end of life. The discussion is based primarily on the investigator's observations and reflections, and focuses on three areas in particular: 1) the changing nature of palliative treatment for older cancer patients, 2) methodological issues related to recruitment and measurement, and 3) the role of family caregivers in monitoring for delirium.

- 
- I. Background
    - 1. Treatment and Disease Course
    - 2. Enrollment
    - 3. Baseline Characteristics
  - II. Study Course
    - 1. Tolerance of Study Protocol
  - III. Delirium Episodes
    - 1. NEECHAM Scores
    - 2. NEECHAM Subscale Scores
    - 3. Delirium Behaviors
    - 4. Vital Function
  - IV. Trajectories of Delirium Vulnerability
    - 1. Cognitive Functioning
    - 2. Depression
    - 3. Physical Functioning
    - 4. Symptom Prevalence and Distress
    - 5. Weight and BMI
    - 6. Phase Angle
    - 7. Etiologic Patterns and Clinical Markers
  - V. Caregiver Monitoring for Delirium
- 

*Figure 3.2. Case study format*

## CHAPTER FOUR

### RESULTS

This chapter presents findings from the three phases of this research. The first phase consisted of secondary analyses of data from the Acute Confusion in Hospitalized Elders Studies to examine delirium in a sample of hospitalized older cancer patients and a subset of the patients who were near the end of life. The second phase was a pilot study investigating the feasibility and burden associated with a protocol for studying delirium in older adults with advanced cancer cared for at home. The findings from the third phase provide an in-depth examination of delirium and delirium vulnerability in a sample of older adults with advanced cancer receiving palliative and end-of-life care primarily at home, as well as a comparison of delirium and delirium vulnerability in this sample and the sample of hospitalized older cancer patients and a discussion of key issues encountered in conducting this research.

#### *Phase I: Delirium in a Sample of Hospitalized Older Cancer Patients*

##### *Analysis 1: The Nature and Course of Delirium*

The first analysis examined the nature and course of delirium in a sample of 76 hospitalized older cancer patients. The goals of this analysis were to: 1) determine the prevalence and incidence of delirium in the sample; 2) examine the course of delirium from admission to discharge; 3) identify etiologic patterns; and 4) compare characteristics and etiologic patterns in the patients with delirium and in those without delirium.

Table 4.1. Characteristics of Hospitalized Older Cancer Patients (N=76)

Variable	n	%
Gender		
Male	41	53.9
Female	35	46.1
Ethnicity		
Caucasian	41	53.9
African-American	32	42.1
Other	3	4.0
Cancer Diagnosis		
Multiple Myeloma	13	17.1
Lung	11	14.5
Prostate	11	14.5
Breast	8	10.5
Lymphoma	6	7.9
Other (12)	27	35.5

Variable	Mean	SD	Range
Age (years)	74.4	7.29	65-96
Education (years)	9.9	4.69	0-20
APACHE II	14.9	4.88	6-30
IADLs	8.5	4.65	0-14
Length of Stay (days)	9.8	8.67	2-43

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### *Patient Characteristics*

Table 4.1 summarizes the characteristics of the sample of hospitalized older cancer patients. The mean age was 74.4 years. Patients were evenly divided by gender and ethnicity; 53.9% were men and 46.1% were non-white. The majority of non-white patients were African-American (91.4%). A total of 17 cancer diagnoses were represented in the sample with the top five being: multiple myeloma (17.1%), lung cancer (14.5%), prostate cancer (14.5%), breast cancer (10.5%), and lymphoma (7.9%). The mean educational level was 9.9 years (SD 4.69; range 0-20). The mean APACHE II score (14.9) indicated moderate illness severity. Similarly, the patients had a moderate level of functional impairment as indicated by a mean IADL score of 8.5. The average length of hospital stay was 9.8 days.

### *Aim 1: Prevalence and Incidence of Delirium in the Hospitalized Older Cancer Patients*

Delirium was present at the time of admission in 29 patients, for a prevalence rate of 38.1%. Fourteen of the 47 patients with no delirium at the time of admission developed delirium at some point during hospitalization, for an incidence rate of 29.8%. The cumulative rate of delirium during the entire hospitalization period was 56.6%, which is defined as the sum of the prevalent and incident cases.

### *Aim 2: Course of Delirium in the Hospitalized Older Cancer Patients*

Table 4.2 shows delirium at admission by NEECHAM category. Of the 29 patients with delirium on admission, 21 (72.4%) had mild delirium (NEECHAM score 20-24) and 8 (27.6%) had severe delirium (NEECHAM score < 20). Twenty-nine patients (38.2%) were at

risk for delirium (NEECHAM score 25-26 or > 26 with risk marker) on admission and 18 (23.7%) exhibited no delirium or minimal risk with a NEECHAM Score  $\geq 27$ .

Table 4.2. Frequency of delirium at admission by NEECHAM category (N=76)

NEECHAM Category	Number and percentage of patients in each category at admission	
	n	%
Severe Delirium	8	10.5
Mild Delirium	21	27.6
At Risk	29	38.2
Low Risk	18	23.7

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Figure 4.1 depicts the course of delirium during hospitalization as represented by changes in mean NEECHAM scores for patients in each NEECHAM category on admission. The mean NEECHAM scores for each category worsened during hospitalization but improved at discharge. In other words, in patients with delirium, delirium worsened during hospitalization but improved prior to discharge. Even in patients with no delirium at admission, mean NEECHAM scores dropped during hospitalization.

NEECHAM scores were relatively unstable in patients admitted with mild delirium and in those at risk for delirium. During hospitalization, 15 of the 21 patients admitted with mild delirium exhibited a clinically significant change of  $\geq 3$  points in their NEECHAM

scores that resulted in a change in delirium category (worsened in 8 and improved in 7). Two additional patients had a 1-or 2-point change in NEECHAM score that resulted in a change in delirium category (worsened in one and improved in one). Eleven of the 29 at-risk patients (38%) developed delirium during hospitalization; 5 developed mild delirium and 6 severe. Three patients who were at risk based on NEECHAM score improved moving into the low-risk category.

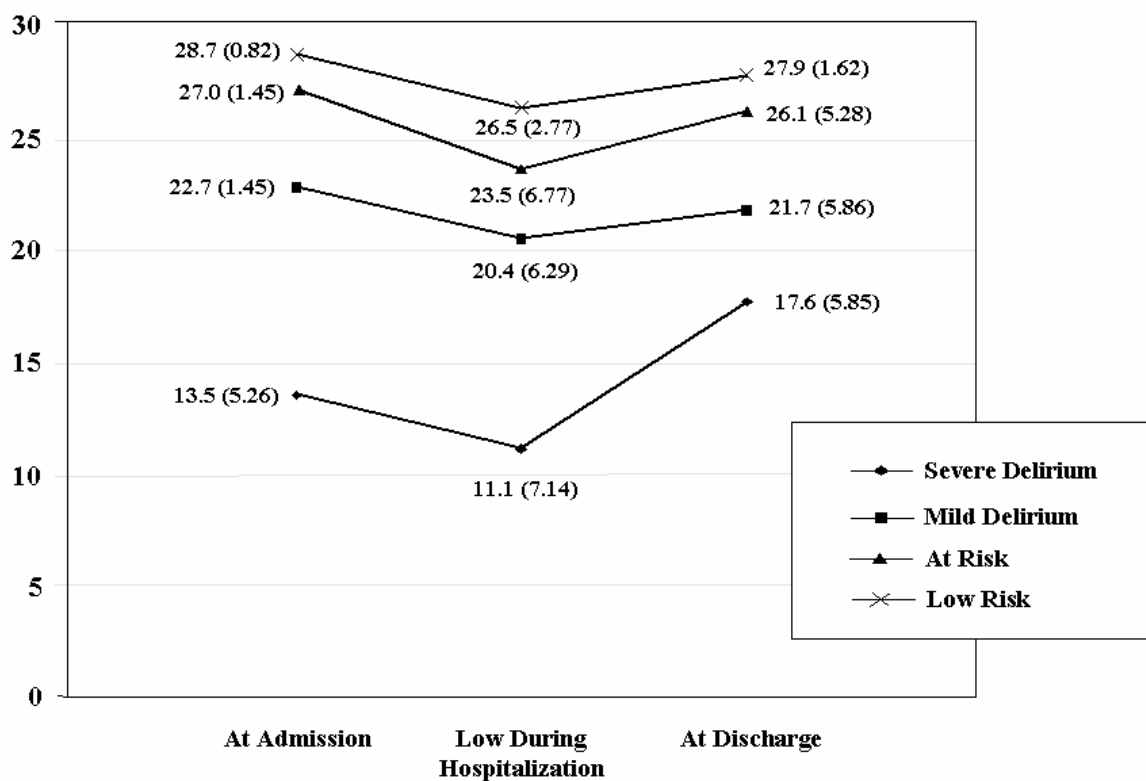


Figure 4.1. Mean NEECHAM scores across hospitalization by NEECHAM category (SD)

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Table 4.3 shows the frequency of delirium at discharge. Delirium was present in 30 (39.5%) patients; 18 (60%) had mild and 12 (40%) had severe delirium. Twenty-one of 29 patients (72.4%) who had delirium on admission had delirium at discharge. Delirium resolved prior to discharge in 13 of 43 patients (30.2%).

Table 4.3. Frequency of delirium at discharge by NEECHAM category

NEECHAM Category	Number and percentage of patients in each category at discharge	
	n	%
Severe Delirium	12	15.8
Mild Delirium	18	23.7
No Delirium*	46	60.5

\* Includes At Risk and Low Risk Categories

### *Aim 3: Etiologic Patterns in the Hospitalized Older Cancer Patients*

Patients were classified into the five etiologic patterns based on the presence of clinical risk markers at admission. Most patients exhibited multiple etiologic patterns ( $M$  2.3;  $SD$  1.07; range 0-5). The most common pattern in hospitalized older cancer patients was metabolic-nutritional (90.8%) followed by hypoxic (61.8%), metabolic-toxic (39.5%), orthostatic-dehydration (35.5%), and chronic cognitive impairment (6.6%).

Five of the hospitalized older cancer patients (6.6%) exhibited markers of chronic cognitive impairment. At admission among these patients, one was at risk for delirium, one had mild delirium, and three had severe delirium. At some point during hospitalization, all of



the patients with chronic cognitive impairment had severe delirium. In addition, at discharge, they all had persistent delirium. Importantly, however, in 3 of the 5 patients, delirium had improved from severe to mild.

*Aim 4: Characteristics and Etiologic Patterns in Patients With and Without Delirium*

Patient characteristics and etiologic patterns in patients who had no delirium were compared with the patient characteristics and etiologic patterns in those who had at least one episode of delirium either on admission, during hospitalization, or at discharge. Table 4.4 presents the characteristics of patients with and without delirium. Patients with delirium were more severely ill (mean APACHE II score 15.9 vs 13.5;  $p = 0.032$ ) and had a greater level of functional impairment (mean IADL score 6.8 vs 10.7;  $p < 0.001$ ). Patients with delirium also exhibited risk markers in more etiologic patterns (mean 2.6 vs 2.1;  $p = 0.045$ ). Although not statistically significant, patients with delirium tended to have a longer length of hospitalization (mean 11.5 vs 7.7 days;  $p = 0.056$ ).

Table 4.4. Characteristics of Patients With and Without Delirium

Variable	Patients with Delirium (n = 43)		Patients without Delirium (n = 33)		Significance Level†
	n	%	n	%	
Gender					
Male	23	53.5	18	54.6	0.927
Female	20	46.5	15	45.4	
Ethnicity					
White	20	46.5	21	63.6	0.138
Non-White	23	53.5	12	36.4	

† Chi square

Table 4.4. Characteristics of Patients With and Without Delirium (continued)

Variable	Mean	SD	Mean	SD	Significance Level††
Age	74.6	7.71	74.1	6.82	0.790
Education	9.9	5.02	10.1	4.35	0.864
APACHE	16.0	5.25	13.5	4.02	0.032
IADLs	6.8	4.75	10.7	3.47	0.000
Length of Stay	11.5	9.66	7.7	6.70	0.056
Etiologic Patterns	2.6	1.05	2.1	1.06	0.045

†† T-test

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Table 4.5 compares the etiologic patterns in patients with and without delirium. Patients with hypoxic pattern markers were more likely to have delirium ( $\chi^2 = 4.410$ ;  $p = 0.036$ ). As previously noted, all of the patients with chronic cognitive impairment ( $n = 5$ ) had delirium at some point during hospitalization.

Table 4.5 Etiologic Patterns in Patients With and Without Delirium

Etiologic Pattern	Patients with Delirium (n = 43)		Patients without Delirium (n=33)		Significance Level†
	n	%	n	%	
Metabolic-Nutritional	41	95.3	28	84.8	0.117
Hypoxic	31	72.1	16	48.5	0.036
Metabolic-Toxic	18	41.9	12	36.4	0.627
Orthostatic-Dehydration	15	34.9	12	36.4	0.894
Chronic Cognitive Impairment	5	11.6	0	0.0	

†Chi-square

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### *Analysis 2: Delirium Resolution*

The purpose of the second analysis was to examine delirium resolution in the 43 hospitalized older cancer patients who had delirium at some point during hospitalization. The specific aims were: 1) to identify trajectories of change in delirium between hospitalization and discharge, and 2) to compare characteristics and etiologic patterns in patients with delirium that resolved by discharge and those with delirium at discharge.

### *Patient Characteristics*

The characteristics of the 43 hospitalized older cancer patients with delirium are presented in Table 4.6. The patients were relatively young with a mean age of 74.6 years. Patients were almost evenly divided by gender and ethnicity. Multiple hematologic and solid

organ malignancies were represented in the sample including multiple myeloma (n=8), leukemia (n=3), lymphoma (n=1), lung (n=9), breast (n=8), prostate (n=4), colon (n=2), liver (n=2), and other (n=6). The mean APACHE II score (16.0) indicated moderate to high illness severity. The patients had a moderate level of functional impairment as indicated by mean IADL score of 6.8. Patients exhibited multiple etiologic patterns with a mean of 2.6. The average length of hospital stay was 11.5 days.

*Aim 1: Trajectories of Change in Delirium*

Forty-one patients (95%) had delirium at some point during hospitalization prior to discharge; 18 (44%) had mild delirium and 23 (56%) had severe delirium. Thirteen patients (30%) had no delirium at discharge. Delirium was present in 30 patients (70%); 18 had mild delirium and 12 had severe delirium.

Table 4.6. Characteristics of hospitalized older cancer patients with delirium (N = 43)

Variable	n	%
Gender		
Male	23	53.5
Female	20	46.5
Ethnicity		
Caucasian	20	46.5
Non-Caucasian	23	53.5
Cancer Type		
Hematologic	12	27.9
Solid Tumor	31	72.1

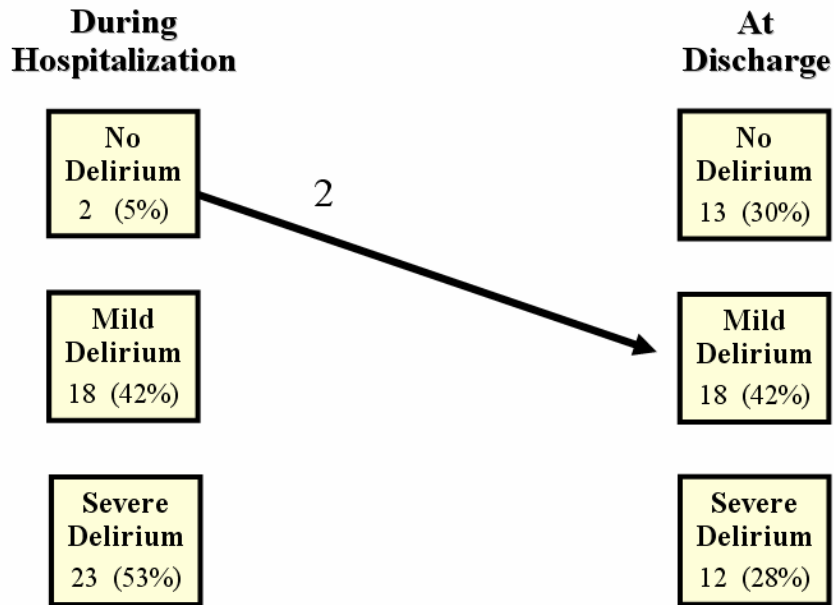
Table 4.6. Characteristics of hospitalized older cancer patients with delirium (continued)

Variable	Mean	SD	Range
Age (years)	74.6	7.71	65-96
Education (years)	9.9	5.02	0-20
APACHE II	16.0	5.25	9-30
IADLs	6.8	4.75	0-14
Length of Stay (days)	11.5	9.66	2-43
Etiologic Patterns	2.6	1.05	1-5

At discharge, delirium persisted in 28 of the 41 patients who had delirium during hospitalization; 16 (57%) had mild delirium and 12 (43%) had severe delirium. In addition, two patients without delirium during hospitalization had mild delirium at discharge. Figure 4.2, Figure 4.3, and Figure 4.4 demonstrate the trajectories of change in delirium between the period during hospitalization and discharge.

Figure 4.2 shows the change trajectory for the two patients with no delirium during hospitalization, but who had mild delirium (NEECHAM score 20-24) at discharge. One of the patients had a 3-point drop in NEECHAM score from 27 during hospitalization to 24 at discharge. The other had a 2-point drop in NEECHAM score from 26 to 24. A change in NEECHAM score  $\geq 3$  points is considered clinically significant.

## Trajectories of Change



*Figure 4.2.* Change trajectory for patients with no delirium during hospitalization but with delirium at discharge

Figure 4.3 shows the change trajectories for patients with mild delirium during hospitalization ( $n = 18$ ). At discharge, delirium had resolved in 12 patients (66%). The mean change in NEECHAM score among the patients with mild delirium that resolved was 5.1 points ( $SD$  2.47; range 2 – 10). All but one of the patients had a change in NEECHAM score  $\geq 3$  points. Six patients (33%) had persistent mild delirium. No patients with mild delirium during hospitalization had more severe delirium at discharge.

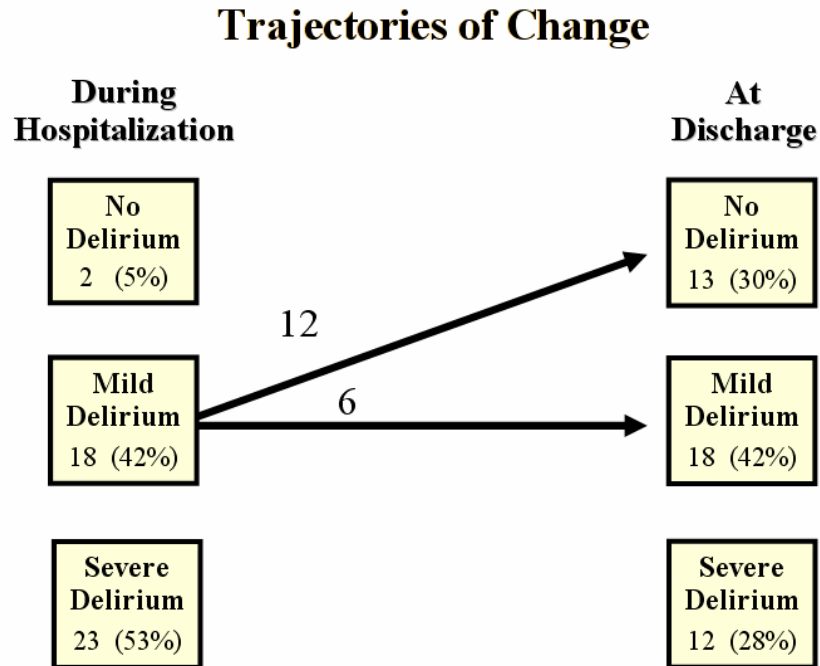


Figure 4.3. Change trajectories for patients with mild delirium during hospitalization

Figure 4.4 shows the change trajectories for patients with severe delirium (NEECHAM score <20) during hospitalization (n = 23). At discharge, delirium had resolved in one patient with severe delirium. This patient's lowest NEECHAM score during hospitalization was 7, and at discharge it was 27. More than half (n = 12; 52%) had persistent severe delirium. Delirium improved from severe to mild in 10 patients (43%). The mean change in NEECHAM score for those that improved was 6.1 points (*SD* 4.38; range 1 – 17). All but one of the patients had a change in NEECHAM score  $\geq 3$  points.

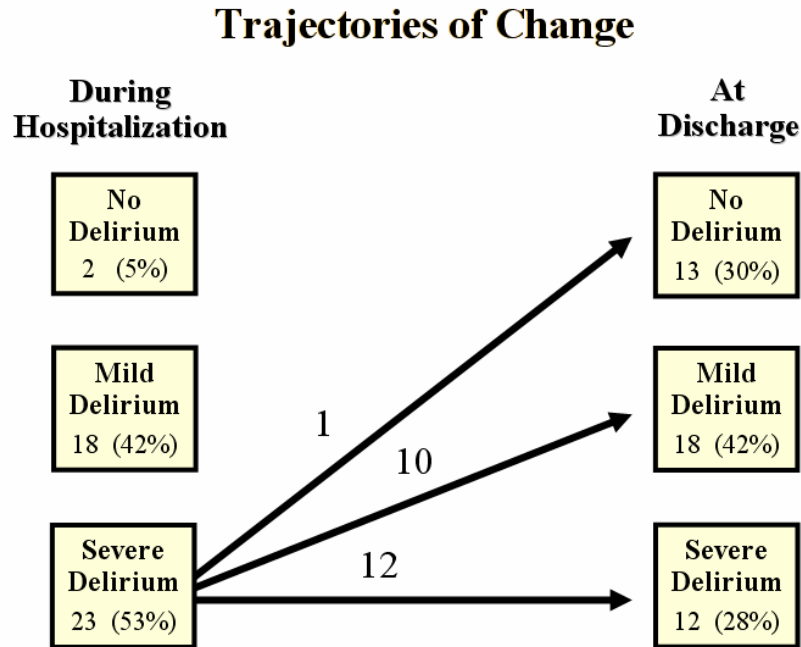


Figure 4.4. Change trajectories for patients with severe delirium during hospitalization

#### Aim 2: Characteristics in Patients With and Without Delirium Resolution

Table 4.7 presents characteristics in patients with and without delirium resolution. Patients with delirium resolution were less functionally impaired (mean IADLs 10.3 versus 5.3) and exhibited fewer etiologic risk patterns (mean frequency 1.9 versus 2.8) (Table 4.7). Patients with delirium resolution also had a shorter length of hospital stay (mean LOS 7.3 versus 13.3). There were no differences among patients with delirium resolution and those without resolution with regard to gender, ethnicity, cancer type, delirium onset, or specific etiologic patterns except for chronic cognitive impairment. All patients with chronic cognitive impairment had delirium during hospitalization that persisted at discharge. Patients with mild delirium were more likely to have resolution than those with severe delirium (Fisher's Exact;  $p < 0.0001$ ).



Table 4.7. Characteristics of Patients With and Without Delirium Resolution

Variable	Delirium Resolution (n = 13)		No Resolution (n = 30)		t Value	Significance Level
	Mean	SD	Mean	SD		
Age	73.0	7.87	75.3	7.67	0.89	0.358
APACHE	16.4	6.09	15.8	4.94	-0.31	0.764
IADLs	10.3	3.42	5.3	4.48	-3.97	0.000
Length of Stay	7.3	2.32	13.3	11.03	2.83	0.008
Etiologic Patterns	1.9	0.86	2.8	1.01	2.81	0.008

*Analysis 3: Delirium in Hospitalized Older Cancer Patients Near the End of Life*

Delirium trajectories and etiologic patterns were examined in 10 of the hospitalized older cancer patients in the Patterns and Interventions Study who died within 3 months of discharge. Table 4.8 summarizes their patient characteristics. Six were men and 7 were African-American. They represented a variety of cancer diagnoses. Their ages ranged from 65-90 years (mean = 76). The patients had moderate to high illness severity (mean APACHE score = 16) and moderate functional impairment (mean PADL = 10.1; IADL = 8.3). The patients exhibited multiple etiologic patterns. Their average length of hospital stay was 12.2 days. While the patients were not considered terminal at admission, their deaths occurred 2 to 70 days after hospital discharge; 5 patients died within 10 days of discharge.

Table 4.8. Characteristics of patients near the end of life (N = 10)

Variable	n	%
Gender		
Male	6	60
Female	4	40
Ethnicity		
Caucasian	3	30
African-American	7	70
Cancer Diagnosis		
Lung	3	30
Prostate	2	20
Multiple Myeloma	2	20
Breast	1	10
Colon	1	10
Gall Bladder	1	10

Variable	Mean	SD	Range
Age (years)	75.9	9.72	65-90
APACHE II	16.0	3.65	12-24
IADLs	8.3	4.11	3-14
Etiologic Patterns	3.2	1.03	2-5
Length of Stay (days)	12.2	8.31	5-30
Time to Death (days)	20.1	21.82	2-70

*Aim 1: Delirium Trajectories in Patients Near the End of Life*

Eight of the 10 patients experienced delirium during their hospitalization (NEECHAM  $\leq 24$ ). The severity and course of delirium varied except in one patient who had persistent severe delirium (NEECHAM  $< 20$ ). Six of the 8 with delirium had intermittent periods without symptoms. All patients with delirium during hospitalization had delirium symptoms at discharge. Based on NEECHAM scores, four delirium trajectories were identified among the older cancer patients near the end of life: no delirium, fluctuating delirium, progressive delirium, and persistent severe delirium.

Figure 4.5 shows the NEECHAM score trajectories for the two patients who had no delirium during hospitalization. One patient remained at low risk for delirium during a 5-day hospitalization. This patient was 65 years old, had multiple myeloma, and died 70 days post-discharge. The other patient fluctuated between being at low risk and at risk for delirium over a 21-day hospital stay. This patient was 66 years old, had breast cancer, and died 21 days following discharge. Her NEECHAM scores were consistently lower toward the end of her hospitalization.

Figure 4.6 shows the NEECHAM score trajectories of the six patients with fluctuating delirium. Throughout their hospitalization, their NEECHAM scores tended to vary widely. Five of the patients had severe delirium at some point; the other fluctuated between mild delirium and no delirium. All but one of the patients had periods without delirium symptoms (NEECHAM score  $\geq 25$ ). At discharge, all of the patients with fluctuating delirium during hospitalization were delirious; 4 had mild delirium and 2 had severe delirium

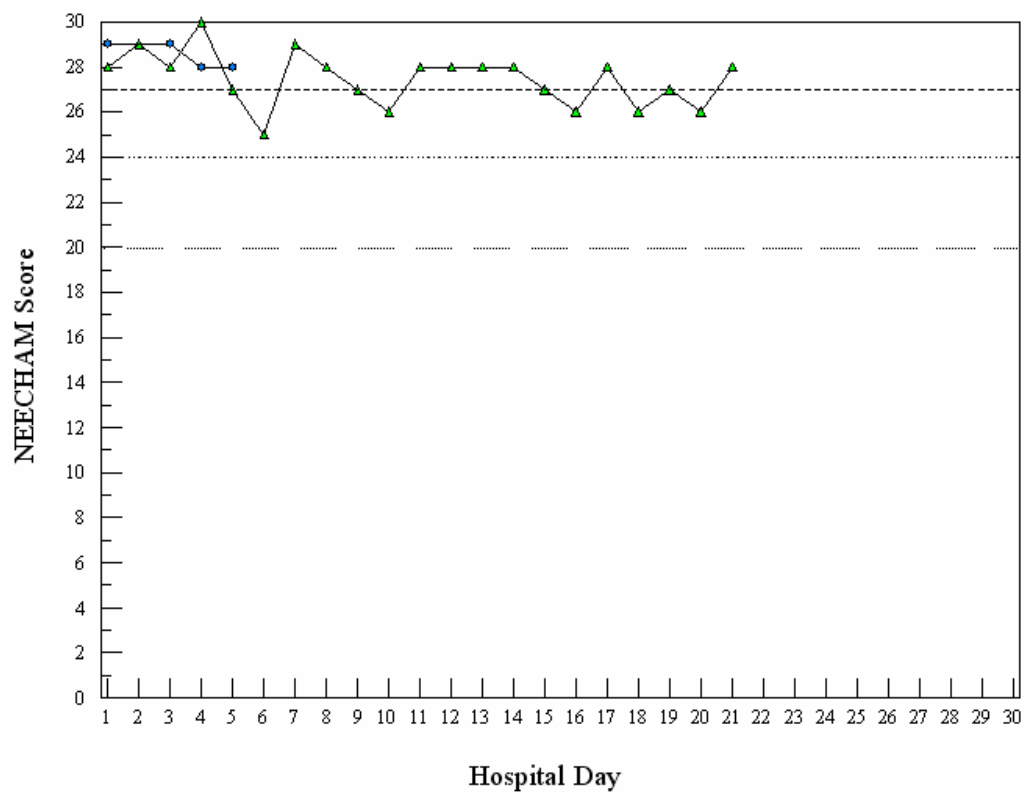


Figure 4.5. NEECHAM score trajectories in patients with no delirium ( $n = 2$ )

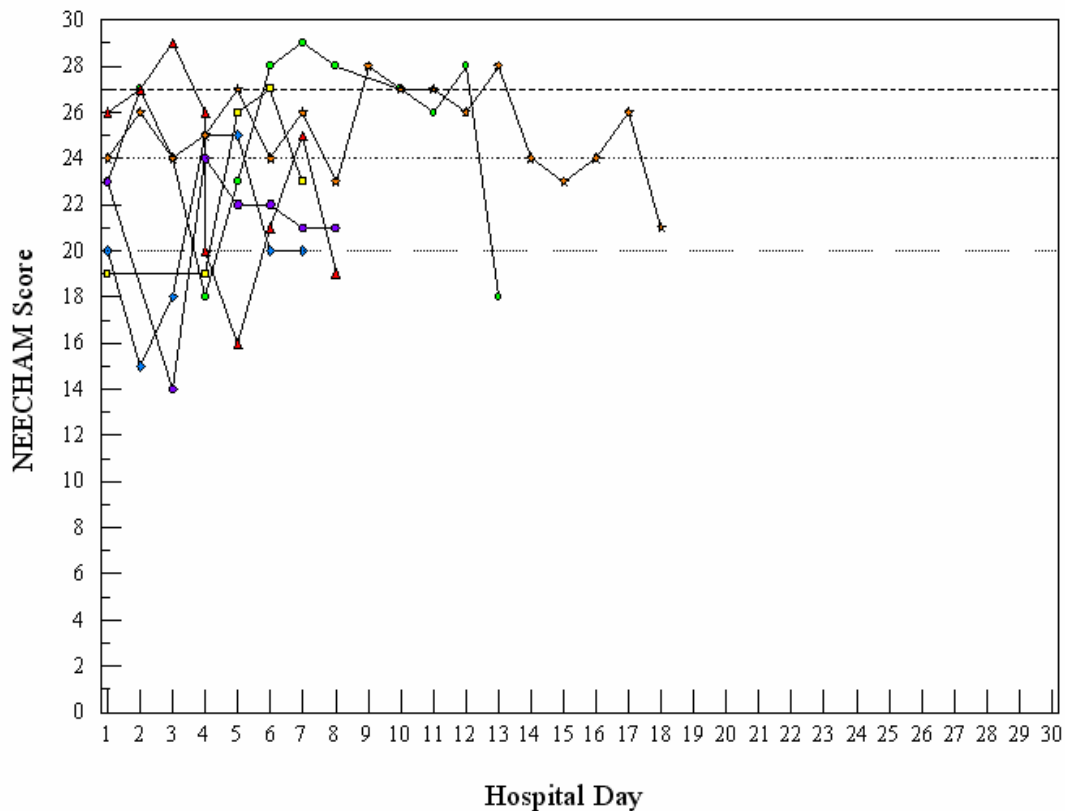
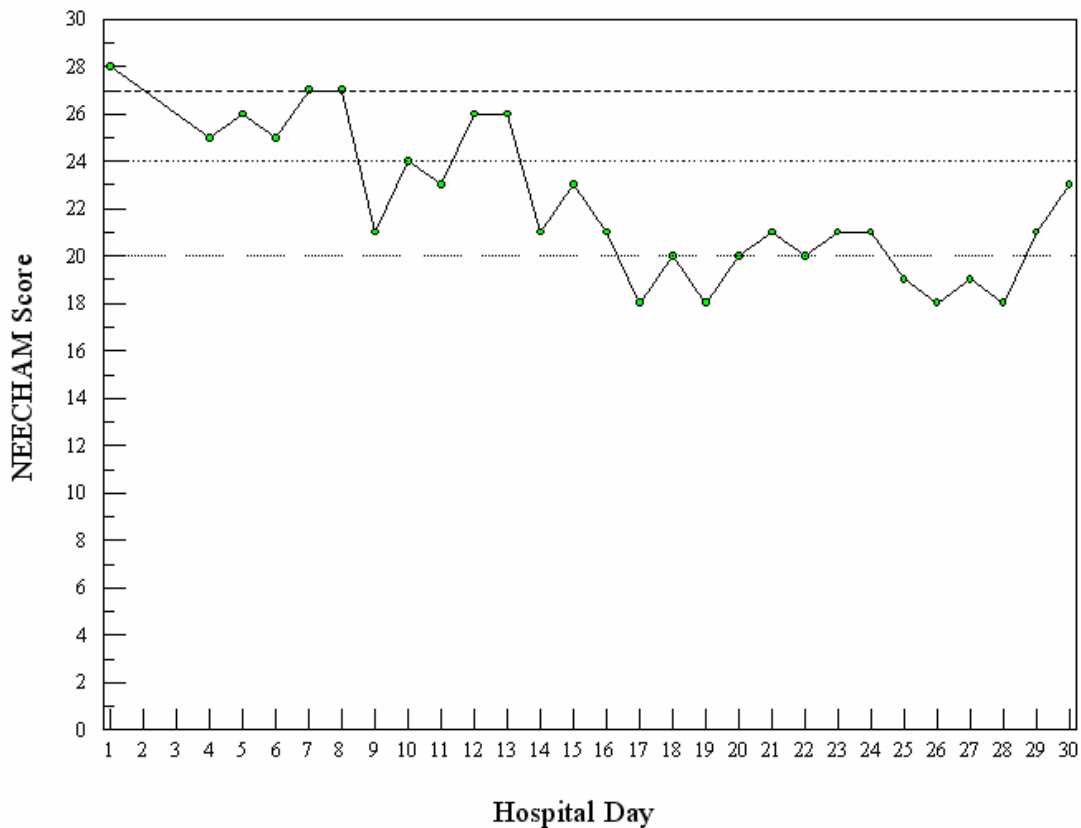


Figure 4.6. NEECHAM score trajectories in patients with fluctuating delirium (n = 6)

Figure 4.7 represents the NEECHAM score trajectory for the patient who had progressive delirium. Although this patient's NEECHAM scores fluctuated during hospitalization, overall, they declined. The patient, a 90-year old, African-American female with colon cancer, was free of delirium at admission and until hospital day 9 when she developed mild delirium (NEECHAM score = 21). Her NEECHAM scores improved over the next 3 days. When she was assessed on day 12 and day 13, she was without delirium symptoms (NEECHAM score = 26). On day 14, she, again, developed mild delirium (NEECHAM score = 21). After that point, she fluctuated between severe and mild delirium until her discharge on day 30. She died 7 days later.



*Figure 4.7.* NEECHAM score trajectory in patient with progressive delirium (n = 1)

Figure 4.8 presents the NEECHAM score trajectory for one patient who had persistent severe delirium from admission to discharge. This patient, a 79-year old, African-American male with cancer of the gallbladder, had severe delirium (NEECHAM score = 16) at admission. Overall, his delirium worsened during his 5-day hospitalization. His NEECHAM scores obtained on hospital day 3 (NEECHAM score = 8) and on hospital day 5 (NEECHAM score = 12), indicated persistent severe delirium. He died at home with hospice care, 2 days after discharge.

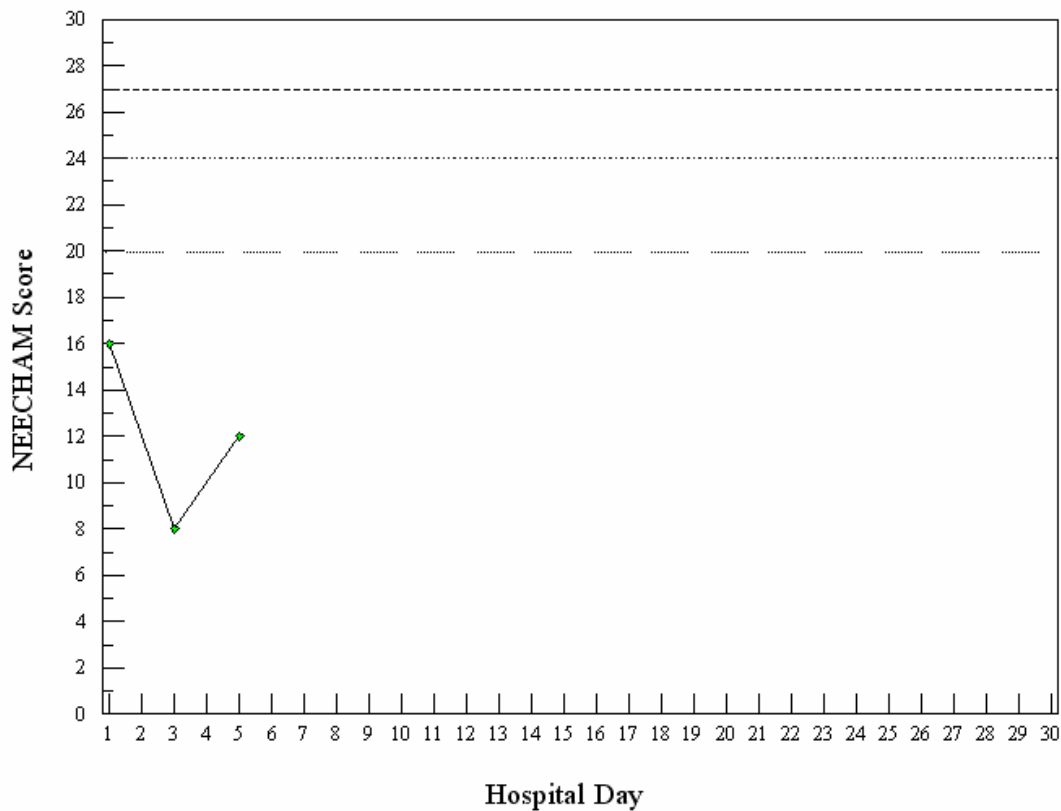


Figure 4.8. NEECHAM score trajectory in patient with persistent severe delirium (n = 1)

#### *Aim 2: Etiologic Patterns in Patients Near the End of Life*

Etiologic patterns were determined by the presence of clinical risk markers at admission. Patients had clinical risk markers for multiple etiologic patterns (Table 4.8). All patients, whether delirious or not, had metabolic-nutritional pattern markers. Seven of the 8 delirious patients had hypoxic markers; 6 had orthostatic-dehydration markers; 4 had metabolic-toxic markers; and 2 patients had markers for chronic cognitive impairment.

*Phase II: Development and Pilot Testing of a Protocol to Study Delirium  
in Older Adults with Advanced Cancer*

The second phase of the research was a pilot study to assess a protocol to study delirium in older adults with advanced cancer receiving palliative cancer treatment and end of life care primarily at home. The specific aims were: 1) to test the feasibility of the protocol, first, in a laboratory and, then, in the home setting; 2) to determine the level of patient and caregiver burden associated with the protocol; 3) to evaluate and refine instruments and data collection procedures; and 4) to identify and resolve methodological issues related to recruitment, consent, measurement, and retention.

*Participant Characteristics*

Three older persons with advanced cancer and their family caregivers were enrolled in the study. Participant #1 was an 87 year-old Caucasian male with metastatic gastric cancer. His cancer was diagnosed in December 2003, and he underwent surgical resection in January 2004. During the study, he was receiving palliative treatment with oral chemotherapy. Participant #2 was a 68 year-old Caucasian male with metastatic gastric cancer that was diagnosed in March 2004. He was receiving infusional chemotherapy throughout the study, except during Week 3, when he had a break between cycles. Participant #3 was a 69 year-old Caucasian female with metastatic colon cancer involving the liver. She had been diagnosed in June 2003. She had been receiving palliative chemotherapy throughout the past year after undergoing an initial surgical resection. All of the participants were being cared for by their spouses.

Family caregivers completed the Caregiver Confusion Checklist twice a day. During the study, all of the participants exhibited possible symptoms of confusion or altered



cognition. The following symptoms were documented on the CCC by their caregivers: being tired, difficulty sleeping, feeling irritable, slowed response, frustration, being withdrawn, feeling drowsy, decreased concentration, fatigue, slowed movements, apathy, being impatient, and foggy. Only one participant (#3) had a suspected episode of delirium following an anaphylactic reaction to Erbitux, a monoclonal antibody that had been added to her regimen when she experienced disease progression. The investigator was not contacted during this episode. Based on information obtained in an interview with the participant's husband following the episode, the participant's NEECHAM Confusion Scale score was estimated to be 16. The participant's caregiver reported observing the following symptoms during the episode: slowed response, slowed movements, simple speech, slurred speech, drowsy, and slowed thinking.

#### *Feasibility and Burden Associated with the Protocol*

Data collection sessions were scheduled at a time that was convenient for patients and their caregivers. Patients and caregivers reported minimal burden associated with the protocol. The initial data collection session was conducted in the Biobehavioral Laboratory in the UNC School of Nursing. During the initial session, the investigator provided informed consent, evaluated cognitive function, obtained sociodemographic data, and completed the protocol for routine data collection. The initial data collection sessions lasted from 1.5 to 1.75 hours. The informed consent process and the collection of sociodemographic data took approximately 20 minutes each. Weekly in-home data collection sessions lasted 1.5 hours on average. The time for completion of questionnaires ranged from 15 to 45 minutes (mean = 22 minutes). Collection of physiological data including equipment set up and clean-up took 20

to 60 minutes (mean = 35 minutes). Interviews with patients and caregivers evaluating research burden lasted from 10 minutes to 45 minutes.

Both patients and caregivers reported minimal burden associated the study protocol and data collection procedures. None of the patients acknowledged physical discomfort with any of the procedures. There were few requests for clarification of questions or instruments. None of the patients asked to take a break during any of the data collection sessions. Additionally, none exhibited signs of fatigue. One patient took more time than the others to complete the questionnaires. He pondered over many of the questions and reported frustration when completing of the Geriatric Depression Scale. All patients felt that they could tolerate the procedure at times when they were feeling less well. Each also indicated that it would not be too burdensome to continue in the study for a longer period of time. One patient, however, stated that weekly data collection session might be confining.

Caregivers reported that they were able to complete the CCC without difficulty. One caregiver reported that it would have been helpful to have more information about the signs and symptoms of confusion or delirium. Caregivers often entered comments or descriptors when patients exhibited signs of confusion. Two patients had a CCC score of 2, but their caregivers did not contact the investigator. In each case, the investigator was scheduled to make a visit for data collection on the following day. The investigator did not determine why the caregivers did not contact him. The caregiver for Patient #3 did not contact the investigator when she was hospitalized following the reaction to Erbitux. He did not complete the CCC during that time even though the patient exhibited signs of confusion. He stated that he was not sure what he should do. Based on these findings several changes were implemented in the follow-up study. Caregivers were provided with more information about

delirium and delirium symptoms. Instructions for contacting the investigator were moved to the bottom of the CCC just below the total score. Finally, caregivers were instructed to complete the CCC twice each day in all care settings and to notify the investigator if the patient is admitted to the hospital or changes care settings.

### *Recruitment Issues*

Several recruiting issues arose during the pilot study. Initially, recruitment was to be done by physicians and nursing staff in the medical oncology clinics. After talking with the staff, it was obvious that the investigator should be more involved in the recruiting process. Therefore, the recruiting strategy was revised and submitted to the IRB for approval. The revised strategy included a limited waiver of HIPAA allowing the investigator to use the medical record to identify prospective participants. Following IRB approval, the investigator attended targeted medical oncology clinics to identify and provide prospective participants with information about the study. Three of 7 patients who were approached agreed to participate in the study. One patient refused during the clinic contact. Three other patients were given a recruitment flyer but did not follow-up with the investigator.

Soon after initiating the pilot study, the investigator determined that hospice patients also should be recruited to participate in the study. An IRB addendum was submitted and approved. The hospice recruitment strategy relied on the hospice staff to identify and approach prospective participants. The investigator met with the hospice team to discuss the study and to provide them with recruitment flyers for prospective participants. One hospice patient who was given a recruitment flyer followed up with the investigator to express an interest in participating. An initial visit was scheduled, but the patient's condition declined

rapidly and his caregiver cancelled the visit. Hospice team members consulted the investigator about three other patients who did not meet inclusion criteria. No hospice patients were enrolled in the study.

### *Summary*

The pilot study was done to evaluate the feasibility and burden associated with a protocol to study delirium and cognitive decline in older adults with advanced cancer cared for at home and to identify methodological issues related to conducting this research. Findings from this study were used to design and conduct the third phase of this research—a longitudinal, multiple case study of delirium in older adults with advanced cancer.

### *Phase III: Trajectories and Patterns of Delirium and Delirium Vulnerability in Older Adults with Advanced Cancer Near the End of Life*

This study was conducted to examine delirium in older adults with advanced cancer near the end of life. The primary aim was to identify and to describe the nature of delirium and trajectories of delirium vulnerability in this population. After providing a description of the entire sample, the research questions will be answered. In the end, there were two groups of participants, those who died during the study and those who lived. Data from all participants will be used to answer the research questions. Following a general discussion, selected data from individual cases will be used to illustrate, in more detail, the nature of delirium and trajectories of delirium vulnerability. An exemplar case study is presented in Appendix E.

### *Participant Characteristics*

The sample consisted of 7 older adults, 6 men and 1 woman, with advanced cancer recruited from the outpatient oncology clinics at a university-affiliated cancer center. Table 4.9 provides detailed characteristics of the individual participants. Their ages ranged from 66-87 years ( $M$  75.6;  $SD$  8.54). Most were married ( $n = 5$ ), one was widowed, and the other was separated. Two of the men were African-American. The participants had varying levels of education—ranging from 6 years of school to having a graduate degree.

Two of the men had non-small cell lung cancer, two had prostate cancer, one had esophageal cancer, and the other had liver cancer. The woman had colon cancer. All but two of the participants had been diagnosed with cancer for more than one year prior to enrollment in the study and had undergone multiple treatments. The two who were recently diagnosed (Mr. B and Mr. F) underwent surgical resections after neoadjuvant treatment.

Table 4.10 summarizes the baseline characteristics of the sample. Overall, the participants had normal baseline cognitive functioning. Although the baseline MMSE scores varied, the mean MMSE was 25, and the median was 27. One participant (Mr. F) had an extremely low baseline MMSE (15/30). However, his baseline NEECHAM score was 28, indicative of normal information processing and behavioral functioning. His low baseline MMSE most likely reflected his 8<sup>th</sup> grade educational level, a low literacy level, and the rural cultural environment in which he lived.

The mean baseline NEECHAM score was 26.7. All of the participants exhibited some deficit in motor functioning, either tremor or slowing. Few showed difficulties with information processing or cognitive functioning, except that some ( $n = 3$ ) had a slowed response to or completion of command, which may have been influenced by their slowed

motor functioning. Most ( $n = 6$ ) had alterations in physiological control, particularly with regard to vital function stability or vital signs. In addition, one participant (Mr. G) was on continuous oxygen, and another (Mr. D) had a long-term indwelling foley catheter.

The level of baseline physical functioning varied among participants. Few exhibited deficits in PADLs, but all needed some assistance with IADLs—particularly needing help with shopping, preparing meals, and with doing housework and yard work. Some also needed assistance with transportation or managing money. Only one participant needed assistance with taking medications. Baseline scores on the PPS demonstrated a moderate level of functional impairment. While the participants were independent in providing self-care, most had a reduced ability to ambulate, were unable to do normal work, and had either normal or reduced food intake.

Although symptom prevalence varied at baseline, on average, the participants reported a high number of symptoms ( $M 11.4$ ;  $SD 4.96$ ). Most likely, the prevalent symptoms were related to the cancer, its treatment, other symptom management, or some combination of each. The most frequently reported physical symptoms were lack of energy ( $n = 7$ ), cough ( $n = 5$ ), lack of appetite ( $n = 5$ ), change in the way food tastes ( $n = 5$ ), diarrhea ( $n = 4$ ), itching ( $n = 4$ ), pain ( $n = 3$ ), difficulty sleeping ( $n = 3$ ), and weight loss ( $n = 3$ ). Two participants reported nausea, shortness of breath, and swelling in arms or legs. The most frequent psychological symptom was feeling irritable ( $n = 5$ ), followed by feeling nervous ( $n = 3$ ), and worrying ( $n = 2$ ) and feeling sad ( $n = 2$ ). The most common cognitive symptom was feeling drowsy ( $n = 5$ ), followed by difficulty remembering ( $n = 3$ ), difficulty concentrating ( $n = 2$ ), and feeling confused ( $n = 1$ ).

Baseline symptom distress also varied among the participants. Global symptom distress scores ranged between 0.16 and 2.06 ( $M$  1.16;  $SD$  0.61). All participants reported a certain level of physical symptom distress ( $M$  0.96;  $SD$  0.58; Range 0.13-1.67), but not psychological symptom distress ( $M$  0.76;  $SD$  0.57; Range 0-1.83) or cognitive symptom distress ( $M$  0.64;  $SD$  0.61; Range 0-1.65). Mr. F reported no psychological symptom distress at baseline. Mr. B and Mr. F reported no cognitive symptom distress.

At baseline, the mean GDS score was 4.6 ( $SD$  2.1; Range 2-7). Three participants (Mr. B, Mrs. C, and Mr. E) had baseline GDS scores  $> 5$ , indicating probable depression. Only one participant (Mr. A) reported a history of depression, and he was on antidepressant medications at the time of enrollment. His baseline GDS score was 4.

The five men who were married lived with their wives and, in some cases, other family members. All but one were cared for primarily by their wives. Prior to his illness, Mr. F was the primary caregiver for his wife who had mild dementia. When he became ill, his daughter and two sons assisted in caring for him and his wife. Mrs. C, a widow, lived alone until 2 weeks before her death. Her daughter and granddaughter-in-law who lived nearby were her primary caregivers. Initially, Mr. G's neighbor assisted with his care, but as he needed more assistance, other family members and friends became involved and provided around-the-clock care in his home.

Table 4.9. Characteristics of individual participants

Case	Age	Gender	Ethnicity	Marital Status	Primary Caregiver	Educational Level	Employment Status
Mr. A	66	Male	Caucasian	Married	Wife	Graduate Degree	Retired
Mr. B	87	Male	Caucasian	Married	Wife	College Degree	Retired
Mrs. C	81	Female	Caucasian	Widowed	Daughter & Granddaughter-in-law	11 <sup>th</sup> Grade	Retired
Mr. D	71	Male	AA	Married	Wife	6 <sup>th</sup> Grade	Retired
Mr. E	84	Male	Caucasian	Married	Wife	Graduate Degree	Retired
Mr. F	74	Male	Caucasian	Married	Daughter & Sons	8 <sup>th</sup> Grade	Retired
Mr. G	66	Male	AA	Separated	Friends & Family	6 <sup>th</sup> Grade	Retired



Table 4.9. Characteristics of individual participants (continued).

Case	Cancer Diagnosis	Date of Diagnosis (Date Enrolled in Study)	Cancer Treatment During Study	Prior Cancer Treatment	Charlson Comorbidity Index	Comorbid Medical Conditions
Mr. A	Non-small cell lung cancer	Initial 03/96 Recurrence 02/04 (04/20/05)	Iressa Sutent	R lung resection; Cisplatin and navelbine; Radiation therapy to chest and brain; Pemetrexed	1	Hypertension; Depression with anxiety; Degenerative joint disease
Mr. B	Hepatocellular carcinoma	04/07/05 (05/23/05)	Surgical resection	Chemo embolization with Mitomycin and Doxorubicin	1	COPD; Degenerative joint disease; Hypertension; Glaucoma
Mrs. C	Colon cancer	02/03 (05/25/05)	Irinotecan and Cetuximab; Globimmune vaccine trial	Surgical resection; 5-FU/Leucovorin; Xeloda; Oxaliplatin; Avastin	2	Hypertension; Atrial fibrillation; Aortic stenosis, Mitral regurgitation; Chronic heart failure
Mr. D	Prostate cancer	10/95 (06/23/05)	Taxotere	Casodex and Proscar; Orchiectomy; Taxotere, carboplatin, and estramustine; Taxotere and estramustine; Taxotere	1	Gout; Chronic renal insufficiency; Long-term indwelling foley catheter
Mr. E	Prostate cancer	01/99 (07/14/05)	Secondary hormone therapy with Ketoconazole and Hydrocortisone; Zometa	Lupron; Orchiectomy	2	Coronary artery disease; 3-vessel CABG; Orthostatic hypotension; Neurogenic bladder; Renal insufficiency
Mr. F	Esophageal cancer	06/27/05 (09/08/05)	Cisplatin and Irinotecan; Concurrent radiation therapy (45 Gy); Surgical resection	None	1	Hypertension; Gastroesophageal reflux disease
Mr. G	Non-small cell lung cancer	06/16/04 (09/26/05)	None	Gemcitabine and Taxol; Pemetrexed; Iressa; Carboplatin/Abraxane Radiation therapy	3	COPD; Hypertension; Coronary artery disease; Degenerative joint disease; Chronic low back pain; Anemia

Table 4.9. Characteristics of individual participants (continued).

Case	Tobacco Use	Alcohol Use	Visual Deficit Correction (Self-Reported)	Hearing Deficit Correction (Self-Reported)	History of Confusion Prior to Cancer Diagnosis	History of Confusion Since Cancer Diagnosis	Self Report of Health at Enrollment
Mr. A	No	Past	Yes Glasses	Yes – some words None	Yes	Yes	Fair
Mr. B	Past	No	Yes Glasses	No	No	No	Fair
Mrs. C	Past	No	Yes Glasses	No	No	No	Fair
Mr. D	Chewing Tobacco	Past Heavy Use	Yes Glasses for reading	No	No	No	Excellent
Mr. E	No	No	Yes Glasses	Yes Hearing aids	No	Yes	Good
Mr. F	No	No	No	No	No	Yes	Good
Mr. G	Past	Past Heavy Use	No	No	No	Yes	Poor

Table 4.10. Baseline characteristics of older adults with advanced cancer (N = 7)

Variable		n
Gender		
Male		6
Female		1
Ethnicity		
Caucasian		5
African-American		2
Cancer Diagnosis		
Lung		2
Prostate		2
Liver		1
Esophagus		1
Colon		1

Variable		Mean	SD	Range
Age	(years)	75.6	8.54	66-87
MMSE	(0-30)	25.0	5.48	15-30
NEECHAM	(0-30)	26.7	2.06	23-29
IADLs	(0-14)	11.0	1.53	9-13
PADLs	(0-14)	13.7	0.49	13-14
PPS	(0-100)	68.6	6.90	60-80
GDS-15	(0-15)	4.57	2.07	2-7
Total # of Symptoms	(0-31)	11.4	4.96	4-18

Table 4.11 provides information about time in study, the frequency and types of visits, and disposition at the end of the study. Participants were enrolled in the study for periods of time ranging from 93 days to 330 days. Three participants died during the study after being followed for 93 days (Mrs. C), 109 days (Mr. G), and 296 days (Mr. D). During the study, two participants, Mr. B who had liver cancer and Mr. F who had locally advanced esophageal cancer opted for surgical treatments that rendered them “cancer-free”. Mr. B and Mr. F were enrolled in the study for 162 and 161 days, respectively. Another participant (Mr. E) was enrolled for 160 days. Although he showed evidence of disease progression with increasing PSA at that time, he and his wife decided not to continue in the study because they were in the process of selling their home and moving into a retirement community. The final participant (Mr. A) was enrolled for 330 days. During the study, he participated in a clinical trial that slowed the progression of his lung cancer and resulted in improved function.

Over the course of the study, a total of 220 assessments were conducted. The total number of assessments per participant varied depending upon the length of enrollment in the study, and the number of delirium and delirium follow-up assessments conducted. Most of the initial delirium assessments were conducted at scheduled weekly assessments—that is, participants were found to be positive for delirium at the time of scheduled weekly assessments. Even though caregivers were monitoring participants daily for signs of delirium using the Caregiver Confusion Checklist (CCC) and had been instructed to contact the investigator for a CCC score  $\geq 2$ , they rarely called to report an increase in CCC score or any other change in the participants’ conditions. Mr. G’s caregivers called twice to report a change in his condition that included signs of delirium—the calls were not triggered by the CCC score.

Table 4.11. Time in study, number of assessments by type, and disposition by participant

Case	Time in Study (Days)	Total # of Assessments	Scheduled Weekly Assessments	Delirium Assessments Triggered by Caregiver Call	Delirium Follow-Up Assessments	Disposition
Mr. A	330	49	47	0	2	Continued Treatment
Mr. B	162	23	21	0	2	Observation
Mrs. C	93	19	12	0	7	Died
Mr. D	296	52	42	0	10	Died
Mr. E	160	22	21	0	1	Observation
Mr. F	161	25	23	0	2	Observation
Mr. G	109	30	16	2	12	Died
Total		220	182	2	36	

*Research Question1: What is the nature and course of delirium in older adults with advanced cancer near the end of life?*

The nature and course of delirium was determined by examining the total NEECHAM score trajectories to identify when delirium occurred. The total NEECHAM score and total NEECHAM score trajectory were used to evaluate severity and duration of delirium. The NEECHAM subscale trajectories and other data were used to identify and describe the cognitive, behavioral, and physiological characteristics of delirium episodes.

First, delirium was examined in each of the participants who died. Second, across case comparisons of delirium trajectories and delirium episodes among the participants who died were made. Third, delirium was examined in the participants who were alive at the end of the study. Finally, reversible episodes of delirium in participants who died were compared to the delirium episodes in participants who lived.

#### *Delirium Episodes in Participants Who Died*

##### *Mrs. C*

Figure 4.9 shows the trajectory of Mrs. C's total NEECHAM scores during the study with the delirium episodes marked. Mrs. C had two delirium episodes determined by positive delirium assessments – NEECHAM score  $\leq 24$  and positive CAM.

Mrs. C's first delirium episode occurred 30 days before her death. She scored positively for delirium at the time of the scheduled weekly assessment. During her first episode, the total NEECHAM score was 21. Mrs. C had only one positive delirium assessment with this episode. She did not score positive for delirium at the follow-up assessment the next day or during assessments over the next three weeks. During this period, her NEECHAM scores were 23 and 24 and the CAM was not positive; she may have been exhibiting subsyndromal delirium or fluctuating delirium.

Mrs. C's second positive delirium assessment was on Day 9 before her death. Her total NEECHAM score was 16 and the CAM was positive. Her NEECHAM scores on Day 7 (10) and on Day 6 (7) demonstrated increasingly severe delirium. From Day 5 until her death, Mrs. C was stuporous and essentially unresponsive. During this period, her

NEECHAM scores were 1 and 0. She exhibited moderate to deep levels of sedation before becoming unarousable 2 days before her death. The CAM could not be scored.

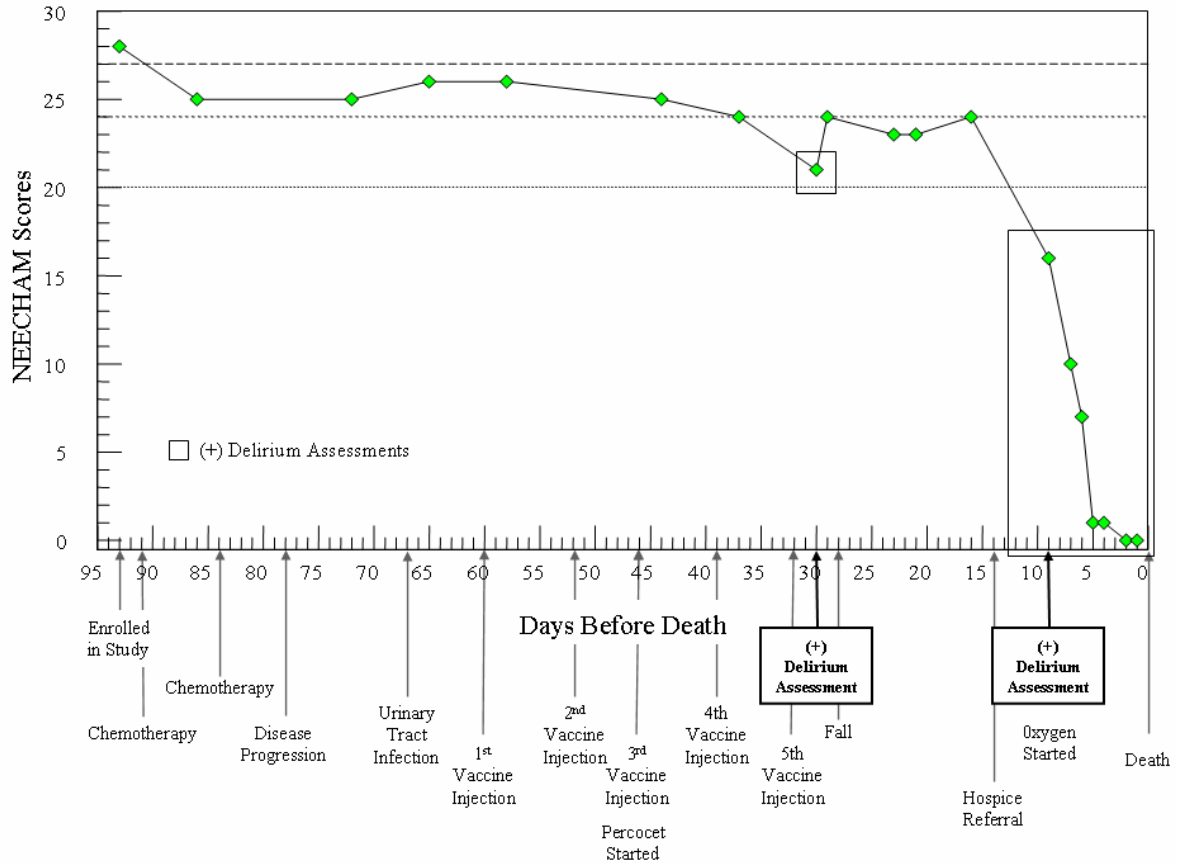


Figure 4.9. Mrs. C's NEECHAM score trajectory with delirium episodes

Figure 4.10 shows the trajectory of Mrs. C's NEECHAM subscale scores. At the time of her first delirium episode, she showed deficits in each of the subscales. Her Level 1: Processing subscale scores were stable prior to the first delirium episode, but dropped during the episode. During the two weeks before the delirium episode, Mrs. C experienced declines in her NEECHAM Level 2: Behavior and NEECHAM Level 3: Physiological Control subscale scores. She exhibited changes in her postural control and appearance, slowed motor

movements, and more limited speech. During the week prior to the first delirium episode, her granddaughter-in-law documented that Mrs. C had been staying in bed more, sleeping a lot, and talking less. She “only talks when you talk to her.”

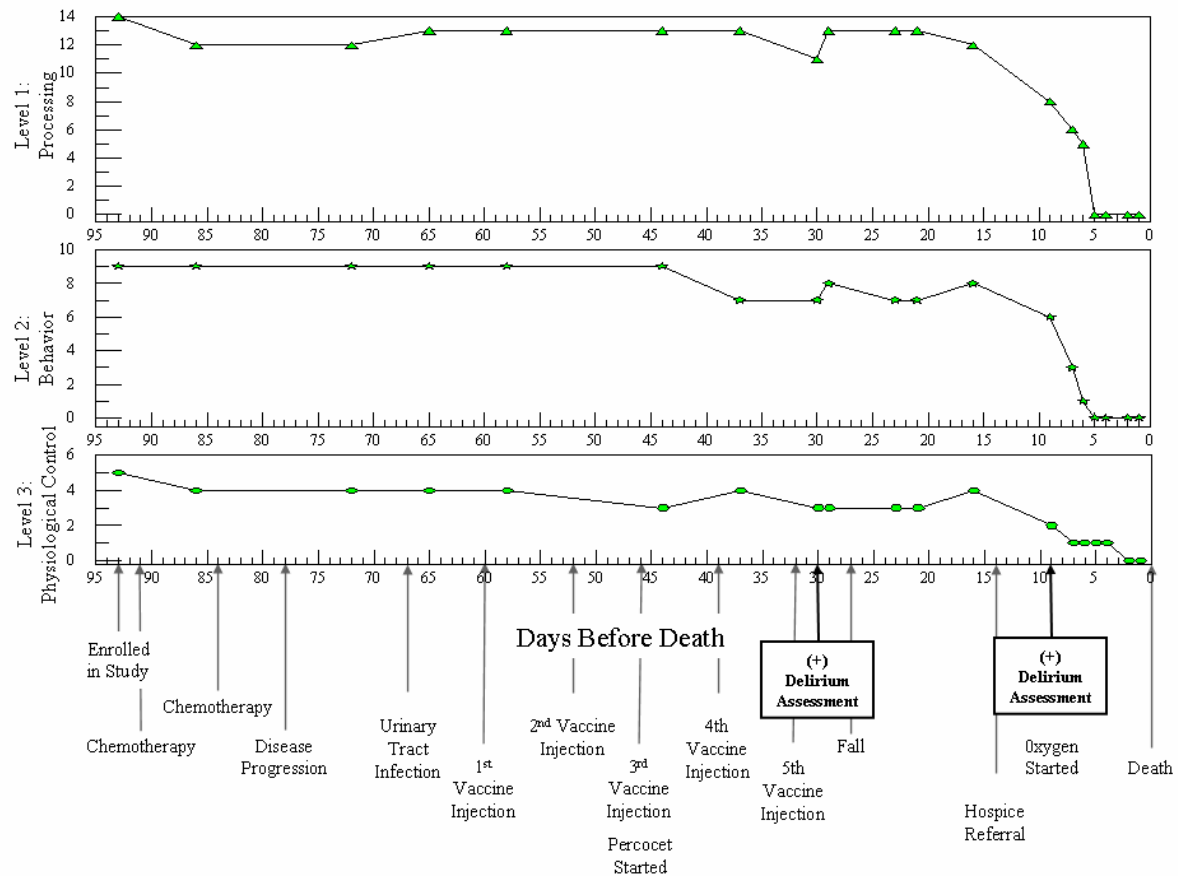


Figure 4.10. Trajectories of Mrs. C’s NEECHAM subscale scores

On Day 16, one week prior to her second delirium episode, Mrs. C’s NEECHAM Level 1: Processing subscale score dropped. Her Level 2 and Level 3 subscale scores were slightly improved. All three subscale scores had declined sharply at the positive delirium assessment on Day 9. At that time, Mrs. C was bedbound and her level of alertness was more diminished. When awake, she tended to stare rather than focus on people at her bedside. She demonstrated little movement of her extremities, but she would drink from a straw placed



near her mouth. Prior to the second delirium episode, she was started on oxygen. She also had intermittent urinary incontinence that became progressively worse.

Mrs. C's first delirium episode was characterized by a decrease in her level of alertness and attention, as well as by slowed motor and verbal behavior. At the time of the positive delirium assessment, she exhibited the following hypoactive delirium behaviors on the Delirium Behavior Checklist: diminished alertness, lethargy, slow speech, slow movements, unawareness, and apathy. No hyperactive behaviors were noted. Mrs. C's score on the sedation subscale of the Richmond Agitation-Sedation Scale (RASS) was -1 (drowsy) and her score on the motor retardation item from the Delirium Rating Scale (DRS-R 98) was 1, indicating a mild reduction in frequency of movement.

Mrs. C's second delirium episode that preceded her death was characterized primarily by hypoactive delirium behaviors. However, on two days, Day 7 and Day 6, she had intermittent periods of restlessness with hallucinations. Otherwise, on these days and on other days, Mrs. C exhibited a decrease in her level of alertness and responsiveness and slowed motor behavior. When Mrs. C exhibited restlessness, her family administered diazepam 2.5 mg. During this episode, Mrs. C became progressively more sedated until she became unresponsive two days before her death. Her RASS sedation subscale scores ranged from -1 (drowsy) to -5 (unarousable).

At the time of her first positive delirium assessment on Day 30, Mrs. C's NEECHAM Level 3 subscale score was 3, indicating deficits in physiological control. She specifically exhibited alterations in her vital function and urinary continence. Figure 4.11 presents Mrs. C's vital function parameters throughout the study. During her first delirium episode, her blood pressure was elevated. It was 167/94 compared to her average during prior

assessments, 135/73. Mrs. C always had an irregular heart rhythm due to atrial fibrillation, but overall her heart rate was controlled with digoxin. At the time of the first positive delirium assessment her heart rate was elevated at 84 beats per minute compared to her average of 65 beats per minute at prior assessments. Mrs. C's temperature also was elevated at 37.6 degrees Celsius. Her respiratory rate, while elevated at 24 breaths per minute, was similar to her usual respiratory rate which had ranged between 20 and 28 breaths per minute.

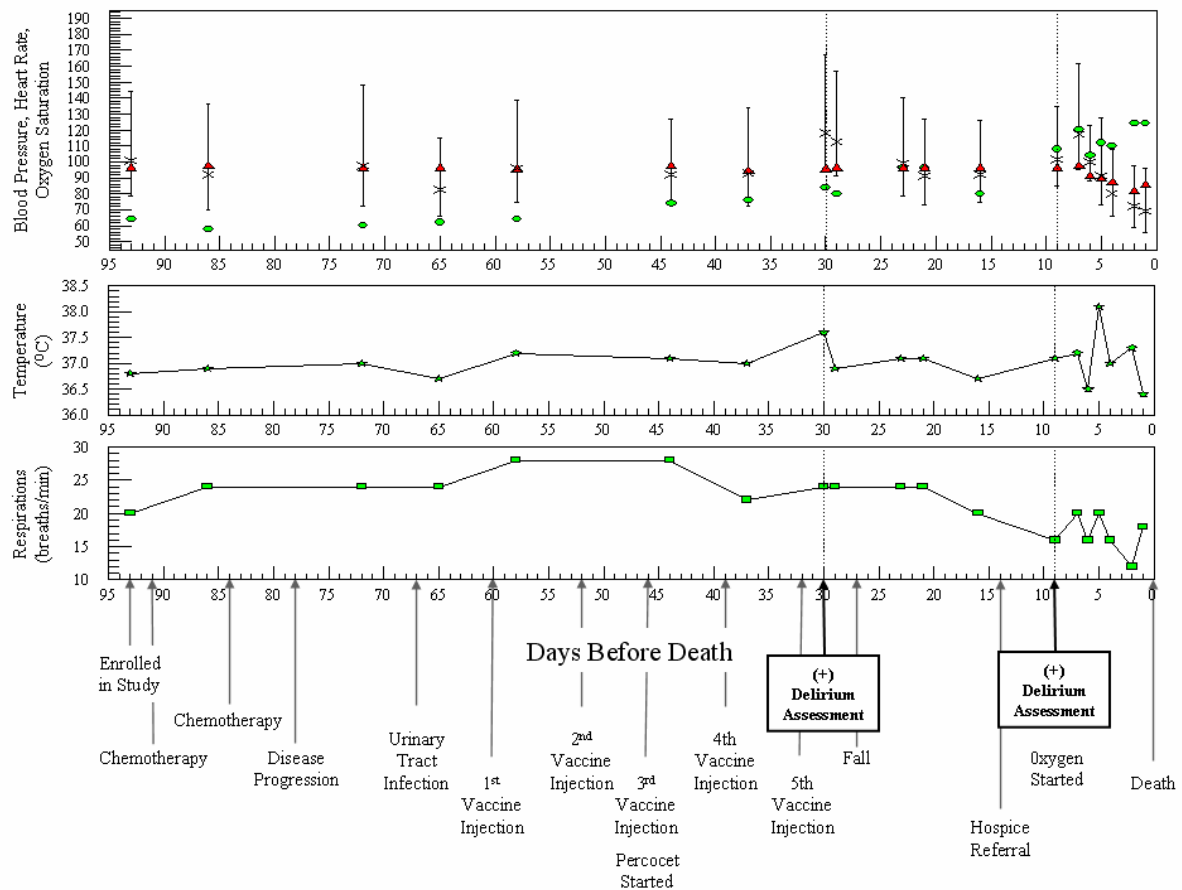


Figure 4.11. Trajectory of Mrs. C's vital function parameters

Mrs. C also exhibited altered physiologic control during her second delirium episode prior to her death. Most notably, her heart rate was increased. On the morning of the second

positive delirium assessment, Mrs. C experienced chest pain and shortness of breath. She was started on supplemental oxygen. At the time of the assessment, later in the afternoon, Mrs. C's oxygen saturation was 97% on oxygen at 2 liters per minute. Her respiratory rate was decreased at 16 breaths per minute. After that point, she exhibited greater physiological instability—hypotension, tachycardia, hyperthermia, and demand for increased oxygen—until her death. During the same time, she had increasingly severe delirium before becoming unresponsive prior to her death.

#### *Mr. G*

Figure 4.12 shows the trajectory of Mr. G's NEECHAM scores with positive delirium assessments noted. Even though Mr. G had two NEECHAM scores  $\geq 27$  early in the study, he was at risk for delirium because of his need for oxygen supplementation. Mr. G had 5 delirium episodes. The first occurred on Day 85 before his death, the second on Day 74, the third on Day 35, the fourth on Day 26, and the fifth on Day 12, respectively. Mr. G's first four delirium episodes resolved. After each of the episodes, his NEECHAM score was  $> 24$  for at least one assessment. His fifth episode persisted until his death.

Each of Mr. G's first 3 delirium episodes consisted of a single positive assessment. His NEECHAM scores during these episodes indicated the presence of mild delirium. His total NEECHAM score was 20 at the first positive assessment, and his NEECHAM score was 21 at the second and third positive delirium assessments. He was not positive for delirium at follow-up assessments conducted one to three days after the initial positive assessments. Mr. G's fourth delirium episode consisted of 3 consecutive positive assessments over 4 days. His total NEECHAM score fluctuated between 19 and 22. Mr. G's fifth delirium

episode began with a positive delirium assessment on Day 12. At the assessment on Day 12, his total NEECHAM score was 22 and the CAM was positive. Although his NEECHAM scores fluctuated, Mr. G remained positive for delirium until his death. On Day 11 at the follow-up assessment, his NEECHAM score was 24. His NEECHAM score was 21 on Day 9 but dropped sharply to 10 on Day 5. Mr. G's NEECHAM score was 19 on Day 4. Although his level of alertness and attention fluctuated during the assessment on Day 4, Mr. G. was more alert primarily because prior to the assessment, the hospice nurse had given him an enema and had attempted to manually disimpact him. After this assessment, his NEECHAM score began to drop again. On Day 2, his NEECHAM score was 11, and on the day before his death it dropped to 7.

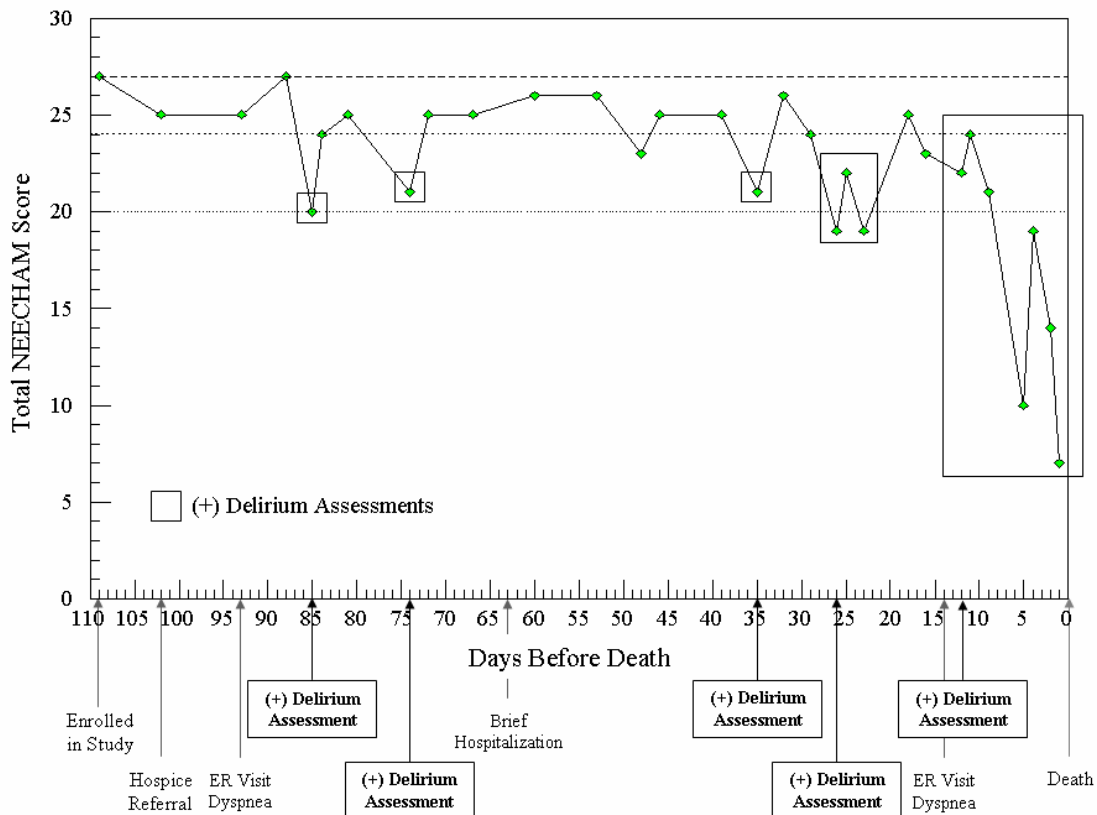


Figure 4.12. Mr. G's NEECHAM score trajectory with delirium episodes

As Mr. G approached the end of his life, the time between delirium episodes decreased and the delirium episodes became progressively longer. Although his NEECHAM scores fluctuated during the later episodes, the scores were lower demonstrating more severe delirium.

Figure 4.13 shows the trajectory of Mr. G's NEECHAM subscale scores. Prior to his first delirium episode, Mr. G had deficits in all of the subscales. The subscale scores dropped further during his first delirium episode. Between the first and second delirium episodes, his Level 1: Information Processing and Level 2: Behavior scores improved but his Level 3: Physiologic Control subscale score remained decreased. At the time of the second delirium episode, his Level 3 score was improved. All of the subscale scores tended to stabilize between the second and third delirium episodes. Four days prior to his third delirium episode, the Level 3 subscale score dropped. During that assessment, his Level 1 subscale score remained stable and his Level 2 subscale score was improved. Mr. G's Level 1 and Level 2 subscale scores fluctuated with delirium episodes. He exhibited more significant fluctuations during his final episode.

During the four delirium episodes that resolved, Mr. G exhibited only hypoactive delirium behaviors. He had a decrease in his level of alertness and attention, as well as slowed motor and verbal behavior. Mr. G's scores on the sedation subscale of the RASS ranged between -1 (drowsy) and -2 (light sedation). His scores on the motor retardation item from the DRS-R 98 ranged between 1 and 2, indicating a mild to moderate reduction in frequency, spontaneity, or speed of movement. Mr. G's final delirium episode was characterized primarily by hypoactive delirium behaviors. Two days before his death, however, he began to exhibit intermittent restlessness. On the day before he died, the periods

of restlessness were more frequent, and he exhibited more motor agitation. At times he would attempt to sit up in bed. He also would take his oxygen off and resist his caregivers' attempts to provide care and assistance.

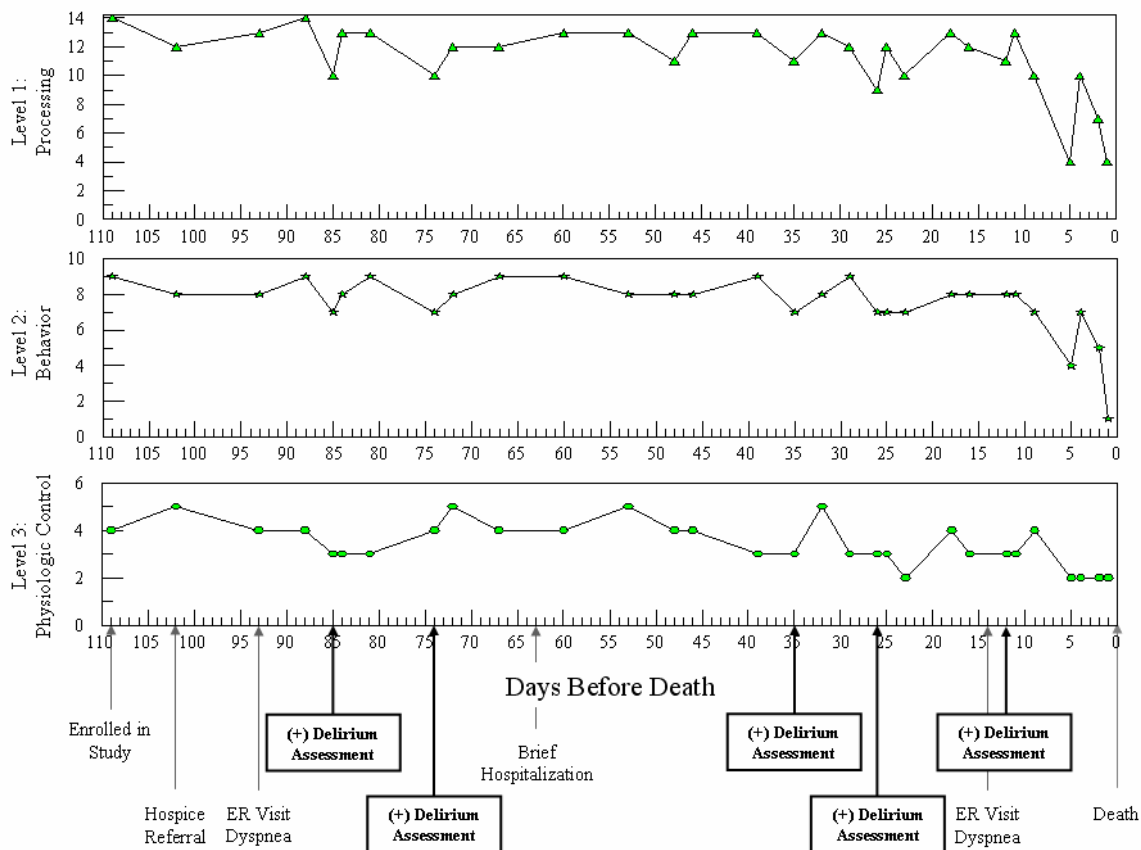


Figure 4.13. Trajectories of Mr. G's NEECHAM subscale scores

Figure 4.14 presents Mr. G's vital function parameters throughout the study. His vital signs often fluctuated with his delirium episodes. At the time of his first positive assessment on Day 85, his heart rate was increased at 118 and his blood pressure was decreased at 112/67. Prior to the episode, his average heart rate and blood pressure were 90 and 135/80, respectively. His temperature and respiratory rate were also increased. His temperature was

37.7 °C, and his respirations were at 24 breaths per minute. His oxygen saturation was decreased at 93%.

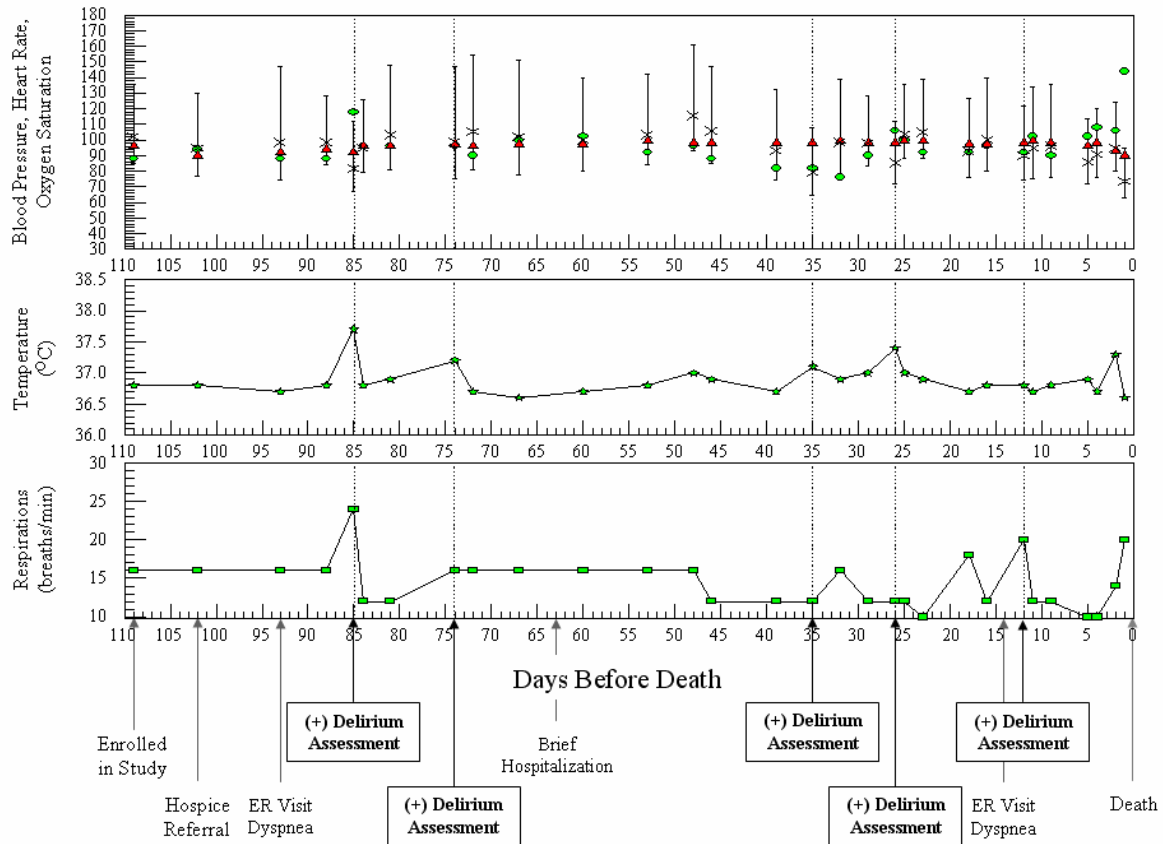
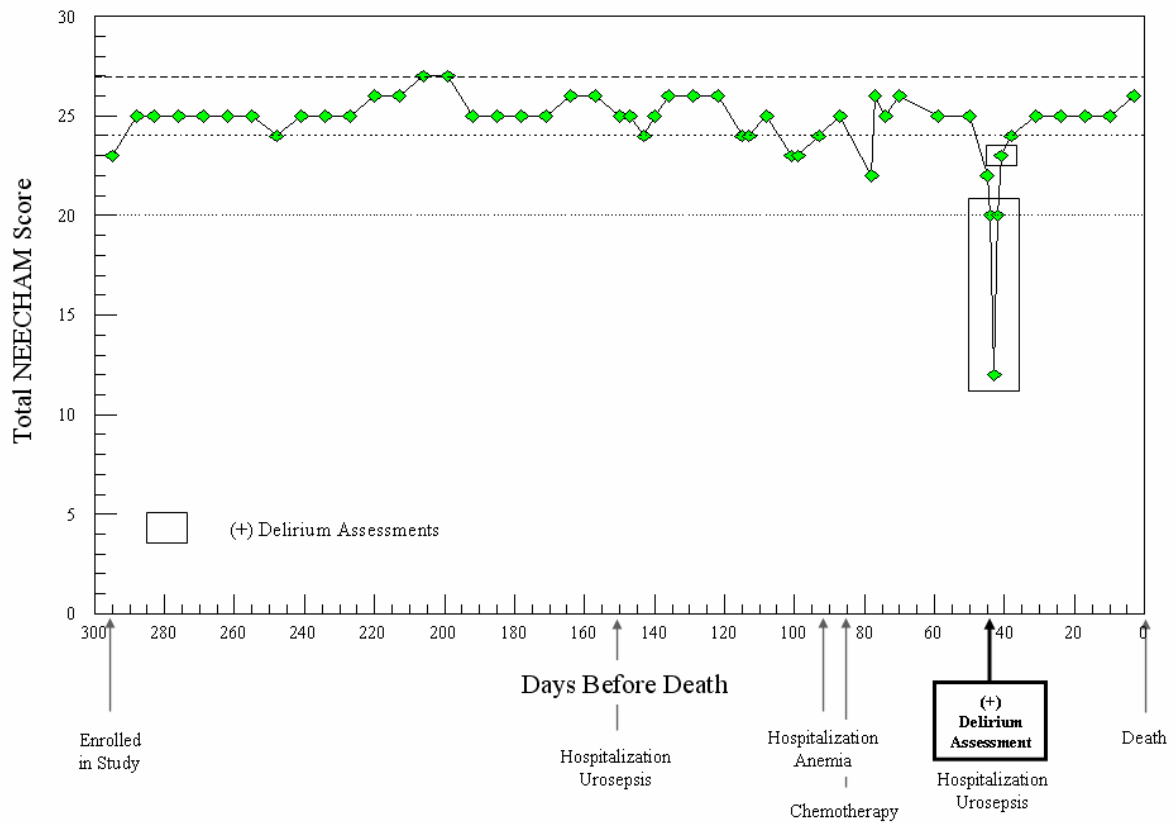


Figure 4.14. Trajectories of Mr. G's vital function parameters

At his second positive delirium assessment (Day 74), overall, Mr. G's vital signs were stable, except that his temperature was slightly elevated at 37.2 °C. Prior to his third episode, his respiratory rate was decreased. From the time of his third delirium episode (Day 35) until his death, Mr. G showed increasing variability in his vital functioning. His heart rate, respiratory rate, and temperature fluctuated. During the last week before his death, and on the day before death, Mr. G's vital functioning was increasingly unstable.

*Mr. D*

Figure 4.15 shows the trajectory of Mr. D's total NEECHAM scores with the delirium episode noted. Mr. D had one documented episode that coincided with a hospitalization for urosepsis—44 days before his death. During the delirium episode, Mr. D had four positive delirium assessments over four consecutive days. His total NEECHAM score at the first positive delirium assessment on Day 44 was 20. His NEECHAM score dropped to 12 at the second assessment on Day 43, but then increased to 20 on Day 42. Prior to his discharge on Day 41, his NEECHAM score was 23. The CAM remained positive. At a follow-up assessment in his home on Day 38, Mr. D's NEECHAM score was 24. The CAM was negative.



*Figure 4.15.* Mr. D's NEECHAM score trajectory with delirium episode



Mr. D's last assessment of the study was conducted on Tuesday, April 11, 3 days before his death. On the morning of Friday, April 14, Mrs. D called to report that Mr. D had died. His death was precipitated by an acute event that caused severe metabolic acidosis and organ failure. At a follow-up visit with Mrs. D after his death, she reported that Mr. D exhibited hyperactive delirium behaviors—agitation and restlessness—prior to being intubated the night before he died. According to his medical record, he was obtunded and had altered mental status upon arrival in the Emergency Room. His mental status fluctuated with treatment prior to being intubated. Mr. D died in the ICU the next morning after the removal of life support.

Figure 4.16 shows the trajectories of Mr. D's NEECHAM subscale scores. Overall, his Level 1: Processing scores improved over the first 60 days in the study, and remained high except during the delirium episode when he showed a sharp drop in his Level 1 scores. Mr. D's Level 2: Behavior scores dropped after his first hospitalization for urosepsis, and throughout the rest of the study remained consistently lower. During his delirium episode his Level 2 score dropped more, but improved. Mr. D's Level 3: Physiologic Control subscale scores show that he had baseline deficits in his physiological functioning. While he always maintained his oxygen stability, Mr. D had variability in his vital functioning which worsened after his initial hospitalization (See also Figure 4.17). In addition, he had a chronic in-dwelling foley catheter due to obstruction from his prostate cancer. During his delirium episode, his Level 3 subscale score improved more rapidly than his Level 1 and Level 2 scores, an indication that information processing and behavior improve after achieving physiologic stability. Similar trends were also seen in Mr. G's case.

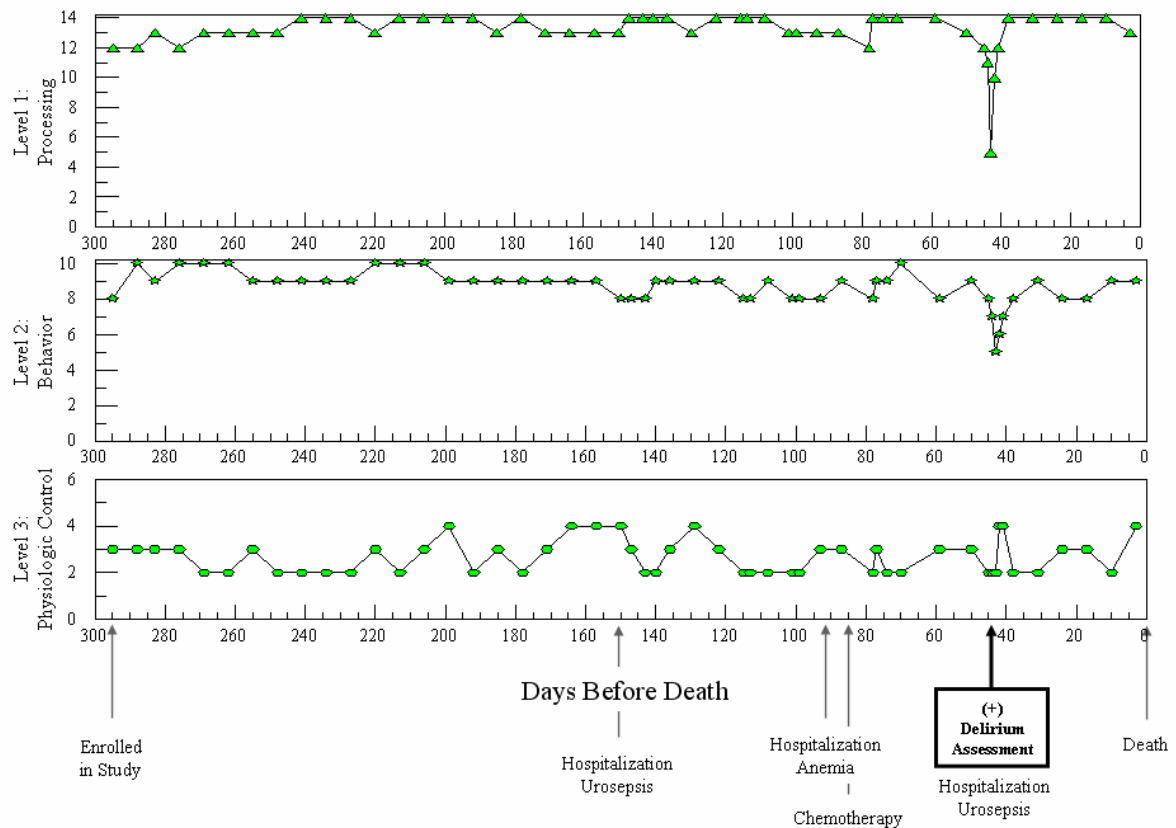


Figure 4.16. Trajectories of Mr. D's NEECHAM subscale scores

Although hyperactive delirium behaviors predominated, Mr. D's delirium episode was classified as of the mixed subtype because he exhibited both hypoactive and hyperactive behaviors. During the first positive delirium assessment on Day 44, Mr. D's mood and behaviors were labile. In addition to being quiet with slowed movements at times, he also became impatient and irritable. The content of his speech was rambling, and occasionally, he laughed inappropriately. When Mr. D was seen in the hospital on Day 43, his hyperactive behaviors were increased. At that assessment, he exhibited the following hyperactive behaviors: hypervigilance, distractability, restlessness, fast and loud speech, easy startling, and tangentiality. Intermittently, he also exhibited hypoactive delirium behaviors including

unawareness and slowed movements. On Day 42, the same behaviors were present but less pronounced. Mr. D also was joking and laughing when interacting with the hospital staff. On Day 41, Mr. D was preparing to be discharged. Most of the behaviors were resolved, but he demonstrated impatience and he talked persistently about his wife coming to pick him up. He also remained easily distracted by people and sounds in the hallway. Overall, his movements were slowed. Mr. D was unable to complete the sentence and drawing on the MMSE because he had significantly limited motion of his right arm and hand which he attributed to arthritis and gout.

Figure 4.17 shows the trajectories of Mr. D's vital function parameters. He shows variability in vital function throughout the study, but it is much more unstable after his hospitalization for urosepsis. His blood pressure and heart rate fluctuated widely. He also developed an occasional irregular heart rhythm. His temperature was more stable except during the episodes of urosepsis.

At the scheduled weekly assessment on Day 45, Mr. D exhibited significant physiological instability. His blood pressure was 71/43 and his heart rate was 104 and irregular. His temperature was slightly elevated at 37.2 °C. Although strongly encouraged to seek medical evaluation that evening, Mr. D and his wife chose not to do so. On the following day, Mr. D was positive for delirium. He remained physiologically unstable. His blood pressure was 77/39, and his heart rate remained irregular and increased at 114 beats per minute. His respiratory rate was 24 breaths per minute, and his temperature was 37.4 °C. Following this assessment, Mr. D was taken to the emergency room and admitted to the hospital. His vital functioning stabilized over the next three days, and his delirium resolved.

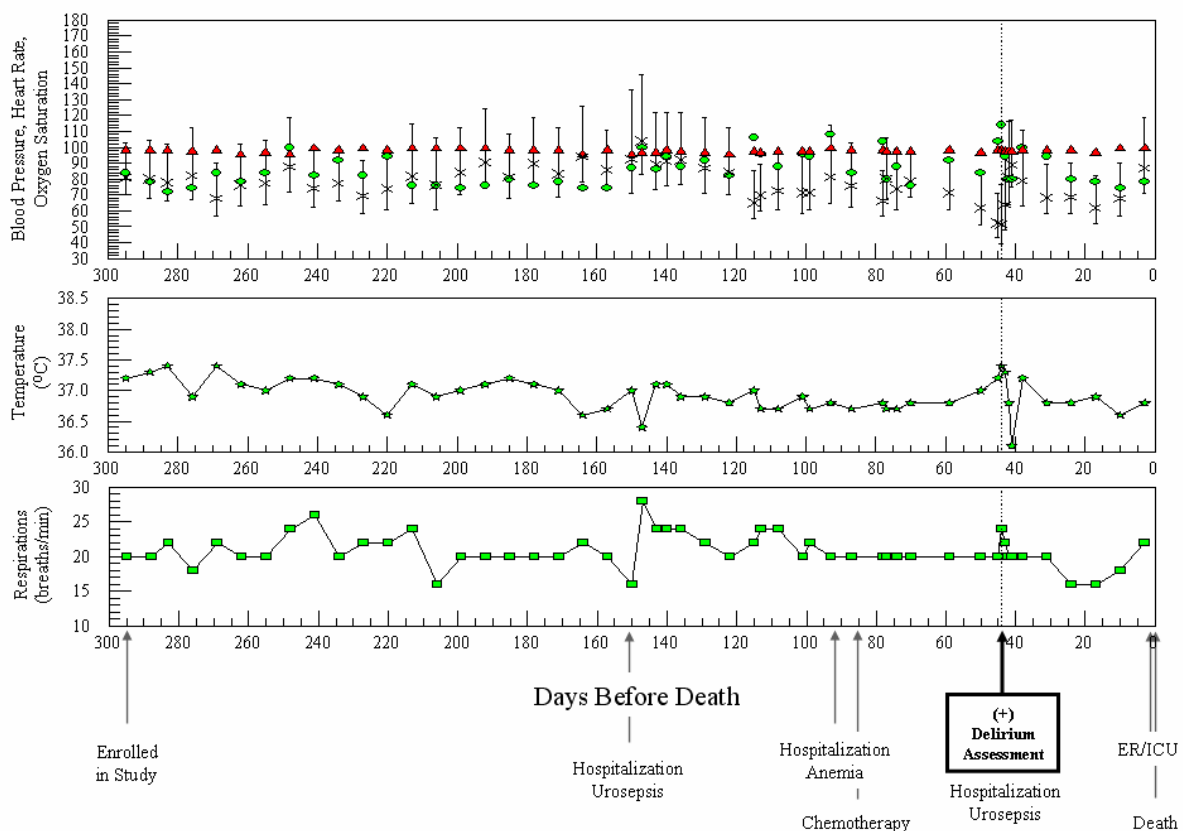


Figure 4.17. Trajectories of Mr. D's vital function parameters

#### *Summary of Delirium Episodes in Participants Who Died*

Mrs. C and Mr. G had two or more episodes of delirium. Both had episodes that either reversed or improved prior to an irreversible episode that preceded their deaths. In each case, the episodes that reversed were shorter and less severe. Mr. G had four episodes that reversed or improved. As he approached the end of his life, the time between delirium episodes decreased and the delirium episodes became progressively longer. Although his NEECHAM scores fluctuated during the later episodes, the scores were lower demonstrating more severe delirium. All of the episodes prior to the terminal episode were characterized by hypoactive delirium behaviors, by decreased alertness and attentiveness, and by altered

physiological functioning. In both cases, the terminal delirium episodes were longer and the delirium was progressively more severe. During their terminal episodes, hypoactive delirium behaviors were predominant. However, Mrs. C and Mr. G exhibited intermittent periods of hyperactive behavior specifically restlessness during their terminal episodes.

Mr. D's dying trajectory and delirium episodes were different from Mrs. C's and Mr. G's. He had one documented delirium episode 44 days before his death that coincided with urosepsis and subsequent hospitalization. Mr. D's death was precipitated by an acute event that caused severe metabolic acidosis and organ failure. His wife reported that he exhibited hyperactive delirium behaviors—agitation and restlessness—prior to being intubated the night before he died. According to his medical record, he was obtunded and had an altered mental status upon arrival in the Emergency Room. His mental status fluctuated with treatments prior to being intubated.

Delirium episodes in patients who died were characterized by significant physiological instability. Physiological parameters tended to stabilize prior to or with resolution of delirium episodes. During the persistent episodes that preceded death, as in Mrs. C's and Mr. G's cases, the physiological parameters demonstrated variability with increasing instability in the days prior to death.

#### *Delirium Episodes in Participants Who Lived*

The four patients who were alive at the end of the study included: Mr. A, Mr. B, Mr. E, and Mr. F. Each had one delirium episode. Their delirium episodes occurred in the context of treatment, except in Mr. E's case. His episode was observed the morning after he returned from an out-of-state trip that included visiting family and attending his sister's funeral. Mr.

A's episode occurred following his 3<sup>rd</sup> 28-day cycle of Sutent, an investigational agent, at a dose of 75 mg per day. During this treatment period, he had experienced significant fatigue and intermittent nausea and vomiting. Mr. B and Mr. F each had a delirium episode postoperatively. Mr. B's delirium episode was documented 6 days following his hepatic lobe resection, and Mr. F's, 3 days after his esophagogastrectomy.

The delirium episodes in the participants who lived were short in duration. Mr. A's delirium episode consisted of 2 consecutive positive assessments, while the other participants' episodes consisted of 1 positive assessment. In each episode, the severity of delirium was mild. NEECHAM scores at the time of positive delirium assessments ranged between 20 and 24.

Each of the delirium episodes in the participants who lived were classified as hypoactive. All of the participants exhibited a decrease in their levels of alertness and attention. They also demonstrated the following hypoactive behaviors: sparse or slowed speech, lethargy, and slowed movements. In addition, staring was observed in three participants (Mr. A, Mr. B, and Mr. E), and apathy in two (Mr. A and Mr. E).

#### *Comparison of Delirium Episodes that Reversed in Participants Who Died to Delirium Episodes in Those Who Lived*

The reversible delirium episodes in participants who died were similar to the delirium episodes in those who lived. The delirium episodes were short in duration. All but one were characterized by hypoactive delirium behaviors. Mr. D's episode coinciding with his urosepsis and hospitalization was mixed but hyperactive delirium behaviors were predominant. The severity of delirium was mild in all episodes in participants who lived. Similarly, the severity of delirium was mild in all but two of the reversible episodes in

participants who died. Mr. G's first three delirium episodes were mild in severity. His fourth episode that preceded his final episode was more severe. His lowest NEECHAM score during this episode was 19. Mr. D's delirium also was severe. His lowest NEECHAM score was 12.

*Research Question 2: How does delirium vulnerability change over time and in relationship to the development of delirium in older cancer patients at the end of life?*

The literature on delirium in the elderly and in cancer patients, previously reviewed, reports a number of risk factors for delirium including: impaired cognitive functioning; limited physical functioning; depression; physical symptoms such as pain; medications; nutritional and metabolic abnormalities, dehydration, and hypoxia. These risk factors, or vulnerability factors, were examined in the older adults with advanced cancer in order to determine how the factors change over time during palliative treatment and at the end of life, and in relationship to the development of delirium.

### *Cognitive Functioning*

Table 4.12 summarizes the participants' MMSE scores. Baseline MMSE scores tended to vary among the participants. Discrepancies in their MMSE scores may be partially attributed to different levels of education and literacy, ethnicity, and other lifestyle and environmental factors. In most participants, MMSE scores fluctuated slightly from assessment to assessment. When measured during episodes of delirium, MMSE scores were decreased.

Table 4.12. Summary of participants' MMSE scores

Participant	Number of Assessments	Mean	SD	Range
Mr. A	49	29.4	0.82	27 – 30
Mr. B	20	27.9	1.57	23 – 30
Mrs. C	-	-	-	-
Mr. D	50	21.9	2.33	14 – 25
Mr. E	22	28.0	1.51	25 – 30
Mr. F	21	18.3	1.87	15 – 22
Mr. G	25	21.9	3.19	14 – 28

Figure 4.18 shows the trajectory of Mr. A's MMSE scores. Interestingly, he scored 30/30 on the MMSE during his first positive delirium assessment. During this assessment, however, he required more direction than usual to remain focused, and it also took him longer to respond to questions and to complete the instruments. Two days later, he remained positive for delirium; his MMSE score was 27—one of his lowest. He was unable to determine the correct date and he was unable to recall two of the three objects that had been presented.



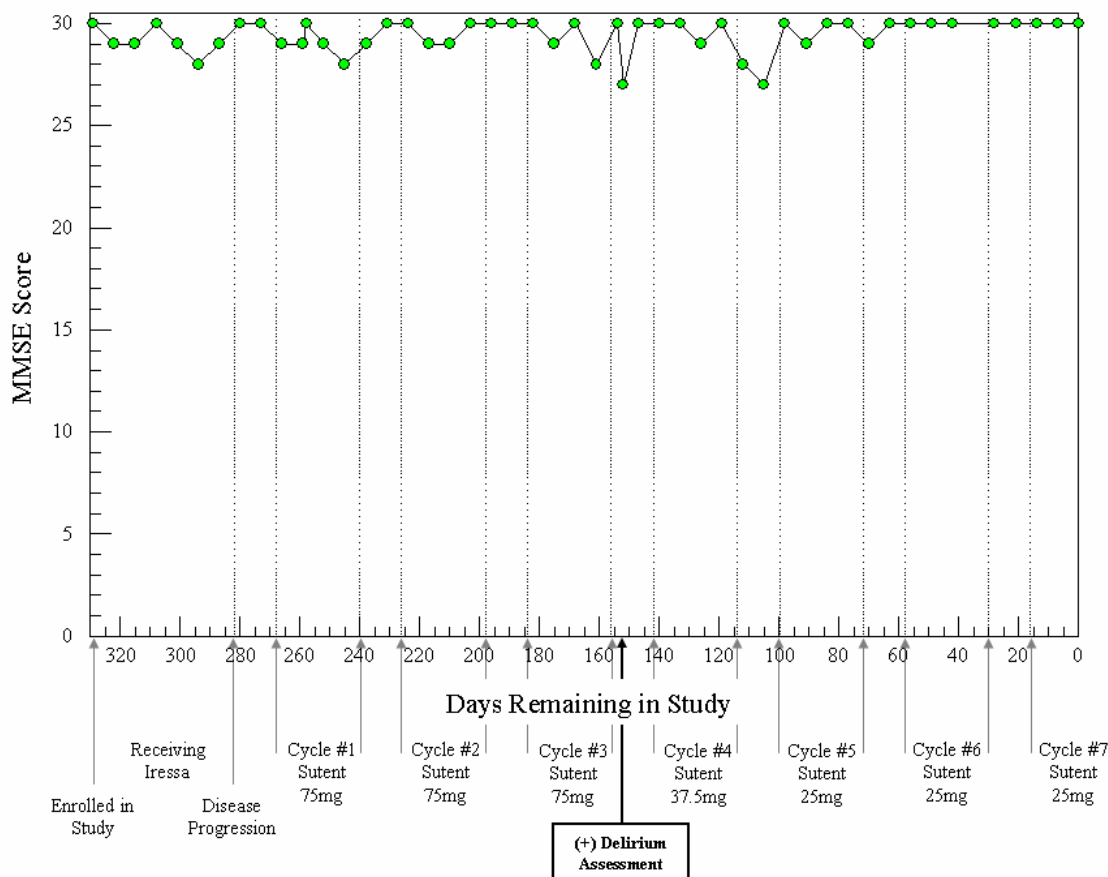


Figure 4.18. Trajectory of Mr. A's MMSE scores

No specific pattern of decline in MMSE scores was noted prior to delirium episodes except in Mr. G's case (Figure 4.19). Overall, his MMSE scores declined over the study as he experienced disease progression and episodic delirium, and as his death approached. Mr. F's MMSE scores increased slightly throughout the study. It is likely that he became more familiar with the instrument and more comfortable with questioning over time. Mrs. C's MMSE trajectory could not be evaluated because she only completed the MMSE completely during three of her first six assessments. Her percentage of correct responses on the MMSE ranged from 0.86 to 1.00.

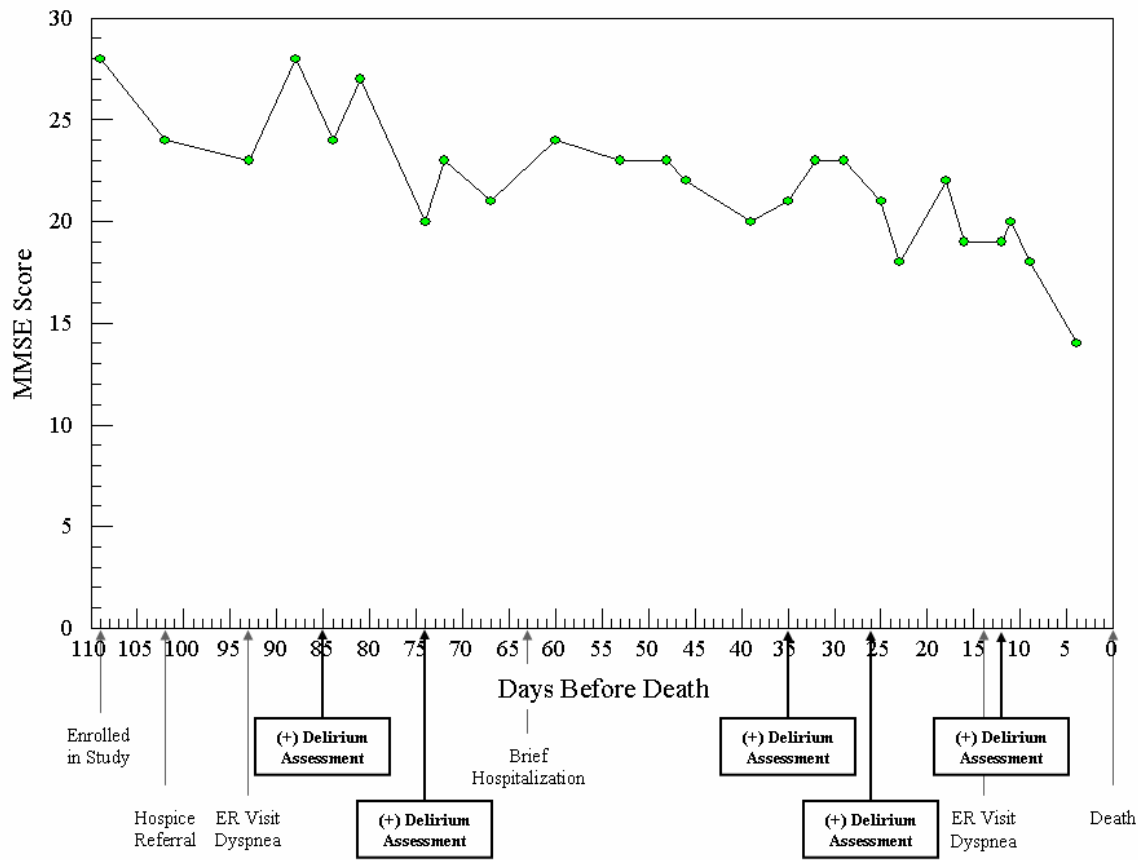


Figure 4.19. Trajectory of Mr. G's MMSE scores

The frequency and distress associated with cognitive symptoms varied among the participants. Five reported frequent cognitive symptoms:  $\geq 2$  symptoms at 60% or more assessments. In contrast, two participants, Mr. A and Mr. F, reported cognitive symptoms at  $\leq 33\%$  of assessments. The most frequently reported cognitive symptom was difficulty remembering ( $n = 103$ ), followed by difficulty concentrating ( $n = 99$ ), feeling drowsy ( $n = 81$ ), and feeling confused ( $n = 64$ ). Among participants, mean cognitive symptom distress scores ranged from 0.15 to 2.40. The participants reporting more frequent cognitive symptoms and higher cognitive symptom distress tended to be older (Mr. B, Mr. E, Mrs. C),

were closer to death (Mrs. C, Mr. G, Mr. D), and/or had baseline cognitive impairment (Mr. E).

### *Physical Functioning*

Overall, particularly among patients who died, physical functioning declined over the course of the study and prior to delirium episodes. After periods of initial stability, Mrs. C and Mr. G experienced drops in their IADL and PADL scores one to two weeks before their first delirium episodes. Mrs. C's scores continued to drop during the period between her first and second delirium episodes. Mr. G's scores showed some variability but, overall, dropped over the study and prior to subsequent delirium episodes. At enrollment, Mr. D's PADL score was 14, indicating that he was independent in all PADLs. His PADL score remained at 14 until his first hospitalization for urosepsis. His initial IADL scores were variable, but then stabilized for a period before his first hospitalization. After the hospitalization, Mr. D's IADL and PADL scores fluctuated. His IADL score never returned to its baseline level. He was independent in his PADLs for a short period after the hospitalization but throughout the remainder of the study he exhibited variability in his ability to perform PADLs.

Figure 4.20 shows the trajectory of Mrs. C's OARS scores. In Mrs. C's case, her PADL score dropped two weeks before her first episode primarily because the frequency of her incontinence increased. After that 2-point drop, her PADL score was stable until the delirium episode. Mrs. C's IADL score dropped steeply over the two weeks prior to her first delirium episode. In Mr. G's case, both his PADL and IADL scores dropped during the week prior to his first delirium episode. His IADL score dropped more sharply than his PADL score.

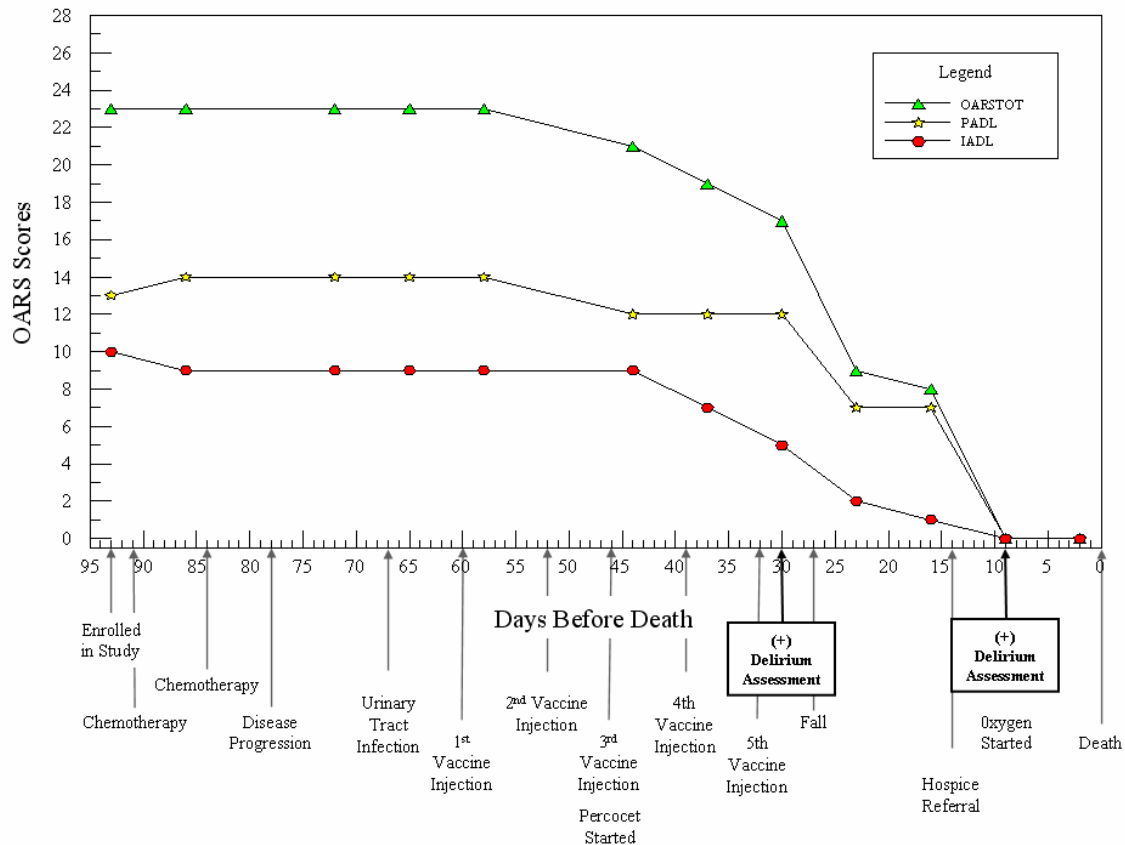


Figure 4.20. Trajectory of Mrs. C's OARS scores

Mrs. C's IADL and PADL scores continued to drop during the 21-day period between her first delirium episode and her second episode preceding her death. Her IADL score dropped steadily during this period, while her PADL score plateaued at 7 for two assessments a week apart. At the time of her second delirium episode, Mrs. C was completely bedbound and dependent in all activities of daily living.

Figure 4.21 shows the trajectory of Mr. G's OARS scores. Mr. G's IADL score dropped sharply during the week prior to his first delirium episode. His PADL score also dropped. During that week, Mr. G had increased shortness of breath and required increased amounts of oxygen supplementation to maintain his oxygen saturation in the low to mid 90's.

He was not able to go out as he normally did, and he required increased assistance from his family and hospice caregivers.

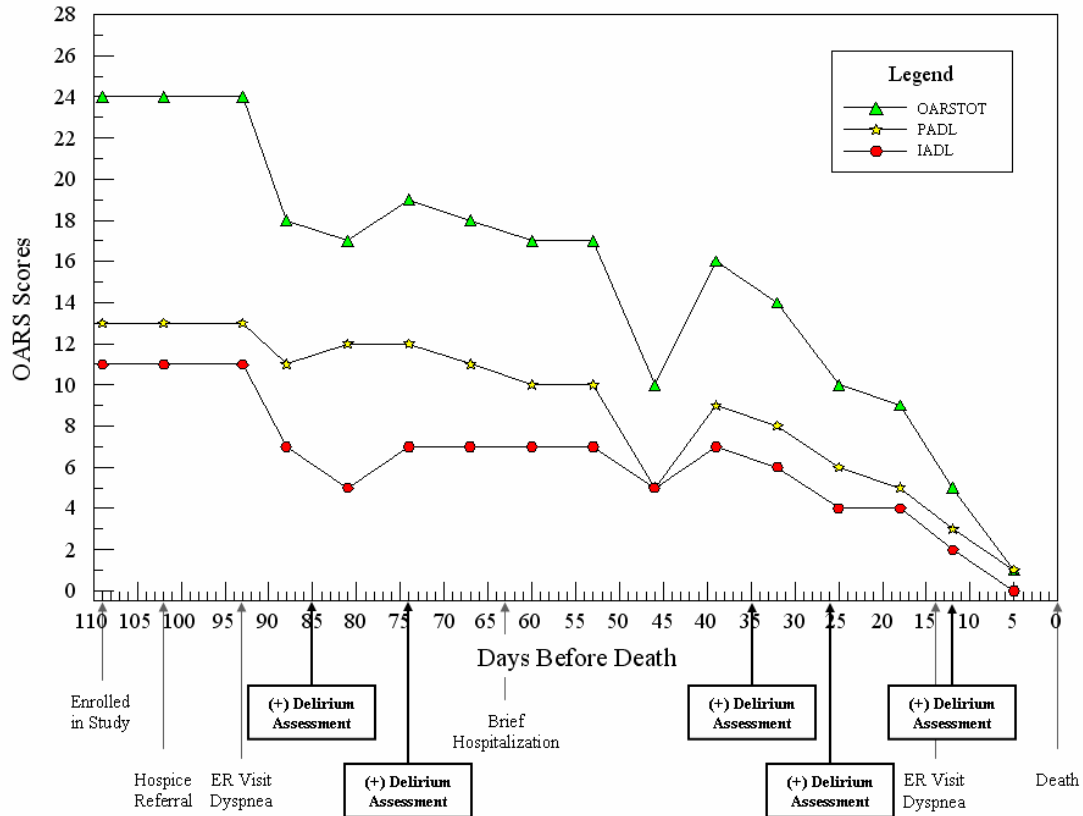


Figure 4.21. Trajectory of Mr. G's OARS scores

After a slight increase, Mr. G's PADL scores dropped slowly but steadily over the remainder study until his death. On Day 46, his PADL score dropped to 5 from 10 at the previous assessment, a week earlier. At the assessment on Day 46, Mr. G also reported an increase in symptoms and symptom distress, and he had a significant increase in his GDS score—from 3 to 11. A week later on Day 39, his IADL and PADL scores rebounded slightly, but then began to drop steadily until his death.

Figure 4.22 shows the trajectory of Mr. D's OARS scores. At the beginning of the study, Mr. D performed his PADLs independently. He initially exhibited variability in his ability to complete IADLs, but after the first 60 days, he achieved stability at an improved level of functioning. After being hospitalized with urosepsis between Day 151 and Day 146, both his PADL and IADL scores, dropped markedly.

After the hospitalization, Mr. D's IADL scores never returned to baseline. His PADL score returned to baseline for a short period, but then fluctuated before stabilizing at a lower level. After the hospitalization, Mr. D stopped driving. In fact, he rarely went out of the house except for clinic appointments. Mr. D spent most of his time either sitting or lying on the sofa or in bed. Mr. D's OARS scores did not show any other significant decline prior to his delirium episode. Following the episode, his IADL score was more decreased. At the assessment prior to his death, Mr. D's PADL score was more decreased.

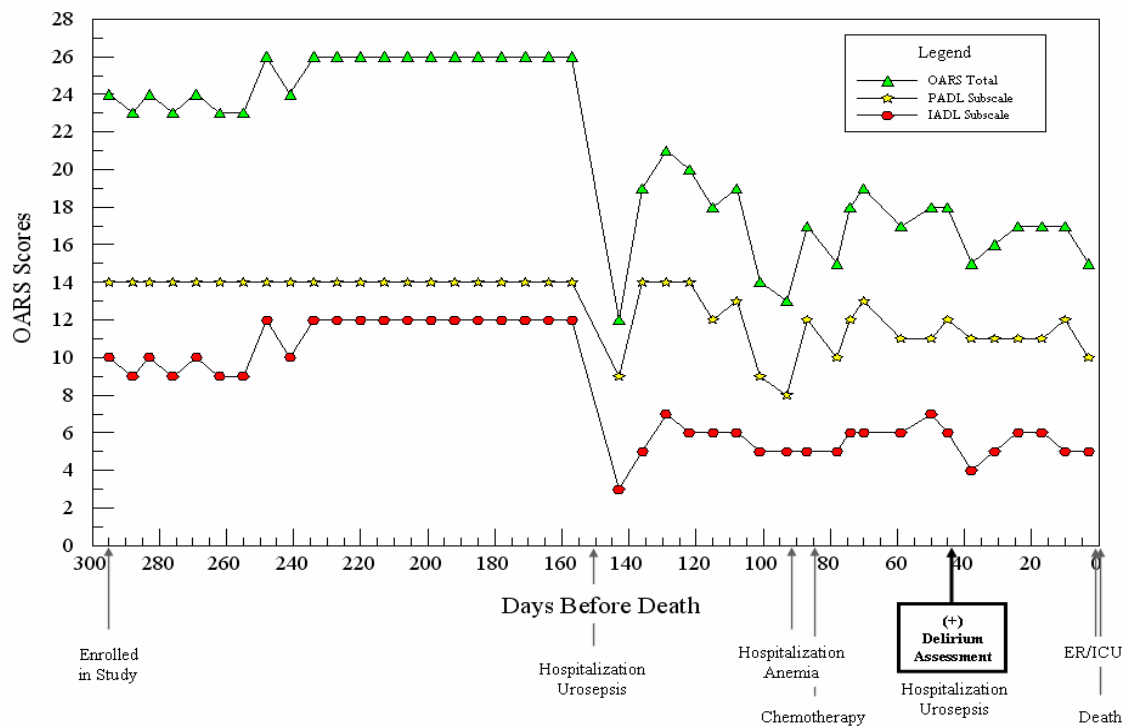


Figure 4.22. Trajectory of Mr. D's OARS scores

Figure 4.23 shows the trajectory of Mr. A's OARS scores. In general, his PADL scores were stable throughout the study. Most of the time, he was completely independent in performing his PADLs. He did experience slight intermittent declines in his PADL scores while being treated with Sutent. In contrast, after a period of initial stability and minimal deficit, his IADL score dropped markedly during the first three cycles of Sutent and prior to his delirium episode. His IADL scores exhibited variability over the remainder of the study but had improved by the end of the study after the Sutent dose was decreased.

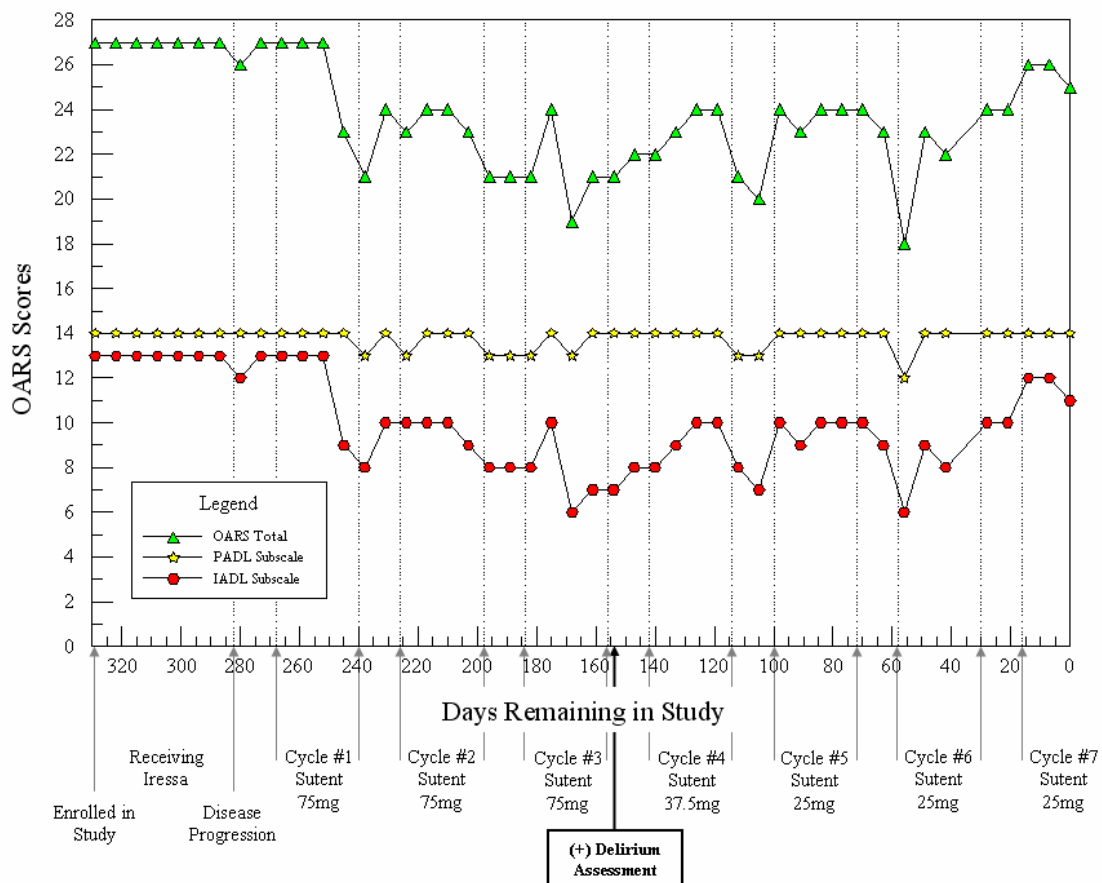


Figure 4.23. Trajectory of Mr. A's OARS scores

Overall, physical functioning declined prior to delirium episodes. Mr. B and Mr. F had delirium while hospitalized during their postoperative periods. As would be expected, during their perioperative periods, their IADL and PADL scores declined (See Figure , p. and Figure , p). While physical functioning was not measured during hospitalizations, both exhibited limited functioning when they developed delirium postoperatively. Their PADL and IADL scores returned to baseline as they recovered. The trajectories of Mr. E's IADL and PADL scores were relatively stable throughout the study (See Figure, p. ). His IADL score was decreased 2 points from his baseline at the assessment on week prior to his positive delirium assessment. His PADL score was unchanged.

### *Depression*

The 15-item Geriatric Depression Scale (GDS-15) was used to identify depression. A score  $> 5$  is indicative of probable depression. Table 4.13 summarizes the participant's GDS scores. Overall, depression scores varied both within and between individuals. All but one of the participants (Mr. F) had intermittent GDS scores indicative of depression. Only one participant (Mr. A) had a prior history of depression that was currently being treated with antidepressant medications.

Depression scores did not show any particular pattern in relation to the development of delirium. Four patterns were identified after examining the GDS score trajectories in relation to other variables: 1) GDS scores  $\leq 5$  (no depression); 2) most GDS scores  $> 5$  (probable depression); 3) most GDS scores  $\leq 5$  but with intermittent spikes, and 4) progressive increase in GDS scores.



Table 4.13. Summary of participants' GDS scores

Participant	Number of Assessments	Mean	SD	Range
Mr. A	46	2.0	2.48	0 – 13
Mr. B	18	6.2	1.46	4 – 10
Mrs. C	4	6.0	0.82	5 – 7
Mr. D	43	3.3	0.97	1 – 6
Mr. E	20	5.8	1.39	4 – 10
Mr. F	20	0.9	0.64	0 – 2
Mr. G	13	6.2	3.17	0 – 11

Table 4.14. Percentage of GDS scores  $\leq 5$  and  $> 5$  by participant

Participant	Number of Assessments	Frequency with GDS score $\leq 5$		Frequency with GDS score $> 5$	
		n	%	n	%
Mr. A	46	43	93.5	3	6.5
Mr. B	18	7	38.9	11	61.1
Mrs. C	4	1	25.0	3	75.0
Mr. D	43	42	97.7	1	2.3
Mr. E	20	7	35.0	13	65.0
Mr. F	20	20	100	0	0
Mr. G	13	7	53.8	6	46.2

Figure 4.24 shows the trajectory of Mr. F's GDS scores. He did not show evidence of depression. His GDS scores were consistently low. His highest GDS score was 2. Even though he had been recently diagnosed and was undergoing intensive treatment, it is likely that Mr. F's overall attitude and outlook on life played a role in his low GDS scores.

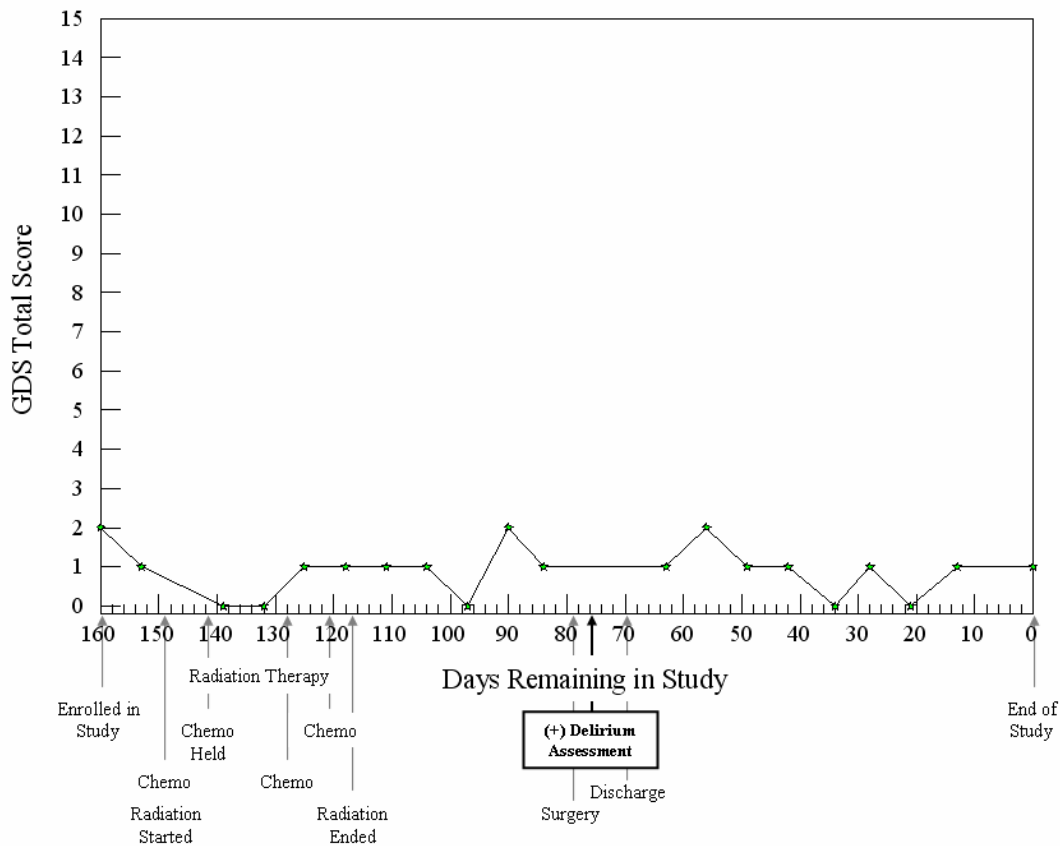
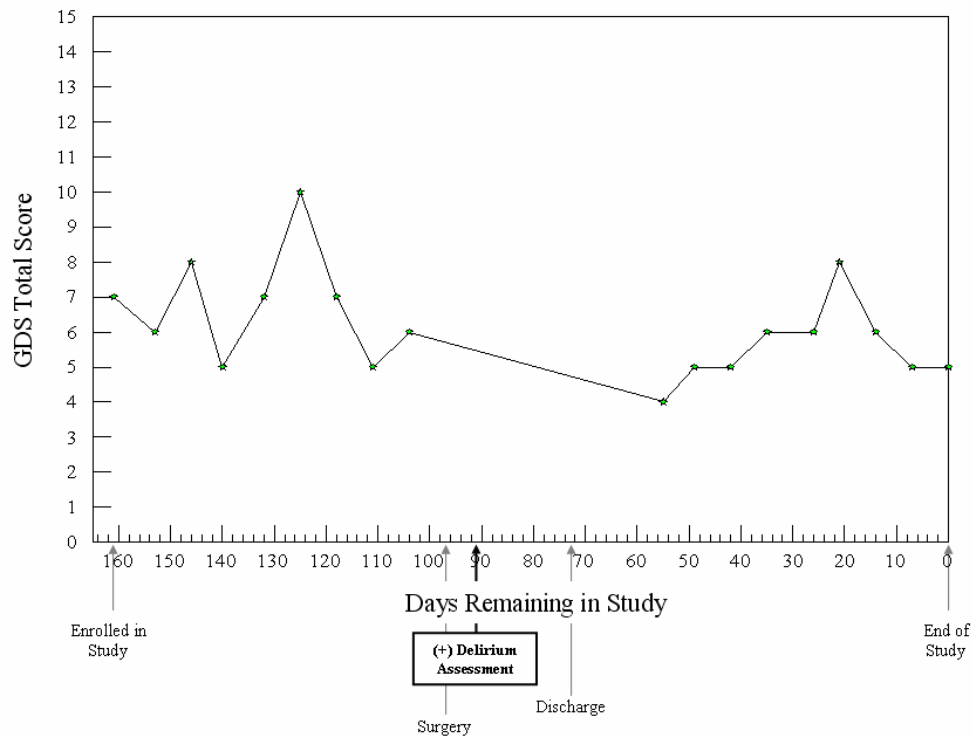


Figure 4.24. Trajectory of Mr. F's GDS scores

Mr. B, Mrs. C, and Mr. E had consistently higher GDS scores—with most  $\geq 5$ . These participants may have been experiencing depression related to their overall conditions or situations—recent cancer diagnosis, disease progression, or impaired function. For example, Figure 4.25 shows the trajectory of Mr. B's GDS scores. He had been recently diagnosed with liver cancer and had undergone chemo-embolization of the tumor, which left him

extremely fatigued and with decreased appetite. He often talked about the negative changes in his overall health and function following this treatment. He did not want to undergo a second chemo-embolization, the usual treatment course, but instead sought surgical resection—even though he was a high-risk surgical candidate. Both Mr. B and Mr. E exhibited some fluctuation in their GDS scores. Intermittent spikes appeared to be associated with increased symptom distress, and in Mr. E’s case, learning of disease progression and preparing for the sale of his house and move.



*Figure 4.25.* Trajectory of Mr. B’s GDS scores

The trajectory of Mr. A’s GDS scores (Figure 4.26) provides an example of the third pattern. Most of his GDS scores were  $\leq 5$  but he had intermittent or occasional spikes in his

scores. At the assessment on Day 112, Mr. A's GDS score following Cycle #4 of Sutent was 13. His MMSE score was 28 and his total NEECHAM score was 27. He reported an increase in his total number of symptoms and an increase in his global, psychological, and physical symptom distress (Figure 4.27). He also reported a decline in his physical functioning, particularly in performing IADLs (Figure 4.28).

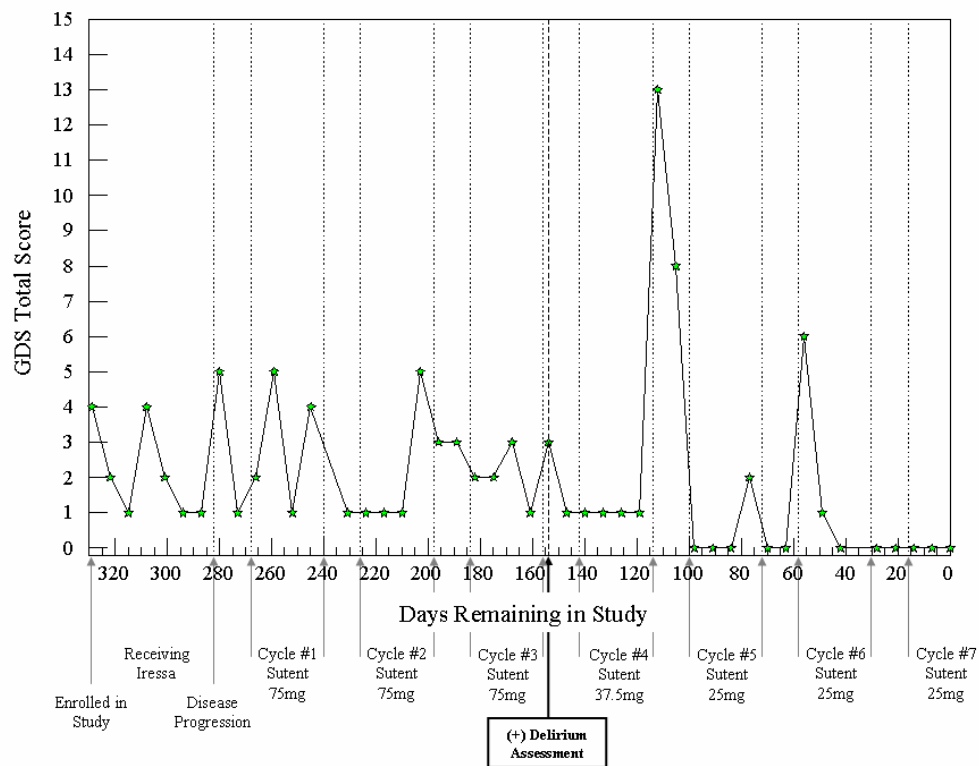


Figure 4.26. Trajectory of Mr. A's GDS scores

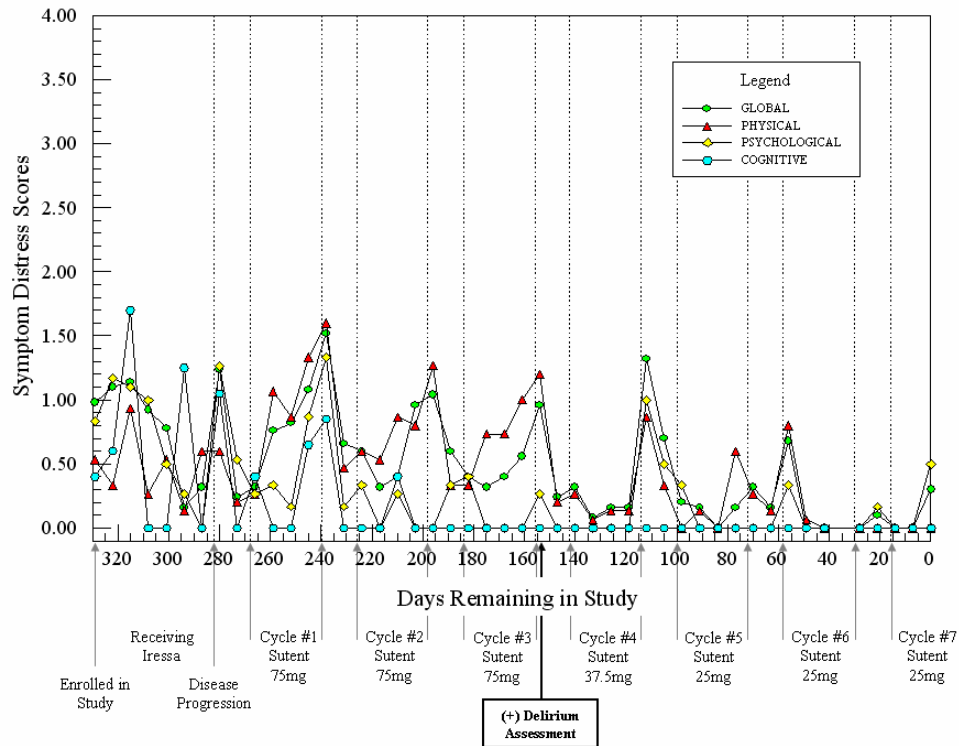


Figure 4.27. Trajectory of Mr. A's symptom distress scores

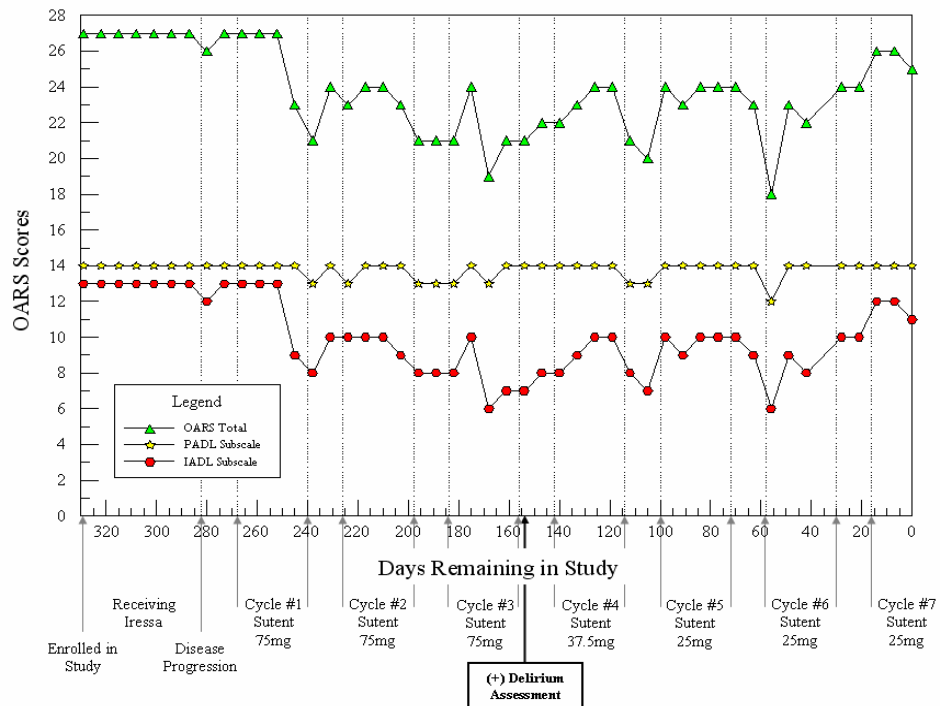


Figure 4.28. Trajectory of Mr. A's OARS scores

As an example of the fourth pattern, overall, Mr. G's GDS score trajectory (Figure 4.29) shows a progressive increase throughout the study as his condition declines and as he approaches death. When Mr. G enrolled in the study, he was living independently and, as part of his usual daily routine, he drove in to town—approximately 25 miles each way—to visit with family and friends. His GDS scores were low. As his condition declined, his scores began to fluctuate, dramatically at times, depending on his functional ability and symptom distress. Near the end of life as his cognitive and physical functioning declined more steadily, his GDS scores remained consistently higher, indicating depression. Although not nearly as dramatic, Mr. D's GDS score trajectory demonstrated a similar pattern.

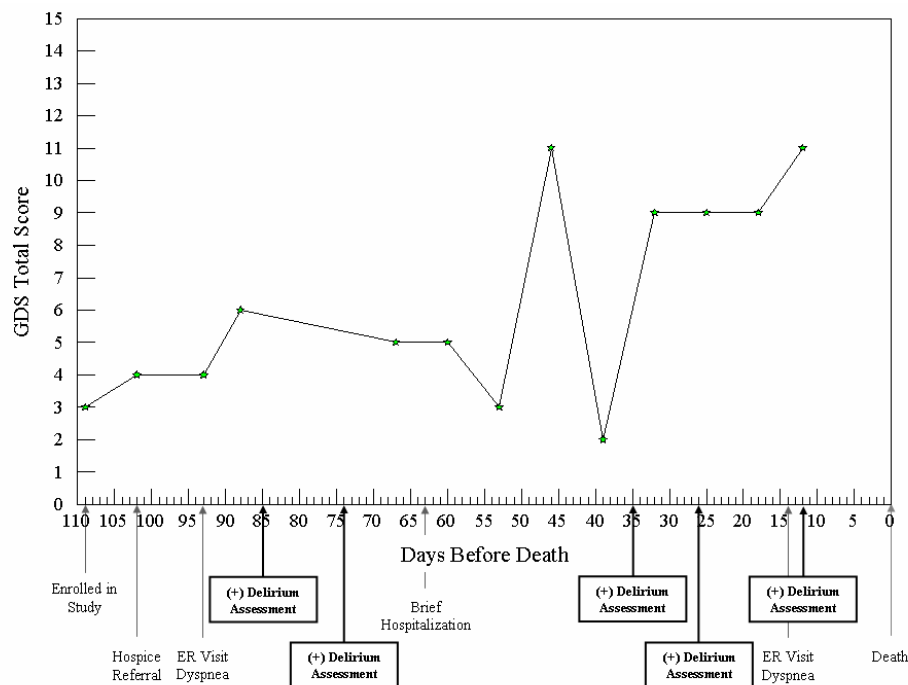


Figure 4.29. Trajectory of Mr. G's GDS scores

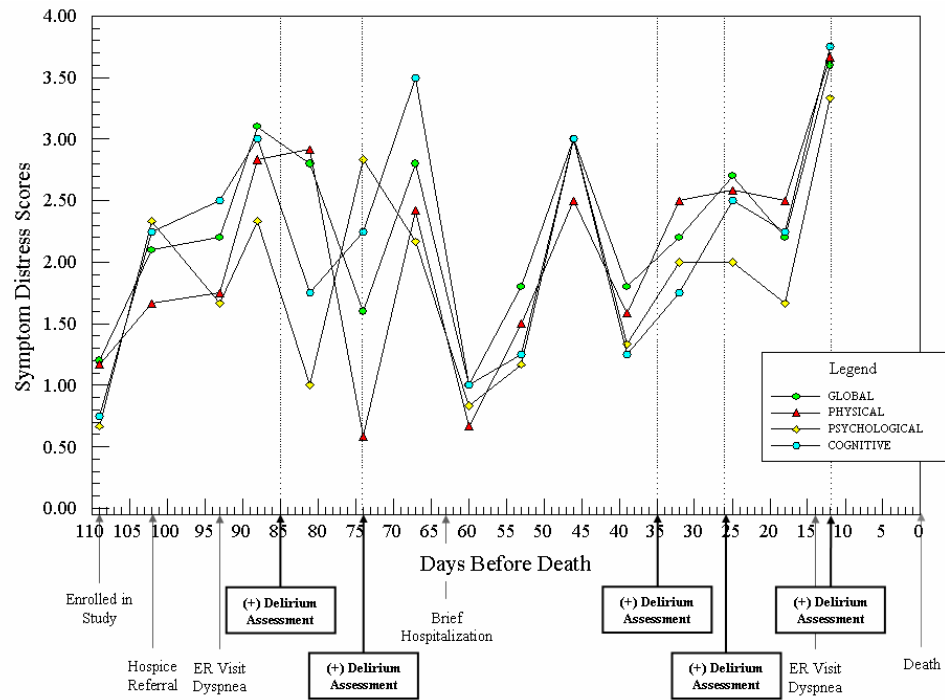


Figure 4.30. Trajectory of Mr. G's symptom distress scores

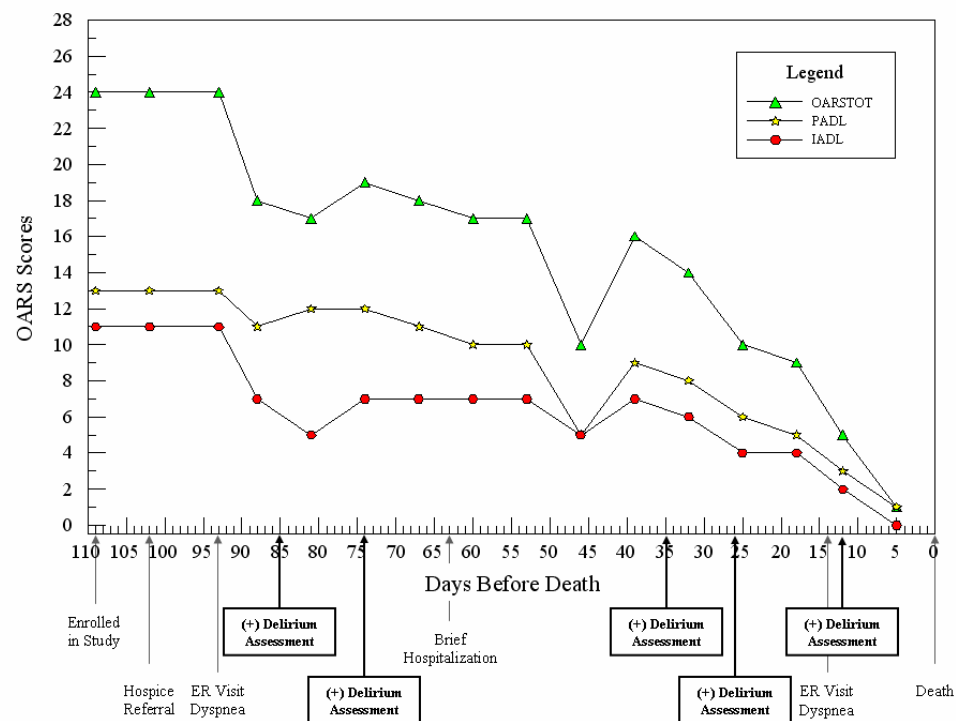


Figure 4.31. Trajectory of Mr. G's OARS scores

### *Symptom Prevalence and Distress*

An adapted version of the Memorial Symptom Assessment Scale – Short Form (MSAS-SF) was used to measure symptom prevalence and distress. The average total number of symptoms reported by participants at each assessment ranged between 3.7 and 22.8. All but one participant (Mr. F) reported, on average, 6 or more symptoms at each assessment. Overall, lack of energy was the most common and most distressing physical symptom. Taste changes and lack of appetite, also common, compound nutritional risk.

Throughout the study, in the patients who died, symptoms and symptom distress increased. Mrs. C showed a pattern of increasing symptoms and symptom distress before she requested to stop completing the instruments. It is likely that this contributed to her request to stop. While Mr. G's symptom distress fluctuated, it was consistently high. His symptom distress increased prior to his first delirium episode, and peaked at the last assessment on Day 12. Mr. D's symptom distress increased after his first hospitalization for urosepsis. Notably, at most assessments, his cognitive symptom distress was higher than his physical or psychological symptom distress.

Mr. A's symptom distress tended to fluctuate with his treatment. He reported increased cognitive distress during the first 50 days of the study while taking Iressa. He reported minimal cognitive symptom distress after that time. After starting the Sutent, his global, physical, and psychological symptom distress fluctuated with his treatment cycles. He reported increased distress at the end of each cycle until the dose was reduced. Among the other participants who lived, symptom distress across the study was relatively stable. Overall, Mr. B and Mr. F had lower levels of distress. On the other hand, Mr. E's symptom distress was high throughout the study. At most assessments, his cognitive symptom distress was



higher than his global distress, physical distress, or psychological distress. Mr. E had pre-existing cognitive impairment and significant symptoms associated with his comorbid medical conditions—orthostatic hypotension and neurogenic bladder.

### *Etiologic Patterns and Risk Markers*

At baseline, the participants who died exhibited risk markers for multiple etiologic patterns. All three had metabolic-nutritional pattern markers. In addition, Mrs. C had orthostatic pattern markers; Mr. G had hypoxic markers, and Mr. D had hypoxic and metabolic-toxic pattern markers. Prior to their first delirium episodes, Mrs. C also had a marker for the metabolic-toxic pattern and Mr. D exhibited a marker for the orthostatic pattern. They also had additional markers for their previously exhibited patterns.

Table 4.15. Etiologic patterns at baseline by participant

Participant	Metabolic-Nutritional	Hypoxic	Metabolic-Toxic	Orthostatic-Dehydration	Chronic Cognitive Impairment
Mr. A	X			X	
Mr. B	X				
Mrs. C	X			X	
Mr. D	X	X	X		
Mr. E	X		X	X	X
Mr. F				X	
Mr. G	X	X			

Table 4.16. Etiologic patterns prior to first delirium episode by participant

Participant	Metabolic-Nutritional	Hypoxic	Metabolic-Toxic	Orthostatic-Dehydration	Chronic Cognitive Impairment
Mr. A	*			*	
Mr. B	*	X	X	X	
Mrs. C	*		X	*	
Mr. D	*	*	*	X	
Mr. E	*		*	*	*
Mr. F	X	X		*	
Mr. G	*	*		X	

\* Pattern markers present at baseline

#### *Metabolic-Nutritional Pattern*

At baseline, all of the participants who died (Mrs. C, Mr. G, and Mr. D), and three who lived (Mr. A, Mr. B, and Mr. E) had metabolic-nutritional pattern markers. Mr. A, Mr. B, Mrs. C, Mr. D, and Mr. G had experienced significant weight loss. Most exhibited other markers including an albumin level < 3.5 g/dl and a lymphocyte count < 1000/cu mm. Mr. E's only marker was a low serum albumin level.

Mrs. C reported that prior to her cancer diagnosis her weight averaged around 164 pounds. Prior to her initial abdominal surgery in January 2003, her documented weight was 136 pounds. Figure 4.32 shows the trajectory of Mrs. C's weight during the study. At the time of enrollment in the study in May 2005, Mrs. C weighed 104.5 pounds. Her body mass index was 19.0. During the study, Mrs. C's weight increased, reflecting generalized fluid

retention and, most notably, progressive abdominal ascites. Her last on Day 16 was 111.4 pounds. Mrs. C's baseline lymphocyte count was low, and it remained low throughout the study. Her baseline albumin level was 3.5 g/dl, but prior to her first delirium episode, it had dropped to a low of 2.7 g/dl.

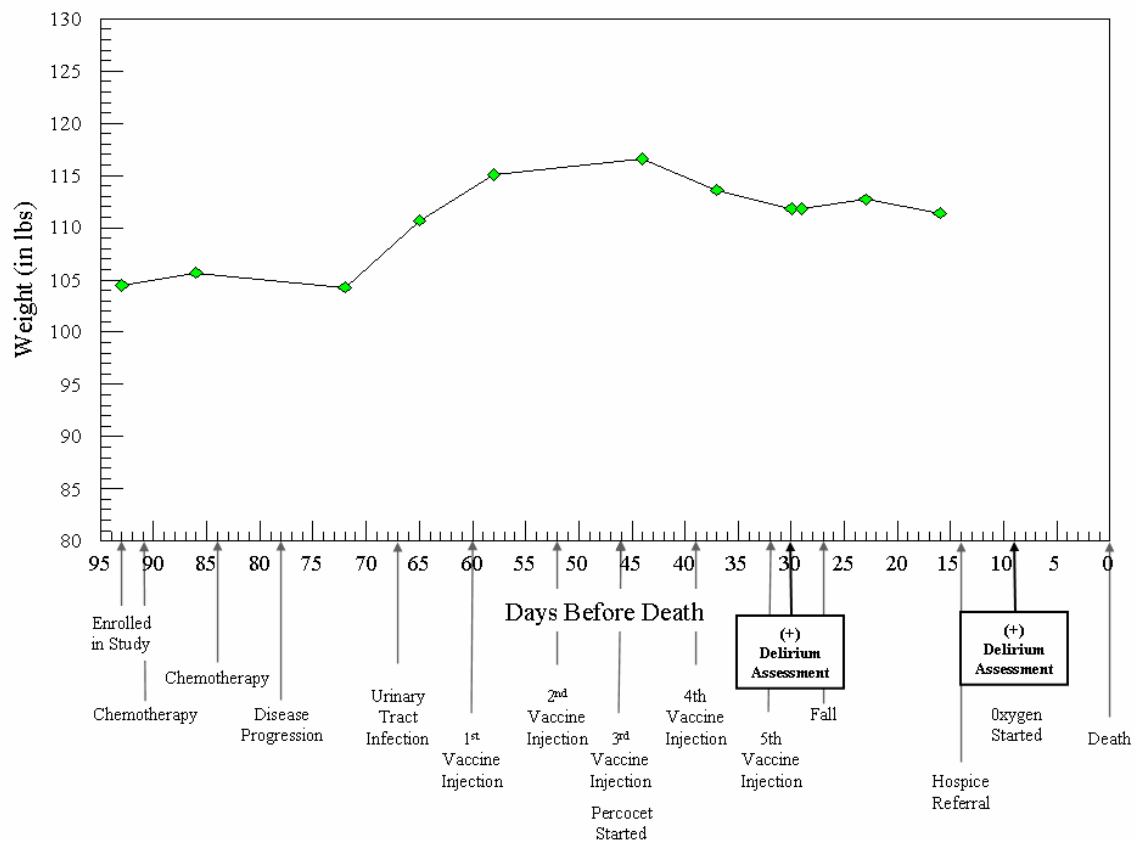


Figure 4.32. Trajectory of Mrs. C's weight

Prior to his cancer diagnosis in May 2004, Mr. G weighed 261 pounds. Figure 4.33 shows the trajectory of Mr. G's weight during the study. Upon enrollment in the study in September, 2005, he weighed 234 pounds. Mr. G's weight declined progressively during the study. His last weight 11 days before his death was 196.2 pounds. Mr. G's lymphocyte count

was decreased upon enrollment and throughout the study. He did not have a recent albumin level documented in his medical record.

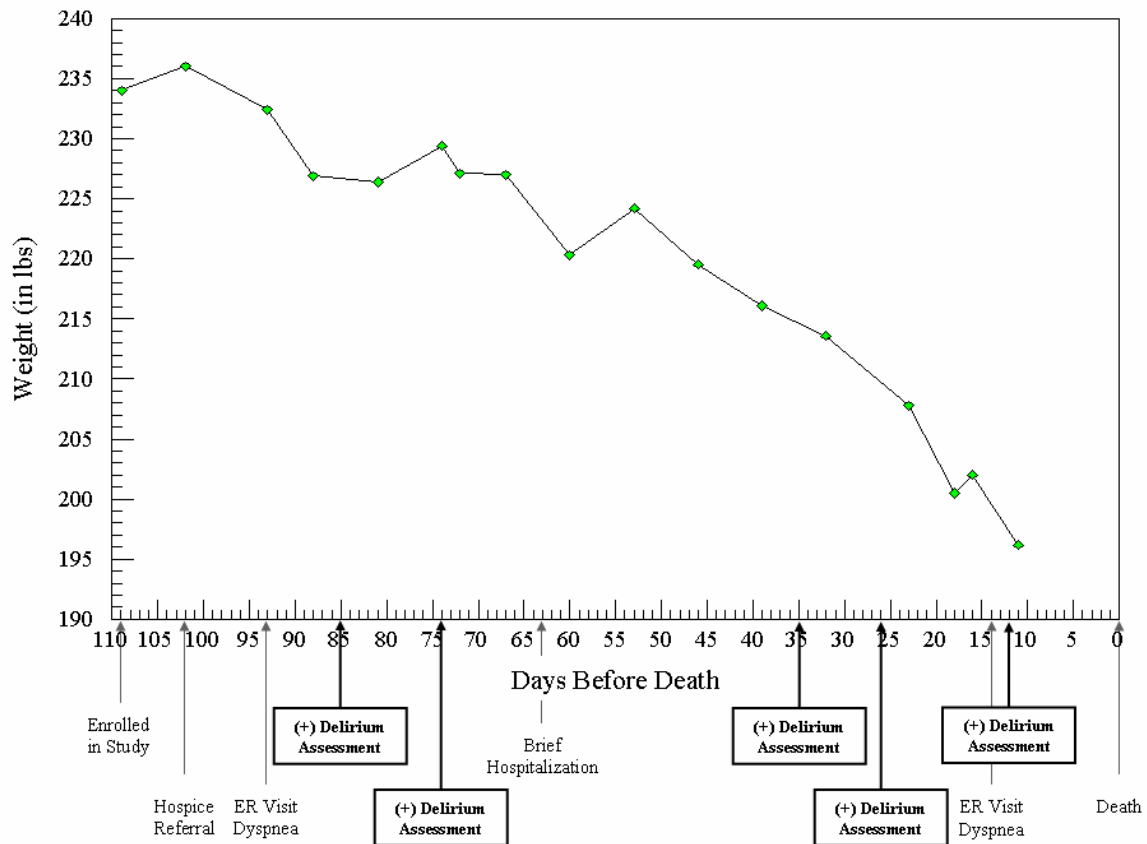


Figure 4.33. Trajectory of Mr. G's weight

Over the 6-month period between January 2005 and June 2005, prior to enrollment in the study, Mr. D had a 17 pound weight loss. Figure 4.34 shows the trajectory of Mr. D's weight during the study. Although Mr. D's weight fluctuated during the study, the overall trend showed a decline—particularly after his first hospitalization. During the study, Mr. D's serum albumin level fluctuated, ranging between 1.8 and 3.5 g/dl. Prior to his delirium episode, his albumin level was 2.8 g/dl—an indicator of metabolic-nutritional and metabolic-toxic risk.

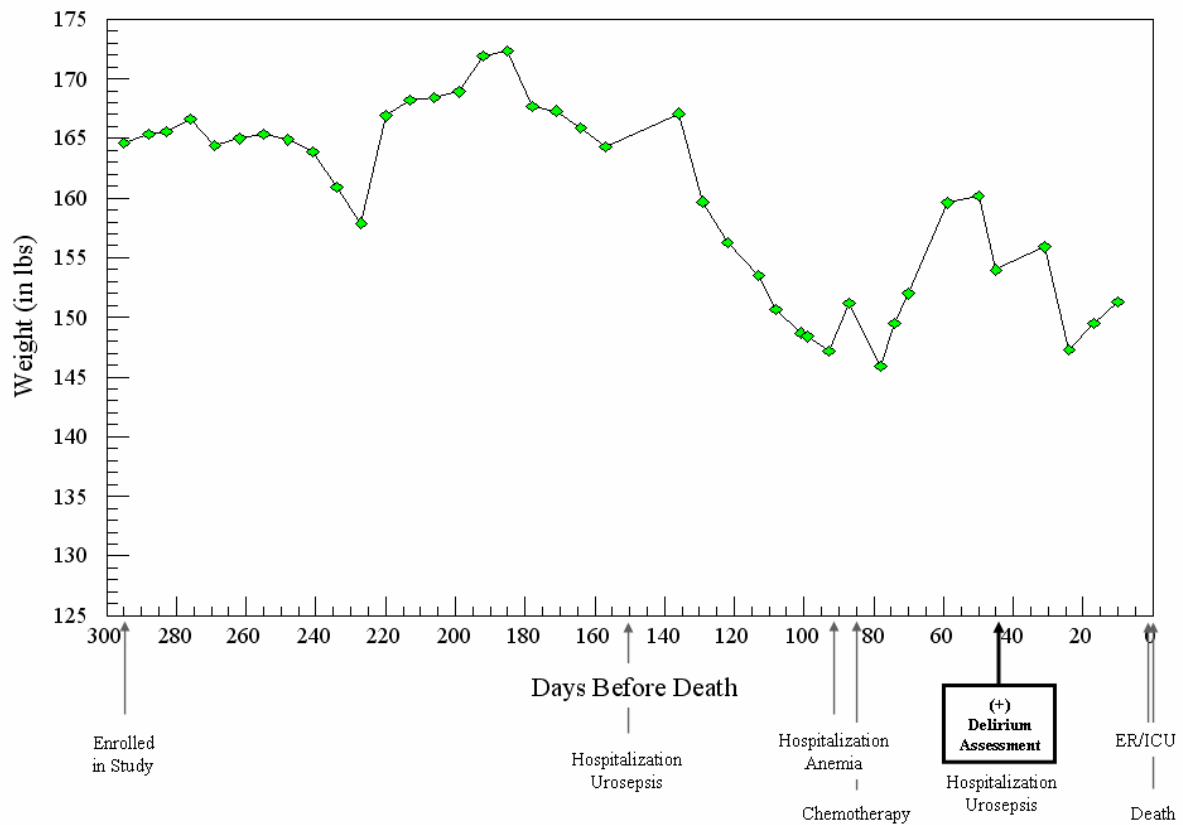


Figure 4.34. Trajectory of Mr. D's weight

Among the patients who lived, Mr. A and Mr. B exhibited metabolic-nutritional risk markers at baseline and prior to their delirium episodes. Over the six months prior to enrolling in the study, Mr. A lost 13.2 pounds. Figure 4.35 shows the trajectory of Mr. A's weight. During the study, his weight fluctuated significantly with fluid retention caused by his treatment. He tended to retain fluid during the two weeks between cycles of Sutent. Despite the fluid retention, over the course of the study, Mr. A lost approximately 13 pounds. His weight at enrollment was 145.9 pounds, and his last weight was 132.8 pounds.

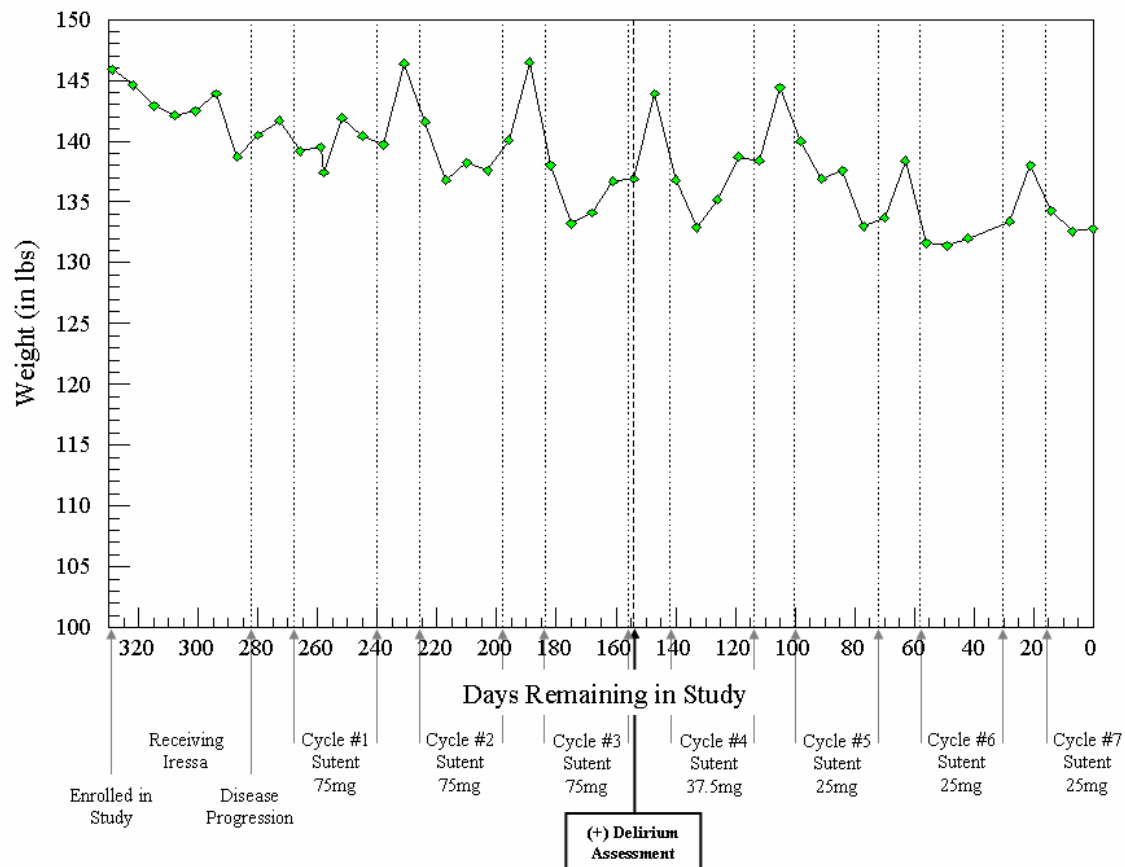


Figure 4.35. Trajectory of Mr. A's weight

During the 6 months prior to enrolling in the study, Mr. B lost 18.5 pounds. His weight during the study prior to his surgery fluctuated between 166 and 170 pounds. His lowest weight, 163 pounds, was documented at the first home visit after his surgery. His last weight was 171 pounds. He often exhibited pedal edema that was worse postoperatively. Therefore, his weights reflect fluid retention most likely related to his low albumin level

### *Hypoxic Pattern*

At baseline, two participants, Mr. G and Mr. D, exhibited hypoxic pattern markers. Mr. G had a long standing history of COPD requiring supplemental oxygen. At the time of enrollment in the study, Mr. G intermittently wore oxygen at 3 liters/minute. He also had a documented history of anemia due to thalisseimia; his baseline hemoglobin was . A week prior to his first delirium episode, Mr. G was admitted to the ER for shortness of breath. Subsequently, his oxygen supplementation was increased to 5 liters/minute. It was thought that hypoxia contributed to Mr. G's first delirium episode. At the time of his first positive delirium assessment, his oxygen saturation on supplemental oxygen at 5 liters/minute was 93%. His oxygen supplementation was increased to 6 liters/minute. At the follow-up assessment the next day, Mr. G's oxygen saturation while receiving oxygen at 6 liters/minute was 97%.

Mr. D's hypoxic risk was related to his low hemoglobin level—thought to be due to bone marrow suppression caused by long-term chemotherapy. His baseline hemoglobin level was 8.8 gm/dl. During the study, Mr. D experienced instability in his hemoglobin level. In January, 2006, Mr. D had increasing shortness of breath. He was hospitalized and transfused with 4 units of packed red blood cells after his hemoglobin was determined to be 5.2 g/dl. When Mr. D was hospitalized with urosepsis in March 2006, he was positive for delirium and his hemoglobin had dropped to 5.3 g/dl. He did not show any evidence of bleeding. It was thought that Mr. D's anemia was due to bone marrow failure caused by long-term chemotherapy administration. Mr. D was transfused again during this hospitalization. His hemoglobin level prior to discharge was 7.3 g/dl. A month later, when hospitalized again, the night before his death, Mr. D's hemoglobin was 4.9 g/dl.

Other participants had hypoxic pattern markers at the time of their positive delirium assessments. At the time of her second delirium episode, Mrs. C exhibited a hypoxic pattern marker—the need for supplemental oxygen. Postoperatively and at the time of his positive delirium assessment, Mr. F, also was receiving supplemental oxygen.

#### *Metabolic-Toxic Pattern*

Risk markers for the metabolic-toxic pattern were common among participants at baseline and at the time of delirium episodes. Although no participant had a baseline diagnosis of liver or renal failure, some exhibited impaired liver or renal function. For example, while receiving the higher dose of Sutent and prior to his positive delirium assessment, Mr. A's bilirubin level was increased at 1.6. Following his hepatic resection and prior to his positive delirium assessment, Mr. B's bilirubin level also was increased at 1.4. Mr. D had chronic renal insufficiency. His baseline creatinine level was 1.5 mg/dl. Each time he was hospitalized for urosepsis and dehydration, Mr. D exhibited worsened renal function. At the first hospitalization, his creatinine level was 4.5 mg/dl. At the second hospitalization when he was positive for delirium, his creatinine level was 2.6 mg/dl. During each hospitalization, his creatinine level returned to baseline with rehydration. Mr. E also had chronic renal insufficiency. Throughout the study, his creatinine level ranged between 1.4 and 1.6 mg/dl. Many of the participants also had low serum albumin levels during the study.

#### *Orthostatic-Dehydration Pattern*

Orthostatic-dehydration pattern markers also were common. Upon enrollment, four of the older adults with advanced cancer had markers for the orthostatic-dehydration pattern; 3



had a BUN/Cr ratio > 20 (Mr. A, Mrs. C, and Mr. F) and the other had orthostatic symptoms (Mr. E). Prior to developing delirium, all of the participants had markers for the orthostatic-dehydration pattern. Among those without markers at enrollment, Mr. B had BUN/Cr ratio > 20 prior to his delirium episode; Mr. G had orthostatic symptoms; and Mr. D had dehydration and hypovolemia with vital function instability. Mrs. C had additional pattern markers prior to her first delirium episode. Her physician thought that she was dehydrated, and she intermittently exhibited orthostatic symptoms.

#### *Chronic Cognitive Impairment Pattern*

Mr. E was the only participant who had pattern markers for chronic cognitive impairment. Mr. E and his wife, as well as his medical record, noted that he had intermittent mental status problems—episodes of confusion. He also needed assistance with taking medications and with completing other IADLs. Although he also had baseline risk markers for other patterns (metabolic-nutritional and orthostatic), Mr. E's delirium episode fit with what is commonly seen in older adults with chronic cognitive impairment or low cognitive reserves. His delirium occurred in the morning after he had returned late the previous night from an out-of-state trip to attend his sister's funeral and to visit with family.

#### *Medications and Treatment*

At baseline, most participants were on multiple medications for the management of chronic illnesses, their cancer, and cancer symptom management. All of the participants except Mr. E were taking their medications independently. Therefore, it was difficult to determine specific dosages of medications taken and whether participants were taking their

medications correctly. In some cases, it is likely that medications and side effects played a role in the development of delirium.

Diagnosed with advanced colon cancer in 2003, Mrs. C had received at least three lines of treatment prior to enrollment in the study. At the time of enrollment she was receiving Irinotecan and Cetuximab. After three cycles of Irinotecan and one cycle of Cetuximab, Mrs. C's disease progressed. She was enrolled in a clinical trial investigating the effectiveness of a vaccine for tumors with Ras mutation. The trial involved five weekly vaccine injections administered in the General Clinical Research Center (GCRC) at UNC. During the course of the vaccine trial, Mrs. C began to exhibit changes in her physical functioning and behavior. She also began to experience increased abdominal and back pain. Up to this point, Mrs. C reported acceptable pain control with Advil and Tylenol. She started on Percocet during the third week of the vaccine trial. Mrs. C noted that one Percocet tablet made her too sleepy. She often took one-half of a tablet during the day, but took a whole tablet at night before going to bed. Mrs. C received the final vaccine and had a CT scan to evaluate the status of her disease on Day 32. On the following day (Day 31), Mrs. C's caregiver noted that she was nauseated and that she ate and drank minimal amounts. Mrs. C took compazine to control the nausea. The next day (Day 30), at the scheduled weekly assessment, Mrs. C was positive for delirium. It is likely that the combination of the above factors contributed to the development of delirium.

Prior to Mr. G's first delirium episode, he was self-administering multiple pain medications including topical fentanyl, percocet, and concentrated morphine solution. After that episode, the hospice nurse changed his regimen to long-acting morphine and immediate release morphine tablets for breakthrough pain. After the episode, Mr. G's family and friends

began to stay with him 24 hours a day. His caregivers administered his scheduled medications including the long-acting morphine, but he still self-administered the morphine for breakthrough pain. For a period, although his level of pain fluctuated, overall, his pain control was improved.

At the time of his scheduled weekly visit on Day 74, Mr. G was positive for delirium—his second episode. He had been to an appointment at the cancer clinic that morning. The clinic note for that visit indicated that Mr. G was somnolent. His caregiver reported that she discovered that he had taken extra doses of pain medication prior to going to the clinic appointment.

After Mr. A experienced disease progression, he was enrolled in clinical trial investigating the effectiveness of Sutent, an antiangiogenesis agent, against non-small cell lung cancer. During the trial particularly while receiving a higher dose of the drug, he experienced – physiologic instability (hypertension), increased fatigue, intermittent nausea and vomiting, weight gain – fluid retention between cycles, variable shortness of breath (increased with fluid retention), hypothyroid, and persistent cough. Mr. A's delirium episode occurred after his 3<sup>rd</sup> 28-day cycle of Sutent. His overall function and symptom distress improved over time as the Sutent dose was decreased.

As previously noted, Mr. B and Mr. F had an episode of delirium while hospitalized following their surgical procedures. Both were receiving pain medications at the time. During the week prior to his positive delirium assessment, Mr. B had an episode of tachycardia that required readmission to the ICU.

*Research Question 3: How is delirium in older adults with advanced cancer near the end of life similar to or different from delirium in hospitalized older cancer patients?*

Similarities were found between delirium in the older adults with advanced cancer near the end of life and delirium in the hospitalized older cancer patients. First, delirium was common in both groups. Fifty-six percent of the hospitalized patients and all ( $n = 7$ ) of the patients with advanced cancer experienced at least one episode of either mild or severe delirium, or both. Mild delirium was more likely to resolve. Persistent delirium was common in the hospitalized older cancer patients and in the older adults with advanced cancer who died. Eight of the 10 hospitalized patients who died had persistent delirium at hospital discharge; one who died two days after discharge had persistent severe delirium. Likewise, two of the older adults with advanced cancer who died had persistent severe delirium in the last two weeks prior to death.

The older adults with advanced cancer near the end of life and the hospitalized older cancer patients exhibited markers for multiple etiologic patterns. Most of the patients in each group had metabolic-nutritional markers. Hypoxic, metabolic-toxic, and orthostatic-dehydration pattern markers were also common. In the hospitalized older cancer patients, pattern markers were assessed at the time of hospital admission. In the older adults with advanced cancer, pattern markers were determined at the time of enrollment into the study, and were examined over time. The type and number of pattern markers increased prior to delirium episodes in these patients.

*Research Question 4: What issues are associated with studying delirium in older adults with advanced cancer?*

Multiple issues were identified in conducting this research. The three specific issues that will be discussed are: 1) the changing nature of palliative cancer treatment in older adults; 2) methodological issues related to recruiting and measurement, and 3) the role of family caregivers in monitoring for delirium.

*Changing Nature of Palliative Cancer Treatment in Older Adults*

One of the most striking observations in conducting this research related to the nature of palliative cancer treatment among the older adults. It was either prolonged or intensive, or both. Five of the seven older adults with advanced cancer had been diagnosed for over a year prior to enrollment in the study. Each of them had received multiple courses of treatment, and in effect almost continuous treatment, from the point of diagnosis or recurrence to enrollment in the study.

Palliative cancer treatments among the older adults also were intensive. Mr. B, an 87-year old gentleman with moderate COPD, initially had chemoablation for a hepatic tumor. Although he was a high-risk surgical candidate, after a two-month recovery period, he had a hepatic lobectomy for definitive treatment. Mr. F, a 74-year old gentleman, underwent triple modality therapy, combined chemotherapy and radiation followed by surgical resection, as part of a clinical trial for esophageal cancer. His treatment was also definitive. Mrs. C, Mr. A, and Mr. G participated in clinical trials after multiple courses of treatment. Mr. D had been on and off chemotherapy for approximately 10 years. During the last four months of his life, it appeared as though he had bone marrow failure associated with long-term chemotherapy

administration. Even with intermittent transfusions, he was unable to maintain a normal hemoglobin level. Mr. E had been on hormone ablation therapy for 5 years.

The prolonged and intensive nature of palliative cancer treatment raises important questions about the impact of treatment in older adults. Over time, how does long-term cancer treatment in older adults, affect their physiological and functional reserves? How do changes in physiological and functional reserves affect treatment response and outcomes? What are the primary markers of decline in reserves? What interventions would help to prevent or slow the loss of reserves?

#### *Issues Related to Recruitment and Measurement*

In preparing to conduct the pilot study, the investigator found that he or a member of his research team needed to be involved in recruiting participants. However, it was helpful to have a supportive introduction by a care team member – physician, nurse coordinator, or clinical research nurse. Six of the seven participants in this study were recruited after a brief introduction of the study and investigator by the care provider. In this study, if prospective participants did not either agree or refuse to participate at the initial introduction of the study, then the investigator requested permission to contact them within two weeks of the initial introduction to see whether or not they would like to participate in the study.

In this study, recruitment was affected by limited human and financial resources. After enrolling a group of participants into the study, the investigator could not be both in the clinic recruiting more participants and in the field collecting data.

The timing of recruitment was also challenging. The investigator did not approach patients during “crisis” periods—at the time of a new diagnosis, just getting established with

new treatment team, making decisions about treatment, and when learning about disease progression. Because of this, some prospective participants may have been missed. Initially, functional status was going to be used as an indicator for eligibility—Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ . However, few patients with a performance status at this level are seen regularly in the oncology clinic. Also based on the findings of this study, functional status may not be a good marker. When functional status begins to drop, life-expectancy may be too short for longitudinal follow-up. If the change in function is associated with a transition into the terminal phase, the patient and family also may feel too overwhelmed to participate in research. There were challenges with recruiting hospice patients. No hospice patients were enrolled into either the pilot study or the follow-up study. Potential issues with hospice patient recruitment will be discussed in Chapter 5.

#### *Role of Family Caregivers in Monitoring for Delirium*

The prevalence of delirium in the home setting is not known, but based on clinical literature and experience it is likely a common problem. Since daily in-home delirium assessments by the investigator were not feasible, identified family caregivers were asked to monitor patients for signs of delirium and, depending on whether or not they lived with the patient, to complete the Caregiver Confusion Checklist (CCC) once or twice a day. Family caregivers were instructed to contact the investigator if two or more signs of delirium were noted. When notified, the investigator would conduct a more in-depth delirium assessment.

Caregivers demonstrated variability in completing the CCC. Some caregivers documented comments about treatment, activities, behavior, and other things. However, the caregiver comments were not always consistent with ratings on the CCC or with the

investigator's observations. For example, at times when Mrs. C's CCC score was noted as 0, her caregiver documented "didn't talk to (sic) much. Mostly quiet!" On other days, she noted that Mrs. C "stayed in the bed off and on – sleepy," but this was not reflected in the CCC score. On the day before Mr. A was positive for delirium at the scheduled weekly assessment, Mrs. A documented notes about changes in his behavior and thinking—"slept most of day" and "responses to questions are a little slow but always appropriate"—but she scored the CCC as 0. Another caregiver, Mrs. E identified and documented alterations in Mr. E's cognitive and behavioral functioning on the CCC and in her comments but did not contact the investigator because she did not want to call attention to Mr. E's impaired functioning. Mr. E was aware of his difficulties and early in the study, he told Mrs. E that he did not want her to note any problems on the CCC. He also expressed disappointment when he performed poorly on the MMSE.

Some caregivers did not complete the CCC on a regular basis. There were blank pages. As in the pilot study, when patients were hospitalized, not all caregivers completed the CCC's consistently. The investigator also occasionally noted caregivers completing several pages at the time of the weekly assessment.



## CHAPTER FIVE

### DISCUSSION

This chapter discusses the findings from this research. First, the discussion focuses on the findings related to delirium in the sample of hospitalized older cancer patients and in the older adults with advanced cancer near the end of life. Second, it discusses delirium vulnerability factors including clinical risk markers and etiologic patterns. Finally, it addresses methodological issues associated with studying delirium in older adults with advanced cancer in the outpatient or home setting. Limitations of the study and implications for future research and practice are integrated into the discussion.

#### The Nature and Course of Delirium

Delirium was common in the hospitalized older cancer patients and in the older cancer patients with advanced disease cared for at home. The prevalence and incidence of delirium in the sample of hospitalized patients were 38% and 30%, respectively. The cumulative rate of delirium was 56%. In another sample of mostly older cancer patients (median age 73 years), Tuma & DeAngelis (2000) found that 34% had confusion at admission, and another 66% developed confusion during hospitalization. In contrast, Ljubisavljevic and Kelly (2003) found a lower incidence of delirium (18%), but their patients were younger (mean age 53.4 years).

Studies of delirium in patients with advanced cancer have found that up to 90% develop delirium in the weeks preceding death (Bruera, Miller et al., 1992; Lawlor, Gagnon

et al., 2000, Massie et al., 1983, Minigawa et al., 1996; Morita et al., 2001). Findings from the secondary analysis and the case studies also show that delirium is common in older cancer patients at the end of life. Eight of the ten hospitalized older cancer patients near the end of life had delirium. In most of the patients, delirium tended to fluctuate. All of the patients with delirium during hospitalization had delirium at discharge. All of the older adults with advanced cancer who died had at least one episode of delirium.

### *Delirium Severity*

The findings suggest that older cancer patients experience different levels of delirium severity. In the hospitalized older cancer patients, 41 patients had delirium during hospitalization prior to discharge; 18 had mild delirium and 23 had severe delirium. At discharge, delirium was resolved in 13 patients, but persisted in 28—mild in 16 and severe in 12. Two additional patients who had no delirium during hospitalization had mild delirium at discharge.

All of the older adults with advanced cancer experienced delirium episodes that resolved or reversed. Reversible episodes tended to be mild and short in duration. In most cases, delirium seemingly resolved on its own without specific delirium-focused interventions. In two patients who died, delirium that preceded death was persistent and more severe.

### *Subsyndromal Delirium*

Subsyndromal delirium is common in hospitalized older patients (Cole, McCusker, Dendukuri, & Han, 2003; Levkoff et al., 1996). In the hospitalized older cancer patients, 21

patients had mild delirium (NEECHAM score 20-24) at admission. It is likely that some of these patients had subsyndromal delirium. Subsyndromal delirium also was noted in the older adults with advanced cancer. They intermittently exhibited delirium symptoms and their NEECHAM scores fell between 20 and 24, but the CAM was not positive.

Two studies of delirium in patients with advanced cancer at the end of life suggest that subsyndromal delirium is common. In a sample of hospice inpatients with cancer, Gagnon et al. (2000) found that the prevalence and incidence of delirium symptoms was higher than confirmed delirium. The prevalence of delirium symptoms was 20.2% whereas the prevalence of confirmed delirium was 13.3%. The incidence of delirium symptoms during hospitalization was 52.1%, while the incidence of confirmed delirium was 32.8%. In the current study, all of the older adults with advanced cancer had at least one positive delirium assessment (NEECHAM score 20-24 and positive CAM). In addition, six of the seven had at least one assessment indicative of subsyndromal delirium (NEECHAM score 20-24 and negative CAM). It is likely that the incidence of subsyndromal delirium in these patients is underestimated due to the frequency of assessments.

In this study, changes in behavioral performance among the older adults with advanced cancer often preceded changes in cognitive functioning and delirium. Typically, in monitoring patients for delirium, the emphasis is place on impaired cognitive functioning (attention, orientation, perception, and memory). However, while altered cognitive functioning is a primary component of delirium, it may not always be the primary manifestation. In the current study, cognitive function was often maintained except during delirium episodes and in some cases, even during delirium episodes, some aspects of cognitive functioning—orientation and memory—were minimally affected. Jenkins et al.

(2000) defined cognitive impairment on the basis of a MMSQ score less than 24/30 or less than 80% if the patient could complete only part of the test. Ten of 91 patients (11%) were found to have evidence of delirium by DSM IV criteria, despite a MMSQ score in the normal range. Behavioral changes may be primary marker of decline and risk, or an early marker of impending delirium.

Sorensen Duppils and Wikklblad (2004) found that most patients demonstrate a pattern of behavioral changes and early symptoms of approaching delirium. They monitored 103 hip surgery patients for behavioral changes prior to delirium. Of the patients who met DSM criteria, 62% exhibited behavioral changes before delirium onset. The most common behavioral changes included anxiety, disorientation, decreased psychomotor activity, memory impairment, increased psychomotor activity, frequent calls for attention, irritation, incoherent speech and reduced level of consciousness. Behavioral changes presented in some patients up to 48 hours before delirium onset, but changes were most evident and more numerous within six hours of onset.

In another study by Levkoff et al. (1994), 69% of hospitalized older patients with incident delirium had prodromal symptoms prior to developing DSM-III-defined delirium. The length of the prodromal period ranged from 1 to 19 days (*M* 2.7; *SD* 3.3). Of importance, they also found that the presence of certain delirium symptoms—disorientation or fluctuating behavior, or both—significantly increased the likelihood of developing delirium.

### *Delirium Subtypes*

Delirium in the older adults with advanced cancer was most often hypoactive. It was characterized by diminished levels of alertness and attention, and by slowed motor and verbal

behavior. Otherwise it was of the mixed subtype and included both hypoactive and hyperactive features. Mr. D's delirium episode was predominantly hyperactive. Mrs. C and Mr. G's terminal delirium episodes were classified as mixed but, in both cases, hypoactive features were predominant. Delirium subtypes were not evaluated in the sample of hospitalized older cancer patients.

In a study examining delirium subtypes in patients with advanced cancer (Lawlor et al., 1998), the hypoactive and mixed delirium subtypes were most common. The hypoactive subtype was most common in terminal delirium episodes occurring within 72 hours of death. In contrast, Steifel et al (1992) reported that the majority of patients in the last week of life had either hyperactive or mixed delirium. However, they used clinical records to identify delirium, and hypoactive delirium presentations may not have been recognized and documented.

The predominance of hypoactive delirium among the older adults with advanced cancer is important. Nurses have not been quick to identify delirious patients, particularly those with mild delirium or hypoactive presentations (Inouye, Foreman, Mion, Katz, & Cooney, 2001; Neelon, Champagne, McConnell et al., 1992). There is a widely held belief that hypoactive delirium is not as distressing for patients and their caregivers. To the contrary, in a study by Breitbart et al. (2002), although more caregivers (88%) reported distress associated with hyperactive delirium, 66% of caregivers of patients with hypoactive delirium reported severe distress. Among patients with delirium recall, hypoactive delirium was just as distressing as hyperactive delirium. In a study by Morita et al. (2004), 34% of caregivers reported that somnolence was distressing or very distressing when it occurred often or very often.

### *Delirium at Discharge and at Home*

Almost 40% of the hospitalized older cancer patients had persistent delirium at discharge; 24% had severe delirium and 16% had mild delirium. Similarly, studies of delirium in hospitalized elderly medical patients have found that a significant number of patients with delirium during hospitalization have delirium or delirium symptoms at discharge and beyond. Levkoff et al. (1992) found that 96% of patients with delirium during hospitalization had symptoms of delirium at discharge. O'Keefe and Lavan (1997) monitored patients with delirium throughout hospitalization and found that 32% had delirium symptoms at discharge. Persistent delirium also has been noted in nursing facility residents with delirium during hospitalization; 72% who survived hospitalization had delirium at discharge (Kelly et al., 2001).

The large number of older cancer patients with delirium or delirium symptoms at discharge has significant implications for post-hospital care and recovery. Naylor, Stephens, Bowles, & Bixby (2005) found that patients with cognitive impairment (delirium, dementia or both) during hospitalization and their family caregivers had multiple unmet needs in the weeks following hospital discharge. In addition, since most oncology treatment is provided in the outpatient setting, the fact that five of the older adults with advanced cancer had at least one episode of delirium at home has implications for their care and their caregivers. Delirium distresses family caregivers (Brajtman, 2003; Breitbart et al., 2002; Morita et al., 2004), in part, because patients with delirium need more assistance with self-care and require close monitoring to prevent injury.

## *Delirium Vulnerability*

### *Severity of Illness and Comorbidity*

Severity of illness and comorbidity are well recognized delirium risk factors. In this study, the hospitalized older cancer patients had a significant level of illness severity. Their mean APACHE II score (14.9) was similar to the APACHE II scores reported in samples of critically ill cancer patients (Sculier, Paesmans, Markiewicz, & Berghmans, 2000; Soares et al., 2004) and general MICU patients (Bo et al., 2003). In the hospitalized older cancer patients, those with delirium were more severely ill than those without delirium (mean APACHE II. score; 16.0 vs 13.5;  $p = 0.032$ ).

The adapted Charlson Comorbidity Index scores among the older adults with advanced cancer ranged from 1 to 3. These scores are similar to the scores found in other samples of older cancer patients. Typically, in older cancer patients, scores on the adapted Charlson are skewed and range mostly from 0 to 3 (Extermann, 2000). In a sample of 203 older cancer patients, only 36% demonstrated comorbidity when rated by the Charlson (Extermann, Overcash, Lyman, Parr, & Balducci, 1998). The median Charlson score was 0, and the range was 0-6, out of a total possible score of 25. Although widely used, the Charlson appears to be a restrictive measure of comorbidity and, therefore, may not account for some conditions or diseases that may affect treatment tolerance and response in older cancer patients. For example, renal impairment is considered a comorbidity only if the serum creatinine level is  $> 3$  mg/dl. In older adults, serum creatinine level and estimations of creatinine clearance do not accurately reflect age-associated reductions in glomerular filtration rate (Wasil & Lichtman, 2005). An older adult with cancer may have a normal

serum creatinine level, but still have renal impairment that is significant enough to require chemotherapy dose adjustments.

### *Physical Functioning*

In the older adults with advanced cancer, physical functioning declined prior to delirium episodes. The decline was most notable in ability to perform IADLs, but in many cases ability to complete PADLs also declined. Mr. G and Mrs. C continued to have progressive declines in functioning after their first delirium episodes. As their functioning decreased, they had additional delirium episodes. Prior to his death, Mr. G had multiple episodes that occurred more frequently, were longer in duration, and were more severe. Mrs. C's second delirium episode preceding death occurred after a steady decline in her physical functioning. At the time of her second delirium episode, her IADL and PADL scores were 0, and her PPS score was 20.

Mercadante et al. (2000) reported similar patterns of increasing delirium symptoms with decreasing function among a sample of 370 patients in a home palliative care program. Symptoms such as drowsiness, weakness, and confusion increased as the cancer progressed and peaked when performance status, as measured by the Karnofsky Performance Scale (KPS), dropped to lower levels. Drowsiness and weakness increased in frequency and severity from KPS 70 to KPS 10. Drowsiness increased significantly at KPS 40, and weakness at KPS 50. Confusion was rare early on but became progressively more frequent and more severe as performance status dropped from KPS 40 to KPS 10—80% of patients at KPS 10 were severely confused.



In the hospitalized older cancer patients, patients with delirium had more functional impairment in IADLs than those without delirium. Patients with delirium resolution were less functionally impaired than those with persistent delirium.

### *Symptom Prevalence and Symptom Distress*

Overall, symptom prevalence and distress fluctuated in the older adults with advanced cancer. While no distinct pattern was observed, in some cases, it appeared as though there may have been interrelationships between physical symptoms—such as fatigue, nausea, vomiting, shortness of breath, and pain—and altered cognitive functioning, and between psychological symptoms and altered cognitive functioning. Cleeland et al (2000) used hierarchical cluster analysis to identify clustering of symptom items from the symptom responses of 527 outpatients receiving cancer treatment. They found a close relationship between clusters of cognitive symptoms and affective symptoms. They also found that a fatigue-related symptom cluster was more closely associated with cognitive and affective symptoms than with other physical symptoms clusters.

As noted above, symptoms like decreased appetite, taste changes, nausea, vomiting, and dry mouth increase metabolic-nutritional risk. In addition, symptoms associated with either decreased fluid intake or increased fluid loss also contribute to orthostatic-dehydration risk. Additional research is needed to more closely examine the complex interrelationships between physical and psychological symptoms, and cognitive symptoms and delirium. As suggested in the study by Cleeland et al., specific-symptom clusters may exist. If so, effective management of the physical and psychological symptoms in the clusters may help to prevent or minimize cognitive symptoms and delirium.

## *Etiologic Patterns and Risk Markers*

### *Metabolic-Nutritional Pattern*

Findings from this research indicate that nutritional risk is a significant problem in older cancer patients. Ninety percent of the hospitalized older cancer patients had metabolic-nutritional risk markers. All ten patients in the subsample who were near the end of life had metabolic-nutritional markers. Six of the seven older adults with advanced cancer had risk markers at baseline, and all had metabolic-nutritional markers prior to their first delirium episodes.

Serum albumin levels and lymphocyte counts were indicative of nutritional risk, but weight loss was the primary risk marker. All but one of the older adults with advanced cancer had significant weight loss—greater than 10% of body weight or 5 kg—either prior to the study or over the course of the study. Five had experienced weight loss prior to enrollment in the study. During the study, two patients, who lost weight initially, gained because of fluid retention—ascites and pedal edema.

Nutritional impairment and weight loss in cancer patients with advanced disease are complex and multifactorial. Typically, in the cancer treatment setting, nutritional intervention and other supportive measures are subsidiary to the cancer treatment itself. The findings from this research indicate that there is a critical need for early intervention to prevent or correct nutritional impairment.

Although limited by small sample size, several studies have shown the effectiveness of nutritional interventions—nutritional assessment, dietary counseling, and nutritional supplements—in patients receiving cancer treatments. Odelli et al (2005) implemented a nutrition pathway in patients with esophageal cancer receiving chemoradiation. Patients were

provided appropriate intervention based on assessed nutritional risk: preventive counseling (low risk), oral nutrition supplements (moderate risk), and enteral feeding (high risk). Outcomes in 24 patients treated before using the nutrition pathway were compared to outcomes in 24 patients treated with the pathway. Patients treated with the nutrition pathway had decreased weight loss, greater radiation therapy completion rates, fewer unplanned hospital admissions, and, when hospitalized, a shorter length of stay. In a randomized trial, Isenring, Capra, and Bauer (2004) evaluated the impact of an early nutritional intervention in GI and head and neck cancer patients receiving radiation therapy. The nutritional intervention involved individualized, intensive nutrition counseling by a dietician and oral supplements, if indicated. Sixty patients were randomized to receive either the nutrition intervention or usual care. Patients who received the nutritional intervention experienced less declines in weight, nutritional status, global quality of life, and physical function. In a pilot study, Bauer and Capra (2005) found that an 8-week nutritional intervention comprised of weekly dietary counseling and consumption of a protein- and energy-rich nutritional supplement with eicosapentaenoic acid (EPA) improved dietary intake, lean body mass, functional capacity, and quality of life in seven patients with advanced pancreatic and non-small cell lung cancer.

The older adults with advanced cancer frequently reported the presence of and distress associated with symptoms that negatively affect nutritional status: lack of appetite, taste changes, nausea and vomiting, and diarrhea (Grant & Kravits, 2000). The timely and effective management of symptoms associated with nutritional risk is paramount in preventing and minimizing nutritional impairment.

### *Hypoxic Pattern*

Hypoxic risk factors also were common in both groups of patients—the hospitalized older cancer patients and the older adults with advanced cancer. In the hospitalized patients, having hypoxic markers significantly increased the risk of developing delirium when compared to those without hypoxic markers. Other studies of delirium in hospitalized cancer patients (Tuma & DeAngelis, 2000) and in patients with advanced cancer (de Stoutz, Tapper, & Fainsinger, 1995; Lawlor et al., 2000; Morita et al., 2001) identified hypoxia as a cause of delirium, which is important because hypoxia is potentially treatable. Neelon, Ng’andu et al. (1996) found that delirium resolved within 24 hours in a significant number of hypoxic patients treated to improve oxygenation. Aakerlund and Rosenberg (1994) found that hypoxemia was the sole cause of post-operative delirium in 5 thoracic surgery patients, and that delirium resolved in all after treatment with supplemental oxygen. de Stoutz et al. (1995) reported that delirium resolved in four terminally ill cancer patients in whom hypoxia was treated.

### *Metabolic-Toxic Pattern*

Metabolic-toxic markers were present at admission in 40% of the hospitalized older cancer patients. Four of the 8 hospitalized patients near the end of life who had delirium exhibited metabolic-toxic pattern markers. In the older adults with advanced cancer, at baseline, two patients had pattern markers; three more acquired markers prior to developing delirium. Four patients had markers indicative of impaired liver or renal function, and three had a serum albumin level  $\leq 3.0$  g/dl. Mr. G did not have a recent albumin level documented in his medical record, but it is likely that his albumin level dropped over the course of the

study as his cancer progressed and as he experienced significant weight loss and nutritional impairment.

The metabolic-toxic pattern is important in older cancer patients because it has significant implications for drug distribution, metabolism, and elimination. At enrollment into the study, the older adults with advanced cancer were taking a large number of medications including those for cancer treatment, for symptom management, and for comorbid diseases and medical conditions. In many cases, multiple medications were added throughout the study.

#### *Orthostatic-Dehydration Pattern*

Common in older adults, dehydration is a well known risk factor for delirium (Mentes, 2006; Mentes, Culp, Maas, & Rantz, 1999; Sheehy, Perry, Cromwell, 1999). Older cancer patients are at risk for dehydration due to age-related physiological changes, the effects of cancer and its treatment, comorbid medical conditions, medications, and symptoms associated with decreased fluid intake and increased fluid loss such as nausea, vomiting, diarrhea, decreased appetite, and taste changes.

Orthostatic-dehydration markers were common in the older cancer patients, particularly in those near the end of life and those with advanced cancer. Thirty six percent of the hospitalized older cancer patients had orthostatic-dehydration markers at admission. Six of the 8 hospitalized patients near the end of life who had delirium exhibited pattern markers, and all of the older adults with advanced cancer had orthostatic-dehydration pattern markers prior to developing delirium. These findings suggest that the orthostatic-dehydration pattern is particularly important in patients with advanced disease.

An abundance of clinical literature addresses concerns about providing artificial hydration at the end of life. The discussion tends to focus on ethical issues related to withholding and withdrawing treatment and other issues such as thirst, quality of life, and prolonging survival. The focus on preventing and managing delirium has been limited.

Studies suggest that hydration in patients with advanced cancer may play an important role in maintaining cognitive functioning and minimizing delirium, particularly in those receiving high doses of opioids, but results have been mixed. Bruera, Franco, Maltoni, Watanabe, and Suarez-Almazor (1995) retrospectively compared the prevalence of agitated delirium in an inpatient palliative care unit before and after the implementation of routine cognitive assessment, and opioid rotation and hydration to manage delirium (cognitive failure). Prior to implementation, agitated delirium occurred in 26% of patients compared to its occurrence in 10% of patients after the implementation. They also found a reduction in the use of neuroleptics and benzodiazepines during the period following implementation. In a similar comparison study, Morita et al. (2003) found that the occurrence of agitated delirium in the last week of life did not change significantly during a period with increased opioid rotation and hydration. In a more recent randomized study, Bruera et al. (2005) found that patients with clinical evidence of mild to moderate dehydration who received 1000 ml of fluid had improvement in myoclonus and sedation compared to patients who received a placebo with 100 ml, but there were no significant differences in improvement in hallucinations or fatigue.

In two studies of delirium in advanced cancer (Lawlor, Gagnon et al., 2000; Morita et al., 2001), treatments were targeted at delirium etiologies. Interventions included opioid rotation for opioid toxicity, rehydration, medication changes, antibiotics for infection,

bisphosphonates for hypercalcemia, and neuroleptics and, if needed to control agitation, benzodiazepines. Lawlor, Gagnon, et al. reported using hydration in patients with clinical or laboratory evidence of dehydration, whereas Morita et al. reported using hydration in conjunction with opioid rotation for opioid toxicity. Reported delirium resolution rates in both studies were positive. In the study by Lawlor, Gagnon, et al., 49% of delirium episodes reversed. Delirium caused by psychoactive medications, including opioids, and dehydration was associated with reversibility. Morita et al. reported symptom improvement in 77% of episodes and complete reversal in 20%. Reversal was higher in delirium related to medications and hypercalcemia. Delirium reversal in episodes associated with other pathologies, including dehydration, was low. The contradictory findings related to delirium reversal and dehydration may result from differences in treatment protocols.

#### *Chronic Cognitive Impairment Pattern*

Preexisting cognitive impairment is a widely recognized risk factor for delirium in medically-ill older adults (Duppils & Wikblad, 2000; Eden et al., 1998; Fisher & Flowerdew, 1995; Francis et al., 1990; Galanakis et al., 2001; Inouye et al., 1993; Pompei et al., 1994; Rahkonen et al., 2001; Rockwood, 1989; Schor et al., 1992). The prevalence of delirium in hospitalized and community-dwelling older persons with dementia ranges from 22-89% (Fick, Agostini, & Inouye, 2002). Ljubisavljevic and Kelly (2003) found that impaired cognitive function was a risk factor for delirium in hospitalized cancer patients.

In the current study, only a small number of the older cancer patients had chronic cognitive impairment. Five patients (6%) in the sample of hospitalized older cancer patients exhibited chronic cognitive impairment at admission. Based on their admission NEECHAM

scores, one patient was at risk for delirium (NEECHAM score  $\geq 25$ ), one had mild delirium (NEECHAM score 20-24), and the other three had severe delirium (NEECHAM score  $< 20$ ). At some point during hospitalization, all of the patients with chronic cognitive impairment had severe delirium. Importantly, at discharge, delirium had improved in three of the five patients, suggesting that even in patients with chronic cognitive impairment, delirium is potentially reversible.

One of the older adults with advanced cancer had reported baseline cognitive impairment. During the study, he had one positive delirium assessment that occurred at a weekly scheduled visit the morning after he returned late the previous evening from an out-of-state trip to visit with one of his children and grandchildren and to attend his sister's funeral. According to his wife and CCC scores, he had additional signs of confusion and impaired cognitive functioning during the study but the investigator was not notified at the time.

In summary, older cancer patients likely have an increased baseline vulnerability or risk for delirium at the time of cancer diagnosis due to age-related physiological changes in multiple organ systems and comorbid medical conditions. Findings from this study suggest that vulnerability increases over time with treatment or disease progression. For example, all of the older adults with advanced cancer exhibited an increase in number of pattern markers prior to their delirium episodes except in the participant with chronic cognitive impairment. In the hospitalized older cancer patients, patients with delirium had more etiologic patterns compared to those without delirium. Therefore, the risk for delirium increases with a greater number of risk markers and patterns. Similarly, Inouye et al. (1993) found that delirium risk increased progressively as the number of risk factors multiplied: cumulative rate of delirium



in patients with no risk factors was 9%; with 1-2 risk factors, 23%; and with 3-4 factors, 83%. Although not examined in these studies, the contribution of specific combinations or clusters of risk markers and patterns may play a key role in determining delirium risk.

Multiple risk markers and etiologic patterns were common in the hospitalized older cancer patients and in the older adults with advanced cancer. Identification of clinical risk markers and etiologic patterns provide specific targets for interventions to prevent and manage delirium in older cancer patients.

### *Methodological Issues*

Descriptive research and qualitative research is used to better understand a problem, to generate hypotheses, and to identify new and important questions about the problem (Grimes & Schulz, 2002; Malterud, 2001a; Malterud, 2001b). This research provides a necessary step to better understand delirium in older cancer patients. It is among the first to examine delirium, specifically in a sample of hospitalized older cancer patients, and to look at delirium in older adults with advanced cancer cared for at home. Findings from the study highlight the magnitude of delirium and delirium vulnerability in older cancer patients, and provide directions for further research and intervention.

Delirium research is methodologically complex and requires significant resources. The longitudinal, multiple case-study, descriptive design using quantitative and qualitative methods facilitated the intense examination of delirium and delirium vulnerability in a small number of older adults with advanced cancer near the end of life.

## *Recruitment*

Limited resources for recruitment and data collection and refusals to participate inhibited the ability to include more cases. Twenty seven patients were approached in the medical oncology clinic regarding participation in the study. Thirteen patients refused to participate either at the initial contact or at follow-up. Four patients were lost to follow-up. One patient's condition declined before he could be enrolled, and two others expressed an interest in study participation but were deemed ineligible—one lacked contact with a regular caregiver and the other was found to have stable disease after further work-up. Patients and family caregivers reported the following reasons for refusal: feeling overwhelmed or too ill, the longitudinal nature of study and weekly commitment, and a lack of understanding about the nature of study. Patients or family members often stated that they (or the patients) were “not having any problems with that right now.”

No hospice patients were enrolled in the pilot study or the follow-up study. Others have described the challenges associated with recruiting and enrolling hospice patients and others into palliative care and end-of-life research (Ewing et al., 2004; Jordhoy et al., 1999; McMillan & Weitzner, 2003). In the current research, the investigator was not directly involved in recruiting hospice patients. The hospice team members (clinical supervisor, nurses, and social worker) agreed to introduce the study to patients and caregivers. In the pilot study they provided a recruitment flyer and stamped envelope, so that those who were interested in study participation could provide contact information to the investigator. This process was changed in the follow-up study. The hospice team members agreed to introduce the study to patients and caregivers, provide them with study brochure, and see if they were willing for the hospice team member to provide the investigator with contact information for

follow-up.

Specific barriers to hospice patient recruitment were not determined. Because research is uncommon in the hospice setting, the hospice nurses may have been unfamiliar with conducting research and they may have felt uncomfortable approaching patients and families about research participation. Another potential barrier to hospice recruitment may be that the transition to hospice care is a crisis period for patients and their families, and that during this period, patients and their families are not able to entertain participating in research. The hospice program in the current study was small with an average daily census around 40 patients, so during the recruitment period, the number of eligible patients may have been limited.

In another study, Kirsh et al. (2004) surveyed 225 hospice nurses to elicit their views on conducting end-of-life research with hospice patients and families. The nurses indicated an openness to research in the hospice setting, but they acknowledged protective attitudes (wanting to control access to patients) and concerns about time constraints. Education and hands-on participation in research in the hospice setting may help address these barriers and counter common beliefs against research with hospice patients and families.

Recruitment in the medical oncology clinic provided benefits, but at times it was difficult to identify the most appropriate patients—those near the end of life. It allowed the investigator to capture the transition from active palliative treatment into the terminal phase. Earlier enrollment also may have prevented attrition at this transition, enabling the investigator to continue the research until death. When patients and families transitioned into the terminal phase, they were familiar with the research protocol and had established a relationship with the investigator. All of the patients and caregivers reported that

participation in the research was beneficial. The frequent assessments and visits from the investigator, who was also a nurse, provided reassurance and support.

Recruitment during the period of active palliative treatment also allowed the investigator to identify whether patients experience cognitive changes and delirium earlier in the treatment course prior to the terminal period. The findings from this study suggest that they do. While the older adults with advanced cancer were at different points in their illness trajectories, all developed delirium. Delirium that occurred prior to the terminal period tended to be mild and transient, and associated with multiple factors. In most cases, it resolved spontaneously as the contributing factors were eliminated or as physiological mechanisms are corrected or restored.

### *Measurement*

Routine screening and monitoring is the first step in the early identification of delirium. Earlier identification could lead to earlier intervention, and improved outcomes. The use of a validated delirium instrument with frequent direct observations is recommended for identifying and monitoring delirium. However, this approach may not always be feasible, especially in the outpatient setting. Today, many older cancer patients are being cared for primarily at home by family members. Therefore, there is a need to develop a methodology to detect and monitor delirium in the home setting. It is a key to advancing delirium research in older cancer patients and to improving their care.

A baseline of cognitive and behavioral functioning is critical for recognizing subtle changes associated with subsyndromal or mild delirium. Therefore, family caregivers may play a key role in identifying early changes and signs of delirium before they progress to

more severe delirium. Fick and Foreman (2000) reported some evidence that family members recognized early changes in behavior in patients that developed delirium.

In the current study, family caregivers were asked to monitor patients for signs of delirium and to complete the Caregiver Confusion Checklist (CCC) once or twice a day. Family caregivers were instructed to contact the investigator if two or more signs of delirium were noted. When notified, the investigator would conduct a more in-depth delirium assessment. Caregivers demonstrated variability in completing the CCC. Some caregivers wrote additional comments that were helpful in understanding what was going on with the patients.

Additional research is needed to study and to establish the role of family caregivers in monitoring for and supporting patients with delirium at home. Educational interventions may help caregivers better understand delirium risk in patients with advanced cancer and increase their ability to identify early changes in cognitive and behavioral functioning associated with developing delirium. Gagnon et al. (2002) developed and provided a psycho-educational intervention to help family caregivers of patients with advanced cancer to better understand and cope with delirium. Caregivers who received the intervention demonstrated an understanding of what delirium is and reported increased confidence in their ability to react appropriately to delirium symptoms. The majority indicated that all family caregivers of patients with advanced cancer should be informed about delirium and delirium risk.

Other measurement concerns relate to the validity and reliability of self-report data in patients with advanced disease and variability in cognitive functioning. Self-reporting may be influenced by environmental, psychologic, physiologic, and pharmacologic factors. Steihauser, Clipp, & Tulsky (2002) point out the problem of non-response bias in end-of-

life research. In the current study, non-response was a problem at times because patients cancelled data collection visits, or they refused to respond to certain questions, or they were not able to respond, or the investigator eliminated instruments in order to decrease participant burden. The use of caregivers as proxy respondents and the use of multiple data sources and data collection techniques can help to address this problem. For example, in this study, the collection of qualitative data (observations and caregiver notes) helped to provide a better understanding of a patient's condition and experience.

This study used multiple instruments with different scaling. In some cases, it made comparison and interpretation of the data more difficult. However, the graphic techniques used in the analysis allowed for visual examination of trends in and among the data.

Another problem encountered in data collection was the inability to obtain accurate, detailed, and specific information about medication use. Most patients were self-administering their medications until their condition or functioning declined. At the time of enrollment, Mr. G was managing a complex medication regimen that included multiple opioids for pain control. After his first delirium episode, the hospice nurses started filling a pill box, and his caregivers began to administer his regularly scheduled medications including long-acting opioids. Mr. G continued to self-administer his short-acting opioids for breakthrough pain. He was not able to accurately report when and how much medication he took over a period of time.

The investigator did not implement pill counts due to intrusiveness. However, this strategy may be necessary in order to accurately monitor medication use. When family caregivers began to administer medications, the investigator provided them with a medication log that could be used to document when medications were given. It was intended not only to

help determine the frequency and dosage of medications administered but also to help caregivers keep track of medication administration.

### Maintaining Reserves in Older Cancer Patients

One of the most striking observations among the older adults with advanced cancer was the prolonged and intensive nature of palliative cancer treatment and its impact on physiological, biochemical, and cognitive reserves. Most of the older adults with advanced cancer received multiple courses of cancer treatment over many years. Others who were more recently diagnosed underwent intensive first line treatment regimens. Findings from this study indicate that functional reserves and reserve capacity are depleted over time in the setting of prolonged and intensive cancer treatment. Diminished reserves lower the threshold of vulnerability in these patients, placing them at increased risk for cognitive and functional decline, delirium, and other poor outcomes.

In older cancer patients, intense and effective supportive care must begin early—at the time of diagnosis—and focus on preventing reserve loss and treatment-related complications. Loss of reserves may be inevitable in older adults with advanced cancer as they approach the end of life. However, early supportive care that continues throughout the treatment course may help to maintain reserves for as long possible.

The findings from this study suggest that the key components of supportive care should include monitoring for and addressing changes in behavior and cognitive and physical function, ongoing nutritional assessment and intervention, monitoring and maintaining adequate hydration, medication management, timely identification and effective management of physical and psychological symptoms, and management of other comorbid medical

conditions. A comprehensive, multicomponent supportive care program would likely have a positive impact on treatment tolerance, cognitive and physical functioning, and overall quality of living and dying.



## Appendix A

### MD Permission Letter and Recruitment Materials



March 15, 2005

Dr.  
Associate Professor  
Division of Hematology/Oncology  
CB#7305, 3009 Old Clinic Building

Dear Dr.:

I am conducting a study to examine and describe the predisposing factors, clinical presentation, and trajectories of delirium in older adults with advanced cancer. I will recruit 15 older adults ( $\geq 65$  years of age) with advanced disease from medical oncology clinics at UNC Hospitals. Participants will be followed for up to 6 months and will undergo weekly in-home assessments with a protocol that uses minimally-invasive instruments and methods to measure a variety of cognitive, behavioral, functional, psychological, and physiological parameters. In addition, family caregivers will complete a short confusion checklist at least once a day. If signs of confusion develop, family caregivers will notify me and I will complete a more in-depth delirium assessment. If new symptoms develop or if changes in a patient's condition are identified, the patient and/or family caregiver will be instructed to follow-up with their medical care provider in the usual manner. The feasibility and burden of the protocol was pilot tested in 3 older adults with advanced GI cancer. Patients and caregivers reported minimal physical or psychological burden with the protocol or data collection procedures. Although no patients developed delirium during the pilot, all either reported or exhibited multiple cognitive symptoms – possible indicators of early delirium or increased delirium risk.

The study has been approved by the Oncology Protocol Review Committee at the Lineberger Comprehensive Cancer Center and the UNC Nursing Institutional Review Board. An abstract of the study and eligibility criteria are enclosed for your review. The study will be monitored by my doctoral research committee and Dr. Steve Bernard, who is a co-investigator.

I am asking for your permission to approach your patients for participation in this study. As you know, older adults with advanced cancer are at increased risk for developing delirium and other cognitive changes associated with their disease and its treatment or other comorbid medical conditions. This descriptive study will improve our understanding of delirium and associated factors in this population. It will also help us to begin to differentiate between potentially reversible delirium caused by correctable pathophysiological mechanisms and irreversible delirium heralding imminent death. An improved understanding of delirium will result in its earlier recognition and treatment.

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THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL  
Biobehavioral Laboratory □ CB#7460, Carrington Hall □ Chapel Hill, NC 27599-7460  
PHONE: 919-966-7598

The identification of risk factors and etiologic mechanisms will provide targets for interventions to prevent and manage delirium. Finally, the ability to differentiate between potentially reversible and irreversible delirium will promote the use of appropriate management strategies consistent with the goals of care and will enable clinicians to better educate and support patients and their family caregivers.

I hope you will grant me permission to approach your patients. Your assistance is crucial to the success of this study. I greatly appreciate your consideration and will be happy to answer any questions or provide additional information. You may contact me by phone at (919) 966-7598 or (919) 636-0122 or by email at [bond@email.unc.edu](mailto:bond@email.unc.edu). As a small token of my appreciation, I will acknowledge your assistance and provide you with any abstracts or publications resulting from this research. I will follow-up with you by email in the near future to ascertain your response.

Sincerely,

Stewart M. Bond, RN, MSN, AOCN  
Doctoral Candidate  
UNC School of Nursing



**Are you an adult (65 years or older) with advanced cancer who would like to help nurses learn more about delirium or acute confusion in older cancer patients?**

If SO.....you and a family caregiver (spouse/partner, sibling, or adult child) are invited to participate in the **Delirium and Cancer Study**, a research project being conducted by nurse researchers at the UNC School of Nursing.

The purpose of the study is to learn more about delirium or acute confusion in older adults with advanced cancer. Delirium (acute confusion) is characterized by new or unusual thoughts, feelings, behaviors, memory problems, or changes in alertness that come on over a short period of time.

You would participate in visits that will be done once a week for no longer than 6 months. Each visit will be in your home at a time that is convenient for you and your caregiver and will last about 1-2 hours. You will be asked questions about your ability to think and care for yourself. You will also be asked questions about your sleep and about other symptoms that may be bothering you. You will have your blood pressure, temperature, heart rate, oxygen level, and body fluid status checked. Your family caregiver will complete a confusion checklist at least once a day. Additional in-home visits may be done if you have any signs of delirium or confusion.

You will receive gift cards or monetary compensation for your time and assistance.

If you are interested in learning more about the study, please contact:

Stewart M. Bond, RN, MSN by cell phone at (919) 636-0122 **OR** by phone at (919) 929-8738 **OR** by email at [bond@email.unc.edu](mailto:bond@email.unc.edu) **OR** you may complete the rest of this form and mail it to me in the self-addressed stamped envelope provided and I will contact you.



Name: \_\_\_\_\_

*Please Print*

Address: \_\_\_\_\_

*Street Address*

*City*

*State*

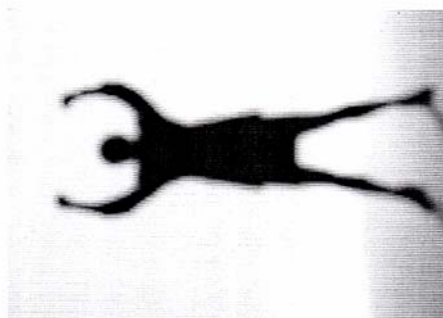
*Zip Code*

Phone Number: \_\_\_\_\_

APPROVED BY THE NURSING IRB  
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

APPROVED 5.25.05 EXPIRES 3.11.06

Are you an **adult (65 years or older) with advanced cancer** who would like to help nurses learn more about delirium or acute confusion in older cancer patients?



If so....you and a family caregiver may be eligible to participate in the **Delirium and Cancer Study** a research project being conducted by nurse researchers at the UNC School of Nursing.

APPROVED BY THE NURSING IRB  
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

APPROVED 5-26-05 EXPIRES 3-11-06 *by*



The University of North Carolina at Chapel Hill



## Why is Delirium a Problem in Persons with Advanced Cancer?

Patients with advanced cancer may experience delirium. Delirium is a



potentially reversible condition. Delirium in patients with

advanced cancer is often caused by multiple factors including:

- the effects of cancer or its treatment, such as:
  - o medication side effects
  - o imbalance of salts and chemicals in the body
  - o nutritional impairment
  - o kidney, liver, lung, or heart problems
  - o infection
- other medical conditions

Delirium can be distressing to both the person with cancer and their family. Patients with delirium may:

- experience unusual thoughts, feelings, and behaviors
- have problems with their



thinking, memory, attention, awareness, and level of alertness

- experience emotional ups and downs



- be irritable, anxious, or depressed
- see or hear things that may not real
- be agitated and restless or, on the contrary, be withdrawn and have slowed reactions
- have alterations in their sleep patterns – staying awake at night and sleeping more during the day

## What is the Delirium and Cancer Study?

The purpose of the study is to learn more about delirium or acute confusion in older adults with advanced cancer.

You will participate in scheduled visits once a week. A nurse researcher will come to your home at a time



that is convenient. Each visit will last about 1-2 hours.

During each visit, the nurse researcher will ask you questions about your ability to think and care for yourself. You will also be asked questions about your sleep, and about other symptoms you may be experiencing. The nurse researcher will check your blood pressure,

temperature, oxygen level, and body fluid status. No needles will be used. Each day



your family caregiver will complete a confusion checklist. Additional visits may be done if needed.


If you are interested in learning more about the study, please contact:

**Stewart M. Bond, RN, MSN, AOCN**  
**(919) 636-0122**  
**(919) 929-8738**  
**bond@email.unc.edu**

Appendix B

Institutional Review Board Approvals

# Memorandum

To: Stewart Bond  
CC: Virginia Neelon  
From: Mary R. Lynn   
Nursing IRB Chair  
Date: 3/11/2005  
Re: Expedited IRB Protocol Review

Review of IRB 922-05 Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

The IRB has completed review of your IRB application and has approved it as "expedited" with a renewal date of March 11, 2006. It was determined that the subjects in this study are at no greater risk than exists in their daily lives (no greater than minimal risk) and there may be no direct benefit to the subjects. Additionally a Limited Waiver of HIPAA is granted for this study for recruitment purposes.

While the IRB will oversee the conduct of your study from the perspective of the protection of human subjects, you remain responsible for the conduct of your research in accordance with the Federal regulations governing the conduct of research with human subjects. This requirement applies equally to all UNC-CH staff, faculty and students. Please be sure that you are aware of these regulations (Code of Federal Regulations, 45 CFR 46), which can be found at the URL address noted below as well as the UNC-CH requirements also referred to below.

Your interactions with the IRB will revolve around changes in your study protocol, adverse events, should any occur, and renewals and project closure. If your **study protocol changes** in such a way that your subjects are treated differently than in the original proposal, you must submit a modification, the form for which can be found on the OHRE web page ([ohre.unc.edu](http://ohre.unc.edu)). Once the modification has been approved you may proceed with the alteration in your protocol.

It is important to note that most addenda require changes in the consent form(s) as well. When consent forms are submitted for review you must submit three different consents – the current one in use, the revised consent with all changes from the previous one noted (bolded, shaded, etc) and the final proposed consent (2 copies). One copy of the approved consent form will be stamped, indicating its expiration date, and returned to you.

**An adverse event**, unanticipated problems or serious adverse events involving risk to human subjects, must be reported to the IRB immediately. Please send the report to the IRB noting it should that it should be given to me.

Each year your study must be **renewed** with the IRB. If there have been a substantial changes in the past year (for which addenda should already have been submitted), you will update your IRB application by incorporating all changes in the protocol, citing the addenda that allowed those

Mary R. Lynn, PhD ([mary\\_lynn@unc.edu](mailto:mary_lynn@unc.edu))  
UNC-CH School of Nursing  
CB # 7460 Chapel Hill, NC 27599-7460



March 11, 2005

changes. Additionally you will submit **an original copy** of any consent form to be used in the next year so it can be stamped. Consent forms are only approved for one year at a time.

If additional personnel become involved with your project, they must meet the human subjects educational requirement in effect at the time they are brought into the study. Please submit to the IRB the ORS certificate for any new research team members. At the current time meeting this requirement is a "one time" event, so once someone has done so there is no need to renew his or her "credentials."

Finally, study **termination** occurs when you no longer will have any access to the subjects and there are no ongoing data analyses warranting the IRB remaining involved. You will complete a brief final report for the IRB to close the study. It is important to note that you must maintain records in accordance with the policy of the University of North Carolina at Chapel Hill, which includes the long-term storage of the original data and consent forms on the UNC-CH campus for a minimum of 5 years. Students may have a copy of the data from their research, but the original copies must be left in the possession of the University. A student's faculty advisor bears the responsibility of being sure this occurs. Additional UNC-CH requirements can be found at the URL also listed below.

As is always the case, if you have any question about the IRB status of your study or any questions related to human subjects, please call me at 966-5450.

**OSR – Responsible Conduct of Research Information**

[http://research.unc.edu/red/responsible\\_conduct.pdf](http://research.unc.edu/red/responsible_conduct.pdf)

**Code of Federal Regulations, 45 CFR 46**

<http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm>



THE UNIVERSITY  
of NORTH CAROLINA  
at CHAPEL HILL

OFFICE OF HUMAN  
RESEARCH ETHICS

NURSING INSTITUTIONAL  
REVIEW BOARD (IRB)

213 CARRINGTON HALL  
CAMPUS BOX 7460  
CHAPEL HILL, NC 27599-7460

T 919.966.8520  
F 919.966.2286  
<http://ohre.unc.edu>

To: Stewart Bond  
CC: Virginia Neelon (Faculty Advisor)  
Date: May 25, 2005  
From: Mary Lynn  
Chair, Nursing IRB

IRB Number: 922-05

Title: Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

Subject: Approval of Modification

The modification of your research project dated May 20, 2005 and received on May 20, 2005 has been reviewed and approved under an expedited procedure because it involves only a minor change to approved research.

Inclusion criteria changed to include patients diagnosed with any advanced non-hematologic malignancy including but not limited to lung, GI tract, breast, head and neck, ovarian, and tumors of unknown primary origin.

Study Protocol has been changed so that for patient's who live alone, the family caregiver will complete the Caregiver Confusion Checklist at least once a day instead of twice a day.

Inducements for Participation has been increased from \$20 (gas cards and long distance telephone cards) to \$25 (gas cards, telephone cards, or cash). Incentive schedule has been changed so that payments will be given after the baseline visit and each month while enrolled in the study.

NOTE:

(1) This Committee complies with the requirements found in Title 21 Part 56 of the Code of Federal Regulations and Title 45 Part 46 of the Code of Federal Regulations. The Nursing IRB's Federalwide Assurance Number is FWA-4801, IRB No. IRB540.

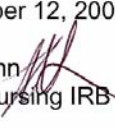
(2) Re-review of this proposal is necessary if (a) any significant alterations or additions to the proposal are made, OR (b) you wish to continue research beyond the expiration date.

# Memorandum

To: Stewart Bond

CC: Virginia Neelon

Date: September 12, 2005

From: Mary Lynn   
Chair, Nursing IRB

IRB Number: 922-05

Title: Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

Subject: Approval of Modification

The modification of your research project has been reviewed and approved under an expedited procedure because it involves only a minor change to approved research.

Modification is to extend the length of the study from 6 months to an additional 6 months on a case-by-case basis. Patients currently in the study have expressed a desire to remain in the study past their 6 month initial enrollment.

## NOTE:

(1) This Committee complies with the requirements found in Title 45 Part 46 of the Code of Federal Regulations. The Nursing IRB's Federalwide Assurance Number is FWA-4801, IRB No. 540.

(2) Re-review of this proposal is necessary if (a) any significant alterations or additions to the proposal are made, OR (b) you wish to continue research beyond the expiration date.

Mary R. Lynn, PhD (mary\_lynn@unc.edu)  
UNC-CH School of Nursing  
CB # 7460 Chapel Hill, NC 27599-7460  
919-966-5450

# Memorandum

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To: Stewart Bond

Date: November 22, 2005

From: Mary Lynn  
Chair, Nursing IRB

IRB Number: 922-05

Title: Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

Subject: Approval of Modification

The modification of your research project submitted on November 18, 2005 has been reviewed and approved under an expedited procedure because it involves only a minor change to approved research.

The approved modification was submitted to extend recruitment to UNC Hospice and to recruit a potential of five hospice patients.

**NOTE:**

(1) This Committee complies with the requirements found in Title 45 Part 46 of the Code of Federal Regulations. The Nursing IRB's Federalwide Assurance Number is FWA-4801, IRB No. 540.

(2) Re-review of this proposal is necessary if (a) any significant alterations or additions to the proposal are made, OR (b) you wish to continue research beyond the expiration date.

Mary R. Lynn, PhD (mary\_lynn@unc.edu)  
UNC-CH School of Nursing  
CB # 7460 Chapel Hill, NC 27599-7460  
919-966-5450

# Memorandum

To: Stewart Bond

Date: March 8, 2006

From: Mary Lynn  
Chair, Nursing IRB

IRB Number: 922-05

Title: Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

Expiration Date: March 11, 2007

Subject: Expedited Protocol Approval Notice-Renewal

The renewal of your research protocol has been reviewed and approved under the expedited procedure since it involves only minimal risk to human subjects. The renewal is valid through the expiration date noted above.

## NOTE:

(1) This Committee complies with the requirements found in Title 45 Part 46 of the Code of Federal Regulations. The Nursing IRB's Federalwide Assurance Number is FWA-4801, IRB No. IRB540.

(2) Re-review of this proposal is necessary if (a) any significant alterations or additions to the proposal are made, OR (b) you wish to continue research beyond the expiration date.

Mary R. Lynn, PhD (mary\_lynn@unc.edu)  
UNC-CH School of Nursing  
CB # 7460 Chapel Hill, NC 27599-7460  
919-966-5450

## Appendix C

### Patient and Caregiver Consent Forms





## CONSENT TO PARTICIPATE IN A RESEARCH STUDY

### Trajectories and Patterns of Delirium in Older Adults with Advanced Cancer

Principal Investigator: Stewart M. Bond, RN, MSN, AOCN  
Coinvestigator: Virginia J. Neelon RN, PhD

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You are invited to take part in a research study being conducted by Stewart Bond, a doctoral student in the School of Nursing at the University of North Carolina at Chapel Hill and Dr. Virginia Neelon. Fifteen older cancer patients and their family caregivers will take part in the study.

**Purpose:** The purpose of this research study is to learn more about delirium or acute confusion (any new or unusual thoughts, feelings, behaviors, memory problems, or changes in alertness that come on over a short period of time) in older adults with advanced cancer.

**Duration and Procedures:** The entire study will last for no longer than 6 months. A nurse researcher will come to your home at least once a week at a time that is convenient to you and your caregiver. During the first visit, you will be asked questions about yourself, your health, and any treatments you have had for your cancer. During the first visit and future weekly visits you will be asked questions that will evaluate your ability to think and take care of yourself. You will be asked questions about your daily activities, about how you are feeling, about how well you sleep, and about other symptoms you have. You will also be asked to give information about the medicines you are taking. You will be asked to let us measure your temperature, heart rate, breathing rate, and blood pressure (lying down and standing up), the oxygen level in your blood by placing a reflecting light sensor on your finger, your weight and height, and your body fluid status.

Your body fluid status will be measured with a bioelectrical impedance analyzer (BIA) while you are lying in bed or sitting in a reclining chair. Adhesive pads or sensors will be placed on your wrists and hands and on your ankles and feet. After the sensors are attached to the BIA, a low-level signal will be sent between the sensors to determine your body fluid status. Measurements will be done on your right side and your left side. The procedure only takes a few minutes and you will not feel anything or have any sensations. Needles will **not** be used in any procedure.

The length of each visit will be about 1-2 hours. You will be allowed to rest as needed during the visit and, if you would like, the information can be collected in two visits.

During the first visit your caregiver will be asked to tell us about himself/herself. Throughout the study your caregiver will monitor you for signs of delirium or confusion. Your caregiver will complete the Caregiver Confusion Checklist at least once a day. If you have any signs of delirium or confusion, your caregiver will call the researcher who will come to your home at the earliest possible convenience to check on you and to learn more about what is going on with you. During this visit you will be asked questions about your thinking and about how you are feeling. You will also be asked to let us measure your vital signs (temperature, heart rate, breathing rate, blood pressure, oxygen level, and body fluid status). Your caregiver will be asked questions that will help us to better understand the changes he/she observed. This portion of the visit will be audiotaped. The researcher will come back to your home the next day to do another check-up visit. You and/or your family caregiver and the researcher will agree upon when additional visits will be done.

In order to learn more about your cancer, cancer treatment, and overall health, we will collect the following information from your UNC medical record: your diagnosis and date of diagnosis; your current and prior cancer treatments; whether you have been hospitalized in the past; the medicines you are taking; results of lab tests, x-rays, and other diagnostic tests; and other medical conditions that you have. During the study, we will look at your medical record at least once each month to get an update on your medical condition and treatment plan. We will collect information about your clinic visits, your treatment plan, your list of medicines, and results of your lab tests, x-rays, and other tests.



If you are admitted to UNC Hospitals during the study, we will visit you there. The visits in the hospital will be like the visits at home. During each hospital visit we will look at your medical record to collect information about your medical treatment plan, the medicines you are taking, and the results of your lab tests, x-rays, and other tests. During the first hospital visit we will also collect the following information: your date of admission, the reason for admission, and your admission diagnosis.

**Audiotaping:** Your caregiver will be audiotaped while he/she is being asked questions if you have any signs of confusion or delirium. You may or may not be present during the audiotaping. The tapes will be used to make sure that all your caregiver tells us is noted accurately. The tapes will be kept in a locked, secure area in the School of Nursing and will be destroyed upon completion of data analysis.

**Risks and Discomforts:** There are no major risks to you as a participant in this study. It is possible that you may feel uncomfortable with some of the procedures and tasks you are asked to do. You might feel tired and frustrated when being asked questions or when filling out forms, especially if you do not feel well. You may also experience emotional or psychological stress when discussing your condition or illness. Please let the researcher know if you need to rest, if you have any questions, or if you are having any other problems. If you become tired or frustrated, you will have the option of taking a rest period of 30-60 minutes or rescheduling the remaining data collection for another time. If the data collection is not completed after a rest period, it will be rescheduled within the next two days if possible.

**Benefits:** You will not benefit directly from this study. You may gain some indirect benefit from frequent contact with the researcher, from frequent check-ups, and from the opportunity to discuss your illness experience. Your participation will help us to learn more about delirium and acute confusion in older adults with advanced cancer. This research may eventually help to improve the care and quality of life of other older adults with advanced cancer.

**Consent Forms:** You will receive a copy of your signed consent form. The investigators will keep the original consent form, as required for 5 years, in a secured locked drawer at the School of Nursing.

**Confidentiality:** Every effort will be taken to protect your identity and confidentiality. Only members of the research team will have access to your data. All data (including paper forms, diskettes, and audiotapes) will be kept in a locked drawer in the School of Nursing. Audiotapes will be destroyed upon completion of data analysis. The results of this study will be used to learn more about delirium in older persons with advanced cancer. The results of this study may be described in a report or health care publication. You will not be identified by name, since all results will be discussed in terms of the whole group.

**Financial Costs of the Research:** The researchers will be responsible for the costs of this research. In the event of physical injury resulting directly from your participation in this research, financial compensation cannot be provided by the University of North Carolina at Chapel Hill. You do not waive any liability rights for personal injury by signing this form.

**Payments to Participants:** You will receive your choice of either a gift card for gas or long-distance telephone calls (\$25 value) or \$25 in cash after the initial visit and each month while you are enrolled in the study.

**Right to Refuse or to Withdraw from the Study:** Your participation in this study is strictly voluntary. You may refuse to participate, or may discontinue your participation at any time without penalty, and without change in the type of medical care or services that you are currently receiving or benefits that you would otherwise be entitled to.

**Institutional Review Board Approval:** This project has been approved by the University of North Carolina at Chapel Hill Nursing Institutional Review Board (IRB). If you have any questions or if you believe that there has been any infringement upon your rights, you may contact this committee by calling (919) 966-5803.

**Other Questions about the Study:** If you have any other questions about the study, you may call the researchers, Stewart Bond at (919) 966-7598 or Dr. Neelon at (919) 966-1410.

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**Participant's Agreement:** I have read the information provided above. I have had the opportunity to ask questions and have had my questions answered. I voluntarily agree to participate in this study. After it is signed, I understand that I will receive a copy of this consent form.

\_\_\_\_\_  
Signature of Research Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

THIS CONSENT FORM SHOULD BE SIGNED ONLY BETWEEN  
5.25.05 AND 3.11.06 *by*  
APPROVED BY THE NURSING IRB  
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL



**CONSENT TO PARTICIPATE IN A RESEARCH STUDY**  
(Caregiver Version)

**Trajectories and Patterns of Delirium in Older Adults  
with Advanced Cancer**

Principal Investigator: Stewart M. Bond, RN, MSN, AOCN  
Coinvestigator: Virginia J. Neelon RN, PhD

---

You are invited to take part in a research study being conducted by Stewart Bond, a doctoral student in the School of Nursing at the University of North Carolina at Chapel Hill and Dr. Virginia Neelon. Fifteen older cancer patients and their family caregivers will take part in this study.

**Purpose:** The purpose of this research study is to learn more about delirium or acute confusion (any new or unusual thoughts, feelings, behaviors, memory problems, or changes in alertness that come on over a short period of time) in older adults with advanced cancer.

**Duration and Procedures:** The entire study will last for no longer than 6 months. A nurse researcher will come to your home at least once a week at a time that is convenient to you and your family member (the patient). During the first visit, you will be asked to tell us about yourself and the care that you provide to your family member. You will be given information about delirium and taught how to complete the Caregiver Confusion Checklist. Throughout the study, you will be asked to monitor your family member for signs of delirium or confusion and to complete the Caregiver Confusion Checklist at least once a day. You will be asked to contact the researcher if your family member has signs of delirium or confusion. The researcher will come to your home at the earliest possible convenience to check on your family member and to learn more about what is going on with him/her. You will be asked questions that will help us to better understand the changes you observed. This portion of the visit will be audiotaped. The researcher will come back to your home the next day to do a follow-up visit. You

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THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL  
Biobehavioral Lab □ CB#7460, Carrington Hall □ Chapel Hill, NC 27599-7460  
PHONE: 919-966-7598



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and/or your family member and the researcher will agree upon the frequency and timing of additional visits.

**Audiotaping:** You will be audiotaped while you are being asked questions if your family member has signs of confusion or delirium. The audiotapes will be used to make sure that all that you tell us is noted accurately. The audiotapes will be kept in a locked, secure area in the School of Nursing and will be destroyed upon completion of data analysis.

**Risks and Discomforts:** There are no major risks to you as a participant in this study. There are no risks of physical harm or discomfort. You may experience some emotional or psychological discomfort or stress when discussing your family member's condition and illness. Please let the researcher know if you have any questions or if you are having any problems or concerns.

**Benefits:** You will not benefit directly from this study. You may gain some indirect benefit from frequent contact with the researcher, from the frequent visits to check on your family member, and from the opportunity to discuss your thoughts, feelings, and concerns about your family member's illness. Your participation will help us to learn more about delirium and acute confusion in older adults with advanced cancer. This research may eventually help to improve the care and quality of life of other older adults with advanced cancer.

**Consent Forms:** You will receive a copy of your signed consent form. The investigators will keep the original consent form, as required for 5 years, in a secure locked drawer at the School of Nursing.

**Confidentiality:** Every effort will be taken to protect your identity and confidentiality. Only members of the research team will have access to your data. All data (including paper forms, diskettes, and audiotapes) will be kept in a locked drawer in the School of Nursing. Audiotapes will be destroyed upon completion of data analysis. The results of this study will be used to learn more about delirium in older persons with advanced cancer. The results may be described in a report or health care publication. You will not be identified by name, since all results will be discussed in terms of the whole group studied.

**Financial Costs of the Research:** The researchers will be responsible for the costs of this research. In the event of physical injury resulting directly from your participation in this research, financial compensation cannot be provided by the University of North Carolina at Chapel Hill. You do not waive any liability rights for personal injury by signing this form.

**Payments to Participants:** You will receive your choice of either a gift card for gas or long-distance telephone calls (\$25 value) or \$25 in cash after the initial visit and each month while you are enrolled in the study.

**Right to Refuse or to Withdraw from the Study:** Your participation in this study is voluntary. You may refuse to participate or may discontinue your participation in the study at any time without penalty and without change in any benefits, services, or care that you or your family member would otherwise be entitled to.

**Institutional Review Board Approval:** This project has been approved by the University of North Carolina at Chapel Hill Nursing Institutional Review Board (IRB). If you have any questions or believe that there has been any infringement upon your rights, you may contact this committee at (919) 966-5803.

**Other Questions about the Study:** If you have any other questions about the study, you may call the investigators, Stewart Bond at (919) 966-7598 or Dr. Virginia Neelon at (919) 966-1410.

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**Participant's Agreement:** I have read the information provided above. I have had the opportunity to ask questions and have had my questions answered. I voluntarily agree to participate in this study. After it is signed, I understand that I will receive a copy of this consent form.

\_\_\_\_\_  
Signature of Research Participant

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Person Obtaining Consent

\_\_\_\_\_  
Date

THIS CONSENT FORM SHOULD BE SIGNED ONLY BETWEEN  
5-25-05 AND 3-11-06 by  
APPROVED BY THE NURSING IRB  
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

3

**HIPAA Authorization for Use and Disclosure of Health Information for Research  
Purposes  
University of North Carolina-Chapel Hill**

IRB Study # 922-05

UNC-Chapel Hill Principal Investigator (Researcher):

Stewart M. Bond, RN, MSN, AOCN  
UNC School of Nursing  
CB# 7460, Carrington Hall  
Chapel Hill, NC 27599-7460

This is a permission called a "HIPAA authorization." It is required by "The Health Insurance Portability and Accountability Act of 1996" (known as "HIPAA") for us to get information from your medical records or health insurance records to use in this research study.

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1. If you sign this HIPAA authorization form you are giving your permission for the following people or groups to give the researchers certain health information about you: **UNC Health Care System—UNC Hospitals, North Carolina Cancer Hospital and Clinics**
2. If you sign this HIPAA authorization form, this is the health information about you that the people or groups listed in #1 may give to the researchers to use in this research study: **information about your cancer diagnosis, your current and prior cancer treatments, other medical conditions that you have, whether you have been hospitalized in the past, and the medicines you are taking; results of lab tests, x-rays, and other diagnostic tests; and information about your ongoing cancer treatment. If you are hospitalized during the study, your admission date, the reason for admission, and your admission diagnosis may be given to the researchers.**
3. The people or groups listed in #1 may give this health information to the researcher listed at the top of this form (UNC-Chapel Hill Principal Investigator) or to another researcher working on this research study.
4. The health information you allow the researchers to get may be seen or used by people who do not have to follow HIPAA rules. You can ask the researchers any questions you have about how they will protect your personal information in this research study.
5. If you do not sign this HIPAA authorization form you cannot be in this research study, but if you do not sign this HIPAA authorization form the people or groups listed in #1 will not change your right to treatment, payment, enrollment or eligibility for anything that is not part of this research study just because you did not sign this HIPAA authorization form,

6. This HIPAA authorization will stop **at the completion of the study.**

7. You have the right to stop this HIPAA authorization at any time. HIPAA rules are that you must stop this HIPAA authorization in writing. You may give your written stop of this HIPAA authorization directly to the people or groups listed in #1 or you may give it to the researcher and tell the researcher to send it to any person or group the researcher has given a copy of this HIPAA authorization. Stopping this HIPAA authorization will not stop information sharing that has already happened.

8. You will be given a copy of this signed HIPAA authorization.

\_\_\_\_\_  
Signature of Research Subject

\_\_\_\_\_  
Date

\_\_\_\_\_  
Print Name of Research Subject

***For Personal Representative of the Research Participant (if applicable)***

Print Name of Personal Representative: \_\_\_\_\_

Please explain your authority to act on behalf of this Research Subject:

\_\_\_\_\_

*I am giving this permission by signing this HIPAA Authorization on behalf of the Research Participant.*

\_\_\_\_\_  
Signature of Personal Representative

\_\_\_\_\_  
Date

THIS CONSENT FORM SHOULD BE SIGNED ONLY BETWEEN  
3.11.05 AND 3.11.06 *bg*  
APPROVED BY THE NURSING IRB  
THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL



## Appendix D

### Phase III: Data Collection Instruments

**The Mini-Mental State Examination**

(Folstein, Folstein, &amp; McHugh, 1975)

Patient instructions: "Now, I'd like for you to answer some questions and follow some instructions. Do your best to respond to each question or instruction. Some will very simple and some will be more difficult."

Points    Points scored

**Orientation**

1. Ask first: "What is the day, date and season?"

If information is omitted, ask as needed:

Year?	1	_____
Season?	1	_____
Date?	1	_____
Day?	1	_____
Month?	1	_____

2. Ask first: What is the same of this place and where is it located

If information is omitted, ask as needed:

State?	1	_____
Country?	1	_____
Town or City?	1	_____
Location (Hospital/Home)?	1	_____
Floor (Room)?	1	_____

**Registration**

3. Name three objects, taking one second to say each. "I am going to give you a list of 3 words, which I want to repeat. The words are \_\_\_\_\_ . Please tell me the three words.

Score first try. Then repeat the objects until all are learned. Tell patient you will ask him to repeat them from memory in a few minutes.

Give 1 point for each correct answer.

Book	Hat	Cup	Cat	3	_____
House	Door	Bed	Tree		
Candle	Car	Train	Chair		

**Attention and Calculation**

4. Serial Sevens. Give one point for each correct answer. How much is 7 from 100, 7 from 93, etc.

(Answer: 100-93-86-79-65. Stop after five answers; you may prompt after each answer. Record in the spaces allowed.)

\_\_\_\_\_ 5 \_\_\_\_\_  
 93 86 79 72 65

If patient missed any calculation, then ask the following: "Now I am going to spell a word forward and I want you to spell it backwards. The word is world: W-O-R-L-D. Spell word backwards." (Answer: D-L-R-O-W; repeat if necessary but not after spelling starts. Record in the spaces). \_\_\_\_\_

**Recall**

5. Ask for names of three objects learned in Question 3.

Give 1 point for each correct answer.

(book, house, candle) 3 \_\_\_\_\_

**Language**

6. Point to a pencil and a watch. Have the patient name them as you point

"What is this?" "Name this?" 2 \_\_\_\_\_

7. Have the patient repeat: "No ifs, ands or buts."

(Stress S's when you say it, S's must be repeated back for a correct response.) 1 \_\_\_\_\_

8. Have the patient follow a three-stage command:

"Take this paper in your right hand.  
 Fold the paper in half with both hands.  
 Put the paper on the bed (table)." 3 \_\_\_\_\_

9. Have the patient read and obey the following:

"CLOSE YOUR EYES." (Code 8 if states that cannot read) 1 \_\_\_\_\_

10. Have the patient write a simple sentence of his or her choice.

(The sentence should contain a subject and a verb and should make sense.  
 Ignore spelling errors when scoring. Code 8 if physically unable to write,  
 i.e. pick up a pencil). 1 \_\_\_\_\_

**Delirium and Cancer Study**

Week # \_\_\_\_\_

Day \_\_\_\_\_

ID# \_\_\_\_\_

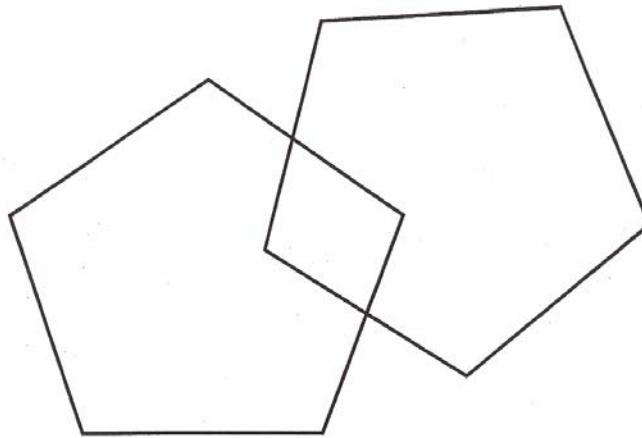
Date \_\_\_\_\_

11. Put the Bender Gestalt design on the top of the clipboard 1 \_\_\_\_\_  
and tell the patient: "Copy that shape." (Give one point if all sides  
and angles are preserved and if the intersecting side form a quadrangle.  
Code 8 if blind or is physically unable to write- i.e. pick up a pencil).

12. Total (Sum 0's & 1's; do not add 8's & 9's) Total 30 \_\_\_\_\_

\*\* If exam is coded as completely refused (9's), unable to answer (8's). Explain coding rationale.

Close your eyes.



Delirium and Cancer Study	Week # _____ Day _____	ID# _____ Date _____
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Memorial Symptom Assessment Scale – Short Form  
(Chang et al, 2000)

Instructions: Below is a list of symptoms. If you had the symptom **DURING THE PAST WEEK**, please check **Yes**. If you had the symptom, please check the box that tells how much the symptom **DISTRESSED** or **BOTHERED** you.

	<b>IF YES:</b> How much did it <b>DISTRESS</b> or <b>BOTHER</b> you?					
Check <b><i>all</i></b> of the symptoms you have had during the <b>past week</b>	Yes (✓)	Not at all (0)	A little bit (1)	Some-what (2)	Quite a bit (3)	Very much (4)
Difficulty concentrating						
Pain						
Lack of energy						
Cough						
Dry mouth						
Nausea						
Feeling drowsy						
Numbness/tingling in hands and feet						
Difficulty sleeping						
Feeling bloated						
Problems with urination						
Vomiting						

<b>Delirium and Cancer Study</b>	Week # _____	Day _____	ID# _____
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	Yes (✓)	Not at all (0)	A little bit (1)	Some- what (2)	Quite a bit (3)	Very Much (4)
Shortness of breath						
Diarrhea						
Sweats						
Itching						
Lack of appetite						
Dizziness						
Difficulty swallowing						
Change in the way food tastes						
Weight loss						
Constipation						
Swelling of arms or legs						
Difficulty remembering						
Other: _____						
Other: _____						



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Below is a list of other common symptoms. Please check **YES** if you had the symptom **DURING THE PAST WEEK**. If you had the symptom, please check the box that tells how often it occurred.

		<b><u>IF YES:</u></b> How <b>OFTEN</b> did it occur?			
Check <b><i>all</i></b> of the symptoms you have had during the <b>past week</b>	Yes (✓)	Rarely (1)	Occasionally (2)	Frequently (3)	Almost Constantly (4)
Feeling sad					
Worrying					
Feeling irritable					
Feeling nervous					
Feeling confused					



**OARS Activities of Daily Living Scale**

(Fillenbaum, 1978)

Instructions: The following questions are about some of your activities of daily living (ADLs), the things that we all need to do as part of our daily lives. I would like to know if you can do these activities without any help at all, or if you needed some help to do them, or if you couldn't do them at all. Please write the number for the best answer in the space provided.

Physical ADLS

1. Can you eat... \_\_\_\_\_  
2 = without help (able to feed yourself completely),  
1 = with some help (need help with cutting, etc.)  
0 = or are you completely unable to feed yourself?
2. Can you dress and undress yourself... \_\_\_\_\_  
2 = without help (able to pick out clothes, dress and undress yourself)  
1 = with some help  
0 = or are you completely unable to dress and undress yourself?
3. Can you take care of your own appearance, for example, combing your hair or shaving? \_\_\_\_\_  
2 = without help  
1 = with some help  
0 = or are you completely unable to maintain your appearance yourself?
4. Can you walk... \_\_\_\_\_  
2 = without help (except for a cane)  
1 = with some help from a person or with the use of a walker, or crutches, etc.  
0 = or are you completely unable to walk?

5. Can you get in and out of bed... \_\_\_\_\_

2 = without any help, grabbing hold of the bedstand, or aids

1 = with some help (either from a person, grabbing hold of a bedstand  
or with the aid of some device)

0 = or are you totally dependent on someone else to life you?

6. Can you take a bath or shower... \_\_\_\_\_

2 = without help

1 = with some help (need help getting in and out of the tub,  
or need special attachment on the tub)

0 = or are you completely unable to bath yourself?

7. Do you ever have trouble getting to the bathroom on time? \_\_\_\_\_

2 = no

1 = yes

If yes, how often do you wet or soil yourself? \_\_\_\_\_

1 = once or twice a week?

0 = three times a week or more?

#### Independent ADLS

8. Can you use the telephone... \_\_\_\_\_

2 = without help, including looking up the number and dialing

1 = with some help (could answer phone or dial operator in an emergency,  
but needed a special phone or help)

0 = or were you completely unable to use the telephone?

9. Can you get to places that are out of walking distances... \_\_\_\_\_

2 = without help (travel alone on buses, taxis, or drive your own car)

1 = with some help (needed someone to help you or be with you  
when traveling)

0 = or were you unable to travel unless emergency arrangements  
were made for a specialized vehicle like an ambulance?

10. Can you go shopping for groceries or clothes (assuming you had transportation) \_\_\_\_\_
- 2 = without help (took care of all shopping needs yourself)
- 1 = with some help (needed someone to go with you in all shopping trips)
- 0 = or were you completely unable to do any shopping?
11. Can you prepare your own meals... \_\_\_\_\_
- 2 = without help (plan and cook full meals yourself)
- 1 = with some help (could prepare something but unable to cook full meals yourself)
- 0 = or were you completely unable to prepare your meals?
12. Can you do your housework or yardwork (cleaning or repairing)... \_\_\_\_\_
- 2 = without help (scrub floors, cut grass, etc.)
- 1 = with some help (could do light work but needed help with heavy work)
- 0 = or were you completely unable to do any of this type of work?
13. Can you take your own medicine... \_\_\_\_\_
- 2 = without help (in the right dose, at the right time)
- 1 = with some help (able to take medicine if someone prepared it for you or reminds you to take it)
- 0 = were you completely unable to take your medicine?
14. Can you handle your own money... \_\_\_\_\_
- 2 = without help (write checks, pay bills, etc.)
- 1 = with some help (could manage day-to-day buying but needed help with managing your check book or paying bills)
- 0 = were you completely unable to handle money?

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**Palliative Performance Scale (PPS)**

(Anderson et al., 1996)

PPS Level	Ambulation	Activity & Evidence of Disease	Self-Care	Intake	Conscious Level
100%	Full	Normal Activity & Work No Evidence of Disease	Full	Normal	Full
90%	Full	Normal Activity & Work Some Evidence of Disease	Full	Normal	Full
80%	Full	Normal Activity with Effort Some Evidence of Disease	Full	Normal or Reduced	Full
70%	Reduced	Unable Normal Job/Work Significant Disease	Full	Normal or Reduced	Full
60%	Reduced	Unable Hobby/House Work Significant Disease	Occasional Assistance Necessary	Normal or Reduced	Full or Confusion
50%	Mainly Sit/Lie	Unable to Do Any Work Extensive Disease	Considerable Assistance Required	Normal or Reduced	Full or Confusion
40%	Mainly in Bed	Unable to Do Most Activity Extensive Disease	Mainly Assistance	Normal or Reduced	Full or Drowsy ± Confusion
30%	Totally Bed Bound	Unable to Do Any Activity Extensive Disease	Total Care	Normal or Reduced	Full or Drowsy ± Confusion
20%	Totally Bed Bound	Unable to Do Any Activity Extensive Disease	Total Care	Minimal to Sips	Full or Drowsy ± Confusion
10%	Totally Bed Bound	Unable to Do Any Activity Extensive Disease	Total Care	Mouth Care Only	Drowsy or Coma ± Confusion
0%	Death	-----	-----	-----	-----

PPS Level \_\_\_\_\_

**Mood Assessment Scale**

(Sheikh &amp; Yesavage, 1986)

- |    |  |     |    |
|----|--|-----|----|
| 1  | Are you basically satisfied with your life?                            | Yes | No |
| 2  | Have you dropped many of your activities and interests?                | Yes | No |
| 3  | Do you feel that your life is empty?                                   | Yes | No |
| 4  | Do you feel bored?   | Yes | No |
| 5  | Are you in good spirits most of the time?                              | Yes | No |
| 6  | Are you afraid that something bad is going to happen to you?           | Yes | No |
| 7  | Do you feel happy most of the time?                                    | Yes | No |
| 8  | Do you often feel helpless?  | Yes | No |
| 9  | Do you prefer to stay at home, rather than going out doing new things? | Yes | No |
| 10 | Do you feel you have more problems with memory than most?              | Yes | No |
| 11 | Do you think it is wonderful to be alive now?                          | Yes | No |
| 12 | Do you feel pretty worthless the way you are now?                      | Yes | No |
| 13 | Do you feel full of energy?  | Yes | No |
| 14 | Do you feel that your situation is hopeless?                           | Yes | No |
| 15 | Do you think that most people are better off than you are?             | Yes | No |



## Sleep Questionnaire

The following questions relate to your usual sleep habits during the past week. Your answers should indicate the most accurate reply for the majority of day and nights in the past week.

1. During the past week, what time have you usually gone to bed at night? \_\_\_\_\_
2. During the past week, how long in minutes has it usually taken you to fall asleep each night? \_\_\_\_\_
3. During the past week, on average how many times did you awaken during the night? \_\_\_\_\_
4. During the past week, what time have you usually gotten up in the morning? \_\_\_\_\_
5. During the past week, how many hours of actual sleep did you get at night? This may be different than the number of hours you spent in bed. \_\_\_\_\_
6. During the past week, how would you rate the overall quality of your sleep?
 

Very good (1)	Fairly good (2)	Fairly bad (3)	Very Bad (4)	_____
------------------	--------------------	-------------------	-----------------	-------
7. During the past week, have you experienced any disturbed dreams that seemed real or caused awakening?
 

Yes (1)	No (0)	_____
------------	-----------	-------
8. During the past week, have you awakened during the night feeling confused or disoriented?
 

Yes (1)	No (0)	_____
------------	-----------	-------

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### Stanford Sleepiness Scale

(Hoddes et al., 1973)

We would like to know how you would evaluate your sleep last night. Please choose the best response to the following questions.

How sleepy or alert do you feel right now? Please mark along the line.

Very Sleepy \_\_\_\_\_ Very Alert

Please circle the number on the scale below that describes how you feel right now:

- 1 Alert, Wide Awake, Energetic
- 2 Functioning at a high level, but not at peak. Able to concentrate
- 3 Awake, but not fully alert
- 4 A little foggy, let down
- 5 Foggy. Beginning to lose interest in remaining awake. Slowed down
- 6 Cannot stay awake. Sleep onset soon.

**Sleep and Rest Subscale – Sickness Impact Profile**  
(John Hopkins University, 1977)

Please respond with either Yes or No to these statements describing your sleep and rest patterns over the past week.

I spend much of the day lying down in order to rest.	Yes	No	_____
			(8.3)
I sit during much of the day.	Yes	No	_____
			(4.9)
I am sleeping or dozing most of the time day and night.	Yes	No	_____
			(10.4)
I lie down more often during the day in order to rest.	Yes	No	_____
			(5.8)
I sit around half-asleep.	Yes	No	_____
			(8.4)
I sleep less at night, for example, wake up too early, don't fall asleep for a long time, and awaken frequently.	Yes	No	_____
			(6.1)
I sleep or nap more during the day.	Yes	No	_____
			(6.0)



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### Physiologic Data

#### Vital Signs

			Age _____
	Lying	Standing 1	Standing 2
Systolic Blood Pressure	_____	_____	_____
Diastolic Blood Pressure	_____	_____	_____
Mean Arterial Pressure	_____	_____	_____
Pulse Rate	_____/_____/_____ (apical/radial/monitor)	_____	_____
Respiratory Rate	_____		
Pulse Oximetry	_____		
Temperature	_____		

#### Anthropometrics

Body Weight	_____
Height	_____
Body Mass Index	_____

#### Bioelectrical Impedance Analysis

	Trial #1		Trial #2		Trial #3		Mean
	R	L	R	L	R	L	
Resistance	_____	_____	_____	_____	_____	_____	_____
Reactance	_____	_____	_____	_____	_____	_____	_____
Impedance	_____	_____	_____	_____	_____	_____	_____
Phase Angle	_____	_____	_____	_____	_____	_____	_____

### NEECHAM CONFUSION SCALE (Neelon, Champagne, & McConnell, 1987)

#### LEVEL 1- PROCESSING

##### PROCESSING-ATTENTION (Attention-Alertness-Responsiveness)

- 4 Full attentiveness/alertness: responds immediately and appropriately to calling of name or touch—eyes, head turn; fully aware of surroundings, attends to environmental events appropriately.
- 3 Short or hyper attention/alertness: either shorted attention to calling, touch, or environmental events or hyper alert, over-attentive to cues/objects in environment.
- 2 Attention/alertness inconsistent or inappropriate: slow in responding, repeated calling or touch required to elicit/maintain eye contact/attention; able to recognize objects/stimuli, though may drop into sleep between stimuli.
- 1 Attention/alertness disturbed: eye open to sound or touch; may appear fearful, unable to attend/recognize contact, or may show withdrawal/combative behavior.
- 0 Arousal/responsiveness depressed: Eyes may/may not open/ only minimal arousal possible with repeated stimuli; unable to recognize contact

##### PROCESSING-COMMAND: (Recognition-Interpretation-Action)

- 5 Able to follow a complex command: "Turn on nurse's call light." (Must search for object, recognize object, perform command.)
- 4 Slowed complex command response: requires prompting or repeated directions to follow/complete a complex command. Performs complex command in "slow/over-attending manner."
- 3 Able to follow a simple command: "Lift your hand or foot MR..." (Only use 1 object.)
- 2 Unable to follow direct command: follows command prompted by touch or visual cue—drinks from glass placed near mouth. Responds with calming affect to nursing contact and reassurance or hand holding.
- 1 Unable to follow visually guided command: responds with dazed or frightened facial features, and/or withdrawal-resistive response to stimuli, hyper/hypoactive behavior; does not respond to nurse gripping hand lightly.
- 0 Hypoactive, lethargic: minimal motor/response to environmental stimuli.

##### PROCESSING-ORIENTATION: (Orientation, Short-term Memory, Thought/Speech Content)

- 5 Oriented to time, place, and person: Thought process, content of conversation or question appropriate. Short-term memory intact.
- 4 Oriented to person and place: Minimal memory/recall disturbance, content and response to questions generally appropriate; may be repetitive, requires prompting to continue contact. Generally cooperate with requests.
- 3 Orientation inconsistent: Oriented to self, recognizes family but time and place orientation fluctuates. Uses visual cues to orient. Thought/memory disturbance common. may have hallucination or illusions. Passive cooperation with requests (cooperative cognitive protecting behaviors).
- 2 Disoriented and memory/recall disturbed: oriented to self/recognizes family. May question actions of nurses or refuse requests, procedures (resistive cognitive protecting behaviors). Conversation content/thought disturbed. Illusions and/or hallucinations common.
- 1 Disoriented, disturbed recognition: Inconsistently recognize familiar people, family, objects. Inappropriate speech/sounds.
- 0 Processing of stimuli depressed: minimal response to verbal stimuli.

#### LEVEL 2- BEHAVIOR

##### BEHAVIOR-APPEARANCE:

- 2 Controls postures, maintains appearance, hygiene: appropriately gowned or dressed, personally tidy, clean. Posture in bed/chair normal.
- 1 Either posture or appearance disturbed: some disarray of clothing/bed or personal appearance, or some loss of control of posture, position.
- 0 Both posture and appearance abnormal: disarrayed, poor hygiene, unable to maintain posture in bed.

##### BEHAVIOR-MOTOR:

- 4 Normal motor behavior: appropriate movement, coordination and activity, able to rest quietly in bed. Normal hand movement.
- 3 Motor behavior slowed or hyperactive: overly quiet or little spontaneous movement (hands/arms across chest or at sides) or hyperactive (up/down. "jumpy"). May show hand tremor.
- 2 Motor movement disturbed: restless or quick movements: Hand movements appear abnormal—picking at bed objects or bed covers, etc. May require assistance with purposeful movements.
- 1 Inappropriate, disruptive movements: pulling at tubes, trying to climb over rails, frequent purposeless actions.
- 0 Motor movement depressed: Limited movement unless stimulated; resistive movements.

**Delirium and Cancer Study**

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Day \_\_\_\_\_

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Date \_\_\_\_\_

**BEHAVIOR-VERBAL:**

- 4 Initiates speech appropriately: able to converse, can initiate and maintain conversation. Normal speech for diagnostic condition, normal tone.
- 3 Limited speech initiation: responses to verbal stimuli are brief and uncomplex. Speech clear for diagnostic condition, tone may be abnormal, rate may be slow.
- 2 Inappropriate speech: may talk to self or not make sense. Speech not clear for diagnostic condition.
- 1 Speech/sound disturbed: altered sound/tone. Mumbles, yells, swears or is inappropriately silent.
- 0 Abnormal sounds: groaning or other disturbed sounds. No clear speech.

**LEVEL 3-PHYSIOLOGIC CONTROL**
**PHYSIOLOGIC MEASUREMENTS:**

Recorded Values:	Normals:
_____ Temperature	(36-37°C) (96.8-98.6°F)
_____ Systolic BP	(100-160)
_____ Diastolic BP	(50-90)
_____ Heart Rate (HR)	(60-100)
_____ Regular/Irregular (circle one)	
_____ Respirations	(14-22)
_____ (count for one full minute)	
_____ O2 sat	(93 or above)
_____ Periods of apnea/hypopnea present? 1=yes 0=no	
_____ Oxygen therapy prescribed? 0=no 1=yes, but not on 2=yes, on now.	

**VITAL FUNCTION STABILITY:** (Count abnormal SBP and/or DBP as one value; count abnormal and/or irregular HR as one; count apnea and/or abnormal respirations as one; and abnormal temperature as one.)

- 2 BP, HR, TEMP, RESPIRATION within normal range with regular pulse
- 1 Any one of the above in abnormal range
- 0 Two or more in abnormal range

**OXYGEN SATURATION STABILITY:**

- 2 O2 sat in normal range (93 or above)
- 1 O2 sat 90 to 92 or is receiving oxygen
- 0 O2 sat below 90

**URINARY CONTINENCE CONTROL:**

- 2 Maintains bladder control
- 1 Incontinent of urine in last 24 hours or has condom cath
- 0 Incontinent now or has indwelling or intermittent catheter or is anuric

\_\_\_\_\_ LEVEL 1 Score: Processing (0-14 points)

\_\_\_\_\_ LEVEL 2 Score: Behavior (0-10 points)

\_\_\_\_\_ LEVEL 3 Score: Integrative physiological Control (0-6 points)

**TOTAL NEECHAM (0-30 points)**

Total Score of :

- |       |  |
|-------|--|
| 0-19  | Moderate to severe confusion                 |
| 20-24 | Mild or early development of confusion       |
| 25-26 | Not confused, but at high risk for confusion |
| 27-30 | Not confused or normal function              |

Delirium and Cancer Study

Week # \_\_\_\_\_

Day \_\_\_\_\_

ID# \_\_\_\_\_

Date \_\_\_\_\_

### Caregiver Confusion Checklist

Each morning and evening please record the presence or absence of these signs of confusion using the following scale: 0 = not present or 1 = present.

	Morning	Evening
Disorientation	_____	_____
Altered Behavior	_____	_____
Inappropriate Communication	_____	_____
Illusions or Hallucinations	_____	_____
Decreased Alertness	_____	_____
Total	_____	_____

**\*\* If the total equals 2 or more -- Notify the investigator \*\***  
**(919) 636-0122 or (919) 929-8738**

Disorientation: Verbal or behavioral manifestations of not being oriented to time or place or self or others

Altered Behavior: Behavior inappropriate to place and situation or behavior that is unusual for the person such as agitated, restless, uncooperative, combative, wandering, easily startled, slowed movements, staring, apathetic, withdrawn

Inappropriate Communication: Communication inappropriate to the place and situation or communication that is inappropriate for the person such as incoherent, rambling, silent, swearing, slowed speech, slurred speech, or unintelligible speech

Illusions/Hallucinations: Seeing or hearing things that are not there; distortions or misperceptions of visual objects

Decreased Alertness: Drowsy, difficulty staying awake, slowed thinking, slowed response to questions

Comments:



Delirium and Cancer Study		ID# _____
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## The Confusion Assessment Method Instrument (CAM)

(Inouye et al., 1990)

### 1. Acute onset and Fluctuate Course

BOX 1

a) Is there evidence of an acute change in mental status from the patient's baseline? No \_\_\_\_

Yes \_\_\_\_

b) Did the (abnormal) behavior fluctuate during the day, that is tend to come and go or increase and decrease in severity? No \_\_\_\_

Yes \_\_\_\_

### 2. Inattention

Did the patient have difficulty focusing attention, for example, being easily distractible, or having difficulty keeping track of what was being said?

No \_\_\_\_

Yes \_\_\_\_

### 3. Disorganized thinking

Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?

No \_\_\_\_

Yes \_\_\_\_

BOX 2

### 4. Altered level of consciousness

Overall, how would you rate this patient's level of consciousness?

\_\_\_ Alert (normal)

\_\_\_ Vigilant (hyperalert, overly sensitive to environmental stimuli, startled very easily)

\_\_\_ Lethargic (drowsy, easily aroused)

\_\_\_ Stupor (difficult to aroused).

\_\_\_ Coma (unarousable)

Do any checks appear in this box?

No \_\_\_\_

Yes \_\_\_\_

If all items in Box 1 are checked and at least 1 item in Box 2 is checked a diagnosis of delirium is suggested.

Adapted from Inouye, SK et al. Clarifying Confusion: The Confusion Assessment Method. New Method for Detection of Delirium. Ann Intern Med. 1990; 113:941-8.

**DSM IV Criteria for Delirium  
(APA, 1994)**

**Disturbance of consciousness with reduced ability to focus,  
sustain, or shift attention** \_\_\_\_\_

- Altered level of consciousness
- Difficult to engage in conversation
- Attention wanders
- Perseverates
- Easily distracted



**Change in cognition** \_\_\_\_\_

- Disorientation to time, place, person
- Memory impairment
- Disorganized thinking
- Language disturbance



**OR**

**Development of a perceptual disturbance** \_\_\_\_\_

- Misinterpretations
- Illusions
- Hallucinations



**Disturbance in behavior and mentation develops over short  
period of time and tends to fluctuate during the course of the  
day** \_\_\_\_\_

**Evidence of a specific organic factor etiologically related to the  
disturbance** \_\_\_\_\_

**Associated features**

- Sleep-wake cycle disturbance
- Increased or decreased psychomotor behavior



## Delirium Motor Patterns

(Trzepacz et al., 2001)

1. **Motor Agitation** (Rate by observation, including from other sources of observation such as by visitors, family, and clinical staff. Do not include dyskinesia, tics, or chorea) \_\_\_\_\_
- 0 No restlessness or agitation
  - 1 Mild restlessness of gross motor movements or mild fidgetiness
  - 2 Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing diapers or catheter
  - 3 Severe motor agitation, such as combativeness or a need for restraints or seclusion
2. **Motor Retardation** (Rate movements by direct observation or from other sources of observation such as family visitors, or clinical staff. Do not rate components of retardation that are caused by Parkinsonian symptoms. Do not rate drowsiness or sleep) \_\_\_\_\_
- 0 No slowness of voluntary movements
  - 1 Mildly reduced frequency. Spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment
  - 2 Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
  - 3 Severe motor retardation with few spontaneous movements

**Delirium Behavior Checklist**

Place a check (✓) next to the behavior if it is present during the assessment:

**Hyperactive Behaviors**

Hypervigilance	_____
Restlessness	_____
Fast or loud speech	_____
Irritability	_____
Combativeness	_____
Impatience	_____
Swearing	_____
Singing	_____
Laughing	_____
Uncooperative	_____
Euphoric	_____
Anger	_____
Wandering	_____
Easy startling	_____
Fast motor responses	_____
Distractability	_____
Tangentiality	_____
Nightmares	_____
Persistent thoughts	_____

**Hypoactive Behaviors**

Unawareness	_____
Decreased alertness	_____
Sparse or slow speech	_____
Lethargic	_____
Slowed movements	_____
Staring	_____
Apathy	_____



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**Richmond Agitation-Sedation Scale**  
(Sessler et al., 2002)

+4	Combative	Combative, violent, immediate danger to caregiver
+3	Very Agitated	Aggressive, pulls at or removes catheter, bandages, or chux
+2	Agitated	Frequent non-purposeful movement
+1	Restless	Anxious, apprehensive but movements are not aggressive or vigorous
0	Alert and Calm	
-1	Drowsy	Not fully alert, but has sustained awakening to voice (eye opening & contact > 10 sec)
-2	Light sedation	Briefly awakens to voice (eye opening & contact < 10 sec)
-3	Moderate Sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep Sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

## Appendix E

### Exemplar Case Study: Mrs. C

Mrs. C

### Background

Mrs. C was an 81 year old white female with adenocarcinoma of the colon. She was widowed and lived alone in a house next door to her daughter. She completed 11 years of school and worked for many years in a hosiery mill. She and her husband had also owned and operated a grill for 15 years. Mrs. C's primary caregivers were her daughter who lived next door and her granddaughter-in-law who also lived nearby. Her daughter worked full-time during the week, so her granddaughter-in-law who was unemployed checked in on Mrs. C throughout the day and took her shopping and to appointments.

In December 2002, Mrs. C began to experience abdominal pain. A computerized tomography (CT) scan revealed a pelvic mass. Around the same time, she had a colonoscopy that revealed a suspicious lesion that was biopsied and found to be malignant. Mrs. C's cancer was diagnosed as Stage IV adenocarcinoma of the colon in February 2003 when she underwent a radical abdominal debulking with total abdominal hysterectomy and bilateral oophorectomy. At the time of diagnosis, the cancer had metastasized to the ovaries, omentum, and pelvis.

### Treatment and Disease Course:

Table E3.1 outlines the course of Mrs. C's treatment. Following surgery in February 2003, Mrs. C underwent 3 six week cycles of 5-fluorouracil (5-FU) and leucovorin which were completed in late July 2003. In October 2003, a follow-up CT scan revealed a pelvic mass and fluid collection in the pelvic floor. An abscess was drained. Follow-up CT scans showed multiple small nodules but was otherwise unchanged. In January 2004 a scan showed interval progression in the size of the pelvic mass and an increase in number and size of the mesenteric soft tissue nodules. In February 2004, she was started on Xeloda at 2000mg per meter squared. A follow-up CT scan in April 2004 showed a mixed response to the Xeloda as well as slight progression with new mesenteric nodules and a slight increase in the size of another nodule. Oxaliplatin at a dose of 130 mg/m<sup>2</sup> every 3 weeks was added to the treatment regimen. In May 2004, Mrs. C was hospitalized for 2 weeks with toxic enterocolitis associated with profound diarrhea, dehydration, hypokalemia, and diffuse lower abdominal pain. Following this episode, treatment was continued with a dose reduction of 50%. In October 2004 scans showed evidence of slowly progressive disease. Avastin at 5 mg/kg was added to the treatment regimen. In March 2005 a follow-up scan showed that the mesenteric nodules and pelvic mass had increased by 25%. In addition loops of bowel appeared adhered to one another. At that time, Mrs. C noted increased gas and slowing of bowel function with significant constipation. Her bowel function markedly improved with initiation of a bowel regimen and Flagyl. She was started on Irinotecan, a topoisomerase I inhibitor, at the end of March 2005. Mrs. C tested positive for expression of epidermal growth factor receptor (EGFR), so Cetuximab, a monoclonal antibody that targets EGFR, was added to the Irinotecan regimen. She was also consented for future participation in a Phase I vaccine trial so that she could be tested for Ras mutation.

Table E3.1. Course of Mrs C's Treatment

Dates	Treatment
02/03	Radical abdominal debulking with total abdominal hysterectomy and bilateral oophorectomy
03/03 – 07/03	3 six week cycles of 5-Flurouracil (5-FU) and leucovorin
02/04 – 04/04	Xeloda 2000 mg/m <sup>2</sup>
04/04 – 05/04	Oxaliplatin 120 mg/m <sup>2</sup> every 3 weeks added
05/04	50% dose reduction due to toxic enterocolitis
10/04-03/05	Avastin 5mg/kg added
03/05	Irinotecan started
05/05*	Cetuximab added
06/05 – 07/05	Phase I vaccine trial
08/12/05	Enrolled in hospice
08/26/05	Death

\*Enrolled in Delirium and Cancer Study on May 25, 2005

### Enrollment

I first met and introduced the Delirium and Cancer Study to Mrs. C and her daughter in the medical oncology clinic. Mrs. C did not have a lot to say except that she had already agreed to participate in the study, thinking that I was talking about the vaccine trial that she had already consented to participate in. Mrs. C's daughter was interested in the study. I suggested that Mrs. C and her daughter discuss participation in the study and told them that I would follow-up with them when they came back to the clinic the next week. When I saw Mrs. C during her next clinic visit, she agreed to participate and her granddaughter-in-law who was with her concurred, so I set up an appointment to obtain consent and to collect baseline data.

I met with Mrs. C, her daughter, and granddaughter-in-law at her home in the late afternoon on May 25, 2005. I sat next to Mrs. C who was in a recliner. Her daughter and granddaughter-in-law sat across the room on a sofa and lounge chair, respectively. Mrs. C was attentive as I reviewed the patient consent form. I then provided Mrs. C and her daughter copies of the consent so that they could review it. Neither Mrs. C nor her daughter had additional questions before Mrs. C signed the consent. I then reviewed the caregiver consent and provided a copy of the caregiver consent to Mrs. C's granddaughter-in-law who agreed to be Mrs. C's family caregiver for the study.

### Baseline Characteristics

#### Cognitive Functioning

Mrs. C's initial NEECHAM Confusion Scale (NEECHAM) score (Range 0-30) of 28 was her highest during the course of the study. During the initial assessment, she exhibited minimal difficulty with information processing or cognitive functioning. However, she

exhibited slight slowing of her motor behavior. She also had an irregular heart rate associated with atrial fibrillation.

Mrs. C's initial mini-mental status examination (MMSE) score (Range 0-30) was 27. Although she knew the month and year, she did not know the exact date. She recalled 2 of 3 objects that were previously presented, but she was unable to accurately draw the intersecting pentagons.

At the initial visit, Mrs. C reported experiencing two cognitive symptoms on the Memorial Symptom Assessment Scale-Short Form (MSAS-SF)—feeling drowsy and difficulty remembering. Her cognitive symptom distress score was 0.75 (Range 0-4). She reported that feeling drowsy was somewhat distressing and that difficulty remembering caused her a little bit of distress. She reported no prior history of confusion. Her family also did not acknowledge any previous episode of confusion. Mrs. C had had a previous hospitalization for acute treatment complications in May 2004. Her medical record did not indicate that she had any change in mental status during that time.

#### Physical Functioning

At the time of enrollment into the study, Mrs. C was living independently with occasional assistance from her daughter and grandchildren. She had stopped driving but went shopping with her family. Her family prepared most of her meals but she was able to warm up the meals and eat them as she wanted. She did her own laundry and household chores (dusting, vacuuming, and dishes). An avid gardener, she also tended several tomato plants and outdoor flower beds. Her instrumental activities of daily living (IADL) subscale score (Range 0-14) was 10. Mrs. C's physical activities of daily living (PADL) subscale score (Range 0-14) was 13. She reported occasional incontinence, once or twice a week. Otherwise, she performed all other PADLs independently.

Mrs. C's baseline Palliative Performance Scale (PPS) score (Range 0-100) was 70. Overall, her ambulation was reduced due to her low energy level, but she was able to do housework and go out with her family. She maintained a full level of consciousness and she was independent in caring for her own physical needs. Her appetite was decreased; thus, her overall food intake was reduced.

#### Symptom Prevalence and Distress

At the initial visit, Mrs. C reported a total of 14 symptoms. Those causing quite a bit or very much distress were pain, low energy, change in taste, constipation, difficulty sleeping, and diarrhea. Those that were somewhat distressing included feeling drowsy, cough, and worrying. Other symptoms that caused a little bit of distress were sweating, itching, lack of appetite, weight loss, and difficulty remembering.

#### Depression

Mrs. C reported no prior history of depression, but her initial Geriatric Depression Scale (GDS) score (Range 0-15) was 6 – indicating that she may be depressed. She reported that she had dropped many activities and interests and that she felt her life was empty. She also reported feeling helpless and pretty worthless. Additionally, Mrs. C noted that her energy level was low and that she preferred to stay at home rather than going out doing new things.

### Nutritional Status and Risk

Mrs. C reported that her usual weight before her cancer was 164 pounds. Pre-treatment weights, documented in her medical record, were 136 pounds in January 2003 prior to her initial abdominal surgery and 136.4 pounds in February 2003 prior to the initiation of chemotherapy. Her weight upon enrollment in the Delirium and Cancer Study was 104.5 pounds. Mrs. C's height was 62.2 inches. Her body mass index (BMI) was 19.0 kg/m<sup>2</sup>, and she appeared thin. On May 13, two weeks before enrollment in the study, Mrs. C's albumin level was 3.5 g/dl (3.5-5.0 g/dl) and her lymphocyte count was 0.8 x10<sup>9</sup>/L (1.5-5.0 x10<sup>9</sup>/L). Therefore, Mrs. C entered the study with markers for the metabolic-nutritional risk pattern. Her initial phase angle was 4.26.

### Overall Health and Comorbidity

Mrs. C rated her overall health as fair at enrollment. She also reported that her health then was about the same as it was 6 months ago. Her adapted Charlson Comorbidity Index score was 2. Mrs. C's comorbid medical conditions included hypertension, mitral regurgitation, aortic insufficiency, and atrial fibrillation. Having quit 30 years ago, Mrs. C had a remote smoking history. She had never used alcohol. Table E3.2 shows the medications Mrs. C was taking when she enrolled in the study.

Table E3.2. Mrs. C's medication list at enrollment

Medication	Dosage
Isosorbide	30 mg QD
Lanoxin	125 mcg QD
Lasix	40 mg as needed
Norvasc	5 mg QD
Metoclopramide	10 mg QID
Prochlorpromazine	10 mg as needed for nausea
Sorbitol	30 ml QD
Quinine sulfate	325 mg Q HS
Ibuprofen	200 mg as needed for pain
Tylenol	650 mg as needed for pain
Caltrate plus	1 tablet QD
Multivitamin	1 tablet QD

### Study Course

Mrs. C was enrolled in the Delirium and Cancer Study for 93 days from May 25, 2005 until her death on August 26, 2005. Figure E3.1 provides a timeline of major events and data collection visits during the study period. During the study period I conducted a total of 19 home visits for data collection, 12 were scheduled weekly visits and 7 were follow-up visits. Mrs. C cancelled the scheduled weekly visits on Day 79) and on Day 51 because she was "worn out" after frequent trips to the cancer center for tests, treatments, and follow-up clinic visits. In addition to the data collection visits, I often saw Mrs. C briefly when she came to the cancer clinic for treatments or follow-up appointments. Table E3.3 shows the medications that were added during the study.

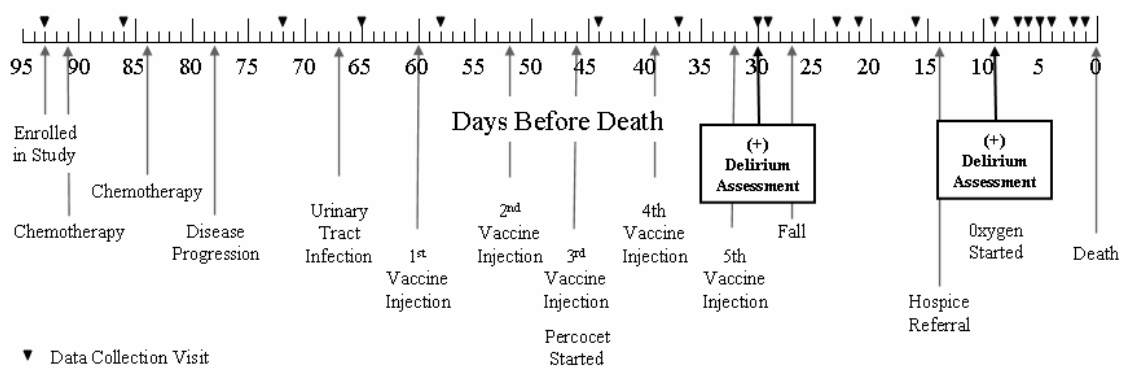


Figure E3.1. Major events and data collection visits during Mrs. C's enrollment in study

Table E3.3. Mrs. C's list of medications added during the study

Medication	Dosage
Hydroxyzine	12.5 mg Q 6 hr prn for itching
Magnesium oxide	400 mg BID
Ciprofloxacin	500 mg BID x 7 days
Amoxicillin	250 mg QID x 10 days
Pyridium	200 mg TID x 5 days
Percocet (5/325)	1-2 tablets Q 4-6 hr prn for pain
Oxycodone (5 mg)	1-2 tablets Q 3-4 hr prn for pain
Morphine solution (20mg/ml)	0.25-0.5 ml prn for pain
Diazepam	2.5 mg Q 6 hr prn for restlessness
Haloperidol	0.5-1 mg q 6 hr prn for
Atropine solution	3 gtts SL prn for congestion
Tylenol suppositories	650 mg PR Q 4-6 hr prn for temperature

When Mrs. C entered the study, she was receiving Irinotecan and Cetuximab. Her last chemotherapy treatment was on Day 84. A scan on Day 79 following two courses of Irinotecan and one course of Cetuximab showed progressive disease in the liver, abdomen, and pelvis. Mrs. C tested positive for the Ras mutation so she was enrolled in the Phase I vaccine trial that involved the administration of five weekly vaccine injections in the General Clinical Research Unit (GCRC). The trial start date was delayed a week when Mrs. C was found to have a urinary tract infection (UTI). The UTI was treated initially with a 7-day course of Ciprofloxacin. Since she continued to have lower abdominal discomfort and microscopic evidence of UTI, this treatment was followed by a 10-day course of Amoxicillin and Pyridium. Mrs. C received her first vaccine injection on Day 60. Following each injection, she had to remain in the GCRC for a 6-hour period of observation. Overall, Mrs. C's condition began to deteriorate during the vaccine trial. A CT scan at the end of the trial showed continued disease progression.

After the clinical trial, Mrs. C received supportive care. For example, on Day 28, she received IV fluids and electrolyte supplementation. During the ride home, after receiving IV

fluids in the clinic, Mrs. C had urinary incontinence in the car. Early in the morning on the following day (Day 27), Mrs. C fell as she went from the bedroom to the kitchen. She was taken to her local MD to evaluate and care for an abrasion on her left forearm. After that time, her daughter placed a “baby monitor” between Mrs. C’s bedroom and her home next door so that she could hear Mrs. C when she got up and down during the night.

Over the next week, Mrs. C’s overall condition improved minimally. She was referred to hospice care at that time—14 days before her death. A hospital bed was set up in Mrs. C’s bedroom. She remained ambulatory with increasing assistance until 10 days prior to her death. On that day she was unable to support her weight when transferring to the bedside commode. On the morning of August 17, 9 days before her death, Mrs. C experienced chest pain and shortness of breath. Her daughter contacted the hospice nurse who instructed her to give Mrs. C pain medication. The nurse also ordered oxygen and other medications (concentrated morphine solution, Diazepam, Haloperidol, Tylenol suppositories, Atropine solution) to have available, if needed, for symptom management. Mrs. C’s caregivers gave her the morphine solution when she was no longer able to swallow pills. Morphine 5-10 mg was given every 6 hours around the clock. On Day 4, the morphine scheduled was changed so that Mrs. C was given a dose every 4 hours. The other medications were used intermittently during the week prior to Mrs. C’s death. Diazepam was given for restlessness. Tylenol was used for fever.

### Tolerance of Study Protocol

Mrs. C agreed to complete all of the study questionnaires during the first five data collection visits. She refused to write a sentence and draw the diagram on the MMSE. At times she mentioned that she did not like having to answer all of the questions. To prevent her from potentially dropping out of the study, from the eighth assessment on, I agreed to limit the formal questions and focus on collecting observational and physiological data. Mrs. C’s granddaughter-in-law monitored Mrs. C for signs of confusion and completed the Caregiver Confusion Scale twice each day during the study. She also documented frequent comments about changes in Mrs. C’s condition.

### Delirium Episodes

Mrs. C had two delirium episodes determined by positive delirium assessments – NEECHAM score  $\leq 24$  and positive CAM. Figure E3.2 shows the trajectory of Mrs. C’s total NEECHAM scores during the study with the delirium episodes noted. Mrs. C’s first delirium episode occurred on July 27, 30 days before her death. She scored positively for delirium at the time of the scheduled weekly assessment. Mrs. C had only one positive delirium assessment with this episode. She did not score positive for delirium at the follow-up assessment the following day or during assessments over the next three weeks. The second positive delirium assessment was on August 17, 9 days before her death. Over the next 3 days, her NEECHAM scores demonstrated increasingly severe delirium until she became stuporous and essentially unresponsive 5 days before her death. During assessments over the last 5 days, Mrs. C’s NEECHAM scores were 1 and 0. She exhibited moderate to deep levels of sedation before becoming unarousable 2 days before her death. The CAM could not be scored



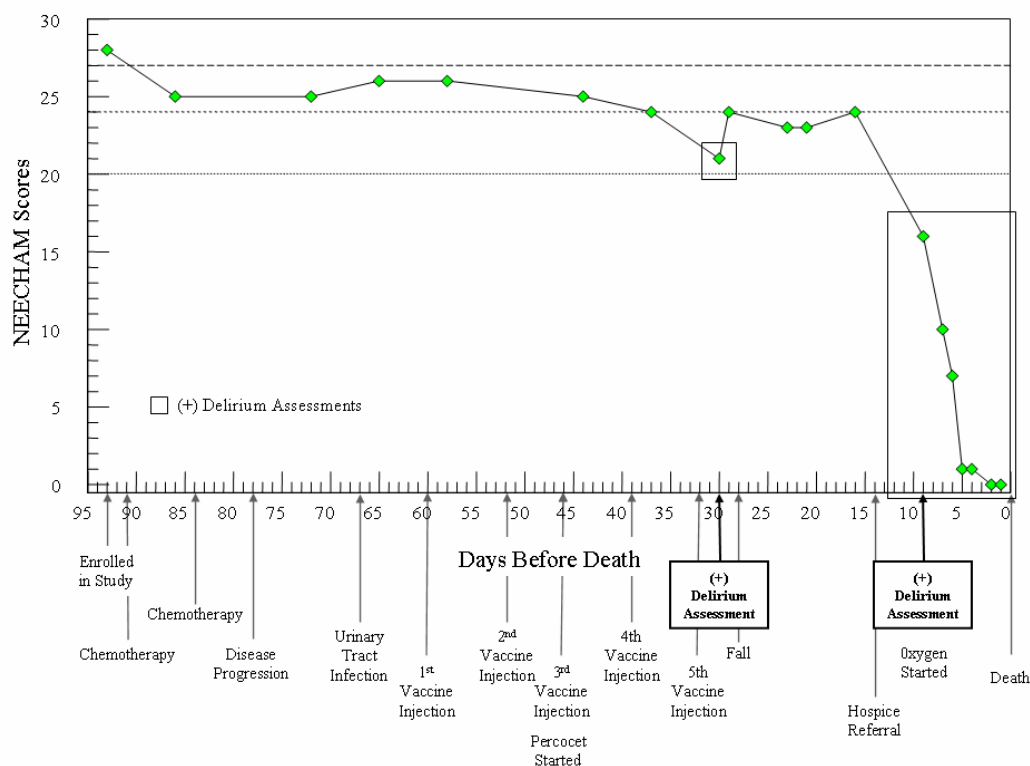


Figure E3.2. Mrs. C's total NEECHAM score trajectory with delirium episodes

### Delirium Episode #1

The first positive delirium assessment occurred during a regular weekly visit on Day 30. Two days before this episode (Day 32), Mrs. C had her final vaccine injection. That afternoon she also had a CT scan to evaluate her disease status. I visited Mrs. C in the GCRC. Both her daughter and granddaughter-in-law were with her. She was drinking liquid contrast in preparation for the scan. When she stood to go to the bathroom, Mrs. C was unsteady and shaky. Her granddaughter-in-law provided assistance, holding her arm as she walked.

During the previous week, her granddaughter-in-law documented in her daily notes that Mrs. C had been staying in bed more, sleeping a lot, and talking less. She “only talks when you talk to her.” Mrs. C also had persistent abdominal pain. She was given a prescription for Tylenol #3 tablets on Day 46. She reported increased drowsiness when she took the Tylenol #3. This was bothersome to her so she limited the amount taking one half of a tablet once or twice during the day and a full tablet prior to bed. As her abdominal pain increased, Mrs. C tended to spend more time in bed. She noted that she felt more comfortable when lying down.

When I arrived for the weekly visit on Day 30, Mrs. C's granddaughter-in-law reported that Mrs. C had been in bed all day and that she was sleeping a lot. She also noted

that Mrs. C had not eaten much over the past two days because “if she thinks of food it makes her nauseated.” She had also taken intermittent Compazine for nausea, but the exact amount and timing of doses was unknown. Mrs. C agreed for me to conduct my assessment in her bedroom. She had always been in the living room for assessments in the past. When I entered the bedroom I noted that Mrs. T was lying on her left side with her eyes closed. She responded briefly to my questions. Her voice was weak. At times I had to repeat questions or commands in order to get a response. Mrs. T did not initiate conversation and she kept her eyes closed throughout most of the assessment.

The total NEECHAM score on the day of the positive assessment was 21 and the CAM was positive. Figure E3.3 shows the trajectories of Mrs. C’s NEECHAM subscale scores. At the time of the positive delirium assessment, her NEECHAM subscale scores were: Level 1: Processing, 11; Level 2: Behavior, 7; and Level 3: Physiologic Control, 3. Her level of alertness and attention were diminished as reflected in the NEECHAM Level 1 subscale score. The Level 2 subscale score had dropped from 9 to 7 at the previous assessment. At that assessment, Mrs. C exhibited changes in her postural control and appearance, slowed motor movements, and more limited speech (verbal interaction). The Level 2 score at the time of the positive assessment was unchanged from the previous assessment. The Level 3 score, which had begun to worsen 2 weeks before, reflected Mrs. C’s physiologic instability.

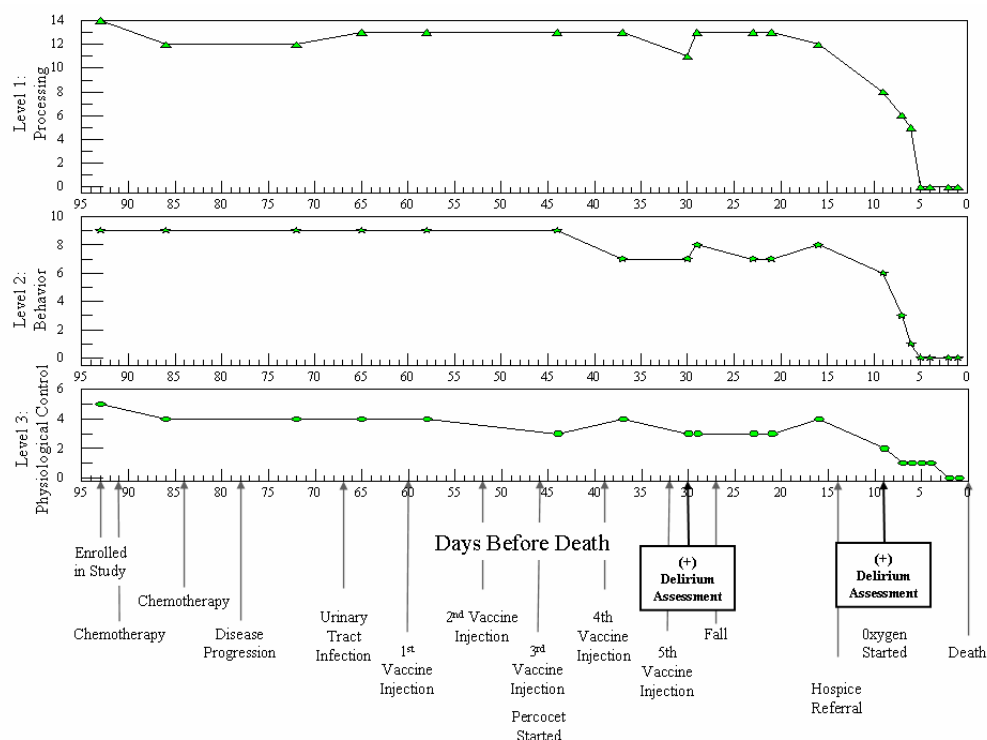


Figure E3.3. Trajectories of Mrs. C’s NEECHAM subscale scores

Figure E3.4 shows the trajectory of Mrs. C’s vital functioning. At the time of the first delirium assessment, she exhibited changes in her physiological functioning. Mrs. C’s systolic and diastolic blood pressure were elevated (167/94). Her temperature also was

elevated at 37.6 °C. Her respiratory rate, while elevated at 24 breaths per minute, did not differ from her average respiratory rate.

There was some question regarding whether Mrs. C had taken her cardiac medications that day. After that episode, Mrs. C's family began to assist her with her medications, putting them in a daily medication organizer. This would allow them to better monitor whether Mrs. C had taken her medications as prescribed.

At the follow-up assessment the next day (Day 29), Mrs. C exhibited increased alertness. She was in bed when I arrived but came into the living room for the assessment. Her NEECHAM score was 24 and the CAM was not positive.

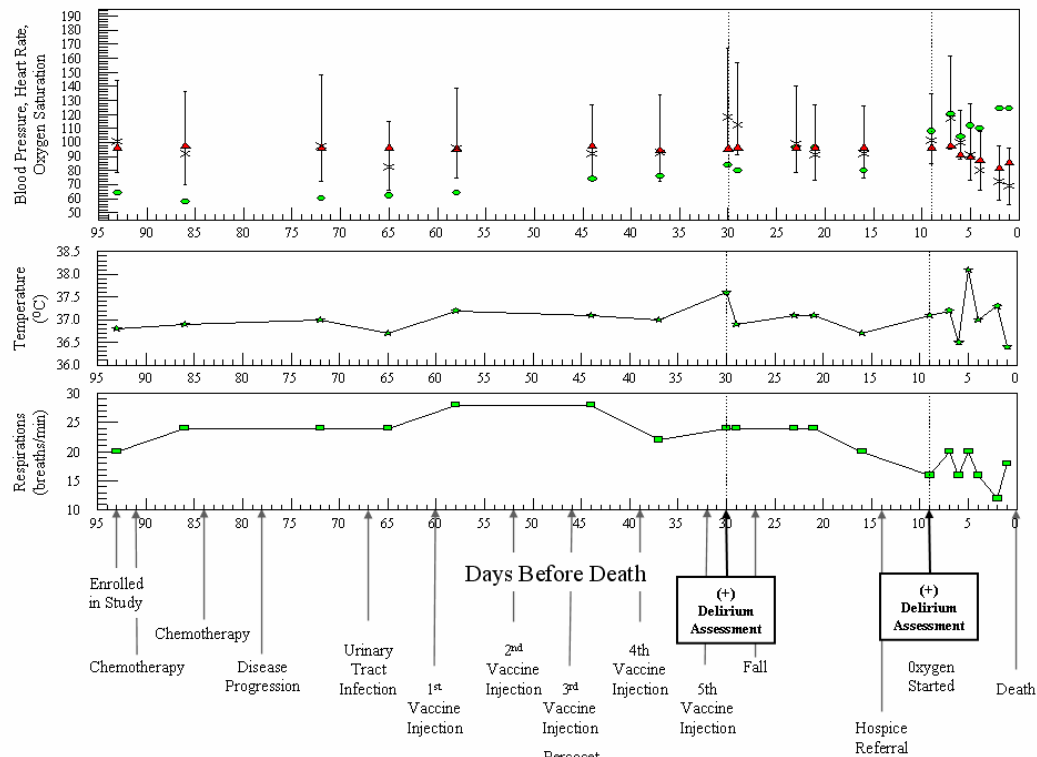


Figure E3.4. Trajectories of Mrs. C's vital functioning

### Delirium Behaviors

The delirium episode was characterized by a decrease in her level of consciousness and attention, as well as by slowed motor and verbal behavior. At the time of the positive delirium assessment, Mrs. C exhibited the following hypoactive delirium behaviors on the Delirium Behavior Checklist: diminished alertness, lethargy, slow speech, slow movements, unawareness, and apathy. No hyperactive behaviors were noted. Consistent with these observed delirium behaviors, Mrs. C's score on the sedation subscale of the Richmond Agitation-Sedation Scale (RASS) was -1, indicating that she was drowsy, and her score on the motor retardation item from the Delirium Rating Scale-Revised-98 (DRS-R-98) was 1.

### Delirium Episode #2:

Mrs. C's second positive delirium assessment was on Day 9, 21 days after the first positive assessment and 9 days before her death. As previously noted, on the morning of the second positive assessment, Mrs. C experienced chest pain and shortness of breath. She was started on oxygen at 2 L/minute, so at the time of the assessment, Mrs. C was wearing oxygen.

At the second positive delirium assessment, the total NEECHAM score was 16 and the CAM was positive. From that point on, Mrs. C's NEECHAM score declined steadily until she became stuporous and essentially unresponsive, 5 days before her death. Mrs. C's NEECHAM scores at the 4 assessments over the three weeks between the first and second positive delirium assessments ranged between 23 and 24. The CAM was negative at each of the 4 assessments – indicating that Mrs. C likely was experiencing subsyndromal delirium during this period.

Mrs. C's cognitive functioning had declined over the two weeks prior to the positive assessment. Her behavioral performance and physiological functioning had also declined. At the time of the positive assessment, the NEECHAM subscale scores were: Level 1 (Processing), 8; Level 2 (Behavior), 6; and Level 3 (Physiologic Control) 2.

At the time of the second delirium assessment, Mrs. C's systolic and diastolic blood pressures were similar to her usual blood pressure readings. Her pulse was elevated and her respiratory rate was decreased. The decreased respiratory rate may have resulted from the initiation of oxygen at 2 L/minute. Her oxygen saturation on oxygen was similar to her baseline on room air. Her temperature was slightly elevated.

After the positive assessment, Mrs. C began to exhibit physiologic instability. Her blood pressure and oxygen saturation fell during the last week, while her pulse increased. Her temperature and respiratory rate were highly variable.

### Delirium Behaviors

At the second positive delirium assessment, Mrs. C exhibited diminished alertness as well as increased slowing of her motor behavior and speech. Her score on the RASS sedation scale was -1 and her score on the motor retardation item of the DRS was 3—severe motor retardation with few spontaneous movements. She exhibited the following hypoactive delirium behaviors on the Delirium Behavior Checklist: diminished alertness, slow speech, lethargy, slow movements, and stare. On Day 7 and on Day 6, Mrs. C exhibited intermittent agitation and restlessness in addition to a diminishing level of consciousness. On Day 7, her caregiver noted, “sleeping off and on...she'll answer you sometimes—you might have to say it 2 or 3 times...talking to her self now. At this point she said she was burning something. Its hot don't you get burned...an went back to sleep...” On Day 6, her caregiver wrote, “Sleeping most of the time now. May or may not answer you when you ask her a question,” and “Talking out loud to her self. Today she was fishing. She had caught some fish.” Most often, she exhibited the hypoactive delirium behaviors noted above. Over the last week, her RASS sedation scores fluctuated, but, overall, showed a decline in her level of consciousness from lightly sedated to unarousable, two days before her death.

## Trajectories of Delirium Vulnerability

### Cognitive Functioning

#### NEECHAM Scores

Figure E3.5 shows the trajectory of Mrs. T's NEECHAM scores. Her NEECHAM scores ranged from 28 at the initial assessment to 0 the day before her death ( $M$  17.3;  $SD$  10.4). Mrs. T's only NEECHAM score in the normal range ( $\geq 27$ ) was at the initial assessment when her NEECHAM score was 28. Otherwise, from Day 86 to Day 44, her NEECHAM scores ranged between 25 and 26 – indicating that she was at risk for developing delirium. On Day 37, one week prior to her first positive delirium assessment, her NEECHAM score was 24. However, the Confusion Assessment Method (CAM) was not positive. Mrs. T was found to be positive for delirium at the weekly assessment on July 27, 30 days prior to her death. Following the positive assessment, Mrs. T's NEECHAM scores improved and ranged between 23 and 24 over the next 2 weeks (Days 29-16). The CAM was not positive during this time. Mrs. T's second positive delirium assessment occurred on August 17, 9 days prior to her death. Her NEECHAM score was 16 and the CAM was positive. Her NEECHAM scores declined steadily and the CAM remained positive over the next four days until she became stuporous and essentially unresponsive.

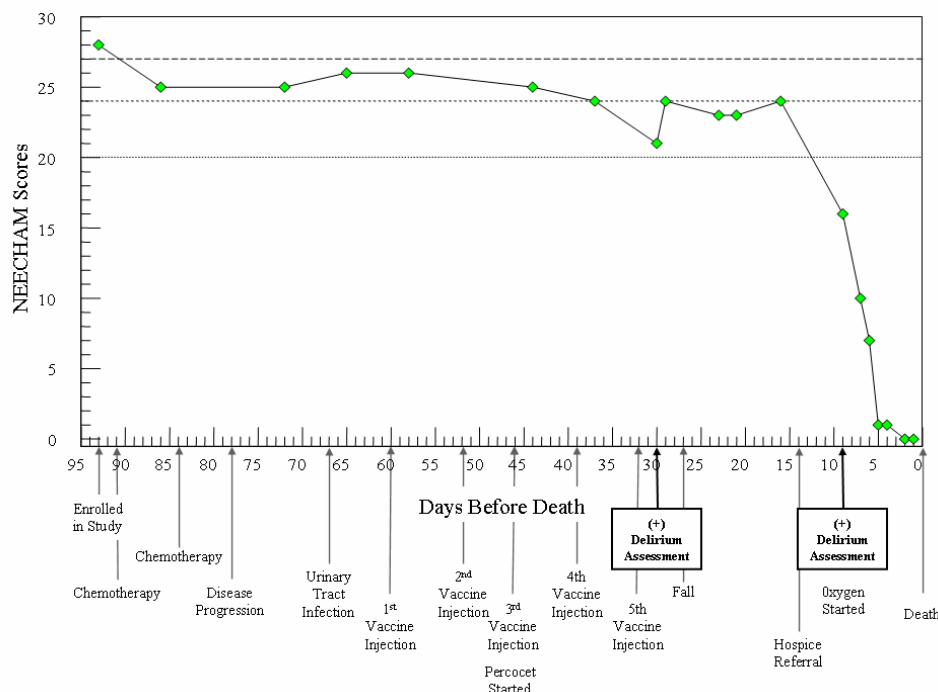


Figure E3.5. Trajectory of Mrs. C's total NEECHAM scores

Figure E3.6 shows the NEECHAM subscale score trajectories. The NEECHAM Level 1 score, representative of information processing and cognitive functioning, was

relatively stable except during delirium episodes. Even when Mrs. C demonstrated slowed cognitive processing and diminished alertness, she was almost always very attentive. For example, she would be sitting silently with a blank stare but would interject appropriately into ongoing conversations. The Level 1 score began to drop more steadily a week prior to the second positive delirium episode. The behavior subscale (Level 2) was initially stable but declined over the two weeks prior to the first positive delirium assessment. After the positive assessment, the Level 2 score remained decreased. The Level 3 subscale score was decreased initially indicating that Mrs. C's delirium risk also was physiologic. Her heart rate was slow and irregularly irregular due to atrial fibrillation and her respiratory rate was often increased. The Level 3 subscale score declined even more two weeks before the first positive delirium assessment.

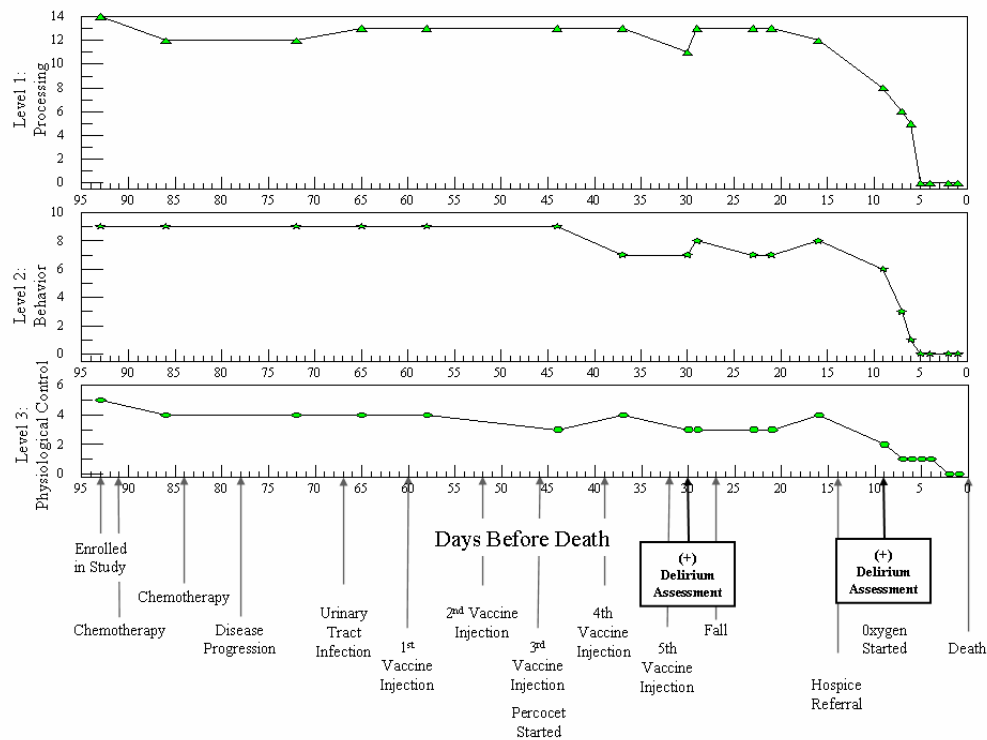


Figure E3.6. Trajectories of Mrs. C's NEECHAM subscale scores

### MMSE Scores

Table E3.4 summarizes Mrs. C's scores on the MMSE. She agreed to complete the MMSE during the first 6 assessments. She refused to complete the drawing during the second and fifth assessments and she refused to write a sentence and to complete the drawing during the sixth assessment. She intermittently had difficulty keeping up with dates and with object recall on the MMSE.

Table E3.4. Mrs. C's MMSE scores

Assessment	Total MMSE Score	Possible Total	Percentage Correct
1	27	30	90
2	25	29	86
3	27	30	90
4	30	30	100
5	27	29	93
6	26	28	93

### Depression

Mrs. C completed the Geriatric Depression Scale (GDS) during the first four assessments. Figure E3.7 shows the trajectory of Mrs. C's GDS scores. Her average GDS score was 6.0 (SD .82), indicating that Mrs. C may have been depressed. Mrs. C did not report a history of depression, but at three of five assessments she reported feeling sad occasionally or frequently (See Table\*\*\*). Following Mrs. C's death, her daughter and granddaughter-in-law questioned whether her changes in behavior over her last weeks of life were related to depression. They noted that she used to enjoy watching television but that she got to where she did not even want the TV on and if it was on she did not watch it but rather just seemed to stare across the room.

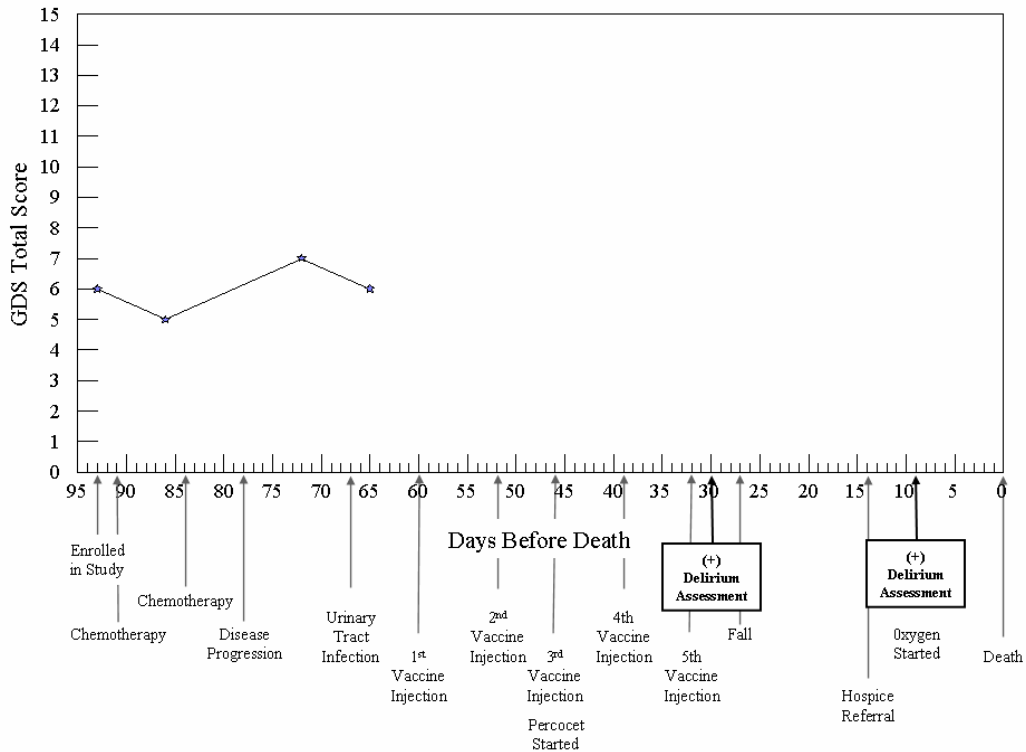


Figure E3.7. Trajectory of Mrs. C's GDS scores

### Physical Functioning

Figure E3.8 depicts the trajectory of Mrs. C's physical functioning measured by the OARS from enrollment in the study until her death. During the last 6 assessments, when Mrs. C was no longer willing or able to complete the OARS, her granddaughter-in-law reported on her ability to perform IADLs and PADLs.

Mrs. C's PADL scores ranged from a high of 14 between Days 86 and 58 to a low of 0, 9 days before her death ( $M$  9.9;  $SD$  5.2). With the exception of occasional incontinence reported at the first assessment, Mrs. C was independent in all of her physical activities of daily living (PADLs). Her PADL subscale score on the OARS remained stable over the first 5 assessments (Range 13-14). Her PADL score dropped to 12 at the 6<sup>th</sup> assessment, 44 days before her death. She reported an increasing frequency of incontinence, three times a week or more. Her PADL score remained at that level until her first positive delirium assessment at the 8<sup>th</sup> assessment on July 27, 30 days prior to her death. During the two weekly assessments following the first positive delirium assessment her PADL score was 7. Nine days before her death when she again scored positively for delirium, her PADL score was 0. Over the previous week, Mrs. C had become completely bedbound, and she began to require total assistance with her PADLs. She remained dependent in all PADLs until her death.



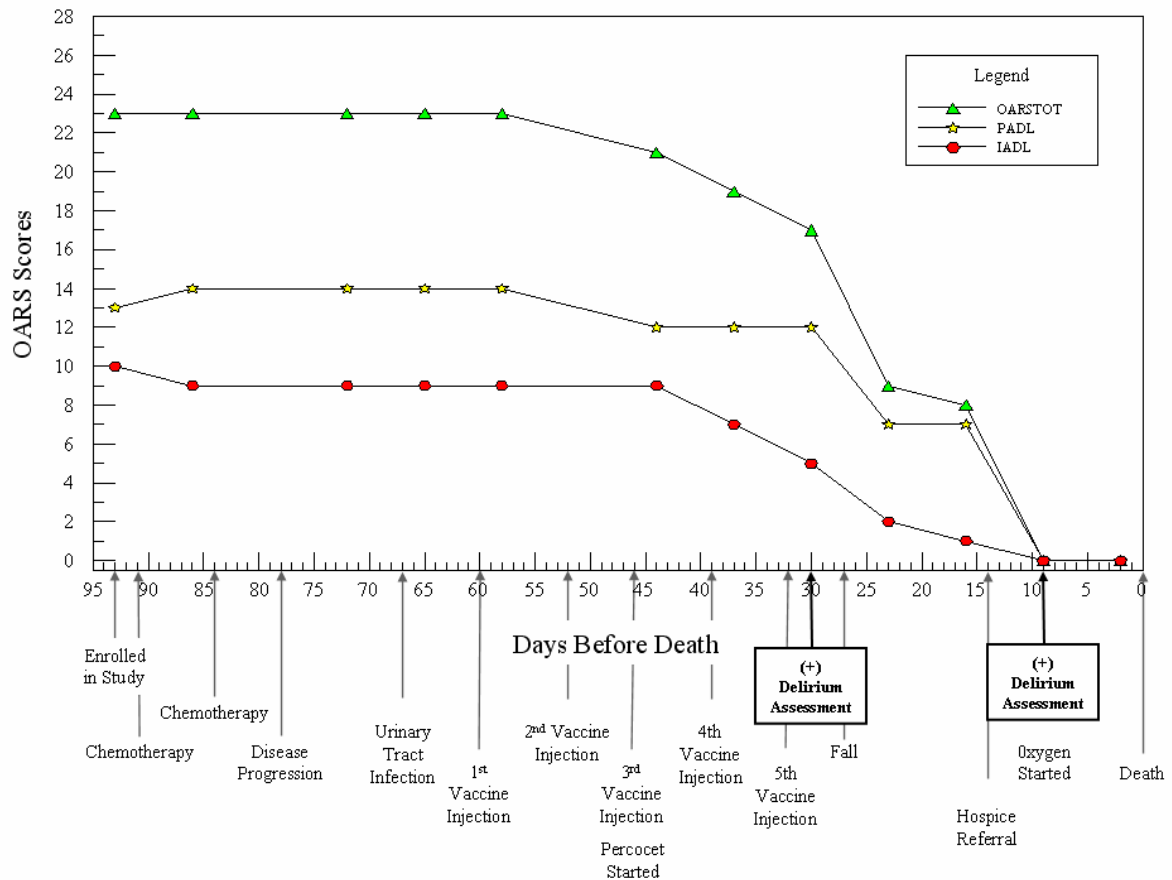


Figure E3.8. Trajectory of Mrs. C's Physical Functioning

As previously noted, Mrs. C required more assistance with her instrumental activities of daily living (IADLs). Her IADL scores ranged from 10 out of 14 at the initial assessment to 0, 9 days before her death ( $M 5.8$ ;  $SD 3.4$ ). At the time of enrollment in the study, her daughter and grandchildren provided transportation. She was able to manage her money and day-to-day buying but her daughter and granddaughter-in-law paid her bills and managed her checkbook. Mrs. C's IADL score began to decline steadily 44 days prior to her death. Her score dropped 4 points over the two weeks prior to the first positive delirium assessment. During this period, Mrs. C was unable to go shopping and do household chores. She also began to need more assistance with managing her money and with taking her medications. After the delirium episode, Mrs. C's IADL scores continued to decline steadily until 9 days before her death when she required total assistance with IADLs and PADLs.

Mrs. C's physical functioning and activity had begun to decline prior to the first delirium episode. She reported increasing incontinence and the need for more assistance with instrumental activities of daily living – shopping and household chores. Her granddaughter-in-law reported that she had been staying in bed more, sleeping a lot, and talking less. At the assessment the week prior to the delirium episode, the IADL subscale score and the behavior subscale of the NEECHAM declined. Mrs. C's PADL score during that time remained stable. Although Mrs. C's NEECHAM scores improved slightly during the two weeks after the first delirium episode, both her PADL and IADL scores continued to decline after the episode.

Mrs. C's OARS scores changed over the 21 days between the first and second positive delirium assessments. Mrs. C's IADL and PADL scores declined steadily between the first and second positive delirium assessments. At the time of the second positive delirium assessment, Mrs. C was completely bedbound and required total assistance with her IADLs and PADLs.

Mrs. C's PPS scores presented in Figure E3.9 demonstrated changes in her overall functioning. Over the course of the study, the PPS score ranged from 70 to 10 ( $M$  40;  $SD$  22.5). The PPS score initially dropped because she was unable to continue doing household chores and other IADLs. It then dropped further because she was less ambulatory and because she needed increasing assistance with PADLs. Mrs. C's PPS score declined steadily over the last three weeks of her life as she required more assistance with her care, became bedbound, and exhibited confusion and a decreased level of consciousness.

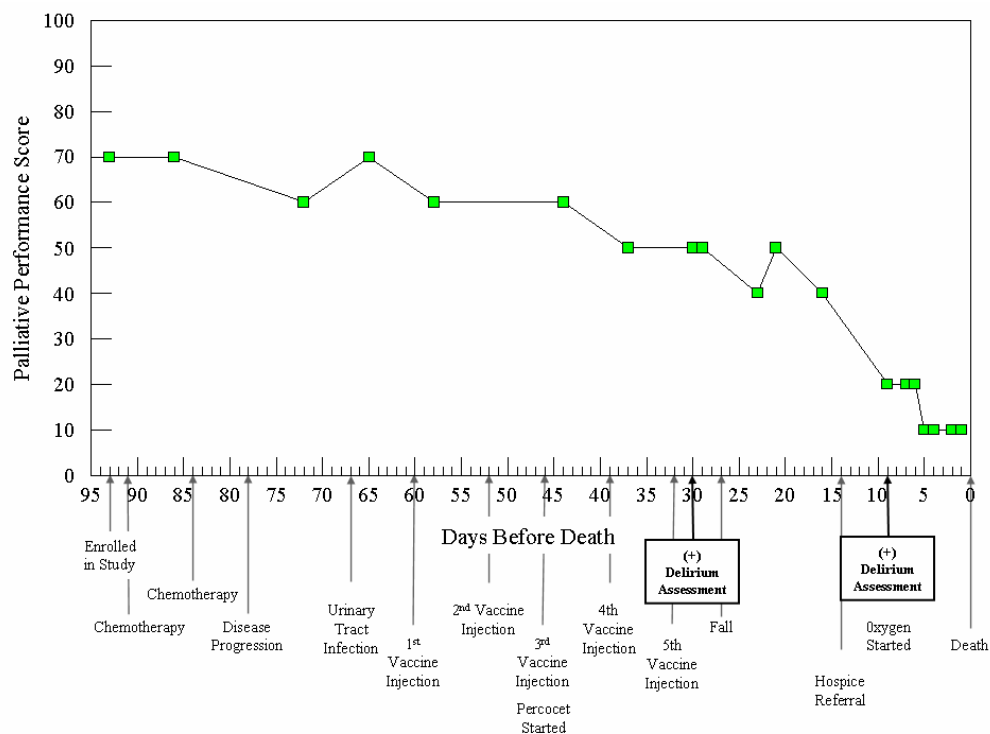


Figure E3.9. Trajectory of Mrs. C's Palliative Performance Scale scores

### Symptom Prevalence and Distress

At each of the first five assessments, Mrs. C completed the Memorial Symptom Assessment Scale—Short Form (MSAS-SF). During the sixth assessment (Day 44), she reported the presence or absence of symptoms but did not rate how bothersome the symptoms were. Figure E3.10 depicts the trajectory of Mrs. C's total number of reported symptoms. She reported having, on average, 13 symptoms ( $SD$  2.7; Range 10-17) at each assessment over the 6 assessments.

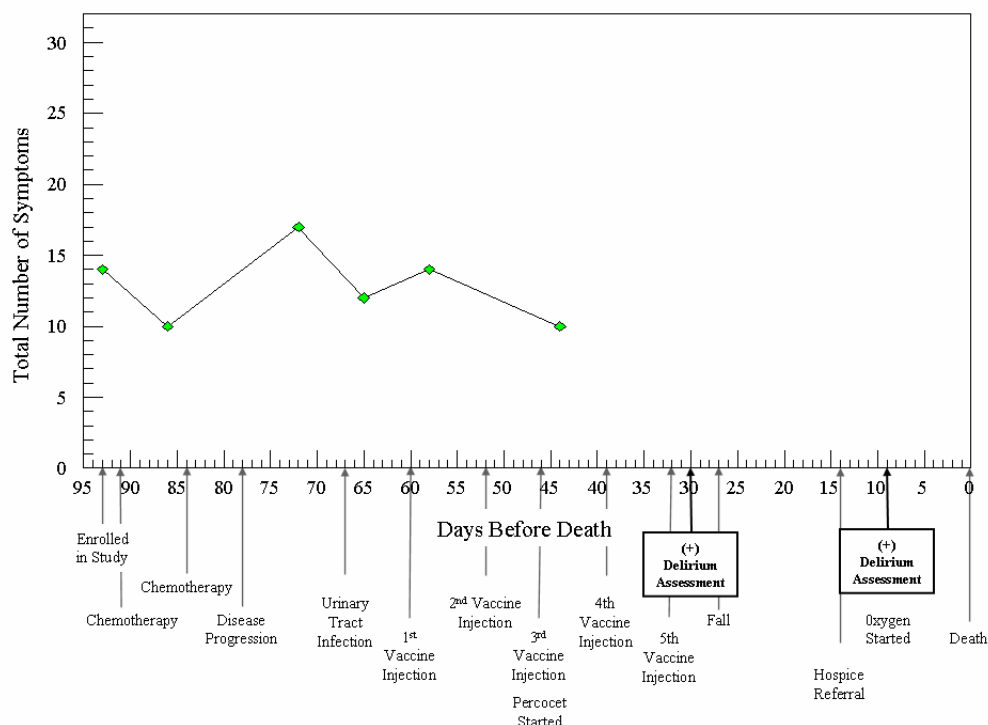


Figure E3.10. Mrs. C's symptom total trajectory

Figure E3.11 shows the trajectory of Mrs. C's symptom distress over the first five assessments. Overall, Mrs. C's symptom distress increased during this period. Her cognitive symptom distress increased sharply between second and third assessments and remained elevated. Her global distress index, physical symptom distress, and psychological symptom distress scores were increased at the fifth assessment. This increase in Mrs. C's overall symptom distress and, in particular, her cognitive symptom distress may have contributed to her request to discontinue the self-report measures during weekly assessments.

Mrs. C's most common physical symptoms, reported at each assessment, were pain, low energy, diarrhea, itching, decreased appetite, and change in taste. Among those, low energy and change in taste were the most distressing, followed by itching, pain, feeling drowsy, decreased appetite, and diarrhea. Table E3.5 shows the distress associated with Mrs. C's most common physical symptoms. Dermatologic reactions, particularly on the trunk and face, are common with Cetuximab. Mrs. C developed a rash on her scalp that caused significant itching. Hydroxyzine was prescribed to relieve the itching. The hydroxyzine, however, caused her to be drowsy. Mrs. C also experienced intermittent diarrhea, a common side effect of Irinotecan.

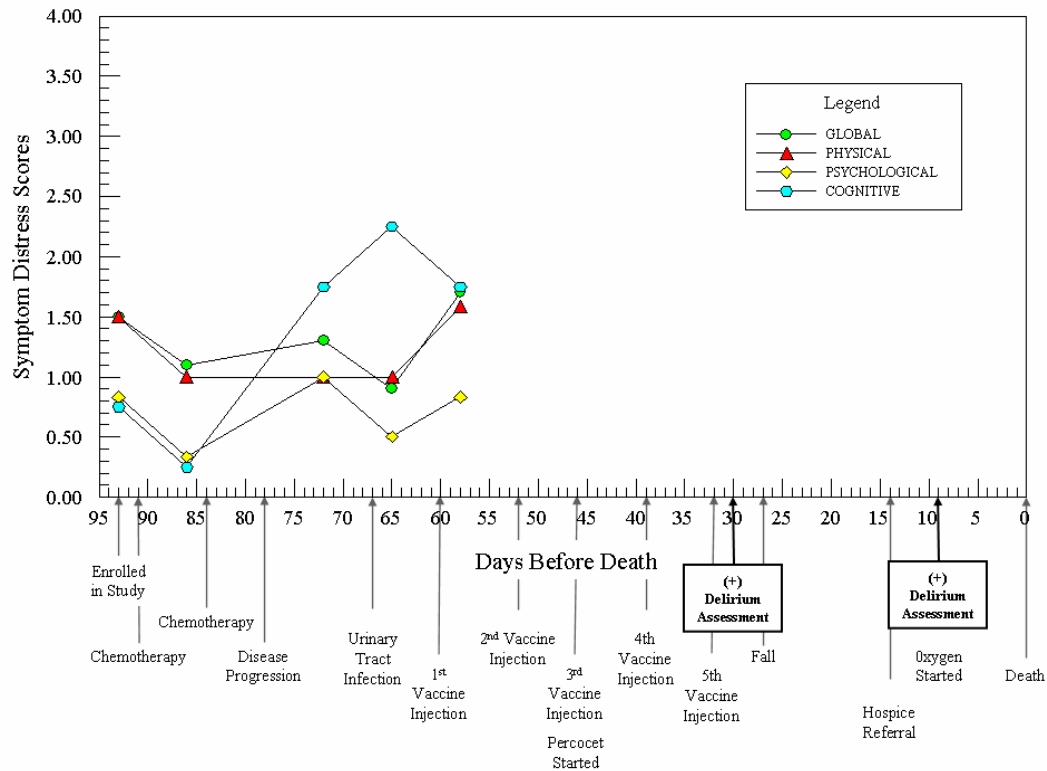


Figure E3.11. Trajectory of Mrs. C's symptom distress

Table E3.5. Distress associated with Mrs. C's most commonly reported physical symptoms.

Symptom	Frequency*	Distress		
		<i>M</i>	<i>SD</i>	Range
Low energy	5	3.36	0.36	3.2 – 4.0
Change in taste	5	3.36	0.36	3.2 – 4.0
Itching	5	2.56	1.04	1.6 – 4.0
Pain	5	2.40	0.80	1.6 – 3.2
Lack of appetite	5	2.40	0.56	1.6 – 3.2
Diarrhea	5	2.24	0.88	1.6 – 3.2

\* Includes first 5 assessments

Throughout the study, Mrs. C identified pain as a troubling symptom. She reported that her pain was associated with arthritis and her cancer. Initially, her pain was controlled with intermittent Ibuprofen and Tylenol. Over the course of the study, Mrs. C had increasing abdominal pain. She was started on Percocet, 46 days prior to her death. Her pain control improved with the Percocet but she experienced increased drowsiness that she disliked. Therefore, she tended to minimize the use of Percocet especially during the day. On Day 14, Mrs. C was given a prescription for Oxycodone 5 mg tablets. The Oxycodone tablets are small and, therefore, easier to swallow than Percocet tablets. In addition, although Mrs. C tended to self-limit the amount of Percocet she took, the recommended daily dosage of Percocet is limited by the amount of Acetaminophen, whereas, the daily dosage of Oxycodone is not limited. About a week prior to her death, when Mrs. C was less responsive, her family started administering concentrated morphine solution. On Day 6, her family began to document the medications and dosages administered. On Day 6, Mrs. C received morphine 20 mg for pain, diazepam 2.5 mg for restlessness, and 3 drops of Atropine solution for noisy lung congestion. Based on the hospice nurse's recommendation and their desire for comfort, Mrs. C's family began to administer morphine 10 mg every 6 hours on Day 5 and then increased the frequency to every 4 hours on Day 4.

Table E3.6 summarizes Mrs. C's reported frequency and distress associated with psychological symptoms. Her most common and most distressing psychological symptom was feeling sad. She also reported worrying. Mrs. C never reported feeling irritable or feeling nervous.

Table E3.6. Reported frequency and distress associated with psychological symptoms

Symptom	Frequency*	Distress		
		<i>M</i>	<i>SD</i>	Range
Feeling sad	3	1.4	1.34	0 – 3.0
Worrying	2	0.8	1.09	0 – 2.0
Feeling irritable	0	-	-	-
Feeling nervous	0	-	-	-

\* Includes first five assessments

Table E3.7 shows the reported frequency and distress associated with cognitive symptoms. Mrs. C frequently reported cognitive symptoms. The most common and most distressing cognitive symptom was feeling drowsy, followed by difficulty remembering, difficulty concentrating, and feeling confused.

Table E3.7. Reported frequency and distress associated with cognitive symptoms

Symptom	Frequency*	Distress		
		<i>M</i>	<i>SD</i>	Range
Feeling drowsy	5	2.40	0.56	1.6 – 3.2
Difficulty remembering	4	1.92	1.21	0 – 3.2
Difficulty concentrating	3	1.12	1.07	0 – 2.4
Feeling confused	3	1.00	1.00	0 – 2.0

\* Includes first five assessments

### Weight and BMI

Figure E3.12 shows the trajectory of Mrs. C's weight. Over the course of her treatment, Mrs. C had lost at least 30 pounds. Her documented weight prior to the initiation of her cancer treatment was 136 pounds. Upon enrollment in this study, her weight was 104.5 pounds; her height was 62.2 inches; thus, her initial BMI was 19.0 kg/m<sup>2</sup>. During the study, her weight increased up to 116.6 pounds because she began to develop ascites and dependent edema. Mrs. C did not stand for her weight during assessments the week of the first positive delirium assessment. Her documented weight in the clinic (111.8 pounds) two days before the positive assessment is reported. The last documented weight on Day 16 was 111.4 pounds. After that assessment, Mrs. C was unable to stand for weight measurements.

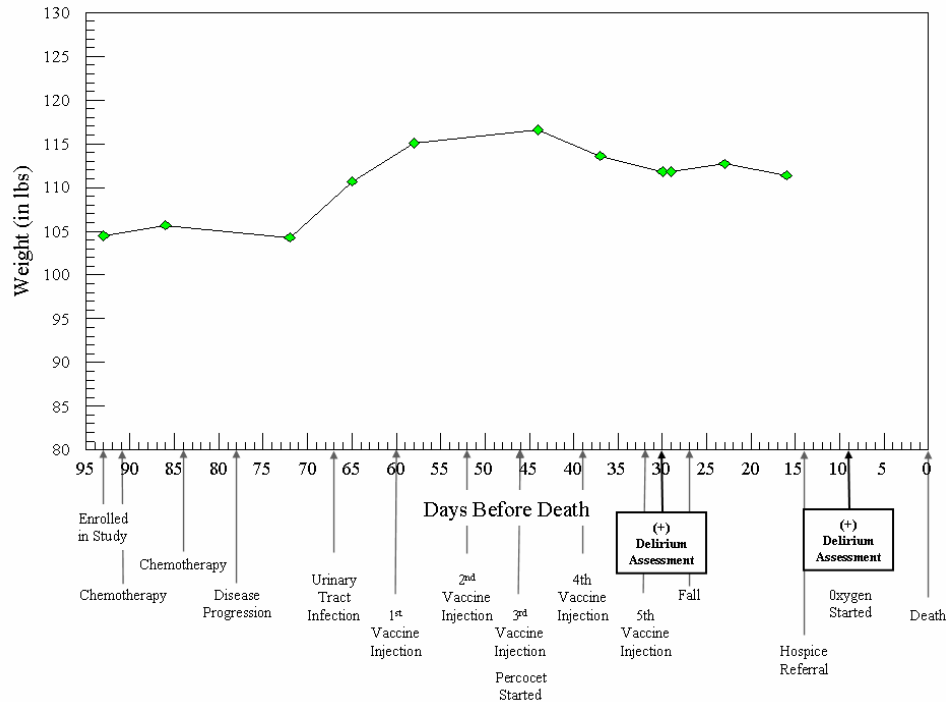


Figure E3.12. Trajectory of Mrs. C's weight

### Phase Angle

Phase angle determined by bioelectrical impedance analysis (BIA) was measured at 16 of the 19 assessments ( $M$  3.29;  $SD$  0.43; Range 2.85-4.26). Figure E3.13 shows the phase angle trajectory. The BIA measures were obtained with Mrs. C sitting in her recliner except when she was in bed. The initial phase angle was 4.26. After the initial assessment the phase angle declined to its lowest point (2.85), 37 days prior to Mrs. C's death and one week prior to the first positive delirium assessment. The phase angle then tended to stabilize except for the measurement done at the first positive delirium assessment. This value may be inaccurate because I was unable to get Mrs. C positioned appropriately. She was partially rotated onto her side and her feet were almost touching each other. When Mrs. C was unable to stand to be weighed, I used the last recorded weight to obtain BIA measures.

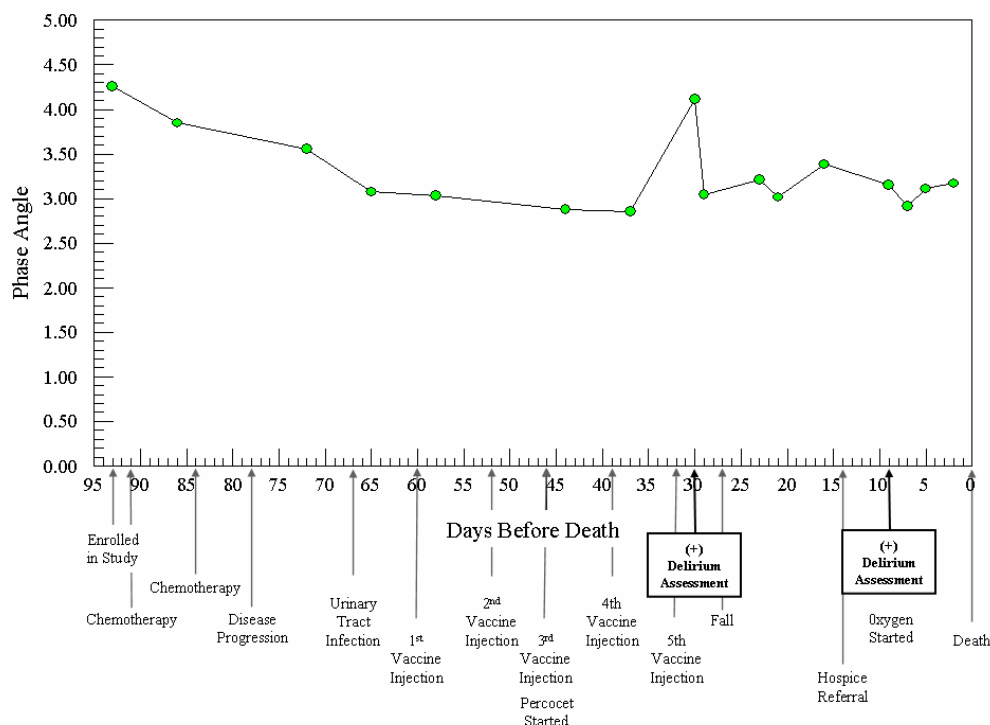


Figure E3.13. Mrs. C's phase angle trajectory

### Etiologic Risk Patterns and Clinical Markers

As previously noted, at the time of enrollment in the study, Mrs. C exhibited clinical markers for the metabolic-nutritional risk pattern. She also had risk markers for the orthostatic-dehydration etiologic risk pattern. Two weeks before enrollment in the study, her BUN/creatinine ratio was 29. In addition, at times throughout the study, Mrs. C noted dizziness with standing or she appeared unsteady when standing. Mrs. C became positive for the metabolic-toxic risk pattern on Day 46, when her albumin level had dropped to 2.7 g/dl. Thus, before her first positive delirium assessment on Day 30, she exhibited clinical markers for three etiologic risk patterns: metabolic-nutritional, orthostatic-dehydration, and metabolic-toxic. At the time of the second positive delirium assessment (Day 9), Mrs. C was on oxygen, a marker for the hypoxic risk pattern. The oxygen had been started earlier that day after Mrs. C experienced chest pain and shortness of breath.

### Caregiver Confusion Checklist

Mrs. C's granddaughter-in-law completed the Caregiver Confusion Checklist (CCC) daily in the morning and in the evening. Figure E3.14 shows the trajectory of the CCC scores over the course of the study. On Day 84, Mrs. C was started on Hydroxyzine to relieve the itching from the rash on her scalp. Two days later on Day 82, her CCC score was 1 in the morning and in the evening due to decreased alertness. Her granddaughter-in-law reported that Mrs. C stayed in bed and slept most of the day after taking 50mg of hydroxyzine during



the previous 24 hours. Mrs. C also had increased sleepiness the following day. However, on Day 80, her granddaughter-in-law noted that she was a “whole lot better.”

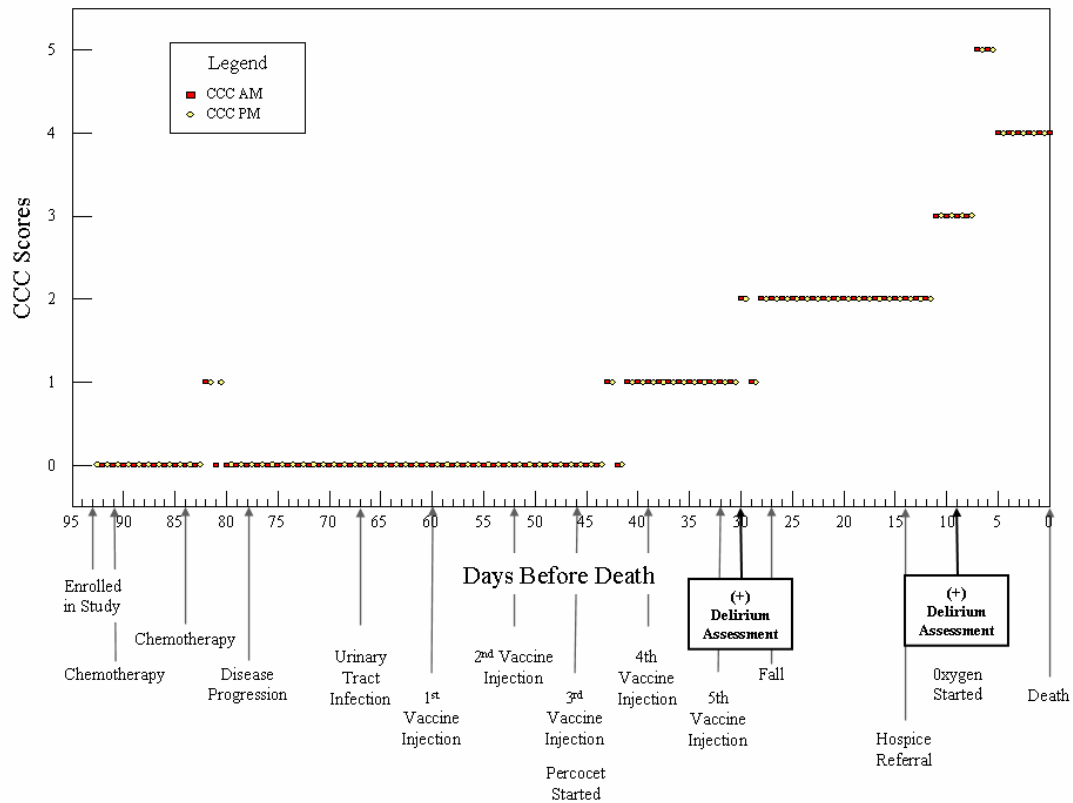


Figure E3.14. Trajectory of CCC scores

After that period, Mrs. C’s CCC scores remained at 0 until 43 days prior to her death. However, on Day 48, her granddaughter-in-law noted that Mrs. C had increased abdominal pain and that she was talking less. The CCC scores did not reflect this change in communication. After I reviewed the CCC’s with Mrs. C’s granddaughter-in-law during my weekly visit on Day 44, she began to note Mrs. C’s silence as inappropriate communication. She did not see it as a change in behavior—being more withdrawn. Over the next 14 days, Mrs. C’s granddaughter-in-law continued to score the CCC at 1, noting that Mrs. C was not talking much. She also documented that Mrs. C was “sleepy”, that she “stayed in the bed off and on”, and that she was “still (having) pain in her stomach”. On many days, Mrs. C’s granddaughter-in-law also documented that Mrs. C was “not feeling good”. The CCC scores did not reflect these changes and Mrs. C’s family never called me to report these changes – potential signs of confusion.

On the day of the first positive delirium assessment (Day 30), the CCC score was 2. Mrs. C’s granddaughter-in-law noted that Mrs. C was silent and drowsy. She continued to score the CCC as 2 except on the following day. On Day 11, she increased the CCC score to 3. On that day, Mrs. C’s granddaughter-in-law indicated that Mrs. C exhibited altered behavior. She noted that Mrs. C had slowed movements and that she was staring. She also

documented that Mrs. C was “very slow at walking”. Mrs. C’s caregivers did not notify me to report these changes. Mrs. C’s granddaughter-in-law continued to score the CCC at 3 throughout the week. When I conducted my scheduled home visit on Day 9, Mrs. C scored positively for delirium. Seven days before her death, the CCC score was 5. Mrs. C’s granddaughter-in-law noted that Mrs. C was disoriented with hallucinations. She noted, “She’ll answer you sometimes. You might have to say it 2 or 3 times”. She also documented that Mrs. C was “talking to herself now”. Mrs. C’s daughter also reported that she had given Mrs. T diazepam for restlessness. On the following day (Day 6), Mrs. C’s granddaughter-in-law noted that Mrs. C continued “talking out loud to herself”. She also noted, “Today she was fishing. She had caught some fish. At this point she is not able to tell you if (she) has to use the bathroom”. The CCC score was 4 for the 5 days prior to Mrs. C’s death. During that time, her granddaughter-in-law noted that Mrs. C was mostly unresponsive – “sleeping just about all the time”. She also noted that Mrs. C “mumbles” at times when you turn her.

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