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Parenteral hydration in advanced cancer patients: A multi-center, double-blind, placebo-controlled randomized trial

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Parenteral Hydration in Advanced Cancer Patients: A Randomized Controlled Trial

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A. INTRODUCTION

Most cancer patients decrease their oral intake before death. This decrease is mostly due to severe anorexia, nausea, dysphagia, or delirium or to patients becoming too frail to take oral fluids or nutrition. Dehydration can cause or aggravate symptoms, such as fatigue, myoclonus, sedation, hallucinations and delirium. In addition, dehydration can increase the accumulation of hydrosoluble active metabolites of the opioids often used in terminally ill cancer patients, thereby producing severe sedation, agitation, or generalized myoclonus. The difficulties associated with determining life expectancy and the complex decision-making process that includes physiologic, psychologic, ethical, legal, social, and practical aspects have contributed to the controversy of whether to give fluid to patients at the end of their lives. This controversy regarding the effects of hydration at the end of life has sparked heated debate in American media and the medical literature [Craig 1994; Mion et al., 2003; Lanuke et al., 2004; Derse, 2005, Hampson and Emanuel, 2005]. In the United States, patients with advanced cancer who have dehydration or decreased oral intake nearly always receive parenteral hydration in acute care facilities but almost never in hospices. There is a nearly complete absence of randomized controlled trials focusing on the potential advantages and disadvantages of parenteral hydration in advanced cancer patients at the end of life [Bruera et al., 2000]. The only randomized, double-blind controlled study on this topic, which was conducted by our group suggested that parenteral hydration decreased symptoms associated with dehydration in advanced cancer patients compared with placebo [Bruera et al., 2005]. In addition, several retrospective studies have suggested that hydration can reduce neuropsychiatric symptoms such as sedation, hallucinations, myoclonus and fatigue [Bruera et al., 1995; de Stoutz et al., 1995].

Our ***long –term goal*** is to understand the effect of parenteral hydration on the quality and quantity of life of the patients with advanced cancer and their primary caregivers. The ***objective of this application***, which is the next step in pursuit of that goal, is to determine the effects of hydration on symptoms associated with dehydration, onset of delirium and overall survival duration in this patient population, and understanding the meaning of hydration to the primary caregiver. The ***central hypothesis*** of this application is that parenteral hydration will improve symptoms associated with dehydration and will delay the onset and reduce the severity of delirium in advanced cancer patients at the end of their lives, and the qualitative analysis will allow us to better describe the meaning primary caregivers attribute to dehydration at the end of patients' lives. Our hypothesis was formulated on the basis of strong preliminary data from a randomized controlled trial to determine the effect of parenteral hydration on overall symptom control in advanced cancer patients with dehydration [Bruera et al., 2005]. The ***rationale*** for the proposed research is that hydration will increase the elimination of active opioid metabolites and other chemicals capable of causing delirium and fatigue and will directly improve brain function by enhancing the intracellular and intravascular volumes in the body. These patient effects may be important to primary caregiver' experiences of last days of their loved ones' lives. In addition to our supportive preliminary data, we are particularly well prepared to undertake the proposed research, because our multidisciplinary research team has the scope and breadth of expertise and experience needed to obtain definitive outcomes, including members with expertise on methodological aspects as well as highly experienced clinicians (see Biographical Sketches). In addition, the work will be conducted in a research environment conducive to its successful completion.

B. SPECIFIC AIMS

We plan to test our central hypothesis and accomplish the objective of this application by pursuing the following four *specific aims:*

1. ***Determine whether parenteral hydration is superior to placebo in improving symptoms associated with dehydration (such as fatigue, myoclonus, sedation, and hallucinations) in advanced cancer patients receiving hospice care.*** Based on our preliminary studies, the working hypothesis is that symptom burden will be lower in patients receiving hydration than in those receiving placebo.

2. ***Determine whether parenteral hydration is superior to placebo in delaying the onset or reducing the severity of delirium in patients with advanced cancer receiving hospice care.*** On the basis of our previous retrospective studies and our preliminary study, we postulate that compared with patients receiving placebo, patients receiving hydration will have a lower severity and later onset of delirium before death.

3. ***Describe the meaning patients and primary caregivers attribute to dehydration and re-hydration at the end of patients' lives.*** There are very limited data on how patients and their primary caregivers experience dehydration and re-hydration issues. This study will allow us to describe primary caregivers' experiences with hydration at the end of patients' lives.

The proposed study is *innovative* because it will use sophisticated methodology previously developed and tested by our group to determine the role of a very simple intervention (hydration) on important clinical variables. The *expected outcomes* are that the administration of hydration will improve symptoms of dehydration (fatigue, myoclonus, sedation and hallucinations), decrease the severity and delay the onset of delirium and increase survival duration. In addition, we will describe the meaning for primary caregivers of this intervention. Such results will have an important *positive impact*, because the identified outcomes have great importance for patients and their primary caregivers and will influence decision making regarding end of life care for the vast majority of cancer patients.

C. BACKGROUND AND SIGNIFICANCE

Pathophysiology of dehydration in advanced cancer patients

Fluid homeostasis depends on the maintenance of a relatively constant and stable composition of body fluids. This maintenance is achieved in normal individuals by matching daily water intake to fluid losses from the body. In normal healthy adults, water constitutes approximately 55-65% of the total body weight. This amount declines with aging and with shifts in body composition resulting in a 10-15% loss of total body water. At the age of 80, water constitutes only 45% of the total body weight. Two-thirds of the total body water is present in tissue cells and is collectively called intracellular fluid. The remaining third is present as extracellular fluid and is divided between the plasma (the intracellular compartment) and the interstitial compartment.

The amount of water lost and consumed every day in healthy adults is about 2.5 liters [Guyton et al., 1996]. Maintaining the correct proportions of extracellular and intracellular volume is vital to proper bodily function. Water is added to the body by two major means [Guyton et al., 1996]: it is injected in the form of liquids or water in the food, which adds about 2100 ml/day to the body fluid, and it is synthesized in the body as a result of oxidation of carbohydrates, which adds about 200 mL/day. The total water intake is of about 2300 mL/day.

Anorexia or cachexia occurs in most cancer patients before death. Profound anorexia may be related to the release of chemicals by the tumor or by the patient's immune system. In addition, patients frequently present with decreased taste, dysphagia, pain in the head and neck region, or psychological depression, all of which are potential causes of anorexia [Bruera et al., 1988] and decreased oral intake [Bruera et al., 1984].

Chronic nausea occurs in the vast majority of patients with advanced cancer [Bruera 1997]. In these patients, chronic nausea is associated with autonomic failure and decreased oral intake [Bruera 1986, 1987]. Therefore, chronic nausea is another major contributor to decreased fluid intake in patients with advanced cancer.

Mood and cognitive disorders are well recognized complications of advanced cancer [Bruera et al.1987; Bruera et al.,1992, Periera et al., 1998]. When patients start to develop delirium they often cannot meet self-care requisites such as maintaining sufficient intake of fluid and food. They may eat and drink less, have a decreased perception of thirst, and not be able to obtain food or fluids [Holm and Soderhamn, 2003]. In previous studies [Bruera et al. 1984, Bruera et al., 1988] we also observed that oral intake was significantly lower and malnourishment significantly frequent in patients with severe depression than in patients without depression. Therefore, both delirium and depression are contributors to decrease fluid intake in patients with advanced cancer.

Theoretical model of the effects of dehydration and parenteral hydration on symptom distress, delirium and survival

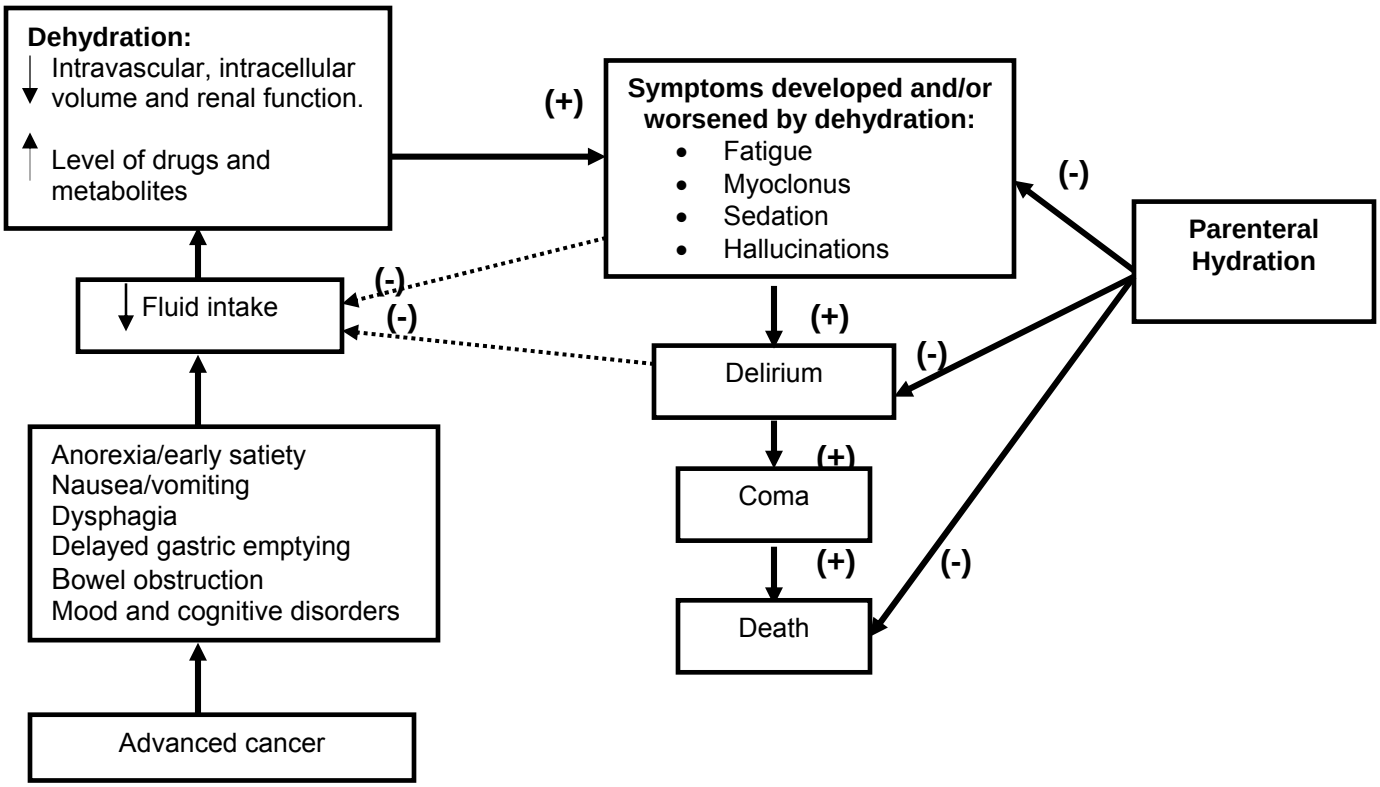
In the normal individual, maintaining a relatively constant volume of water and a stable composition of body fluids is essential for homeostasis. Therefore, the daily water intake must be balanced to match the daily loss of fluid from the body. The great majority of patients in the terminal phase of their illness experience severely reduced oral intake before death.

Figure 1. summarizes the theoretical model of the effects of dehydration and parenteral hydration on symptom distress, delirium and survival. Patients with advanced cancer experience profound anorexia/early satiety, nausea or vomiting, dysphagia, delayed gastric emptying, bowel obstruction, severe mood disorders, and cognitive impairment. These symptoms may lead to decreased oral intake and dehydration with resulting in decreased intravascular and intracellular volume, and decreased renal function and progressive accumulation in the blood level of drugs and metabolites. These changes result in the development and/or aggravation of existing symptoms including fatigue, myoclonus, sedation and hallucinations. These symptoms can further decrease the patient's ability to obtain and drink fluids and therefore increase dehydration. Small changes in fluid balance can move the patient into delirium, mostly precipitated by worsening renal function. Accumulation of

opioids or their metabolites may reach levels toxic enough to induce symptoms. The natural progression of delirium is towards coma and death, unless the symptom is successfully reversed.

We hypothesize that parenteral hydration will maintain intravascular and intracellular volume and renal function, which will decrease some of the symptoms related to dehydration, delay the onset of delirium and coma, and ultimately the moment of death.

Figure 1. Theoretical model of the effects of dehydration and parenteral hydration on symptom distress, delirium and survival.



Clinical manifestations in cancer patients with dehydration

Fatigue is reported by 60-90% of patients with advanced cancer as their most frequent and debilitating symptom [Vogelzang et al., 1997]. Fatigue consists of three major components: easy tiring and reduced capacity to maintain performance; generalized weakness (i.e., the anticipatory sensation of difficulty in initiating a certain activity); and mental fatigue, (i.e. the presence of impaired mental concentration, loss of memory, and emotional lability. Fatigue can interfere with a patient's ability to perform daily physical and social activities. In most patients with advanced cancer, fatigue is a syndrome caused by a number of physiological and psychological mechanisms [Hwang et al., 2003; Stone et al., 1999]. Cancer produces tumor by-products or induces immune cytokines capable of producing fatigue directly or indirectly by causing cachexia, muscle loss or deconditioning [Ahlberg et al., 2003; Mock 2001]. Decreased renal function results in increased metabolite levels of medications that patients receive to treat their symptoms (i.e. opioid) and that can cause neurocognitive changes and hypogonadism, which are associated with fatigue [Chlebowski et al., 1982; Rajagopal et al., 2003; Rajagopal et al., 2004]. Decreased intravascular and intracellular volumes resulting from decreased oral intake further the intensity of fatigue. In our preliminary study, all patients with decreased oral intake or dehydration reported moderate to severe fatigue [Bruera et al., 2005, Burge 1993].

Myoclonus is a neurological movement disorder characterized by brief, involuntary, twitching or "shock-like" contractions of a muscle or muscle group. These movements may be accompanied by periodic, unexpected interruptions in voluntary muscle contraction. The cortex and brain stem are thought to be the most common origins of this dysfunctional signaling [Caviness, 1996; Clouston et al., 1996]. The cause of myoclonus varies. In cancer patients, myoclonus may be associated with chronic opioid therapy [Mecadante 1998]. Hyper-excitability, hyperalgesia and myoclonus may be elicited by high doses of morphine and meperidine, which result in the accumulation of their excitatory metabolites [Woolf, 1981; Potter et al., 1989]. Other authors speculate that the neuroexitatory metabolites of opioids, such as morphine and hydromorphone, may be responsible for the simultaneous development of myoclonus and a hyperalgesic state in cancer patients treated with high doses of

opioids [Labella et al., 1989; Sjogren et al., 1993]. However, myoclonus was reported in 64% of cancer patients, regardless of the use of opioids [Steiner and Siegal, 1989]. Yoon et al. observed two patients who developed myoclonus as a result of dehydration without other medical or neurological causes, and these patients achieved complete resolution of myoclonus by hydration only [Yoon et al., 2005]. In our previous study, 71% of patients with decreased oral intake or with dehydration reported experiencing myoclonus [Bruera et al., 2005]. Taken together, these results suggest that in patients with advanced cancer, dehydration can cause myoclonus by allowing the accumulation of neuro-excitatory metabolites of opioids and other drugs.

Sedation is a symptom that consists of decreased arousal and somnolence. It is frequently an independent and distressing syndrome. Patients with severe sedation can be difficult to arouse. Sedation may result from the accumulation of sedative opioid metabolites, or it may simply be one of the manifestations of hypoactive delirium. Several retrospective studies have suggested that hydration can reduce sedation [Bruera et al., 1995; de Stoutz et al., 1995].

Hallucination is a visual, auditory, olfactory, or other sensory experience that seems real but lacks external stimuli. Hallucinations may occur as an independent manifestation of delirium or as part of a syndrome, such as delirium or acute psychosis. Our previous prospective study and retrospective studies suggested that hydration could reduce neuropsychiatric symptoms such as hallucinations [Bruera et al., 1995; de Stoutz et al., 1995, Bruera et al., 2005].

Delirium is an acute state of confusion that results from a diffuse organic brain dysfunction [Meagher, 2001; Casarett et al., 2001]. This syndrome may or may not be associated with perceptual abnormalities, such as illusions or hallucinations, delusional thoughts, psychomotor agitation or retardation, or fluctuating level of consciousness (sedation). Delirium occurs in 28 to 86% of advanced cancer patients admitted to hospice or a hospital palliative care unit [Lawlor et al., 2000; Bruera et al., 1992]. In advanced cancer patients, delirium may be due to organic failure or to non-organic factors. It is unclear how a distant tumor may alter brain physiology, but cytokines (such as interleukin or interferon) and other inflammatory mediators may contribute [Dunlop et al., 2000]. One of the most widely accepted hypotheses regarding the pathophysiology of delirium is the cholinergic hypothesis, which contends that delirium is mediated by a deficit of acetylcholine or a predominance of dopamine [Trzepacz, 2000]. Delirium can be induced by anticholinergic drugs and can be reversed with cholinergic agonists such as physostigmine or neuroleptics [Brown, 2000]. Delirium in advanced cancer is considered a multi-factorial process. Drugs, metabolic abnormalities, sepsis, dehydration, and direct cancer involvement of the central nervous system are all possible [Massie et al., 1992; Lipowski 1983]. Decreased oral intake results in dehydration and decreased renal function, which may increase the concentration of drug metabolites. Drugs are the main precipitating factor of delirium in advanced cancer patients [Karlsson, 1999]. Opioid metabolites have been found to be associated with the development of delirium [Doorley et al., 2004; Slatkin et al., 2004]. A variety of drugs may be required for symptom control in advanced cancer patients (e.g., metoclopramide, antihistamines, corticosteroids, quinolone, or anti-convulsant), and the combination of these drugs may alter cognitive function and precipitate an acute state of confusion in patients. Hyperactive delirium seems to be more frequent in liver failure, opioid toxicity or corticosteroid therapy [Tuma et al., 2000]. Hypoactive delirium has been associated with dehydration [Centeno et al., 2004]. Other common etiologies of delirium include accumulation of drug metabolites and hypercalcemia, both of which can improve rapidly with replacement of fluids. Although the prevention of delirium in patients with cancer has not been systematically examined, studies in patients with advanced cancer and the elderly have found that hydration of these patients can prevent the development of delirium [Seymour et al., 1980; Bruera et al., 1995; Inouye et al., 1999]. Hepatic and renal function deteriorate with advanced illness or as the time of death approaches, and patients become more vulnerable to delirium [Lawlor et al., 2000, Tiziana et al., 2000].

Coma and Death: Nutrition and hydration often are seen as essential aspects of human needs to support life. When oral intake is insufficient to maintain adequate hydration and appropriate organ functioning, patients will suffer progressive decrease from reduced intravascular volume to hypovolemia, hypotension, decreased renal function, shock, delirium, coma, and finally death.

Parenteral hydration in advanced cancer

When oral intake is insufficient to maintain adequate hydration, most advanced cancer patients in traditional hospitals receive parenteral fluids [MacDonald et al., 1996; Bruera et al., 1996]. In contrast, advanced cancer patients receiving hospice care almost never receive parenteral fluid [Dunphy et al., 1995; Dunlop et al., 1995; Bruera et al., 2000]. Specialists in hospice care argue against parenteral fluids and for a less aggressive approach to patient care. Furthermore, the per diem hospice funding mechanism makes the administration of parenteral fluid difficult to finance.

Advantages and disadvantages of parenteral hydration in advanced cancer patients

Our group has previously summarized these arguments for and against hydration in terminally ill patients [Fainsinger et al., 1991; Fainsinger et al., 1995]. *Arguments in favor of parenteral hydration in patients with advanced cancer are as follows:* dehydration can cause confusion, restlessness, and neuromuscular irritability; oral hydration is given to dying patients reporting thirst and therefore parenteral hydration should also be administered; parenteral hydration is the minimum standard of care in the acute care setting, and withholding parenteral fluid from dying patients may result in withholding therapies from other compromised patient groups; and dying patients have poor quality of life, so parenteral hydration should be given to reduce dehydration associated symptoms, and thus improve comfort and quality of life. *Arguments against parenteral hydration* in patients with advanced cancer are as follows: comatose patients do not experience symptom distress; less urine results in a reduced need to void or use catheters; dehydration results in less gastrointestinal fluid, nausea and vomiting and respiratory tract problems, and in a decreased frequency and severity of edema and ascites, dehydration may act as a natural anesthetic for the central nervous system, and parenteral hydration is uncomfortable and limits the patients' mobility.

One of the goals of hydration is to prevent or reverse distressful symptoms attributable to dehydration. One of the most critical arguments related to the hydration in terminally ill cancer patients concerns the relationship between delirium and symptoms of opioid-induced neurotoxicity with hydration status. Some studies have shown that the incidence of delirium in hospitalized patients may be substantially reduced by administration of fluids [Pereira et al., 1997, Bruera et al., 1995]. The adoption of a vigorous hydration program in a palliative care unit in Canada was partly responsible for the diminished incidence of delirium[Bruera et al., 1995]. Other studies have demonstrated that therapeutic interventions can reverse or improve 30-70% of episodes of delirium [Gagnon et al., 2000; Maddocks et al., 1996; Tuma et al., 2000; Breitbart et al., 2002]. In these studies, the use of opioids or other psychoactive medications, and dehydration were the most frequent causes of reversible delirium.

The common disadvantages of hydration are related to complications of intravenous fluids administration such as increased peripheral edema, ascites and pleural effusion [Morita et al., 2005] and other complications such as interferences with acceptance of the terminal condition, prolonged suffering, and the dying process, increased pulmonary secretions, cough, choking and congestion, and pain due to intravenous therapy [Dalai and Bruera, 2004]. Notably, the main argument set forth by hospice personnel for not hydrating terminally ill cancer patients is about the complexity and discomfort associated with the administration of intravenous fluids. In addition, intravenous injection requires that the patient be hospitalized and thus spend time away from home. This argument may become moot if subcutaneous hydration, a safe and simple method of parenteral hydration, is adopted in the home setting. Life prolongation might be considered a negative effect in patients who are suffering great distress, while it might be considered a positive effect in patients who are in relatively good symptom control. Unfortunately, the role of hydration on life duration has not been established in clinical trials and it is therefore impossible to determine the effects of fluids or lack of fluids in a given patient with regard to duration of life.

Volume of hydration in terminal cancer patients

In some studies [Bruera et al., 1996], adequate hydration has been achieved in terminally ill cancer patients with a much lower fluid volume than that needed by the average medical or surgical patient. The lower water requirement in this population is related to a combination of factors, which may include age, body weight, decreased insensible losses, and decreased clearance of free water. Most patients with advanced cancer are elderly and because of the shifts in body composition, the total body water content by 10-15% lower compared with that of younger adults [Guyton and Hall, 1996]. In addition, cancer-related cachexia and weight loss decrease the water required [Bruera et al., 2003, Bruera et al., 1999]. Although the daily water requirement of a 70-kg man might be about 2,100 mL, but a loss of 30 kg in body weight would reduce this requirement to 1,200 mL. In terminally ill cancer patients, who are less physically active than healthy adults or are bedridden, the water requirement drops to 800-1,000 mL/day.

There are several reports of terminal cancer patients suffering from respiratory distress due to pulmonary edema while receiving parenteral fluids; these patients received exceedingly high volumes of fluids relative to their diminished needs [Bruera et al., 1996]. In most circumstances, approximately 1,000 mL of fluid is sufficient for a 24-hour period and allows for normal urine output and adequate clinical hydration. Fainsinger et al., reported in a prospective open study of 100 consecutive patients dying in a Palliative Care Unit, 69 of whom received subcutaneous hydration for an average of 14 ±18 days, and the treatment was well tolerated in patients with an average volume of 1203 ± 505 mL per day [Fainsinger et al., 1992]. The same infusion site was maintained for an average of 4.7 ± 5.4 days. Results from our preliminary study suggest that clinical symptom

improvement can be observed with a volume of hydration of 1,000 mL per day, and that a total volume of 1,000 mL over 4 hours given subcutaneously can be easily achieved at home [Bruera et al., 2005]. Our study showed that subcutaneous infusion was well tolerated, the mean intensity of pain at the injection site was 2.10± 2.95 for patients received 1,000 mL over 4 hours and 1.75 ± 2.55 for patients received 100 mL over 4 hour (*P* =0.1). The mean scores for swelling at the injection site were 0.82 ±1.13 and 1.41 ± 1.66 for the hydration and placebo, respectively (*P* = .64).

Methods of Parenteral Fluid Administration

Intravenous route (IV): Artificial hydration has traditionally been given intravenously and usually with a peripheral line. The peripheral IV route for hydration may be problematic for terminally ill cancer patients and poses a potential problem in the home-care setting. Other disadvantages of intravenous route for hydration in such patients include pain associated with needle insertion, the need for frequent site changes, difficulty in finding venous access, the need for immobilization of the arm, impediments to mobility, the risk of increasing agitation and accidental catheter removal in patients with delirium, the need for hospitalization, high cost, need for specific training in surveillance and care and complications such as thrombophlebitis and infection. Central venous catheters have considerably improved the comfort and safety of chemotherapy in cancer patients, but they are associated with an increased risk for major adverse events including arterial puncture [Yilmazlar et al., 1997], infection [Diener et al., 1996], and thrombosis [Devie-Hubert et al., 1996].

Subcutaneous Route (hypodermoclysis): The term hypodermoclysis was initially used to describe the infusion of fluid into the subcutaneous space; it also describes the delivery of medications for symptom control. There is a good evidence showing that subcutaneous absorption of fluid is equivalent to intravenous administration [Bruera et al., 1995]. This method of parenteral fluid administration was widely accepted in clinical practice until the 1940s and 1950s [Berger, 1984], when it was replaced by intravenous infusion and is rarely used today in acute care settings. As a result, many physicians and nurses are unfamiliar with this safe and effective technique. In recent years, there has been a renewed interest in this method as an alternative to the intravenous route, and several studies and clinical experience have demonstrated its safety and practical advantages [Fainsinger et al., 1994; Slesak et al., 2003; Farrand et al., 1996; Lipschitz et al., 1991]. Initial research focused on elderly patients, but subsequent studies with terminally ill cancer patients helped establish the safety, efficacy, and tolerability of hypodermoclysis in this patient group [Fainsinger et al., 1994; Bruera et al., 1990; Bruera et al., 2005]. Although hypodermoclysis is suitable for fluid administration in a variety of clinical settings (e.g., hospital or home), its current use is primarily restricted to the geriatric or palliative care, where parenteral fluid administration is often considered for providing hydration or comfort.

Hypodermoclysis has a low incidence of adverse effects. Schen reported local edema as the only complication in 4/270 patients [Schen et al., 1981], and in another report of 634 patients, they reported that edema or heart failure resulting from volume overload occurred in 9 patients, local infection in 1 and ecchymosis in 2 [Schen et al., 1983]. Hypodermoclysis involves the simple and minimally distressful procedure of inserting a butterfly needle subcutaneously and attaching a line for fluids to be administered via an infusion pump or gravity in the home setting [Steiner et al., 1998, Ross et al., 2002]. In ambulatory patients, the abdomen, upper chest, and area above the breast may be used as the subcutaneous infusion site. In bedridden patients, preferred sites are the thighs, abdomen, and outer aspects of the upper arm [Waller at al., 1996; Sasson et al., 2001]. In a prospective study conducted at a palliative care unit, the mean duration of a subcutaneous site for the administration of narcotics was 7 days [Bruera et al., 1988]. Other advantages of Hypodermoclysis are that it is easy to manage in the home care setting and that the tubing can be connected and disconnected from the needle by primary caregivers after minimal training. In this proposed study, all patients who do not have intravenous access will receive fluid subcutaneously.

Primary caregivers' experiences with hydration at the end of patients' lives

Decision-making regarding hydration at the end of a patient's life is a source of great distress for patients and their primary caregivers [Bruera and Lawlor, 1998]. The concept of patients dehydrating or starving to death often raises strong feelings among patients, their primary caregivers, and members of the community [Morita et al., 2004; Choi and Billings, 2002]. Healthcare professionals also heatedly debate the importance of hydration and the potential benefits and disadvantages of artificial hydration. Early discussion with patients and primary caregivers about the goals of care and treatment choices, including the expected benefits and burdens, based on the best available evidence of possible end-of-life interventions (including hydration), is ethically appropriate, respects patient and family autonomy, and facilitates informed decision making. Very limited data are available on how patients and primary caregivers experience hydration and dehydration issues. Since patients vary in their ability to express their needs, and since professionals do not as a whole understand patients' views, those who

are alerted to potential needs will be quicker to respond to the earliest cues. Patients have described professionals who respond in unhelpful ways; those who were aware of the patients' perspective may be less likely to ignore important concerns or to respond in inappropriate ways [Cohen et al., 2000]. Knowledge of patterns of needs will provide a more effective base for clinical interactions and decision making. Cohen's prior research has shown that people are willing and able to describe their symptoms and health care experiences and that they can articulate the meaning of these experiences.

Ethical Considerations

Ethical analyses and justifications for this study must address, 1) a study design that includes a placebo arm, and 2) the risk-benefit analysis with special consideration of potential risks and harms to study subjects. Regarding subjects randomized to the placebo arm, these subjects will in fact be receiving “standard of care” because in the United States patients with advanced cancer at the end of life and enrolled in hospice almost never receive parenteral hydration. Thus, the placebo-arm subjects will not be denied a symptom management strategy that they would otherwise receive. Regarding the risk-benefit analysis, as stated previously, the long-term goal of the study is to understand the effect of parenteral hydration on the quality and quantity of life in terminally ill cancer patients and their primary caregivers by decreasing the symptoms associated with dehydration. In our preliminary study [Bruera et al., 2005], parenteral hydration was well tolerated and did not result in increased incidences of edema or respiratory distress in subjects receiving parenteral hydration. Further, in the preliminary study, our results suggested that hydration was able to improve the combined target symptom score and decrease myoclonus and sedation in the treatment group compared with the placebo group. A trend towards perception of overall benefit for patients in the treatment group was also observed. Thus, we believe that there is a favorable benefit-versus-risk calculation as we initiate this new study.

Team Function

Bruera, as principal investigator, has been responsible for the design of the study. Bruera and Drs. Gomez and Trumble of Odyssey Health Care, Merkelz of Vitas Hospice, Strauch of Houston Hospice and Palliative Care System, and Silverado Hospice will interact on all the logistic aspects regarding patient recruitment. These physicians have successfully interacted with M.D. Anderson Cancer Center in clinical and educational activities for many years. Bruera has collaborated with Cohen and Anderson on a number of ongoing research grants and projects. Bruera has collaborated with Palmer, biostatistician, Willey, Clinical Protocol Administration Manager, Shen, Sr. research nurse and Zhang, Sr. data coordinator in more than 100 different projects and publications. This is an experienced group of investigators with a track record of successful, harmonious, and highly effective interaction.

Anderson has actively participated in the preparation of this proposal particularly in the development of the theoretical framework and the evaluation of symptom assessment tools. Anderson will participate in the monthly investigators’ meetings and help to address administrative and patient and family assessment related issues, and will be actively involved with the data analysis and interpretation.

Cohen has actively participated the preparation of this proposal particularly in the development of the theoretical framework and development of the qualitative component of the understanding of the primary caregivers’ experiences with the hydration. Cohen will participate in the research nurses training and in the regular refresher sessions, she will participate in monitoring the quality of the interviews, the monthly investigator’s meetings and help address administrative and methodological issues, and will actively participate in the analysis, interpretation, and presentation and publication of the results. Cohen, with the help of the research nurses, will supervise and verify verbatim transcription of the audiotapes of each interview. The transcriptionist will use a common editorial software program such as Microsoft Word for transcription.

Palmer has participated in all aspects of the design of this study with particular emphasis on the theoretical framework, sample size calculation and data analysis. She will participate in the monthly investigator’s meetings and will help resolve administrative and methodological problems. She will be the main statistician leading the data analysis required for presentation, publication of our results and manuscript preparation.

Willey, in her role as project manager, has actively participated in the design, literature search, methodology development, budgeting preparation, and proposal preparation. She will coordinate training of the research nurses and actively participate in the curriculum, coordinate the monthly investigator’s meetings, and will oversee the daily operation of the study with regard to patient accrual, quality assurance, and links with clinicians, institutions, and investigators. She will participate in the data monitoring, interpretation and assisting with the preparation of abstract, manuscript and publication.

Poulter, Research Nurse Supervisor, has extensive clinical research experience in oncology, and now in palliative care and symptom research. She will be involved in coordinating hiring new staff, training the research nurses, overseeing the daily operations of the study, transferring of care to the hospice from M.D. Anderson,

coordinating the research nurse's schedule to provide adequate coverage of the hospice patients, ensuring data collection quality on the data collection forms, and will provide nursing coverage for the research nurses when they are unavailable. In addition, if the hospice census is particularly high, she will provide research nursing care, as needed to the study patients.
Pei, Sr. research nurse, will be responsible for screening patients for eligibility, patients accrual, data collection, and study administration. She will be participating in monthly research meeting to discuss problems and issues related to the study with the PI, project manager, research nurse supervisor and hospice physicians.
Zhang, will be the project data manager. She will participate in the monthly investigators meetings, be responsible of the creation and maintenance of the files, and be actively involved in the process of data management, analysis, and preparation of the results for presentation and publication.
Smith, as a full-time Clinical Ethicist for eighteen years and also with extensive experience serving on Institutional Review Boards (IRBs), participated in the preparation of the proposal, particularly by helping the team reflect on ethical aspects and issues related to the proposal design. He will be an ongoing member of the team, assisting in the writing of the protocol, abstract and informed consent form to be submitted to the M. D. Anderson IRB; and by actively participating in team meetings as scheduled, helping to address ethical issues as they arise.

Summary

Many patients in the terminal phase of their illness experience reduced oral intake before death. When oral intake is not adequate, dehydration and its symptoms result. Our preliminary study demonstrated that parenteral hydration rapidly resulted in less sedation and myoclonus and hallucinations [Bruera et al., 2005]. Other researchers' studies have also indicated that appropriate hydration can contribute to patient comfort [Bruera et al., 1995; Lawlor et al., 2000; Mercadante et al., 2000; de Stoutz et al., 1995]. Most studies on hydration in patients with advanced cancer are limited by methodological issues, and do not provide enough of the evidence-based practice of hydration therapy. In this study, we aim to determine if parenteral hydration is superior to placebo in improving symptoms associated with dehydration such as delirium, sedation, myoclonus and fatigue in advanced cancer patients receiving hospice care. By using appropriately powered, randomized, double-blind study with longer treatment period and more investigator-measured clinical outcomes than our preliminary study, The proposed project will help us to resolve some of issues that were not answered by our previous study.

Significance

Almost all cancer patients who die in acute care facilities receive intravenous fluids, whereas almost no patients who die in hospice do. Very few areas of cancer care have such a significant practice variation. Our proposed study will be the first randomized controlled trial evaluating the relative benefits and disadvantages of parenteral hydration in patients near the end of their lives. Because parenteral hydration can easily be implemented both in hospitals and in the community, the results of our study will provide data for evidence based practice with immediate implications on the care of for vast majority of patients who die of cancer. In addition, the results of our study will allow physicians, patients, and primary caregivers to better understand and decide about the appropriateness of giving or withholding parenteral fluids to patients who are near the end of their lives. Finally, the results of this study will provide important information for the design of future clinical trials addressing different modalities of hospice and community based hydration as well as research projects to better delineate the best volume and type of parenteral fluids to administer at the end of life.

D. PRELIMINARY STUDIES

The principal investigator's (PI's) initial studies on the management of dehydration in advanced cancer patients allowed us to establish the frequency of dehydration in the palliative care cancer patient population. Our group has conducted multiple retrospective studies and clinical trials on hydration in terminally ill cancer patients.

Our previous study results demonstrated that subcutaneous hydration is well tolerated in patients with advanced cancer and that patients were capable of maintaining excellent hydration with approximately 1000 mL of fluid daily [Fainsinger and Bruera. 1991, Fainsinger et al.,1994]. Retrospective studies conducted by our group revealed that parenteral hydration alone or with opioid rotation resulted in improved control of dehydration symptoms and decreased agitation among advanced cancer patients and that patients were capable of improving their symptoms and maintaining appropriate hydration with 1,000-1200 mL of parenteral fluid daily [De Stouz et al., 1995, Bruera et al., 1995]. In a retrospective study, 203 consecutive cancer patients who died in an acute palliative care unit received a mean daily volume of 1,015 ± 135 mL of fluids, and 30 patients who died in a cancer center received a mean daily volume of 2,080 ± 720 mL of fluids ($p<0.001$) [Bruera et al., 1996]. Thus, the amount of fluid that cancer patients receive in hospitals may be much higher than necessary to maintain hydration.

Traditional methods of subcutaneous hydration infusion require the regular administration of 300 U of hyaluronidase per liter of infusion. Hyaluronidase is an enzyme that reversibly hydrolyzes hyaluronic acid polymers in the extracellular space, allowing the infusion fluids to spread through a larger area and be better absorbed. We conducted a randomized controlled trail comparing 300 U and 150 U of hysluronidase before a 500 mL infusion of normal saline over one hour. We found no significant differences in swelling, edema, rash, or leakage, or the blinded preference by the patients and investigators between the two concentrations of hyaluronidase [Bruera et al., 1995]. We concluded that hyaluronidase was not routinely necessary for the administration of subcutaneous hydration.

Our previous prospective studies suggested that parenteral hydration was safe and effective in patients with advanced cancer, and our retrospective studies suggested that there might be some beneficial effects of parenteral hydration on a number of neuropsychiatric symptoms. Therefore, we conducted a pilot randomized controlled trial to determine the effect of parenteral hydration on overall symptom control in terminally ill cancer patients with evidence of mild to moderate dehydration [Bruera et al., 2005]. In this study, patients were randomly assigned to receive 1,000 mL of normal saline (hydration group, n=27) or 100 mL of normal saline (placebo group, n=22) as an infusion over 4 hours daily for 2 days. Patients who already had an intravenous access (n=12) received infusion intravenously, and patients with no intravenous access received infusion subcutaneously (n=37). We chose four target symptoms (sedation, fatigue, hallucination, and myoclonus) on the basis of results from our retrospective studies [Bruera et al., 1995; de Stouta et al., 1995; Bruera et al., 1988; Fainsinger and Bruera, 1991] and our clinical experience. Patients scored the intensity of each symptom on a scale from 0 to 10 (0 = absence of symptom, and 10 = worst possible symptom). A symptom was considered present when the score was 1 or higher, and an improvement was defined as a decrease of 1 point or more. Hydration resulted in decreased sedation and myoclonus and a trend toward decreased hallucinations (table 1). These benefits may have resulted from hydration per se or simply from an increased elimination of active opioid metabolites from patients, all of whom were receiving opioids for their pain. Our findings also suggest that clinical symptom improvement can be observed with a volume of hydration of approximately 1,000 mL over 4 hours per day.

Table 1. Symptom improvement between hydration and placebo group

	Treatment Group (n=27)		Placebo Group (n=22)		
Symptom	No. of patients with the symptom	No. of patients with Improved symptom (%)	No. of patients with the symptom	No. of patients with Improved symptom (%)	P Value
Hallucinations	11	9 (82%)	14	7 (50%)	.208
Myoclonus	18	15 (83%)	17	8 (47%)	.035
Fatigue	26	14 (54%)	21	13 (62%)	.767
Sedation	18	15 (83%)	15	5 (33%)	.005
Total symptom burden	73	53 (73%)	67	33 (49%)	.006

* A decrease of 1 point from the baseline determination on a numeric scale 0 to 10 was considered an improvement.

The main limitations of that study included the small sample size and the fact that the final assessment was conducted at the end of the infusion on Day 2, which means that the final assessment comparing the differences between the hydration and placebo groups was less than 36 hours after the intervention. It is likely that those patients receiving hydration would continue to experience significant improvement over several days while those receiving placebo would continue to deteriorate as a consequence of progressive dehydration. In our proposed study, we will conduct assessments on Day 4 (+/- 2 days), Day 7, and every three to five days until patient death. Our study will also be conducted with a much larger sample, and because of the expected deterioration in patients' ability to complete self assessment, will include a number of assessments to be completed by caregivers and the research nurses. Overall survival duration will also be included as an outcome of the proposed study. Finally, the random allocation of patients to receive fluid is a new intervention; therefore, testing the effect of hydration at the end of life may have implications for cancer care.

Delirium is a common neuropsychiatric complication in patients with advanced cancer. The Memorial Delirium Assessment Scale (MDAS) is an instrument for diagnosing and assessing the severity of delirium. We conducted a prospective study to assess the clinical utility, factor structure, and validity of the MDAS in a relatively homogenous population of patients with advanced cancer [Lawlor et al., 2000]. The previous MDAS validation study reported an optimum MDAS diagnostic cutoff score of 13 [Coyle et al., 1994], but we found a sensitivity of only 51% at this cutoff. Breitbart and colleagues acknowledged the potential limitations of the

MDAS as a diagnostic instrument, especially in the case of mild delirium [Breitbart et al., 1997; Breitbart, 1994]. Our own results demonstrated that a diagnostic cutoff score of 7 was optimal (sensitivity, 98% and specificity, 96% [Lawlor et al., 2000]. In a retrospective study, we observed that patients often present mild symptoms of cognitive failure for many days before agitation occurs, and that a relatively low volume of fluid (approximately 1 liter) per day may help prevent agitated delirium by promoting the excretion of metabolites [Bruera et al., 1995].

Co-investigator Dr. Cohen has conducted research with several patient groups. This research has included obtaining descriptions of perceptions of patients, their primary caregivers, nurses, and other healthcare professionals. Cohen has observed that patients vary in their ability to express their needs and that professionals do not as a whole understand these patients' views, professionals who are alerted to potential needs will be quicker to respond to the earliest cues. For example, in several studies, patients spoke of fearing death, but these fears were sometimes mentioned in jokes or indirectly, and the patients described nurses responding in unhelpful ways; nurses who were aware of the fear of death may be less likely to ignore the concern or to respond in other inappropriate ways [Cohen et al., 2000]. Knowledge of these patterns of needs will provide a more effective base for clinical interactions and decision making. Dr. Cohen's prior research has also shown that people are willing and able to describe their health care experiences and that they can articulate the meaning of these experiences. These people have included African Americans and Latinos. In addition, interventions have been suggested by these descriptions, and we expect in this study they will help us better understand the important aspects of hydration. Descriptions obtained from Cohen's prior research have also been useful to health care professionals who have not had the experiences being described. The "insider" experiences yield insights that provide a fuller understanding of the experiences, and our expectation is that the information obtained from analyzing the interview with primary caregivers will add new, more detailed, understanding of the important aspects of hydration. The purpose of the qualitative components of this study is to elucidate the meaning of the experiences of both symptoms and hydration.

E. RESEARCH DESIGN AND METHODS

E1. Study Design

The proposed research will evaluate the efficacy of parenteral hydration as compared to placebo in patients with advanced cancer receiving hospice care. In this randomized, double-blind trial, patients will be randomly assigned to receive 1,000 mL of normal saline (the hydration group) or 100 mL of normal saline (the placebo group) over 4 hours daily until the patient is unresponsive, develops progressive coma, or dies. Assessments will take place at baseline and daily until discontinuation of the study or death (Table II). A total of 150 advanced cancer patients with decreased oral intake or dehydration receiving hospice care will be recruited to the study.

E2. Performance Sites

This proposed study will be conducted at The University of Texas, M.D. Anderson Cancer Center. The principal investigator, co-investigators, and biostatistician are all faculty members of the institution. The research nurses, or assigned research study coordinator, from the institution's Department of Palliative Care and Rehabilitation Medicine will enroll patients into the study, administer protocol procedures in patients' homes, perform assessments and collect data. The data manager from this department will create the protocol specific database, and enter the data. All data monitoring and analysis will be performed at M.D. Anderson Cancer Center.

In acute care hospitals, all terminally ill cancer patients admitted to hospital inpatient units receive parenteral fluid. It may be difficult to randomly assign hospital cancer patients to receive no fluid. On the other hand, hospice patients receive no parenteral fluid. Thus we will recruit patients only from hospices. Seven hospices (Odyssey Health Care of Houston, Odyssey Health Care of Conroe, the Vitas Healthcare Corporation-Houston, Houston Hospice and Palliative Care System, VistaCare Hospice, Silverado Hospice, and CHRISTUS VNA Hospice) will participate in the study by screening and providing potentially eligible patients. All patients recruited for the study will be under home hospice care:

1. Odyssey HealthCare-Houston provides end-of-life care and supports to thousands of patients and their primary caregivers across the great Houston area. With 4 full time physicians, 24 full time registered nurses and 11 full time licensed vocational nurses, it provides home hospice care for cancer and non-cancer patients. On an average, 220 patients are admitted to home hospice and inpatient hospice each month. Approximately 32% of patients are diagnosed with advanced cancer. Odyssey HealthCare-Houston will be actively recruit patients for study participation. The medical director, Dr. Joseph Trumble, will be responsible for screening potential eligible patients and coordinating with the PI and the research nurses.

2. Odyssey HealthCare –Conroe is located in North Houston, with 2 full time and 8 part time physicians, and 72 nurses (RNs and LVNs). It provides home hospice and inpatient hospice care to thousands of patients at the end of life. Average admission per month is about 225. Approximately 35% of patients are diagnosed with advanced cancer. The medical director, Dr. Sandra Gomez, will be responsible for screening potential eligible patients and coordinating with the PI and the research nurses.

3. Vitas Healthcare Corporation has been a leader in the American hospice movement for the past 25 years. Headquartered in Miami, Florida, VITAS serves patients from 34 hospice programs in major metropolitan markets in 12 states including Texas. With one fulltime physician, 15 part-time physicians, 40 registered nurses, 40 licensed vocational nurses, VITAS-Houston provides home hospice and inpatient hospice care to patients in the great Houston area. Approximately 220 patients are admitted to hospice care and 65% of patients have a diagnosis of cancer. The medical director, Dr.Kenneth Unger, will be responsible for screening potential eligible patients and coordinating with the PI and the research nurses.

4. Houston Hospice, a nonprofit organization, has been providing end of life care to Houston and surrounding communities since 1980. Hospice care is provided in a home, or residential facility such as a nursing home, with the Hospice interdisciplinary team of healthcare professionals and volunteers providing services and support. Houston Hospice and Palliative Care System serve the community from four sites in the Houston area. There are eight physicians on staff and 85 registered nurses and licensed vocational nurses, approximately 195 patients are admitted to Houston Hospice each month. 62% of patients have a diagnosis of cancer. The vice president for medical affaires, Dr. Elizabeth Strauch, will be responsible for screening potential eligible patients and coordinating with the PI and the research nurses.

5. VistaCare is a leading provider of hospice care services nationwide. VistaCare provides hospice care primarily designed to reduce pain and enhance the quality of life of patients facing life-limiting illness. This hospice care is most commonly provided in the patient's home or other residence of choice, including hospitals, assisted living communities and nursing homes through their interdisciplinary teams of physicians, nurses, home healthcare aides, social workers, spiritual and other counselors and volunteers. VistaCare offers a wide range of supportive services to terminally ill patients and their families. Our staff not only treats physical pain and symptoms, but also provides emotional, social, and spiritual support for the individual and their loved ones. We also work collaboratively with area physicians and clinicians.

6. Silverado Hospice is a provider of national hospice care services, including the Houston area and surrounding communities. Its mission is to care for people afflicted with chronic disease, by maximizing their quality of life at all stages and helping their family and loved ones understand and transition through the disease and the grieving process to be one with their loved ones. Their goals include: Help the patient live each day fully and comfortably by providing effective pain control and symptom management; tailor medical, emotional, and spiritual support to the patient and the family; and comfort the family with personal counseling, resources, and bereavement support. Silverado Hospice is owned and operated by Silverado Senior Living, established in 1996 in Escondido California. There are two hospice locations in the Houston area. The administrator is Cindy S. Scott, RN, OCN, and she will be responsible for screening potential eligible patients and coordinating with the PI and assigned research staff at MDACC.

7. CHRISTUS VNA Hospice and Palliative – Houston is a nonprofit Medicare certified and licensed hospice currently serving 41 patients and their families in the greater Houston area. The hospice's interdisciplinary team includes medical doctors, nurses, hospice aids, chaplains, social workers, volunteers and support staff. They provide care to patients in their home, assisted-living facilities, personal-care homes, nursing homes and hospitals. The hospice recently completed a focused CHAP survey with no deficiencies. Clinical management of CHRISTUS VNA Hospice is provided by Dr. Carol Strickland who has been the Medical Director of the hospice for over 10 years and Debra Raught, RN, Clinical Supervisor who has 10 years of hospice clinical nursing and management experience. Joining Dr. Strickland and Ms. Raught in this hospice ministry is Tom Scott, Director of Hospice Services.

Permission to conduct the study will be obtained from the Institutional Review Board of M.D, Anderson Cancer Center, the Odyssey Health Care Corp, the Vitas Healthcare Corp., Silverado Hospice, CHRISTUS VNA and the Houston Hospice. The Protection of Human Rights Guidelines will be followed during all study related activities.

E3.Subjects

A total of 150 patients will be recruited to participate in this study. If patients meet the inclusion and exclusion criteria, and patients and their primary caregivers are willing to participate in the study, patients and their primary caregivers will be asked to provide a written informed consent. Primary caregiver is defined as a

partner, sibling, or child, older than 18 years of age who resides with the patient, and is responsible for most of patients' care. The hospice physicians (Drs. Trumble, Gomez, Unger, Strauch, Strickland and Ms. Scott), or designated hospice nurses will contact the research nurses, or study coordinators, at M.D. Anderson Cancer Center who are responsible for the study, and the PI regarding a patient's participation. While patients are on the study, routine hospice care will continue to be provided by the hospice physicians and nurses. Data from the six hospices indicate that we will be able to enroll 150 patients during a 36-month period (Average 4 to 5 patients per month)(see Study Time Line).
The gender breakdown and the race and ethnicity breakdown of the study participants will be proportional to the gender and the race and ethnicity of all patients admitted to the hospices. Information obtained from all **Seven** hospices indicates that 58% of the patients are female and that approximately 65 % of patients are white, 15 % Hispanic, 15 % African American, and 5 % Asian and others. Because the research nurses from M. D. Anderson Cancer Center will administer the fluid and will perform the assessments in patients homes, geographic limitation is required, therefore, all patients to be recruited for the study will reside within 60 miles of M.D. Anderson.

E3.1 Eligibility for participating in the study:

E3.11 Inclusion criteria for patients::

1) Patients with advanced cancer (local recurrence or metastatic disease) admitted to hospice care.
2) Patients have reduced oral intake of fluids, as determined by clinical assessment.
3) Patients exhibit evidence of mild or moderate dehydration as defined by decreased skin turgor in subclavicular region (more than 2 seconds), plus a score of ≥ 2/5 in the clinical dehydration assessment (Appendix A-11).
4) In addition to fatigue (expected to be present in all patients based on our pilot study), patients must score ≥ 1 on a 0 to 10 scale (0=no symptom, 10=the worst possible symptom) of two of the three other target symptoms (hallucinations, sedation and myoclonus).
5) Patients are 18 years of age or older.
6) Patients have life expectancy ≥ 1 week as determined by their treating physicians.
7) Patients who score < 13 (normal range) in the Memorial Delirium Assessment Scale (MDAS) and are able to give written informed consent.
8) Patients must be able to tolerate the parenteral treatment application device (butterfly cannula or intravenous access)
9) Patients must have a primary caregiver.
10) Patients must reside within 60 miles of M.D. Anderson Cancer Center. Exception to this is for patients referred from Odyssey Health Care of Conroe, patients referred from this site must reside within 75 miles of M.D. Anderson Cancer Center.

E3.12 Exclusion Criteria of patients:

1) Patients refuse to participate in the study or are not competent to give informed consent.
2) Patients are suffering from severe dehydration defined as decreased blood pressure or low perfusion of limbs, decreased level of consciousness, or no urine output for 12 hours.
3) Patients have history or clinical evidence of renal failure. Creatinine >1.5 x ULN. (M.D. Anderson Cr ULN=1.5 mg/dl). Therefore, a patient with Creatinine of > 2.25 mg/dl will be excluded.
4) Patients have history or clinical evidence of congestive heart failure.
5) Patients are not able to complete the baseline assessment forms.
6) Patients have history of bleeding disorders demonstrated by clinical evidence of active bleeding, hematuria, hematoma, ecchymoses and petechiae.
7) Patients with brain metastasis, leptomeningeal disease or primary brain tumors will be eligible for participation in this study as long as there is no evidence of altered mental status as demonstrated by a normal score on the Memorial Delirium Assessment Scale (MDAS).

E3.13 Inclusion Criteria for family caregivers:

1) The family caregiver is the patient's spouse, parent, sibling, child or significant other.
2) The family caregiver must reside with the patient and be responsible for the care of the patient. Exception to this is for patients who are admitted to In Patient hospice or nursing homes/rehabilitation centers and are under the care of the hospice.
3) The family caregiver must be 18 years of age or older.

4) The family caregiver must be willing to be interviewed by the research nurse and sign written informed consent.

E3.14 Exclusion Criteria of family caregivers:
1) The family caregiver refuses to participate in the study.
2) The family caregiver has difficulty understanding the intent of the study.

E3.2 Procedures

E3.21 Research personnel training All investigators (PI, Co-PI, collaborators and research staff) will undergo a two-day training session at M.D. Anderson, where they will review all aspects of protocol related issues and logistics of conducting the clinical trial, such as, patient screening process, communication between hospice physicians and the research nurses, pharmacy orders and infusion bag preparations, method of data collection including interviewing skills case report forms, as well as methods of patient enrollment.

At each participating hospice, the collaborator will request an approval of the protocol from the Institutional Review Board (IRB). Each collaborator will be responsible for complying with legal and regulatory requirements. Written confirmation of IRB approval will be obtained from each site, as well as the name of the committee chair and a list of committee member.

Research nurses from the department of Palliative Care and Rehabilitation Medicine at M.D. Anderson will be assigned to conduct this study. Only M.D. Anderson research staff will obtain informed consent. One Infusion Research Nurse who is not blinded to the amount of fluid to be given will be responsible for delivering the fluid bag, preparing the infusion, and initiating the infusion. One Assessment Research Nurse, or Research Assessment Study Coordinator, who is blinded to the amount of fluid given will be responsible for obtaining informed consent as delegated by the principal investigator, and assessing patients after an infusion is completed.

The Assessment Research Staff**,** who also conduct the interviews with the patients and their primary caregivers will undergo a training program conducted by the principal investigator [EB], the project manager [JW], and co-investigator [MC]. Instructions of symptom assessment using Edmonton Symptom Assessment System (ESAS) and Nursing Delirium Screening Scale (Nu-DESC) will be provided to primary caregivers. Mock interviews will be recorded, reviewed, critiqued, and discussed. Training on the other study instruments (described in "Outcome Measures" below will consist of several mock interviews that will be observed and critiqued. The research staff will evaluate study patients and primary caregivers only after they have successfully completed training. Interview training will include reducing interviewer bias, preventing the introduction of assumptions and leading statements, reflecting informants' views rather than suggesting views, and helping informants elaborate on and clarify their perceptions. Co-investigator Dr. Cohen will review the audiotapes and discuss them with the interviewers throughout the project. This procedure discussed by Tripp-Reimer [Tripp-Reimer 1985] and used by Cohen in prior research, has been successful in obtaining rich phenomenological data. The techniques in phenomenological interviewing are exactly what are required in this study. In addition, videotape Instruction for the Unified Myoclonus Rating Scale will be reviewed. The research nurses will conduct a mock practice under the supervision of the principal investigator (EB), the project manager (JW), research nurse supervisor (EP).

A monthly research meeting attended by all key personnel and research nurses of the study will be held at M.D. Anderson to discuss patient accrual, treatment and issues related to patient care.

The infusion bag of 1000 mL of 0.9% Sodium Chloride will be prepared by the M.D. Anderson investigational pharmacy. Only the infusion research nurse will not be blinded to the amount of fluid in the infusion bag. The rate of infusion will be set by an infusion research nurse according to the treatment group the patient is assigned to.

E3.22 Randomization Patients will be stratified at the time of randomization by accrual site to ensure an approximately equal representation of patients in each arm, by site. Separately for each site, a total of 150 patients will be randomly assigned to one of two treatment groups. The hydration group (n=75) will receive parenteral hydration (a 1,000 ml infusion), and the placebo group (n=75) will receive a 100 mL infusion. The randomization schema will be based on parameters input into RANLST, a randomization program developed at M.D. Anderson and supported by an NCI grant. Initially a randomization list containing order information for both arms will be made. Information about treatment assignment will then be deleted from the list given to research nurses. Patient names in sequence will be recorded on each list as the patients are entered and both lists will match patient name and identification number. Only the M.D. Anderson pharmacist and the primary statistician, and the two infusion research nurses will know the complete list of the order of randomization into the two arms

until the end of the study. However, knowledge about an individual patient's assignment to a treatment arm may be disclosed early and the patient removed from the study if the primary treating physician requests it due to adverse events. Otherwise, no other persons will know the assignment of patients to treatment arms until the end of the study.

E3.23 Treatment Plan: Patients who are enrolled in the study will continue in their routine hospice care provided by their hospice physicians. All patients will be treated in inpatient hospice or home hospice by M.D. Anderson research nurses. Treatment plan as follows:

1. Assessments will be performed at baseline and during the study (Table 2).
2. Patients will receive 1,000 ml or 100 mL of normal saline (0.9% Sodium Chloride) parenterally over 4 hours daily.
3. The fluid will be given parenterally. Patients who already have an IV access (central venous catheter or Port-a-cath) may receive the infusion intravenously. Patients who have no IV access will receive the infusion subcutaneously. Most patients (approximately 80%) in the participating hospices will have no intravenous access and therefore will receive their infusion subcutaneously. Subcutaneous injection procedures will be followed according to the "Patient Education Manual- Hypodermoclysis" which is approved by The University of Texas M.D. Anderson Cancer Center Patient Education Office © 2004 (Appendix A-1).
4. The rate of infusion will be 25 mL per hour for the placebo group and 250 mL per hour for the hydration group. An Infusion Research Nurse who will not be blinded to the patient treatment group will regulate the infusion rate, cover the IV pump and place the pump in a backpack, and will ensure the completion of the infusion. Gemstar Infusion Pump will be used for this study.
5. Each day, 2 hours [+/- 3 hours] after the completion of the infusion, patients will be assessed for symptoms and treatment related adverse effects (AEs) by an assessment research nurse, or research assessment study coordinator, who is blinded to the patient treatment group.
6. Infusions will be continued until the patient or the family refuses to continue the study, the patient develops a severe AE related to hydration, or the patient dies. The assessment research nurse, or research assessment study coordinator, will discuss the discontinuation of the infusion with the hospice physician, the PI and the patient's family. All patients will be off study at day 14 [+/- 3 days] and off study assessments will be done by the Assessment Research Staff. If the patient or caregiver wishes to continue receiving hydration fluids after the study has been completed [day 14 +/- 3 days]; they can discuss this option with their attending hospice physician. Patient may receive 1,000 ml normal saline each day subcutaneously by gravity. Treatment will be given by hospice nurse. Fluid will be provided at no cost to the patients.
7. If unexpected serious side effect occurs (during the double blind phase, the blind code will be broken), the patient will be taken off study and appropriate interventions will be provided.
8. Data collection after patients become unresponsive, unable to (i.e. severity of physical symptoms etc.) or refuse to answer questions: During the study patients may become unresponsive, unable to answer questions due to severity of physical symptoms, or refuse to answer questions. In order to minimize missing data, we will use the tools that provide accurate information about the patient's status even when the patients are unresponsive. With regards to specific aim #1, fatigue can be determined by the caregiver using the ESAS (Nekolaichuk et al., 1999), myoclonus can be assessed by the observation of the research nurse (Unified Myoclonus Rating Scale) and the caregiver, sedation will be assessed by the research nurse using RASS, and hallucinations will be assessed by the research nurse (MDAS item 7) or by the caregiver (ESAS – hallucination). With regards to specific aim #2, delirium can be assessed by the nurse (MDAS, RASS, and Nu-DESC). Specific aim #3 is related to patients' and caregivers' experiences of hydration. If patients are unresponsive, unable to (i.e. severity of physical symptoms etc.) or refuse to answer questions they will, of course, not be included in for the qualitative components of the study, and patient self-report symptom assessments and functional assessment portion of the UMRS will not be performed. This event will be documented, but will not be considered as study violation.

E3.3 Outcome Measures

Specific Aim #1: D*etermine whether parenteral hydration is superior to placebo in improving symptoms associated with dehydration (such as fatigue, myoclonus, sedation, and hallucinations) in advanced cancer patients receiving hospice care.*

We hypothesize that there will be a decreased sum of the target symptoms between baseline and day 4 (+/- 2 days) in patients receiving hydration compared with those receiving placebo. The patient, the main caregiver and the assessment research staff will complete the assessments. Patients will continue for as long as they are able to complete the assessments. The main caregiver and the assessment research staff will continue to assess the patient until the patient's death.

E3.31 Measures of Fatigue

The *patient* will rate fatigue by using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) (Appendix A-2) at baseline, day 7, and then every 3-5 days until patient is off study. The FACIT-F fatigue subscale has been used primarily in cancer patients to measure fatigue during the last 7 days. The subscale consists of 13 items. Patients rate the intensity of fatigue and its related symptoms on a scale of 0-4, from 0 "not at all" to 4 "very much". Test-retest reliability coefficients for the fatigue subscale have ranged from 0.84-0.90. This scale has demonstrated strong internal consistency (alpha=0.93-0.95) [Cella et al., 1993].

The *patient* will rate fatigue by using the Edmonton Symptom Assessment System-Fatigue (ESAS) (Appendix A-3) at baseline and daily for the first week, then every 3-5 days until patient is off study. This tool is designed by our group [Bruera et al., 1991] to assist in the assessment of nine symptoms common in cancer patients: pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, feelings of well-being and a line labeled "Other Problem". The severity at the time of assessment of each symptom is rated from 0 to 10 on a numerical scale, 0 meaning that symptom is absent and 10 that it is of the worst possible severity. The instruments and techniques are both valid and reliable in the assessment of the intensity of symptoms in cancer populations [Chang et al., 2000]. The instrument is designed for both patient and caregiver (if the patient is cognitively impaired or for other reasons cannot independently do the ESAS) to complete [Bruera et al., 1991].

E3.32. Measures of Myoclonus

The *Assessment Research* Staff will complete Section 2 and Section 5of the Unified Myoclonus Rating Scale (UMRS) at baseline, day 4 (+/- 2 days) , day 7 and every 3-5 days until patient is off study:

The UMRS (Appendix A-4) is a statistically validated clinical rating instrument for assessing patients with myoclonus [Frucht et al., 2000]. Section 2 assesses myoclonus at rest, and Section 5 assesses performance of functional tests. Because the other six sections of the UMRS can be influenced by the patient's underlying illness or symptoms or can be evaluated only if a patient completes all the sections, we will use only section 2 and 5 for our study. In section 2, each item is rated on a scale of 0 to 4, 0 "no jerks", 4 "≥ 10 jerks" in 10 seconds. In section 5, each item is rated on a scale of 0 to 4, 0 "normal", 4 "can not complete the task". The assessment will be performed according to "Videotape Instruction for the Unified Myoclonus Rating Scale" (see Appendix A-4).

The *patient* will rate the symptom score at baseline and daily for the first week, then every 3-5 days until patient is off study by using the ESAS-Myoclonus. In addition to measuring a patient's response to ten common symptoms, ESAS includes other symptoms to be measured. For the purpose of this study, we will measure myoclonus in the past 24 hours using a 0 to 10 numerical scale. 0 "no jerks", 10 "worst possible jerks". This is one of the four dimensions of the ESAS that were identified as target symptoms in our preliminary study [Bruera et al., 2005].

E3.33 Measures of Sedation

The *Assessment Research* Staff will complete this assessment at baseline and daily for the first week, then every 3-5 days until patient is off study by using The Richmond Agitation-Sedation Scale (RASS) (Appendix A-6). RASS was designed to have precise, unambiguous definitions for levels of sedation that rely on an assessment of arousal, cognition, and sustainability using common responses (eye opening, eye contact, physical movement) to common stimuli (spoken voice, physical stimulation) presented in a logical progression. RASS has five levels of sedation in addition to level 0, which corresponds to a calm, alert state. RASS can be administered in 30-60 seconds, using three sequential steps: observation, response to auditory stimulation, and response to physical stimulation. RASS has been validated and has shown high reliability and validity in medical, surgical, sedated and non-sedated adult patients in an intensive care unit [Sessler C et al., 2002].

The *patient* will score drowsiness at baseline, daily for the first week, then every 3-5 days until patient is off study by using the ESAS-Drowsiness. The sedation/drowsiness item in the ESAS will be used to measure patient's levels of sedation in the last 24 hours.

E3.34. Measures of Hallucinations

The *Assessment Research* Staff will complete this assessment to assess patients' hallucinations at baseline and daily for the first week, then every 3-5 days until patient is off study by using The Memorial Delirium Assessment Scale-Item 7 (Perceptual Disturbance) (Appendix A-5). The Memorial Delirium Assessment Scale (MDAS) is a clinician rated 10-item severity rating scale. Each item is scored from 0 to 3 depending on its intensity and frequency (possible range, 0-30). It has been successfully used in a variety of settings [Marcantonio et al., 2001; Fann et al., 2002]. Items included in the MDAS reflect the diagnostic criteria for delirium in the DSM-IV as well as symptoms of delirium from earlier or alternative classification systems. Scale items assess disturbances in arousal and level of consciousness, as well as several areas of cognitive functioning (e.g., memory, attention, orientation, disturbances in thinking) and psychomotor activity. Item 7 (Perceptual Disturbance) is to evaluate a patient's misperceptions, illusions, and hallucinations inferred from inappropriate behavior during the interview or admitted by the subject and those elicited from the nurse or family accounts of the past several hours or of the time since last examination. The scale is 0 "none", 1 "mild" misperceptions or illusions related to sleep, fleeting hallucinations on 1-2 occasions without inappropriate behavior; 2 "moderate" hallucinations or frequent illusions on several occasions with minimal inappropriate behavior that does not disrupt the interview; 3 "severe", frequent or intense illusions or hallucinations with persistent inappropriate behavior that disrupts the interview or interferes with medical care.

The *patient* will score the symptom at baseline and daily for the first week, then every 3-5 days until patient is off study by using the ESAS-Hallucinations. In addition to measure patient's responses to ten common symptoms, the ESAS includes two extra symptoms to be measured. For the purpose of this study, we will measure hallucinations in the past 24 hours using a 0 to 10 numerical scale. 0 "no hallucinations", 10 "worst hallucinations". This is one of the four dimensions of the ESAS that were identified as target symptoms in our preliminary study [Bruera et al., 2005].

Specific Aim #2: Determine whether parenteral hydration is superior to placebo in delaying the onset or decreased severity of delirium in patients with advanced cancer receiving hospice care

Overtime, we expect that approximate 85% of our patients will become delirious and unresponsive. We hypothesize that compared with placebo, hydration will delay the onset delirium and reduce its severity. In order to accomplish this aim, we will use the following instruments to diagnose and determine the severity of delirium:

E3.35 Measures of Delirium

The *Assessment Research* Staff will complete the assessment of delirium by using the MDAS to measure the severity of delirium, the RASS to the characteristics of delirium (agitation versus sedation), and the Nursing Delirium Screening Scale (Nu-DESC) to capture the day-to-day fluctuations in the overall syndrome of delirium.

The Memorial Delirium Assessment Scale (MDAS) (Appendix A-5) is a clinician rated 10-item severity rating scale and is used to assess patient's severity of delirium in the past several hours. Each item is scored from 0 to 3 depending on its intensity and frequency (possible range, 0-30). The 10 Items are anchored with statements reflecting the severity or intensity of the symptom and were reviewed by experienced clinicians to ensure ease of administration and ability to generate accurate (reliable) ratings. The resulting scale, which requires approximately 10 minutes to administer, integrates behavioral observations and objective cognition testing. When items cannot be administered, scores can be prorated from the remaining items to an equivalent 10-item score. The MDAS is highly correlated with existing measures of delirium and cognitive impairment, yet offers several advantages over these instruments for repeated assessments which are often necessary in clinical research [Breitbart et al., 1997]. The MDAS has been validated in an advanced cancer population: a diagnostic cutoff score of 7 gave optimum results in relation to the presence or absence of delirium with sensitivity of 97% and specificity of 95% [Lawlor et al., 2000]. This assessment will be performed at baseline and daily for the first week, then every 3-5 days until patient is off study

The Richmond Agitation-Sedation Scale (RASS) (Appendix A-6): Psychomotor agitation is one of the most distressing aspects of delirium, particularly for the families of affected patients (Bruera, et al., 1992). Patients with similar levels of delirium may have very different levels of agitation. The Richmond Agitation-Sedation Scale (RASS) measures the predominant features of delirium (agitation or sedation) in a very precise, unambiguous way on a daily basis. Previous observations by our team (Bruera, et al., 1995) suggest that hydration had a major effect in decreasing psychomotor agitation. RASS will be used daily to determine the predominant features of delirium.

Nursing Delirium Screening Scale (Nu-DESC) (Appendix A-7): Nu-DESC is a brief observational instrument that does not require patient participation and therefore it is very well suited for daily assessment of the fluctuating elements of delirium. This five-item scale includes four items of the **Confusion Rating Scale (CRS) and a brief nursing delirium screening instrument** that does not require patient participation and is adapted to the fluctuating nature of delirium, because it provides continuous cognitive status assessment as well the delirium symptoms monitoring. The Symptoms, such as **disorientation, inappropriate behavior, inappropriate communication, illusions or hallucinations, and psychomotor retardation** will be assessed. Each symptom is rated from 0 to 2 based on the presence and intensity of that symptom. The total score ranges from 0 to 10. The Nu-DESC, which takes less than 2 minutes to complete, is psychometrically valid and has a sensitivity of 85.7% and a specificity of 86.8% [Gaudreau et al., 2005]. In oncology inpatient settings, the Nu-DESC is a widespread clinical assessment tool and has shown promise as a research instrument. In our proposed study, the assessment research nurse, or study coordinator, will use the Nu-DESC daily to assess patient's delirium status by direct observation and by questioning the main caregivers. The patient's primary caregiver will be instructed to observe for the five symptoms during the two 8-hour periods following the nurse's assessment and rate the symptom severity. The scores provided by the primary caregiver will give us important information regarding the patient's delirium status, however, the nurse's assessment will be primary outcome for the diagnosis of delirium.

The Nu-DESC is not able to characterize the abnormalities in cognition, thought process, perceptions, and level of consciousness as the MDAS does, but it provides for a simple and reliable estimation of the presence of delirium. We believe these two tools are complementary because the Nu-DESC will be able to capture the day-to-day fluctuations in the overall syndrome of delirium while the MDAS will be able to define in much better detail the different specific abnormalities as they develop over time as a consequence of dehydration. One possible outcome of this study is that the onset of delirium (as measured by MDAS and Nu-DESC) may not be delayed or avoided by hydration, but agitation (as measured by RASS) may be reduced. In that case the hydration group would experience no difference in MDAS and Nu-DESC scores compared with the placebo group but significantly low agitation scores in the RASS. The fluctuation of symptoms of delirium will be monitored using Nu-DESC. We will compare the results of the Nu-DESC at baseline and during follow-up in both patient groups. The fluctuation in the symptoms of delirium will not likely have an impact on the early symptoms before patients developed delirium (main outcome of our study) as well as on the moment of onset (another major outcome) or the overall survival.

Specific Aim # 3: Describe the meaning patients and primary caregivers attributed to dehydration and re-hydration at the end of patients' lives

D3.36 Collection of patient and family caregiver experiences: We developed an interview guide for both patients and family caregivers on a very small pilot study to address its feasibility. Four pairs (4 patients and 4 corresponding family members) were approached in the inpatient palliative care unit. Two pairs did not want to talk, one because they had just gotten some upsetting news, and the other because the patient was in considerable pain and staff members were working on pain management. The other pairs were willing to talk. While the content of their views on hydration of the other two pairs may well differ from those of patients who are not hospitalized, but both patients viewed hydration as "medicine", and said it was not food because they did not feel full after getting the hydration. Both had experienced dehydration during their illnesses, and it had resulted in visits to the emergency room and hospitalization. The caregivers described in detail how they work to manage fluids and other medication for their loved ones. One spouse kept notes, and had a "schedule" of what he needed to do and when each procedure was needed. He developed these both from watching nurses at the hospital, and from discussing this with a nurse who "sat down, said 'You'll be fine,' and then helped me work out what I needed to do." In this proposal, we will seek to understand the meaning of the hydration for both patients and their caregivers. From our pilot interviews we developed the following beginning interview guide for patients: (1) Please tell me what it has been like for you to get fluids. We are interested in what is important about these fluids; (2) Are these fluids more like food or more like medicine? Please describe your response; (3)Have you ever gotten dehydrated? Please tell me about that; (4) How do you manage your care? We will also seek to obtain information about caregiver distress or feelings about the hydration and the care that caregivers are providing by asking the caregivers: (1) Please tell me what it has been like for you for your family member to get fluids. We are interested in what is important to you about these fluids; (2)Are these fluids your family member is getting more like food or more like medicine? Please describe your response; (3) Has your loved one ever gotten dehydrated? Please tell me about that; (4) How do you manage your loved one's care? As in all phenomenological interviews, the interviewer will take the lead from the person being interviewed, and follow

their conversation. The interviewer will ask for examples, have the person being interviewed "say more about that", and ask for more details and clarification.

If patients are unresponsiveness on day 4 of the study, they will of course not be included for the qualitative components of the study.

These questions will be asked at baseline and on day 4 (+/- 2 days) of the treatment. This interaction will be tape recorded, transcribed verbatim and analyzed. The project manager will conduct weekly quality improvement with all the research nurses by discussing the content of the interviews. Focus will be on appropriate techniques for interviewing. Co-investigator Dr. M. Cohen, who will be analyzing these transcribed interviews, will also alert the research manager and staff should problems be noted in the techniques the nurses are using. She will meet with the research nurses to discuss any issues or changes in the quality or consistency of these interviews.

E3.37 Other Assessments

The *patient and primary caregiver* will score patients' symptoms by using:

The Edmonton Symptom Assessment System (ESAS) (Appendix A-3): As mentioned under "Measures of fatigue" the ESAS measures responses to 10 common symptoms (pain, fatigue, nausea, depression, anxiety, drowsiness, constipation, shortness of breath, appetite, feelings of well-being). Patients and their caregivers rate the intensity of symptoms during the last 24 hours on 0 to 10 numerical scales from 0 "no symptom" to 10 "worst possible symptom". The instruments and techniques are both valid and reliable in the assessment of the intensity of symptoms in cancer populations [Chang et al., 2000]. The instrument is designed for both patient and caregiver (if the patient is cognitively impaired or for other reasons cannot independently do the ESAS) to complete [Bruera et al., 1991]. The reliability of symptom rating has been tested in patient with advanced cancer, nurse and family caregiver [Nekolaichuk C, et al., 1999]. The ESAS will be assessed at baseline, daily for the first week, and then every 3-5 days until patient is off study.

Global Symptom Evaluation (Appendix A-9): This instrument is used to estimate the minimal important difference in symptoms (fatigue, myoclonus, sedation, hallucinations and delirium) before and after treatment. Patients will be asked about their symptoms (worse, about the same, or better) after starting treatment. If their answer is "better", they will be asked to rate how much better their symptoms are (almost the same, hardly any better at all, a little better, somewhat better, moderately better, a good deal better, a great deal better, or a very great deal better). If their answer is worse, patients will be asked to rate how much worse their symptoms are (almost the same, hardly worse at all, a little worse, somewhat worse, moderately worse, a good deal worse, a great deal worse, or a very great deal worse). This tool has been used in a number of symptom researches [Redelmeier et al., 1996; Guyatt et al., 1993]. Global Symptom Evaluation will be assessed on day 4 (+/- 2 days) and day 7.

Perception of Treatment Received (Appendix A-10): This questionnaire is used to assess the perception of the treatment the patient received during double blind clinical trials of the patients and their primary caregivers. It consists of one question ("What kind of study treatment do you think you or your loved one received in the last 3 days?") with a choice of three answers (Hydration, placebo, and I don't know). We have used this questionnaire for several of our double-blind clinical trials [Bruera et al., 2004, Bruera et al., 2005]. This assessment will be performed on day 4 **(+/- 2 days) and 7.**

The Assessment Research Staff will complete the following assessments at baseline, daily for the first week and 3-5 days until patient is off study:

Peripheral Edema (Appendix A-11) The severity of peripheral edema will be determined through the examination of seven regions: the hands, forearms, upper arms, feet, lower legs, thighs and trunk. Peripheral edema severity is scored based on the degree of increased skin thickness in the middle of each region (0=none; 1=mild, thickness of < 5 mm; 2=moderate, 5-10 mm; 3=severe, >10 mm). If peripheral edema is asymmetric, the more severe side will be rated unless the asymmetry was caused by a unilateral vascular obstruction; in this case, the non-obstructed side will be rated. The peripheral edema score (range 0-21) will be calculated as the total of the severity scores for the seven regions. A higher score indicates more severe edema. This assessment method has been used in patients with advanced cancer [Morita et al., 2005].

Respiratory Tract Secretion (death rattle) (Appendix A-11): Bronchial secretion is defined as sounds audible at the bedside produced by the movement of secretions in the hypopharynx or the bronchial tree in association with respiration [Ellershaw et al., 1995]. An increase in bronchial secretions has been expressed as one

potential side effect of parenteral hydration [Regnard and Mannix, 1991;]. Bronchial secretions, also known as "death rattle", occur in approximately 50% of patients who die of cancer; however, prospective studies have not observed an association between the level of hydration and the development of respiratory tract secretions [Ellershaw et al., 1995]. In this study, we will use a scale of 0 to 3 [Back et al., 2001] to assess the volume of noise produced by the respiratory tract secretion, 0=inaudible; 1=audible only very close to the patient; 2=clearly audible at the end of the bed, in a quiet room; 3=clearly audible at about 20ft (9.5m) (at the door of the room).

Other side effects (Appendix A-11): All side effects related to treatment will be recorded according to NCI common toxicity criteria. If unexpected serious side effects occur, the nurse will report them to the PI and hospice treating physician immediately, and appropriate medical action will be taken immediately according to standard clinical practice. Serious side effects will be reported according to M. D. Anderson Cancer Center Toxicity Reporting Guidelines, and the patient will be withdrawn from the study.

Clinical Dehydration Assessment (Appendix A-11): This dehydration assessment scale has been used in a prospective study in cancer patients [Morita et al., 2005]. The degree of dehydration will be assessed on the basis of three physical findings, moisture on the **mucous membranes of the mouth** (0=moist; 1=somewhat dry; 2=dry), **axillary moisture** (0=moist; 1=dry) and **sunkenness of the eyes** (0=normal, 1=slight sunken, 2=sunken). These signs are selected due to their significant correlations with biological dehydration, as previously confirmed in elderly patients [Eaton et al., 1994; Gross et al., 1992; McGee et al., 1999]. Empirical studies have found that the sensitivity/specificity of each sign in identifying dehydration is 85% and 58%, 50% and 82% and 62% and 82%, respectively [Eaton et al., 1994; Gross et al., 1992; McGee et al., 1999]. The dehydration score (range 0-7) is calculated as the total of these three scores. A higher score indicates a higher level of dehydration.

Laboratory Test (Appendix A-8): The level of dehydration will be measured by biochemical parameters. The results of biochemical parameters will allow us to establish the effectiveness of rehydration in the treatment group compared with progressive dehydration in the placebo group. The results will also allow us to analyze whether the level of symptom improvement is related to the severity of dehydration upon admission. Serum samples will be collected at baseline and on day 7 (+/- 2 days) for biochemistry analysis including osmolality, atrial natriuretic peptide, creatinine, BUN, albumin, hemoglobin, sodium, and calcium. Blood sample will be collected by the assessment research nurse and sent to the MD Anderson Diagnostic Center for processing. The atrial natriuretic peptide is a cardiac hormone synthesized mainly in the atria [Winaver et al., 2000]. This factor is a highly sensitive measure of intravenous volume in cardiac and hemodialysis patients [Wilkins et al., 1997; Wolfram et al., 1996]. Several studies have demonstrated the role of ANP in the sensation of thirst in healthy and non-cancer populations with dehydration [Morita et al., 2001]. The secretion of ANP is directly determined by intravenous volume as compared to other more traditional parameters of dehydration, such as urea and osmolality that are potentially influenced by a number of other physical conditions such as renal dysfunction or intestinal bleeding. Therefore, ANP can be an effective indicator of hydration status in advanced cancer patients. B-type Natriuretic peptide (BNP) is commonly regarded as exclusively ventricular-derived hormone. It shares structural and physiologic features with ANP [Omland, 2008]. Previous studies have shown that saline infusions increase plasma NT-proBNP [Lang et al., 1993], water consumption during exercise in the heat, i.e., with dehydration increases BNP [Mudambo et al., 1997]. In this proposed study we will use either ANP or BNP to monitor intravenous volume.

Measure of Functional Status (Appendix A-13): The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale will be used to assess the health care provider's estimate of the patient's functional status. The ECOG scale is a 5-point measure of functional ability, ranging from fully active (able to carry on all pre-disease performance without restriction) to completely disabled (cannot carry on any self care; totally confined to bed or chair). The ECOG Performance Scale has demonstrated excellent reliability and validity in numerous ECOG clinical trials and descriptive studies [Cleeland et al., 1997]. ECOG will be assessed at baseline, day 7 and every 3-5 days until patient is off study.

Recording of concomitant medication All concomitant medications use will be directed by the treating physician. Active metabolites of some of the opioid analgesics and neuroleptics may accumulate. However, this is one of the frequent indirect effects of dehydration rather than simply an effect of the drugs. Therefore, an expected outcome in the hydration group would be the elimination of active metabolites and opioids and other drugs with consequent reduced production of delirium. We will record the name, dosage and indications of all the medications.

The *Infusion Research Nurse* will perform the following assessments daily:

Intravenous injection (IV) site (Appendix A-12): If patients have intravenous access, the IV site will be assessed daily prior to each infusion by the *Infusion Research Nurse*. NCI common Toxicity Criteria version 3

will be used to rate the severity. Grade 1: Pain, itching, erythema; Grade 2: Pain or swelling, with inflammation or phlebitis; Grade 3: Ulceration or necrosis that is severe, operative intervention indicated.

Subcutaneous injection site (Appendix A-12): If patients have subcutaneous injection site, the site will be assessed prior to each infusion by the *Infusion Research Nurse.* Symptoms include pain (rated 0-10, 0=no pain, 10=worst possible pain), swelling (0=none; 1=mild, not measurable; 2= <5 cm; 3= 5-10 cm; 4= >10cm), erythema (0=none; 1=mild, not measurable; 2= < 5cm; 3= 5-10 cm; 4 >10 cm), ecchymosis (0=none; 1=mild, not measurable; 2= <5 cm; 3= 5-10 cm; 4 >10 cm), and leakage at the injection site (absent, present). This tool has been used in our previous studies [Bruera et al., 1990; Bruera et al., 1995]

Demographic and cancer variables (Appendix A-8): The variables including age, gender, education, race, ethnicity, cancer diagnosis will be collected at baseline from the participants. In addition, among hospice patients who refuse to participate in the study, we will collect their reasons for refusing.

The Patients Assessment Burden

In summary, in order to avoid extensive burden to the patients, they will only be required to complete the FACIT-F (it takes approximate 5 minutes to complete); the ESAS and its additional measures (2 minutes), the Global Symptom Evaluation (30 seconds) and Perception of Treatment Received questionnaire (30 seconds) (Table 2). The remaining measures will be assessed by the caregiver or by the research nurses.

Table 2. Treatment and Evaluation During Study

Intervention/Assessments*	Baseline	Day 1	Day 2	Day 3	Day 4 (+/- 2 days	Day 5	Day 6	Day 7	Daily Day 8-14	Every 3-5 days between day 8-14
Patient										
FACIT-F	X							X		X
Patient and Primary Caregiver										
Edmonton Symptom Assessment System (ESAS)	X	X	X	X	X	X	X	X		X
Global Symptom Evaluation					X			X		
Perception of Treatment Received Questionnaire					X			X		
Meaning of hydration at the end of life	X				X					
Primary Caregiver and Research Nurse										
Nursing Delirium Screening Scale	X	X	X	X	X	X	X	X	X	
Research Nurse										
Parenteral infusion		X	X	X	X	X	X	X	X	
Memorial Delirium Assessment Scale	X	X	X	X	X	X	X	X		X
Richmond Agitation-Sedation Scale	X	X	X	X	X	X	X	X		X
Unified Myoclonus Rating Scale	X				X			X		X
Assessment of adverse event	X	X	X	X	X	X	X	X		**X**
Clinical Dehydration Assessment	X	X	X	X	X	X	X	X		**X**
ECOG performance status	X	X	X	X	X	X	X	X		**X**
Infusion site assessment		X	X	X	X	X	X	X	X	X
LAB (osmolality, atrial natriuretic peptide or pro BNP, creatinine, BUN, albumin, hemoglobin, sodium, calcium)	X							X		
Opioid and concurrent medication	X	X	X	X	X	X	X	X		X

Baseline assessment: Before first infusion; Symptom assessments: 2 hours [+/- 3 hours] after the end of the infusion.

Statistical Considerations

Prior to inferential procedures, extensive descriptive statistical analyses of the outcome and predictor variables will be conducted. Standard descriptive statistics (including means, standard deviations, ranges, frequencies, and 95% confidence intervals) will be computed where appropriate. Distributional characteristics of relevant variables will also be more closely examined using boxplots and histograms. If the data do not appear to be approximately normally distributed, transformations will be made to the data or nonparametric methods will be used. Bivariate associations will be explored using Pearson's Product Moment correlation coefficients, scatterplots, and contingency tables.

The primary endpoint of this study is reduced symptom burden and will be defined as the change in the sum of the four symptoms (fatigue, sedation, myoclonus and hallucinations) from baseline to four days later as

measured by the ESAS.

We analyzed information from a subset of patients from our previous study (Bruera et al, 2005) who experienced at least two of the three symptoms we will use for patients' eligibility in the proposed study: sedation, myoclonus and hallucinations. These patients (15 or 16 per arm) showed a change in two-day sum scores of four symptoms of –9.33 and –5.5 in the hydration and placebo arms, respectively. Although the standard deviation was wider for the placebo arm than for the hydration arm (10.1 versus 5.2), the differences found could have been considered statistically significant if a larger number of patients had been enrolled. We base the sample size for the proposed study on this available information and allow for a maximum 15% dropout rate [Bruera et al., 2004; Bruera et al., 2004]. For the proposed study, we will be able to detect changes between treatment arms at least as large as the previous study if we evaluate 64 patients per arm, with a two-sided significance level of 0.05 and 80% power. We will increase this number of patients to 75 per arm to allow for up to a 15% dropout rate.

In addition to this measure of symptom burden, we will also test for differences between treatment arms of the study for other continuous variables, such as the FACIT-F, the RASS, the MDAS, the Nu-DESC, and other symptoms of the ESAS, using the same statistical methods that will be used for the primary endpoint. Given the available sample size (64 evaluable patients), changes between baseline and day 4 (+/- 2 days) that are at least as large as 50% of the associated standard deviation will be declared statistically significant at a two-sided significance level with 80% power.

The effect of the interventions on physiological symptoms and psychological symptoms will be tested using ANCOVA in SAS (SAS Institute, Cary, NC). The outcome variable will be regressed onto the treatment arm variables with covariance adjustment for the baseline value of the outcome variable. Standard residuals-based diagnostic procedures will be used to test model assumptions and influential observations. Normalizing or variance stabilizing transformations will be made as necessary. Although the randomization procedure will most likely ensure that these simple treatment comparisons are valid, additional covariance adjustments will be included in the models for age, gender, socioeconomic status, and ethnicity. These variables will be forced in the model in a single step. The magnitude and significance of the treatment condition variables will thus represent the effect of the interventions after adjustment for the covariates. Separate analyses will be conducted for the outcome measures for each follow-up time point. To prevent inflated Type I error rates due to multiple comparisons, p-value adjustment will be conducted using the bootstrap resampling approach described by Westfall and Young, 1993. This approach is less conservative than the standard Bonferroni approaches, while at the same time preserves the overall desired Type I error rate. Algorithms for this procedure are currently available in SAS.

Additional analyses will also be conducted in which all follow-up time points will be analyzed simultaneously using mixed model ANCOVA in SAS. In mixed model ANCOVA, repeated measures data can be included by including random effect regression terms that provide adjustment for the correlation structure that exists across measures from the same individual. At a minimum, a random effect term corresponding to the individual will be included in the model. Additional covariance structure among observations from the same individual will be modeled by selecting the best fitting variance-covariance matrix using the procedure described by Wolfinger [Wolfinger, 1993]. A separate time variable will be included in the model to allow simple trends to be tested. An interaction term between time and treatment arm will be added to test for differential patterns of change across time between the two treatment conditions. Similar covariance adjustment for age, gender, socioeconomic status, and ethnicity will be included as described above.

We will also determine at day 4(+/- 2 days) which variables, such as the FACIT-F, the RASS, or the MDAS are significantly associated with changes in the symptom of burden score. This will initially be made by examining correlations between change scores in the symptom burden score (day 4 (+/- 2 days) minus baseline score) with day 4(+/- 2 days) values of these variables. We will also perform a multivariate regression analysis at day 4 (+/- 2 days) to determine which variables in combination are associated with our primary endpoint, reduced symptom burden. The independent variable will be the change in symptom burden from baseline to day 4(+/- 2 days) . Dependent variables will include those from the univariate analyses that show some signs of a significant association ($p<0.10$). We will use stepwise regression methods to help us identify the best model to predict change in symptom burden at day 4(+/- 2 days) . We will also analyze the data for differences between baseline and day 7, but may have a reduced sample size available due to the expected deaths of some of the patients by this time point.

We could not locate publications about the timing of the onset of delirium in a hospice population, although we estimate that delirium will develop in 85% of the patients before their death [Bruera et al., 1992; Centeno et al., 2004]. To determine whether parenteral hydration is superior to placebo in delaying the onset of

delirium, we will determine the length of time to delirium for all patients and then compare the average times (or the distribution of the times between treatment arms). We will use a t-test or an equivalent nonparametric test (depending on the distribution of the data) to test for these differences. In addition, we will test for differences in the severity of delirium between the two arms using similar methods. Given an estimated 54 evaluable patients with delirium (85% of 64 patients per arm), differences between treatment arms that are at least as large as 54% of the associated standard deviation will be declared statistically significant at a two-sided significance level with 80% power. We will also compare the proportion of patients with delirium in each arm by using a binomial test. With 64 patients per arm, we will be able to detect differences that are 11% or larger with a two-sided significance level of 0.05 and 80% power.

For our third objective, we will use standard survival analysis procedures and a log rank test to determine any significant differences between the two treatment arms in survival times. We estimate that median survival will be 15 days [Virnig et al., 2002; Schonwetter et al., 1990] in the placebo arm. Given our available sample size (75 per arm), we will be able to declare as significant a 24-day median survival in the hydration arm (a difference of 9 days). This calculation assumes a 2-sided significance level of 0.05 and 80% power. It also assumes an accrual rate of 4 to 5 patients per month for 36 months. In survival analyses we will include information from all patients even if they withdraw from the treatment arm early.

Power Considerations: We also estimate power in terms of Effect Size Index (ESI), which renders the detectable difference in terms of population standard deviation units (Cohen, 1988). For example, an ESI of 0.5 represents an effect size of 0.5 standard deviation units. We anticipate that we will be able to recruit approximately 150 participants during the recruitment period. With a maximum attrition rate of 15% by the 4-day follow-up, we will have approximately 64 participants per each of the two arms available for analysis. Using a simple t-test for two main effects comparisons at the 4-day follow-up and assuming a two-tailed type I error rate of 0.05 and a sample size of 64 participants per each main effects arm, we will have 80% power to detect a true effect size of 0.50 standard deviation units. By the end of the main accrual period, at 7days, we may experience up to a 30% dropout rate, or have 53 patients per each main effects arm remaining in the study. Using a simple t-test for two main effects comparisons at the 7-day follow-up and assuming a two-tailed type I error rate of 0.05 and a sample size of 53 patients per each main effects arm, we will have 80% power to detect a true effect size of 0.55 standard deviation units. ESIs of this magnitude are approximately what Cohen describes as a medium (0.5) effect. These are consistent with what we found in our pilot study.

Covariance adjustment for the baseline score of the outcome measure and other important covariates using ANCOVA will increase power, as will the use of all follow-up measures in the mixed-model ANCOVA analysis described above.

Missing Data: To allow for up to 15% of patients dropping out of the study before its completion after 4 days of treatment, we will recruit a total of 75 patients per arm, or a total of 150 patients. This is based on our previous studies [Bruera et al., 2004; Bruera et al., 2004]. Missing data will continue to occur throughout the data as patients die under hospice care. For this reason, we will keep our primary analysis methods as simple as possible, but will also explore other methods of analysis and other methodologies for estimating missing data (Palmer, 2004). We will initially assume that missing data will give unbiased estimates of the intervention effects provided that the probability of having missing data depends only on the covariates in the model. We will check this assumption by looking at predictors of missing data. If the assumption is violated we will perform sensitivity analyses to determine the effect of varying the assumptions about the mechanisms for missing data. Other methods of accounting for missing variables will also be employed in sensitivity analyses.

Schedule for Interim and Final analysis:

Interim analysis: 64/128 pts are fully evaluated & off study. It will determine if symptoms in the primary hypothesis are significantly different ($p<0.001$) in the two arms & if unexpected SAE's occurred. Final analysis: 128 pts are fully evaluated & off study.

Qualitative Analyses: This study will involve interviews with 20 primary caregivers, each longitudinally at 2 times, or 40 interviews. In order to understand the essential elements in experience, sufficient numbers of informants must be selected to provide a detailed and clear description of the experience under investigation. The usual way to determine sample size is through saturation, which means researchers conduct interviews until they no longer hear new statements from informants and the data are increasingly redundant. For the purposes of operational and budgetary planning, we will use previous experience and research to project a point at which saturation, and a detailed description might be expected. In prior research this has meant that the themes identified were present in the majority of informants' descriptions. For example, Cohen and Ley (Cohen and Ley, 2000] interviewed 20 BMT patients who were long-term survivors, Cohen and Sarter [Cohen and Sarter, 1992] interviewed 32 nurses to describe the experience of oncology nursing, and Cohen, Haberman, and Steeves [Cohen et al., 1994] conducted

a multi-site study of the meaning of oncology nursing with 76 interviews with 38 nurses. Wilson and Morse [Wilson and Morse, 1991] included data from 48 interviews with 15 husbands of women undergoing chemotherapy. These numbers of informants were sufficient to obtain detailed descriptions of the experiences under study. Morse and colleagues [Morse et al., 2000] recently described using qualitative data to identify interventions and evaluate outcomes. While our project differs in many ways from what they describe, the idea that applies to this project is that qualitative data are useful to understand the hydration intervention and the primary caregivers' experiences with hydration for persons with advanced cancer. Other strategies Morse et al. found to be useful have been included here, such as including clinicians on the research team. As they note, this strategy addresses both process and outcome and thus enhances the applicability to complex clinical experiences. These strategies will enhance our ability to use these data to understand what is important to primary caregivers in hydration intervention. The aim is to balance variability and homogeneity. Limiting the sample to patients from four institutions will make it easier to describe the clinical context in detail. However, the variability of the patients should provide enough heterogeneity to allow a wide exploration of the primary caregivers' experience of this intervention.

Data Analysis and Interpretation: Qualitative data analyses will help accomplish aim 4: Analysis will follow the approach based on the hermeneutic phenomenological approach, also called the Utrecht School of Phenomenology or simply phenomenological research [Cohen and Sarter, 2000; Cohen et al., 1994]. Data analysis will occur simultaneously with data collection. The goal of analysis will be a thick description which captures the experience from the perspective of the informant in its fullest and richest complexity [First et al., 1997]. This analysis will provide a detailed description of the meaning of the intervention. Co-investigator Dr. Cohen and the research team will jointly conduct analysis using a process similar to what they have used in prior research. Dr. Cohen's prior research has demonstrated the advantages of having a team work together to analyze a large volume of data. Once an understanding of the overall text is obtained, phrases in the text will be underlined and tentative theme names written in the margin of the text. The data will then be examined line by line and all important phrases labeled with tentative theme names. An example from previous research is the analysis of the following passage:

> "I got the shingles. I never knew what shingles were, and I didn't know and I got so scared. And I come there and they're like, 'Oh, don't worry, that usually happens to bone marrow transplants after.' And I said, see, no one told me this. You should have told me because I started stressing out... I just think they should prepare people before they go in, of what is going to happen to you after, and what really a transplant is."

This passage was identified as an exemplar (bits of textual data in the language of the informant that captures essential meanings of themes) and coded as "information needs." As this example illustrates, analysis of data includes elements within themes.

After exemplars are identified, they will be clustered according to observed similarities into themes for each individual informant. Themes and exemplars will be compared for similarities and differences with each informant, across all informants. Important contextual features, such as ethnicity, and how the experiences vary with these features will be included in the analysis. This analysis will identify patterns and relationships among the various informants and form a coherent picture of the whole. Data will also be analyzed to obtain an understanding of the meaning of hydration. The computer program Ethnograph or a similar one will be used to facilitate this thematic analysis.

Bias Control: The general rule for bias control in qualitative research, whether it is phenomenological or from another school or method, is to open all decision making to inspection by informants, peers and others who have no special attachment to or interest in the specific results of data analysis. Bias control will be accomplished through the use of several procedures developed by Cohen [Cohen, 1995]. The first procedure will be to use of the research team and the collaborators as a review panel. This panel will be given interviews and asked to identify tentative themes in the text. Next the panel will be given a sample of exemplars and a description of themes and asked to match the exemplars with a theme. The level of agreement among the panel members will be determined. Significant disagreements will be discussed and analysis refined until consensus is reached. Cohen will coordinate this procedure.

Triangulation: Linking analysis of qualitative and quantitative data will help accomplish aim 4. Phenomenological data will be analyzed with phenomenological techniques, and statistical analysis will be conducted on quantitative measures) [Lincoln and Guba, 1985]. These data will then be linked in several ways. Groups will be formed on the basis of scores on the structured measures (e.g., symptoms associated with dehydration). In addition, we will develop major qualitative themes or results (e.g., different meanings attached to hydration) and examine how variation in the qualitative data link to variation in the quantitative data. Matrices will be developed that combine and compare the qualitative and quantitative data [Morse, 1991; Breutmayer et al., 1993]. We will add the major phenomenological themes to enhance our understanding of the factors associated with various patterns. In addition, we will develop exemplar cases, for example, cases that illustrate different meanings. In

these cases, the diverse sources of data will provide a more comprehensive understanding of the meaning of hydration. The data linking will serve multiple purposes, including describing the understanding of the meaning of the hydration in more detail than is possible without the qualitative data. Co-investigator Dr. Cohen has experience with triangulation and will provide guidance for the processes used to link the qualitative and quantitative data.

Time Line for Grant Activities (Months)

Task	1-4	5-12	13-18	19-30	31-34	35-40	41-48
Staffing							
Training							
Study initiation							
Patients enrollment							
Data collection							
Data entry and monitoring							
Data analyses							
Abstract and manuscript preparation							

F. Human Subjects

This application is to obtain support for a clinical trial that will determine whether parenteral hydration will provide symptom relief in patients with advanced cancer as compared to placebo.

Protection of Human Subjects

Permission to conduct the study under this grant will be obtained from the Institutional Review Board of M.D. Anderson Cancer Center. The Protection of Human Rights Guidelines will be followed during all study-related activities. In each participating hospice, the investigator will request an approval of the protocol from the institutional review board (IRB). Each investigator will be responsible for complying with legal and regulatory requirements. Written confirmation of IRB approval will be obtained from each investigator, as well as the name of committee chair and the IRB membership list.

Permission to conduct the study will be obtained from the Institutional Review Board of M.D, Anderson Cancer Center, the Odyssey Health Care of Houston, the Odyssey Health Care of Conroe, Vitas Healthcare Corp., the Houston Hospice, VistaCare Hospice, Silverado Hospice and CHRISTUS VNA. The Protection of Human Rights Guidelines will be followed during all study related activities.

1. Clinical Setting and Patient Screening

Advanced cancer patients with decreased oral intake/dehydration receiving hospice care from the Odyssey Health Care of Houston, Odyssey Health Care of Conroe, the Vitas Healthcare Corp-Houston, Houston Hospice, VistaCare Hospice, Silverado Hospice and CHRISTUS VNA will be screened for patient eligibility. If patients meet the inclusion criteria and are willing to participate in the study, patients will be asked to provide a written informed consent. The research nurse, or assigned study coordinator, responsible for this study will be informed about the patient participation by the hospice physician, or nurse. All patients participating in the study are under inpatient or home hospice care.

2. Eligibility for participating in the study including:

Inclusion criteria:

1) Patients with advanced cancer (local recurrence or metastatic disease) admitted to home hospice care.
2) Patients have reduced oral intake of fluids, as determined by clinical assessment.
3) Patients exhibit evidence of mild or moderate dehydration as defined by decreased skin turgor in subclavicular region (more than 2 seconds), plus a score of ≥ 2/5 in the clinical dehydration assessment (Appendix A-11).
4) In addition to fatigue (expected to be present in all patients based on our pilot study), patients must score ≥ 1 on a 0 to 10 scale (0=no symptom, 10=the worst possible symptom) of two of the three other target symptoms (hallucinations, sedation and myoclonus).
5) Patients are 18 years of age or older.
6) Patients have life expectancy ≥ 1 week as determined by their treating physicians.

7) Patients who score < 13 (normal range) in the Memorial Delirium Assessment Scale (MDAS) and are able to give written informed consent.
8) Patients must be able to tolerate the parenteral treatment application device (butterfly cannula or intravenous access)
9) Patients must have a primary caregiver.
10) Patients must reside within 60 miles of M.D. Anderson Cancer Center.

Exclusion Criteria of patients:
1) Patients refuse to participate in the study or are not competent to give informed consent.
2) Patients are suffering from severe dehydration defined as decreased blood pressure or low perfusion of limbs, decreased level of consciousness, or no urine output for 12 hours.
3) Patients have history or clinical evidence of renal failure. Creatinine >1.5 x ULN. (M.D. Anderson Cr ULN=1.5 mg/dl). Therefore, a patient with Creatinine of > 2.25 mg/dl will be excluded.
4) Patients have history or clinical evidence of congestive heart failure.
5) Patients are not able to complete the baseline assessment forms.
6) Patients have history of bleeding disorders demonstrated by clinical evidence of active bleeding, hematuria, hematoma, ecchymoses and petechiae.
7) Patients have primary CNS malignancies, brain metastasis, or leptomeningeal disease.
E3.13 Inclusion Criteria for family caregivers:
1) The family caregiver is the patient's spouse, parent, sibling, child or significant other.
2) The family caregiver must reside with the patient and be responsible for the care of the patient.
3) The family caregiver must be 18 years of age or older.
4) The family caregiver must be willing to be interviewed by the research nurse and sign written informed consent.
E3.14 Exclusion Criteria of family caregivers:
1) The family caregiver refuses to participate in the study.
2) The family caregiver has difficulty understanding the intent of the study.

3. Data collection

We will review patient medical charts and assessment tools to collect data for the clinical trial. Data will be collected specifically for this research purpose, and existing data from medical charts (i.e., demographic data) will be incorporated.

4. Patient rights and confidentiality

Patients will be informed that refusing to participate in the study or deciding to terminate their participation will not affect their current treatment plan. The patients will be given a written and verbal description of the study during the informed consent teaching interview. Guidelines regarding Institutional Review Board, Human Rights Protection will be strictly followed.

Study subjects will sign an IRB-approved written informed consent form after having the study explained to them in person by the hospice physician, hospice nurse, or MDACC research staff (ie, research nurse or study coordinator). Included in this explanation will be a reassurance that lack of participation in the study will not bear a relationship to their care for cancer or its symptoms. Circumstances of obtaining informed consent will be documented in patient medical records.

We will maintain confidentiality by assigning a study number to all study subjects. Data collected will be identified and tracked using this number. No names or other identifying information will be attached to the data collection.

4. Benefits

We expect benefits to result from this study. The study will provide data that will help us further understand the effect of hydration in advanced cancer patients. Hydration will likely decrease dehydration related symptoms, including fatigue, myoclonus, sedation, and hallucinations, provide comfort to patients and ease primary caregivers' distress by knowing that their loved one is receiving fluid, and delay the onset or decrease the severity of delirium; and possibly prolong survival. However, these benefits may be temporary.

6. Risks

AEs associated with parenteral hydration at rate of 1000 ml per day include the possibility of swelling around the site where the catheter is inserted. Patients may experience some pain or discomfort near the infusion, although this is uncommon. Infection can develop at the site where the catheter is inserted. Patients may not be able to tolerate additional fluid because of fluid overloading. Swelling in other parts of the body may develop. Patients may experience aggravation of respiratory tract secretion at the end of life (the death rattle). The potential AEs will be monitored daily during the study period,

7. Inclusion of women and minority

The subject selection procedure provides equal access to both genders. Data from the four participating hospices suggest approximately equal gender distribution for the home hospice patients (58 % female and 42 % male). This proportion will be maintained in our study population. Our eligibility criteria do not exclude potential subjects by race or ethnicity. We will ask each patient to self-identify their race and ethnicity. During 2004, the average population in the five participating hospices was approximately 65% white, 15% African-American, 15% Hispanic, and 5% Asian and other. This racial and ethnic distribution will be reflected in our study population.

Target/Planned Enrollment Table: Total of 150 patients and 150 caregivers will be enrolled.

Ethnic Category	Females (Patient/Caregiver)	Males (Patient/Caregiver)	Total (Patient/Caregiver)
Hispanic or Latino	26 (11/15)	20 (12/8)	46 (23/23)
Not Hispanic or Latino	148 (64/84)	106 (63/43)	254 (127/127)
Ethnic Category: Total of All Subjects	174 (75/99)	126 (75/51)	300 (150/150)
Racial Categories			
Asian and other	10 (5/5)	6 (3/3)	16 (8/8)
Black or African American	26 (11/15)	20 (12/8)	46 (23/23)
Caucasian	138 (59/70)	100 (60/40)	138 (119/119)
Racial Categories: Total of All Subjects	174 (75/99)	126 (75/51)	300 (150/150)

8. Inclusion of children

The assessment and treatment of multiple symptoms of cancer and cancer therapy affect the care and quality of life in children as well as adults. Limited studies on cancer symptom management for children, such as a recent study on fatigue [Hockenberry-Eaton & Hinds, 2000], indicate that participation in these types of studies results in minimal risk to the patients. However, we will not include patients younger than 18 years old in our trial because the assessment tools we propose to use were designed and validated for adult cancer patients and because the number of pediatric cancer patients admitted to the four participating hospices is very limited.

Data and Safety monitoring

The M.D. Anderson IRB reviews and approves the data and safety monitoring plan for all clinical trials. In addition to ongoing monitoring by the PI and research staff, data and safety monitoring for this project will be conducted by two independent M.D. Anderson entities set up specifically to address these issues, the IRB and the Data Monitoring Committee (DMC). Plans and procedures for maintaining data integrity, defining and reporting adverse events/experiences, and IRB and DMC oversight and monitoring of this project are described below. These procedures include monitoring of participant eligibility and accrual, adverse events, interim data analyses.

1. Monitoring by IRB

During the protocol review and approval process, the IRB determines the level of safety monitoring required for that protocol. The minimum monitoring requirements include investigator monitoring of

participant safety, adverse event (AE) reporting in compliance with IRB, NIH, and FDA guidelines, and participation in the Continuing Review process with the IRB. The Data Monitoring Committee (DMC) also monitors clinical trials. The outcomes of IRB and DMC reviews are conveyed to the PI via the administrative support staff in the Office of Protocol Research (OPR).

For all protocols conducted at the M. D. Anderson, the PI is responsible for submitting AEs to the IRB. The institution's policy for AE submission has been defined and approved by the IRB and must be included as an appendix to all protocols. AEs are submitted to OPR, entered into the Protocol Data Management System (PDMS) and forwarded to the designated IRB vice chairperson for review. Attached to each AE, is a listing of all prior AEs submitted for that protocol. Any comments, questions or changes the IRB requests to the protocol as a result of this review are conveyed to the PI. The PI response and protocol modification process is monitored by the IRB vice chairperson and OPR support staff. The vice chairperson presents the report on AE review to the full committee at the next IRB meeting.

All protocol participants must be registered in the Protocol Data Management System (PDMS). PDMS is a clinical trials database designed to meet the regulatory needs of the M.D. ANDERSON clinical research enterprise, allow PIs to collect their protocol data electronically, and allow electronic data transfer to NIH and industry sponsors. The Office of Protocol Research (OPR) creates a file in PDMS of each human subjects protocol submitted for review and approval. After the title, PI, collaborators and other protocol specific information is entered, the system assigns the protocol a unique number that will be used to track the protocol through review and approval, participant registration, adverse event collection, continuing review and participant data collection processes.

The system tracks the reviewers and the committee dates and outcomes of each protocol through the scientific review and IRB review processes. Once the protocol has IRB approval and all other issues are satisfied, the protocol may be "activated". The Activation Process involves entering into PDMS the eligibility criteria, any dose information, and the date of the most current IRB approved informed consent document. Once activated, participants may be registered in the database. Activation is an independent step in the review and approval process and must be specifically requested by the PI.

It is the M.D. Anderson policy that all participants in a clinical trial must be registered in PDMS. To register a participant, the PI or research coordinator must enter some demographic data and then answer all the eligibility criteria that are specific for that protocol. The system is programmed with the logic to determine which eligibility criteria are not met based on the Yes/No response of the person registering the participant. For protocols sponsored by NIH, no participant may be registered unless they completely meet all eligibility criteria. This real time, continuous monitoring of participant eligibility increases participant safety by ensuring that only individuals that meet the criteria are enrolled.

The PDMS also contains a field that is visible during the participant registration process that indicates the date of the current IRB approved informed consent document. The OPR staff updates this field each time the IRB approves a modification to an informed consent document. The IRB approved informed consent document is stamped, dated and signed only when a protocol is activated. No document without the stamp can be used. Stamping, signing and dating the document are the final step in the activation process. Comparing the date on the informed consent document with the date in PDMS enables the registering individual to make sure the correct informed consent document was used.

The OPR also uses PDMS as a tool for monitoring participant safety using menus designed for reporting, tracking and reviewing adverse events. All adverse events (AEs) submitted to the IRB are submitted to OPR, which provides the administrative support to the committee. Each AE for a participant treated at M.D. Anderson is entered into PDMS in the electronic file for the protocol upon which the participant was enrolled. The AE form and any additional information supplied to OPR are forwarded to an IRB Vice Chair who is responsible for reviewing AEs. In addition to the submitted information, a report is generated from PDMS summarizing all previous AEs submitted for that protocol and supplied to the IRB Vice Chair. This allows the reviewer to see the entire safety history of the protocol and identify trends much sooner than in situations where the safety information is reviewed together only once a year during an IRB review.

It is during this continuous AE review that the IRB will request PIs to modify the informed consent documents if new safety issues arise, or to modify to reduce the potential toxicity to participants or modify any other aspect of the protocol to enhance participant safety. This real time, continuous AE review and protocol/informed consent modification process is an important component of the M.D. Anderson continuous monitoring of participant safety.

Part of the information in the database for each protocol is the maximum accrual approved by the IRB. Since each participant is registered on the protocol in the database, monitoring the progress of the research by examining protocol accrual is a simple and routine process carried out by OPR. Every six months reports are generated for categories of Low, Slow, No Accrual and Approved but not yet activated. The PI of any protocol that falls in one of these categories is sent a memo requesting input on why the protocol is not accruing at the expected rate. Depending on the response, the protocol is closed or the protocol is continued and re-reviewed 6 months later.

In addition, the PDMS sends an automatic email message to the OPR who in turn notifies the PI when a protocol is within 5 participants of reaching maximum accrual. The system sends another email message when accrual is reached and OPR then closes the protocol to new participant entry. With this system, protocols cannot accrue more participants than was approved by the IRB.

The OPR also uses the PDMS to determine the auditing eligibility, evaluability, on-study dates, and off-study dates of each research subjects in a protocol. The OPR performs audits on both a random and for-cause basis although its major focus is the operation of an elaborate and intense training program for research coordinators. It is the belief of the M.D. Anderson Office of Research Administration that while auditing can identify problems, education can prevent them. That is why that office has used OPR to stress an educational, proactive approach to research quality. In addition, OPR contains an ombudsman function that confidentially assists research personnel who believe that a study may not be operating in a manner consistent with Good Clinical Practice. A report to this function may trigger an audit or some other type of investigation. Every report is investigated fully and confidentially to assure no repercussions to the reporter or to the research team performing the research in question unless a true violation is identified. Most Phase 1 and 2 trials at M.D. Anderson are monitored daily by the research teams performing the research. In addition the IRB may require frequent reporting on toxicity of any trial the IRB identifies as having risks warranting an increased monitoring frequency.

The requirements for AE reporting are extensively reviewed with all key personnel on grant applications during the mandatory IRB-sponsored training. In addition, every protocol must have the AE reporting requirements attached to it prior to IRB approval. Every AE report is reviewed by a Vice Chairperson of the IRB and duly reported to the entire IRB at the next meeting. IRB meetings occur every two weeks. If immediate action is required (protocol closure, information dissemination to other PI's doing studies with similar agents) that is done by the IRB Vice Chair via the Office of Protocol Research. All of these actions are coordinated through the PDMS computer system. Plans for assuring that any action resulting in a temporary or permanent suspension of an NIH-funded clinical trial is reported to the NIH grant program director responsible for the grant.

For the most part, the closure of the trial will occur due to actions coordinated within the OPR, whether this is due to a poor audit, an IRB action, or unexpected AEs. The OPR will work with the IRB to notify all parties requiring such notification (e.g., NIH, FDA, sponsor).

2. Monitoring by the DM

The Data Monitoring Committee (DMC) is an officially constituted committee of M.D. Anderson designed to oversee the data and safety monitoring of clinical trials. The primary objectives of the DMC are to;

- Ensure that participants in a trial are protected;
- Ensure that participants' interests are not made secondary to the interests of the scientific investigation; and
- Monitor all clinical trials that originate at M.D. ANDERSON or that are coordinated or analyzed by the M.D. Anderson.

  The DMC has the following responsibilities to accomplish the above objectives:
- To review interim analyses of outcome data (prepared by the study Statistician or other responsible person at the time points defined in the protocols approved by the IRB), and to recommend, if necessary, whether the study needs to be changed or terminated based on these analyses;

- To determine whether and to whom outcome results should be released prior to the reporting of study results from this trial at the time specified in the protocol;
- To review interim toxicity data and efficacy of treatment;
- To review major modifications to the study proposed by the PI prior to implementation (e.g., termination, dropping an arm based on toxicity results from this trial or results of other trials, increasing target sample size);
- To communicate information and recommendations to appropriate persons at M.D. Anderson regarding the assessment of issues or problems and effective resolutions for educational purposes and improved participant care and risk prevention.

The Committee consists of not more than 15 members (including the Chairman). A majority of members attending meetings of the DMC constitute a quorum. Appointments are made based on the breadth of backgrounds and experience. The committee includes scientists and statisticians from within and outside the institution selected based on their experience, reputation for objectivity, absence of conflicts of interest, and knowledge of good clinical trial methodology. At least fifty one percent of the voting members are not affiliated with M.D. Anderson. DMC members represent participant interests, and not that of the institution.

The DMC meets at least once a year, and more often if necessary. Each randomized clinical trial protocol has specified interim analyses times. Information provided to the DMC include: title of study, PI, date start of study, expected termination date, expected total number of participants, number of participants entered currently, data from interim analyses, date of interim analyses, toxicity concerns, and the next formal monitoring date as specified in the protocol. The PI may prepare a report addressing specific toxicity concerns or other concerns about the conduct of the study during the open session. A copy of the statistician's report may be sent to the DMC Chair for presentation during the closed portion, but not to any other individuals not on the DMC. The report may contain recommendations on whether to close the study, whether to report the results, whether to continue accrual or follow-up and whether DMC discussion is needed.

The review of each trial may include two parts. The first part will be an open session in which members of the study team may be present at the request of the DMC to answer questions. In this part, the focus is on accrual, compliance and toxicity issues. Following this open session, there will be a closed, executive session in which the DMC discusses interim outcome results by treatment arm, what action needs to be taken, and then votes. At the executive session, those present are limited, to DMC members, alternates, and ex officio members. If a decision is made by the DMC to modify or discontinue a trial - recommendations will be made as to whether and how participants are to be informed and by whom and communicated to the PI in writing. Copies of such communication will be preserved in the official Committee Minutes.

DMC recommendations are based upon results for the current study being monitored as well as upon data available to the DMC from other related studies. The PI will assure that the DMC is advised about relevant non-confidential results from other related studies that become available. It will be the responsibility of the DMC to determine the extent to which this information is relevant to decisions to continue or modify the current study. The DMC will provide recommendations in writing to the PI to change or stop a study, or part thereof (e.g., one arm), or to continue a study unchanged. Special consideration will be given to participants already in treatment.

In the event that a study change is recommended for participant safety reasons (including early stopping of inferior therapy), the PI acts to implement the change as expeditiously as possible to ensure safety of all participants on the study. In the unlikely situation that the PI does not concur with the DMC recommendation, then the Vice President for Research Administration must be informed of the recommendation of the DMC and of the PI's reason for disagreeing with the recommendation. The Vice President for Research Administration and the PI, in consultation with the DMC Chair, are responsible for reaching a mutually acceptable decision about the study. Confidentiality is maintained during these discussions. In the event that a change in a study is recommended for reasons other than participant safety (e.g., to extend accrual because of a lower than expected accrual rate), the DMC provides to the PI as much rationale for the proposed change as can be made without jeopardizing the conduct of the study. The PI is responsible for having an amendment prepared and submitted to the IRB the recommendations of the DMC and providing the rationale for the changes. IRB approval of the amendment will be required prior to implementation of the change, although a decision to override the DMC's recommendation is made only in the most exceptional circumstances.

All documents, investigative reports or information and conversations relating to this committee's work are strictly confidential and are not shared with anyone other than other committee members. Although committee documents are subject to legal privileges as set forth in statutory and case law and are not subject to discovery during a litigation process, the privilege may be lost if committee documents are given to, shown to or discussed with non-committee members without an official DMC request to do so.

No communication of the deliberations or recommendations of the committee, either written or oral, is made outside of the committee except as provided for in these policies and procedures. All DMC members or alternates will sign statements of confidentiality at the beginning of an appointment period. Outcome (efficacy) results are strictly confidential and are not divulged to non-members (excepting the PI and Associate Vice President for Clinical Investigations) until the recommendation to report the results are accepted and implemented.

Individuals invited to serve on the DMC disclose to the Group Chair any potential, real or perceived, conflicts of interest. These include professional interest, proprietary interest and miscellaneous interest considerations. Potential conflicts that develop during the conduct of a trial should also be disclosed to the PI.

Compliance with Requirements Regarding the Reporting of Adverse Experiences (AEs)

1. Adverse Experiences Requiring Immediate Reporting: Two types of Adverse Experiences require prompt reporting to the IRB and the study sponsor, serious and unexpected. For these AEs, we will submit a written report to the OPR within 10 working days of the AE. Unexpected fatal or life-threatening AEs will be phoned immediately to the OPR, and the OPR will notify the appropriate sponsors within 3 days. In our trial, a serious AE is defined as a clinical event occurring subsequent to the administration of an agent or intervention which can be characterized as fatal, life-threatening, permanently disabling, requiring hospitalization, or an overdose.

It is expected that patients under hospice care will die within days or weeks during or after completion of this study due to their advanced disease. Hydration with normal saline is considered as low risk intervention. Therefore, we will report expected death during IRB continuing review. Death information will be recorded and will be placed in the study binder.

Unexpected AE is defined as a clinical event that is not identified in nature, severity, or frequency in the investigator's brochure, protocol, or other pertinent supporting literature. At times, the occurrence of an unexpected adverse experience might not be suspected until more than one event has occurred. Once the clinical event has been identified, all cases should be reported. No degree of unexpected toxicity is specified, but practically, it is unusual to be able to discern less than grade 2 toxicity.

2. AEs that do not require immediate reporting: AEs that are not serious or not unexpected (as defined in the previous paragraph) will be submitted in written to the OPR every month.

3. AEs Associated with Participating in the Intervention: The toxicities associated with parenteral hydration at rate of 1000 ml per day include the possibility of swelling around the site where the catheter is inserted. Patients may experience some pain or discomfort near the infusion, although this is uncommon. Infection can develop at the site where the catheter is inserted. Patients may not be able to tolerate additional fluid causing fluid overloading. Swelling in other parts of the body may develop. Patients may experience aggravation of respiratory tract secretion at the end of life (the death rattle).

In addition to the monitoring that is conducted by the M. D. Anderson DMC, patients are closely followed by the investigator/the research nurse daily during the study. Patients will be provided the telephone number of the PI and the research nurse in case they feel they need to reach someone immediately.

4. Adverse Experiences Associated with Self-Report Questionnaires: This study will involve the use of questionnaires and interviews that could reveal sensitive information (e.g., assessment of mood or other psychiatric disturbance). Procedures are in place to protect participant confidentiality. Such instruments are administered only by trained staff and after careful explanation to the participants about their purpose and use

in this study. The instruments are not used to communicate psychiatric diagnosis to the participant. However, the PI or one of the co-investigators reviews the results and if in their clinical judgment the results reveal a degree of disturbance that requires further professional consultation, the participant is contacted. Possible outcomes of this contact include referral to the participant's primary care physician and/or other physician, and/or other mental health providers.

5 .Assuring that Action Resulting in Suspension of Trial is Reported to NCI Grant Program Director Responsible for the Grant

Any human subjects research that is not being conducted in compliance with applicable institutional policy and Good Clinical Practices will be suspended by the IRB. An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include the necessary and appropriate notifications of such actions to the institution's administration, funding agency, NCI or other sponsor.

Data Quality and Integrity

Because of the ongoing monitoring of the project, study investigators and staff are responsible for ensuring that data quality assurance procedures are developed and maintained. Several procedures will be used to maintain the integrity of the data. All databases will be stored in a centralized location on one of the departmental servers, which is backed up daily, with access limited to specific users at the discretion of the PI. The PI will assure that audits of selected subsets of data are performed and that appropriate safeguards of participant privacy are maintained. Privacy safeguards will include appropriate password protection and physical security for all computer systems. Patient names will not be stored in data files; records linking participants' names with the computer identifiers will be kept in a separate file and encrypted.

A relational database will be created in Microsoft ACCESS to store all project-related data. ACCESS can accommodate complex relationships among tables, allowing large quantities of data to be integrated into a single database. Relational databases such as ACCESS also allow for powerful and flexible queries and reports. ACCESS can be easily customized using Visual Basic for Applications (VBA) code, allowing the inclusion of many design features ideal for behavioral science research. These features include more user-friendly interfaces, the ability to specify valid ranges for variables, and double-entry systems for data, all of which help to maintain data integrity. We will use the built-in security features of ACCESS to restrict user access.

Additional quality assurance procedures include a data collection protocol documented in a protocol manual; a two-stage editing procedure for survey data collection consisting of the initial review of the data collection form by a project member immediately following data collection, and a second review by a project member who will record any significant deviations from the protocol; and regular meetings between the study statistician, the PI, data managers, and other project staff to review problems and solutions, and discuss concerns. Data entry systems, whether via scannable forms, or hand entry with verification, specifically provide field checks, range checks for continuous variables and valid value checks for categorical variables; checks for legitimate dates and times and logical consistency. A specific audit trail system that identifies the date, time, and individual making changes on the database will be part of the data-entry system. During data collection, we will either issue reports weekly or following any new data entry, depending on the needs of the project. Queries and reports will be provided to the study statistician and the PI.

G. Vertebrate Animals not applicable

H. Literature Cited

Ahlberg K, Eckman T, Gaston-Johnansson F, Mock V. Assessment and management of cancer-related fatigue in adults. The Lancet 2003; 362:640-650.

Back IN, Jenkins K, Blower A, Beckhelling J. A study comparing hyoscine hydrobromide and glycopyrrolate in the treatment of death rattle. Pallia Med 2002 16(5): 449-450.

Berger EY. Nutrition by hypodermoclysis. J Am Geriatr Soc 1984; 32:199-203.

Breitbart W, Rosenfeld B, Roth A, et al. The Memorial Delirium Assessment Scale. J Pain Symptom Manage 1997; 13(3):128-137.

Breitbart W. Re: Memorial Delirium Assessment Scale and commentary. J Pain Symptom Manage 1974; 15:75.

Breitbart W. Gibson C, Tremblay A. The delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. Psychosomatics 2002; 43:183-194.

Breitmayer B, Ayres L, Knafl K. Triangulation in qualitative research: Evaluation of completeness and confirmation purposes. *Image* 1993; 25(3): 237-243.

Brown TM. Drug-induced delirium. Semin Clin Neuropsychiatry 2000; 5:113-124.

Bruera E, Belzile M. Watanabe S, Fainsinger RL. Volume of hydration in terminal cancer patients. Support Care Cancer 1996; 4:147-150.

Bruera E, Brenneis C, Michaud M. Use of the subcutaneous route for the administration of narcotics in patients with cancer pain. Cancer 1988; 62:407-411.

Bruera E, Carraro S, Roca E, Cedaro L, Chacon R. Association between malnutrition and caloric intake, emesis, psychological depression, glucose taste, and tumor mass. Cancer Treat Rep. 1984 Jun;68(6):873-6.

Bruera E, Catz Z, Hooper R, Lentle B, MacDonald RN. Chronic nausea and anorexia in patients with advanced cancer: A possible role for autonomic dysfunction. J Pain Symptom Management 1987; 2:19-21.

Bruera E, Chadwick S, Fox R, Hanson J, MacDonald N. Study of cardiovascular autonomic insufficiency in advanced cancer patients. Cancer Treat Rep 1986; 70:1383-1387.

Bruera E, Chadwick S, Weinlick A. Delirium and severe sedation in patients with terminal cancer. Cancer Treat Rep 1987; 71:787-788.

Bruera E, de Stoutz ND, Fainsinger RL. Comparison of two different concentrations of hyaluronidase in patients receiving one-hour infusions of hypodermoclysis. J Pain Sympt Manage 1995; 10:505-509.

Bruera E, Franco JJ, Maltoni M. Changing pattern of agitated impaired mental status in patients with advanced cancer: Association with cognitive monitoring, hydration and opioid rotation. J Pain Symptom Manage 1995; 10:287-291.

Bruera E, Kuehn N, Miller M, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. J Palliat Care. 1991 Summer;7(2):6-9.

Bruera E, Lawlor P. Defining palliative care interventions. J Palliat Care 1998; 14:23-24.

Bruera E, Legris MA, Kuehn N, Miller MJ. Hypodermoclysis for the administration of fluids and narcotic analgesics in patients with advanced cancer. J Pain Symptom Manage 1990; 5:218-220.

Bruera E, MacDonald N. To hydrate or not to hydrate: How should it be? J Clin Oncol 2000; 18:1156-1158.

Bruera E, MacDonald RN. Nutrition in patients with advanced cancer: An update and review of our experience. J Pain Symptom Management 1988; 3:133-140.

Bruera E, Macmillan K, Hanson J, et al. The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. Pain 1989; 39:13-16.

Bruera E, Miller L, McCallion J, et al. Cognitive failure in patients with terminal cancer: A prospective study. J Pain Symptom Manage 1992; 7:192-195.

Bruera E, Miller L, McCallion J, Macmillan K, Krefting L, Hanson J. Cognitive failure in patients with terminal cancer: a prospective study. J Pain Symptom Manage 1992; 7(4):192-5.

Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Thalidomide in patients with cachexia due to terminal cancer: preliminary report. Ann Onc 1999; 10: 857-859.

Bruera E, Neumann CM, Pituskin E, Calder K, Hanson J. A randomized controlled trial of local injections of hyaluronidase versus placebo in cancer patients receiving subcutaneous hydration. Ann Oncol 1999; 10(10): 1255-1258.

Bruera E, Palmer JL, Bosnjal S, Rico M, Moyano J, Sweeney C, Strasser F, Willey J, Bertolino M, Mathias C, Spruyt O, Fisch M. Methodone versus morphine as a first-lin strong opioid for cancer pain: a randomized, double-blind study. J Clinc Oncol 2004; 22:185-191.

Bruera E, Sala R, Rico MA, Moyano J, Centeno C, Willey J, Palmer JL. Effects of parenteral hydration in terminally ill cancer patients: A preliminary study. J Clin Oncol 2005; 23:2366-2371.

Bruera E, Seifert L, Watanabe S, Babul N, Darke A, Narsanyi Z, Suarez-Almazor M. Chronic nausea in advanced cancer patients: a retrospective assessment of a metoclopramide-based antiemetic regimen. J Pain Symptom Manage 1996; 11(3):147-153.

Bruera E, Strasser F, Palmer JL, Willey J, Calder K, Amyotte G, Baracos V. Effect of fish oil on appetite and other symptoms in patients with advanced cancer and anorexia/cachexia: A double-blind, placebo-controlled study. J Clin Oncol 2003; 21: 129-134.

Bruera E. Clinical management of anorexia and cachexia in patients with advanced cancer. Oncology 1992; 49(suppl 2):35-42.

Bruera E., Moyano J, Sala R, Rico M, Bosnjak S, Bertolino M, Willey J, Strasser F, Palmer JL. Dexamethasone in addition to metoclopramide for chronic nausea in patients with advanced cancer: a randomized controlled trial. J Pain Symptom Manage 2004; 28(4):381-8.

Burge FI, Dehydration symptoms of palliative care cancer patients. J Pain Symptom Manage 1993; 8:454-464.

Casarett DJ, Inouye SK. Diagnosis and management of delirium near the end of life. Ann Intern Med 2001; 135:32-40.

Caviness JN. Myoclonus. Mayo Clin Proc 1996; 71:679-688.

Cella DF, Tulsky DS, Gray G eta l. The Functional Assessment of Cancer Therapy scale. J Clin Oncol 1993; 11: 570-579.

Centeno C, Sanz A, Bruera E. Delirium in advanced cancer patients. Palliat Med. 2004; 18(3):184-94.

Chang V, Hwang S, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. Cancer. 2000 May ;88(9):2164-71.

Chio Y, Billings J. Changing perspectives on palliative care. Oncology. 2002;16:515-522.

Chlebowski RT, Heber D. Hypogonadism in male patients with metastatic cancer prior to chemotherapy. Cancer Research 1982; 42(6):2495-2498.

Cleeland C, Ginin R, Baez L, Loehrer P, Pandya K. Pain and treatment of pain in minority patients with cancer. The Eastern Cooperative Oncology Group Minority Outpatient Pain Study. Ann Intern Med. 1997 Nov 1;127(9):813-6.

Clouston, PD, Lim CL, Fung V, et al. Brain-stem myoclonus in a patient with non-DOPA-responsive Parkinsonism. Mov Disord 1996;11:401-410.

Cohen J. Statistical Power Analysis for the Behavioral Sciences. New Jersey: Lawrence Erlbaum Associates; 1988.

Cohen M, Ley C. Bone marrow transplantation: the battle for hope in the face of fear. Oncol Nurs Forum. 2000; Apr;27(3):473-80.

Cohen M. the experience of surgey: Phenomenological clinical nursing research. In: Omery A, Kasper C, Page G (eds.). In search of Nursing Science. Sage, Thousand Oaks; CA 1995: 159-174.

Cohen MZ, Haberman M, Steeves R. The meaning of oncology nursing: A phenomenological investigation. *Oncology Nursing Forum* 1994; 21(Suppl 8):5-8.

Cohen MZ, Kahn D, Steeves R. Hermeneutic phenomenological research: A practical guide for nurse researchers. Sage, Thousand Oaks, CA 2000.

Cohen MZ, Sarter B. Love and work: Oncology nurses' view of the meaning of their work. *Oncology Nursing Forum* 1992; 19(10): 1481-1486.

Coyle N, Adelhardt J, Foley KM, et al. Character of terminal illness in the advanced cancer patient: Pain and other symptoms during the last four weeks of life. J Pain Symptom Manage 1990; 5:83-93.

Coyle N, Breitbart W, Weaver S, Portenoy R. Delirium as a contributing factor to "crescendo" pain: three cases reports. J Pain Symptom Manage 1994; 9:44-47.

Craig GM. On withholding nutrition and hydration in the terminally ill: has palliative medicine gone too far? J Med Ethics 1994; 20:139-143.

Dalal S, Bruera E. Dehydration in cancer patient: To treat or not to treat. The J of Supportive Oncol. 2004; 2(6):467-483.

Day HB. The treatment of infantile diarrhea by saline injections. Practitioner 1913; 91:58-64.

De Stoutz ND, Bruera E, Suarez-Almazor M. Opioid rotation (OR) for toxicity reduction in terminal cancer patients. J Pain Symptom Manage 1995; 10:378-384.

Derse A. Limitation of treatment at the end-of-life: withholding and withdrawal. Clin Geriatr Med. 2005; 21(1):223-38.

Devie-Hubert I. Carlier M, Pozzo-DiBorgo C. Venous thrombosis on central catheters in oncology. Rev Med Inteme 1996; 17(10):821-825.

Diener JR, Coutinho MS, Zoccoli CM. Central venous catheter-related infections in critically ill patients. Rev Assoc Med Bras 1996; 42(4):205-214.

Doorley J, McNeal W. The role of neuroleptics in managing morphine-induced terminal delirium: implications for the clinical nurse specialist. Clin Nurse Spec 2004;18(4):183-185.

Dunlop RJ, Campbell CW. Cytokines and advanced cancer. J Pain Symptom Manage 2000; 20:214-232.

Dunlop RJ, Ellershaw JE, Baines M, et al. On withholding nutrition and hydration in the terminally ill: Has palliative medicine gone too far? A reply. J Med Ethics 1995; 21:141-143.

Dunphy K, Finlay L, Rathbone G, et al. Rehydration in palliative and terminal care: If not, why not? Palliat Med 1995; 9:221-228.

Eaton D, Bannister P, Mulley G. Connolly M. Auxiliary sweating in clinical assessment of dehydration in ill elderly patients. Bri Med Journal 1994; 308:1271.

Ellershaw JE, Sutcliffe JM, Saunders CM. Dehydration and the dying patient. J Pain Symptom Manage 1995; 10(3):192-197.

Fainsinger RL, Bruera E. Hypodermoclysis for symptom control vs the Edmonton Injector. J Palliat Care 1991; 7:5-8.

Fainsinger RL, Bruera E. The management of dehydration in terminally ill patients. J Palliat Care 1995; 10:55-59.

Fainsinger RL, Bruera E. When to treat dehydration in a terminally ill patient? Support Care Cancer 1997; 5:205-211.

Fainsinger RL, MacEachern T, Miller MJ, Bruera E, Hanson J. The use of hypodermoclysis for rehydration in terminally ill cancer patients. J Palliat Care 1992; 8:70.

Fainsinger RL, MacEachern T, Miller MJ, et al. The use of hypodermoclysis for rehydration in terminally ill cancer patients. J Pain Symptom Manage 1994; 9:298-302.

Fann JR, Roth-roemer S, Burington BE, et al. Delirium in patients undergoing hematopoietic stem cell transplantation. Cancer 2002; 95:1971-1981.

Farrand S, Campbell AJ. Safe, simple subcutaneous fluid administration. Br J Hosp Med 1996; 55:690-692.

Ferry M, Dardaine V, Constans T. Subcutaneous infusion of hypodermoclysis: a practical approach. J Am Geriatr Soc 1994; 47:93-95.

First M, Spitzer R, Gibbon M, Williams J. Structured clinical interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV), American Psychiatric Press, Washington, DC. 1997.

Frucht S, Leurgans S, Hallett M, Fahn S. The Unified Myoclonus Rating Scale (UMRS): a statistically valid clinical rating instrument. Mov Disord 2000;15 (Suppl 3):7-8

Gagnon P, Allard P, Masse B, DeSerres M. Delirium in terminal cancer: a prospective study using daily screening, early diagnosis, and continuous monitoring. J Pain Symptom Manage 2000; 19:412-426.

Gaudreau J-D, Gagnon P, Harel F, Tremblay A, Roy M-A. Fast, systematic, and continuous delirium assessment in hospitalized patients: The Nursing Delirium Screening Scale. J Pain Symptom Management 2005; 29(4):368-375.

Gross C, Lindquist R. Wooley A. Clinical indications of dehydration severity in elderly patients. J Emerg Med 1992; 10:267-274.

Guyatt G, Feeny D, Patric D, Measuring health-related quality of life. Ann Intern Med. 1993; 118(8):662-9

Guyton A, Hall J. The body fluid compartments: extracellular and intracellular fluids, interstitial fluid, and edema. In Textbook of Medical Physiology. 9th ed. Philadelphia, Pa: WB Sauders; 1996:297-313.

Hampson L, Emanuel E. The prognosis for changes in end-of-life care after the Schiavo case. Health Affaires 2005, 24(4):972-975.

Hays H. Hypodermoclysis for symptom control in terminal cancer. Can Fam Physician 1985; 31:1253-1256.

Holm B, Söderhamn O. Factors associated with nutritional status in a group of people in an early stage of dementia. Clin Nutrition 2003; 22(4):385-389.

Hwang SS, Chang VT, Montse R, Kasimis B. Multidimensional independent predictors of cancer-related fatigue. J Pain Symptom Management 2003; 26:604-614.

Inouye SK, Bogardus St Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999; 340:669-676.

Karlsson I. Drugs that induce delirium. Dement Geriatr Cogn Disord 1999; 10:412-415.

Labella FS, Pinsky C, Havlicek V. Morphine derivatives with diminished opiate receptor potency show enhanced central excitatory activity. Brain Res 1989; 174:263-271.

Lanuke K, Fainsinger R, DeMoissac D. Hydration management at the end of life. J Palliat Med 2004; 7(2):257-63.

Lawlor PG, Gagnon B, Mancini IL, et al. Occurrences, uses, and outcome of delirium in patients with advanced cancer. A prospective study. Arch Intern Med 2000; 160:786-794.

Lawlor PG, Nekolaichuk C, Gagnon B, et al. Clinical utility, factor analysis, and further validation of the Memorial Delirium Assessment Scale in patients with advanced cancer. Cancer 2000; 88:2859-2867.

LincolnY, Guba E. Naturalistic Inquiry; Sage, Beverly Hills, CA 1985.

Lipowski ZJ. Transient cognitive disorders (delirium, acute confusional states) in the elderly. Am J Psychiatry 1983; 140:1426-1436.

Lipschitz S, Campbell AJ, Roberts MS, et al. Subcutaneous fluid administration in elderly subjects: validation of an under-used technique. J Am Geriatr Soc 1991; 39:6-9.

MacDonald N, Fainsinger R. Indications and ethical considerations in the hydration of patients with advanced cancer. In: Bruera E, Higginson I (eds). Cachexia-Anorexia in Cancer Patients. New York, NY, Oxford University Press, 1996, pp 94-109.

Maddocks I, Somogyi A, Abbott F, Hayball P, Parker D. Attenuation of morphine-induced delirium in palliative care by substitution with infusion of oxycodone. J Pain Symptom Manage1996; 12:182-189.

Marcantonio ER, Flacker JM, Wright RJ, et al. Reducing delirium after hip fracture: A randomized trial. J Am Geriatr Soc 2001; 49:516-522.

Massie MJ, Holland JC. The cancer patient with pain: psychiatric complications and their management. J Pain Symptom Manage 1992; 7:99-109.

McGee S, Abernethy W, Simel D. Is this patient hypovolemic? JAMA 1999; 281:1022-1029.

Meagher DJ. Delirium: optimizing management. BMJ 2001; 322:144-149.

Mecadante S. Pathophysiology and treatment of opioid-related myoclonus in cancer patients. Pain 1998; 74:5-9.

Mercadante S, Ripamonti C, Casuccio A, et al. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. Support Care Cancer 2000; 8:188-191.

Mino L, O'Connell A. Parenteral hydration and nutrition in the geriatric patient: Clinical and Ethical Issues. J of Infusion Nursing 2003;26(3):144-152.

Mock V. Fatigue management: Evidence and guidelines for practice. Cancer 2001; 92(6 Suppl):1699-1707.

Morita T, Hirai K, Sakaguchi Y, Tsuneto S, Shima Y. Family-perceived distress from delirium-related symptoms of terminally ill cancer patients. Psychosomatics 2004; 45:107-113.

Morita T, Hyodo I, Yoshimi T, Ikenga, M et al. Association between hydration volume and symptoms in terminally ill cancer patients with abdominal malignancies. Annals of Oncol 2005; 16:640-647.

Morita T, Tei Y, Tsunoda J, Inoue S, Chihara S. Determinants of the sensation of thirst in terminally ill cancer patients. Support Care Cancer. 2001 May;9(3):177-86.

Morse J, Penrod J, Hupcey J. Qualitative outcome analysis: Evaluating nursing interventions for complex clinical phenomena. *J Nursing Scholarship* 2000; 32(2):125-130.

Morse JM. Approaches to qualitative-quantitative methodological triangulation. *Nursing Research* 1991; 40:120-123.

Nekolaichuk CL, Maguire TO, Suarez-Almazor M, Rogers WT, Bruera E. Assessing the reliability of patient, nurse and family caregiver symptom ratings in hospitalized advanced cancer patients. J Clin Oncol 1999; 17: 3621-3630.

Palmer JL. Analysis of missing data in palliative care studies. Journal of Pain and Symptom Management, 28 (6), 612-618, 2004.

Palmer JL. Analysis of missing data in palliative care studies. *Journal of Pain and Symptom Management,* 28 (6): 612-618, 2004.

Pereira J, Hanson J, Bruera E. The Frequency and Clinical Course of Cognitive Impairment in Patients with Terminal Cancer. Cancer 1997; 79:835-842.

Potter JM, Reid DB, Shaw RJ, et al. Myoclonus associated with treatment with high doses of morphine. The role of supplemental drugs. Br Med J 1989; 299:150-153.

Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. J Pain Symptom Management 2003; 26:1055-1061.

Rajagopal A, Vassilopoulou-Sellin R, Palmer JL, Kaur G, Bruera E. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. Cancer 2004; 100:851-858.

Redelmeier D, Guyatt G, Goldstein R. Assessing the minimal important difference in symptoms: a comparison of two techniques. J Clin Epidemiol. 1996 Nov;49(11):1215-9.

Ross JR, Saunders Y, Cochrane M, Zeppetella G. A prospective, within-patient comparison between metal butterfly needles and Teflon cannulae in subcutaneous infusion of drugs to terminally ill hospice patients. Palliative Med 2002; 16:13-16.

Sasson M, Shvartzman P. Hypodermoclysis: an alternative infusion technique. Am Fam Physician 2001; 64:1575-1578.

Schen RJ, Singer-Edelstein M. Hypodermoclysis (letter). JAMA 1983; 250:1694-1695.

Schen RJ, Singer-Edelstein M. Subcutaneous infusions in the elderly. J Am Ger Soc 1981; 24:583-585.

Schonwetter R, Teasdale T, Storey P, Luchi R. Estimation of survival time in terminal cancer patients: an impedance to hospice admission? Hosp J. 1990; 6(4): 65-79.

Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166: 1338-1344.

Seymour DG, Henschke PJ, Cape RD, Campbell AJ. Acute confusional states and dementia in the elderly: The roles of dehydration/volume depletion, physical illness and age. Age Aging 1980; 9:137-146.

Sjogren P, Dragsted L, Christensen CB. Myoclonic spasm during treatment with high doses of intravenous morphine in renal failure. Acta Anaesthesiol Scand 1993b; 37:780-782.

Slatkin N, Rhiner M. Treatment of opioid-induced delirium with acetylcholinesterase inhibitors: a care report. J Pain Symptom Manage 2004; 27(3):268-273.

Slesak G, Schnurle JW, Kinzel E, Jakob J, Dietz PK. Comparison of subcutaneous and intravenous rehydration in geriatric patients: a randomized trial. J Am Geriatr Soc 2003; 51:155-160.

Steiner L, Siegal T. Muscle cramps in cancer patients. Cancer 1989; 63:571-577.

Steiner N, Bruera E. Methods of hydration in palliative care patients. J Palliat Care 1998; 14:6-13.

Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A, A'Hern R. Fatigue in advanced cancer: A prospective controlled cross-sectional study. British J Cancer 1999; 9:1479-1486.

Tiziana M, Bianchette A, Trabucchi M, Lawlore PG, Gagnon B, Mancini IL, Pereira JL, Hanson, Suarez-Almazor M, Bruera E. Delirium as a predictor of survival in older patients with advanced cancer. Archive of Internal Medicine 2000; 160: 2866-2868.

Tripp-Reimer T. Research in cultural diversity: reliability issues in cross-cultural research. Western J of Nursing Research 1985; 7(3): 391-392.

Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000; 5:132-148.

Tuma R, DeAngelis LM. Altered mental status in patients with cancer. Arch Neurol 2000; 57:1727-1731.
Virnig B, McBean M, Kind S, Dholakia R. Hospice Use Before Death: Variability Across Cancer Diagnoses. Medical Care 2002; 40(1): 73-78.

Vogelzang N, Breitbart W, Cella D, et al. Patient, caregiver, and oncologist perceptions of cancer-related fatigue: results of a tri-part assessment survey. Semin Hematol. 1997; 34(Suppl 2): 4-12.

Waller A, Carolin NL. Subcutaneous infusions. In: Waller A, Carolin NL (eds). Handbook of Palliative Care in Cancer. Boston, MA, Butterworth Heinemann; 1996:449-456.

Westfall PH, Young SS. Resampling-Based Multiple Testing. New York: John Wiley & Sons, Inc.; 1993.

Wilkins M, Redondo J, Brown L. The natriuretic-peptide family. Lancet 1997; 349:1307-1310.

Wilson, S., & Morse, J. Living with a wife undergoing chemotherapy. Image - *The Journal of Nursing Scholarship*, 1991;23, 78-84.

Winaver J, Abassi Z, Green J, Skorecki K. Control of extracellular fluid volume and the pathophysiology of edema formation. In: Brenner BM (ed) The Kidney, 6th edn. Saunders, Philadelphia, p 795-865.

Wolfinger R. Covariance structure selection in general mixed models. *Communications in Statistics: Simulation and Computation* 22(4):1079-1106, 1993.

Wolfram G, Sitter T, Gottsmann M, Gerzer R, Schiffl H. Assessment of dry weight in haemodialysis patients by the volume markers ANP and cGMP. Nephrol Dia Transplant 1996; 11 (suppl 2):28-30.

Woolf CJ. Intrathecal high dose morphine produces hyperalgesia in the rat. Brain Res 1981; 209:491-495.

Yilmazlar A, Bilgin H, Korfali G, Eren A, Oskan U. Complications of 1303 central venous cannulations. J Roy Soc Med 1997; 90(6):319-321.

Yoon W, Lee W, Chung E, Youn J. Dehydration-induced myoclonus: Report of two cases. 16th International Congress on Parkinson's Disease and Related Disorders. (Abstract). June 5-9, 2005, Berlin, Germany.

Mudambo KS, Coutie W, Rennie MJ. Plasmaarginine vasopressin, atrial natriuretic peptide and brain natriuretic peptide responses to long-term field training in the heat: effects of fluid ingestion and acclimatization. Eur J Appl Physiol Occup Physiol 1997; 75:219-25.

Lang C, Choy A, Turner K, Tobin R. Coutie W, Struthers A. The effect of intravenous saline loading on plasma levels of brain natriuretic peptide in man. J Hypertens 1993;11:737-41.

Omland T. Advances in congestive heart failure management in the intensive care unit: B-type natriuretic peptides in evaluation of acute heart failure. Cri Care Med 2008; 36(1):S17-S27.

H. CONSORTIUM/CONTRATUAL ARRANGEMENTS Page 74

I. RESOURCE SHARING

None

J. LETTERS OF SUPPORT/AGREEMENT