

Grant Number: 5R01AT001006-03
PI Name: KUTNER, JEAN S.
PI Email: jean.kutner@uchsc.edu
PI Title: ASSOCIATE PROFESSOR & ACTING DIVISION HE
Project Title: Efficacy of Massage Therapy at the End of Life

Abstract: DESCRIPTION (provided by applicant): Relief of physical and emotional symptoms is a key component of end-of-life care. However, there is a significant burden of unrelieved symptoms among terminally ill patients. Individuals with advanced cancer often suffer from multiple symptoms; the pharmacologic interventions used for alleviation of one symptom may exacerbate other symptoms. Studies of the efficacy of therapies that have potential to mediate these symptoms deserve our highest priority. For these reasons, the goal of this application is to evaluate the efficacy of massage therapy for alleviation of symptom distress and improvement of quality of life for patients with advanced cancer who are receiving hospice/palliative care. The specific aim of this study is to demonstrate the efficacy of massage therapy for treatment of pain, reduction of physical and emotional symptom distress, and improvement of quality of life among cancer patients at the end of life. This will be a multi-site randomized clinical trial comparing massage therapy plus usual hospice care with a control group receiving "non-moving touch" plus usual hospice care. The study will be conducted in a community-based hospice/palliative care research network. Data will be collected at baseline, immediately preceding and following each intervention (massage therapy) or control (non-moving touch) session, and weekly for the three weeks of each patient's participation in the study. Analyses will determine the independent influence of the intervention (a series of massage therapy sessions) on the identified outcomes (pain, physical and emotional symptom distress, quality of life).

Institution: UNIVERSITY OF COLORADO DENVER/HSC AURORA
P.O. BOX 6508, GRANTS AND CONTRACTS
AURORA, CO 800450508

Fiscal Year: 2005

Department: MEDICINE

Project Start: 15-JUL-2003

Project End: 31-MAR-2007

ICD: NATIONAL CENTER FOR COMPLEMENTARY & ALTERNATIVE
MEDICINE

IRG: ZRG1

RESEARCH PLAN

Introduction to Revised Application

This application has been substantially revised in response to reviewers' comments and has been updated to reflect progress in the Investigators' current research. Changes have been clearly marked in the body of the Research Plan by highlighting. Where an entire section has been extensively modified, only the section heading is highlighted to indicate that the entire section has been changed. We refer to specific reviewers' comments and changes made within the Research Plan below.

Research Team Modifications: The research team has been greatly enhanced by the addition of Diane Fairclough, PhD as a Co-Investigator (see Key Personnel and biosketch). Dr. Fairclough, who recently assumed an appointment at the University of Colorado Health Science Center as a member of the Colorado Health Outcomes Program, has significant expertise in statistical issues relevant to this study, including longitudinal data collection with repeated measures, particularly related to measurement of quality of life. Dr. Fairclough has and will provide advice on the design, analyses and interpretation of the proposed study. Dr. Fairclough replaces Dr. Stanley Xu as biostatistician for this proposal.

Jeanette Ezzo, CMT, MPH, PhD (see biosketch and letter) has replaced Ann Gill Taylor as expert consultant. Dr. Ezzo has been particularly helpful in working with us to select the control exposure for the revised protocol. She will consult throughout the proposed project on study design, training of on-site personnel and interpretation of study results.

The position of Linnea Hemphill, MSN, nurse massage therapist, who was listed as a massage consultant on the previous version of the proposal is now listed as "TBA". Ms. Hemphill, who ran a formalized massage therapy program for oncology patients at the Denver Veterans Administration Medical Center between 1993 and 2001, remains closely involved with the study, working with Co-Investigator Marlaine Smith to design the intervention and control protocols and conducting the pilot data collection. However, given her current full-time employment by the Denver Veterans Administration Medical Center, we were restricted from listing Ms. Hemphill as receiving salary support from this federally-funded proposal. Should this proposal be funded, the Division of General Internal Medicine at the University of Colorado Health Sciences Center will hire Ms. Hemphill on a part-time basis, permitting her to receive salary support from this project for her involvement. Ms. Hemphill's position is currently listed as "TBA" in the grant application.

Methodological Issues

The reviewers commented on a number of methodologic areas that required strengthening. Specifically, the reviewers requested attention to: the methods for patient selection and eligibility criteria, assurance of treatment integrity, choice of the control exposure and site selection.

The current Research Plan addresses the reviewers' comments as follows.

Study setting/site selection: We have added more specific criteria for study site selection and narrowed the list of potential study sites to those that actually meet these specified criteria. Potential study sites were asked to complete a questionnaire that addressed their ability to meet site eligibility criteria, including access to an adequately trained massage therapist and availability of on-site personnel for study coordination, data collection and control sessions. In addition, potential study sites were queried regarding their patient census, percent with cancer, percent with at least moderate pain and whether they used a local IRB. Responses to these queries are presented in the "Study Setting" section. The list of potential collaborating sites has been revised to include only sites that have met explicit eligibility criteria. Supporting letters from these sites are included in the Appendix.

Sample - Patient selection: We agree with the reviewers' comments that the previous characteristics for patient selection were somewhat vague. Specifically, eligibility criteria have been modified to limit the study population to persons enrolled in participating hospice organizations for whom cancer is their primary diagnosis and who have experienced at least moderate pain (at least a level 4 on a standardized 0 – 10 pain scale) at least some of the time in the week preceding study enrollment. We have not limited the type of pain (e.g. somatic, visceral or neuropathic) that participants might experience. This decision is discussed on the "Sample" and "Data Collection" sections of the proposal. We have also clarified that assessment of patient eligibility will be made prior to study enrollment, thus preserving the evaluable N of 440.

Treatment groups: We have changed the control exposure to "non-moving touch" plus usual hospice care from the originally-proposed usual hospice care only, as recommended by the reviewers and our expert consultants. The selection of "non-moving touch" as the control exposure was made after extensive literature review and consultation with experts in the field. From our review of the literature (see "Background" section), it does not appear that there is any uniformly-accepted control exposures for massage trials. The "non-moving touch" protocol described in this proposal mirrors that being used currently in an NCCAM-funded R21, one of whose objectives is to determine if a sham-bodywork therapy regimen can be used as an effective control for clinical trials of massage therapy.¹

The revised control exposure is described in the "Description of Treatment Groups". While there is no study design that will eliminate all potential sources of bias, selection of this "active" control exposure will increase our ability to discern the true therapeutic effects of the object of this study, massage therapy. That is, by use of a control exposure that includes elements of the intervention being studied, specifically touch and attention, we will be able to control for these elements of the intervention being studied. Determination of which elements of the intervention actually impart the therapeutic effect have important implications for application of these study findings to clinical practice. Since use of an "active" control comparison group will likely decrease observed effect sizes, the study *Sample Size* has been appropriately adjusted to preserve the power of this study to detect clinically significant differences. The study budget has also been modified to reflect the addition of an "active" control arm. Given the reviewers' comments and reconsideration of the optimal study design to evaluate the intervention and outcomes of interest, we did consider a 3-arm study design, comparing massage therapy plus usual hospice care to "non-moving touch" plus usual hospice care to usual hospice care alone. We decided against this option due to the tremendous sample size and resources necessary for conducting a 3-arm study in this population and study setting.

On-site study personnel: We have clarified that on-site study personnel will consist of an on-site study coordinator, on-site data collector, on-site massage therapist and on-site personnel (volunteers) conducting the "non-moving touch" sessions. We have clarified the roles of each of these individuals (see "Data Collection" section). We agree with the reviewers' concerns regarding potential difficulties presented by turnover or unanticipated availability of on-site personnel, particularly the massage and "non-moving touch" therapists. We have clarified that we will train one primary and one back-up massage therapist and one primary and one back-up "non-moving touch" person at each study site. Additional training of on-site personnel will occur throughout the course of the study as needed both to accommodate addition of new personnel and to assure treatment integrity (see "Description of Treatment Groups" and "Data Collection" sections).

Training and assurance of integrity of the study exposures: The description of the training sessions for the on-site personnel, particularly for the massage therapists and personnel conducting the "non-moving touch" sessions, has been expanded. We have also more explicitly stated the purpose and

content of site visits to be conducted throughout the course of the study (see “Description of Treatment Groups” and “Data Collection”). The budget has been modified to accommodate additional site visits and additional training of on-site personnel.

Statistical Issues: The statistical analysis and power calculation sections have been re-written to address the larger sample size required by having an “active” control arm.

Mechanisms of intervention effect

The reviewers expressed disappointment at the “lack of attention to theory or mechanism” by which massage effects are obtained. This issue has been addressed in the “Background and Significance” section under “Conceptual Framework for Efficacy of Massage Therapy” and is referred to in the “Measurement” section. While the primary focus of the proposed project is pragmatic rather than explanatory, i.e. to determine the efficacy of massage therapy for the treatment of pain in the specified population rather than specific mechanisms of or subgroups for which massage therapy is most likely to be efficacious, we plan to include sufficient data elements to begin to explore these explanatory issues with this study population.

Study Setting

The description of the study setting has been updated to reflect growth of the Population-based Palliative Care Research Network (PoPCRN) since the previous application.

Resources

The Resources section has been updated to reflect changes since the previous application.

Preliminary Studies

The research team has begun pilot testing of the study enrollment and data collection instruments and procedures as well as the massage therapy intervention protocol. Data from this pilot data collection are included in this section. In addition, this section has been updated to reflect progress in the investigators’ current work since the previous application.

Budget

The budget has been revised to reflect the addition of Diane Fairclough, PhD as a co-investigator, the inclusion of additional resources to assure fidelity to the study protocol at each of the participating sites, and the larger sample size required by having an “active” control arm.

A. Specific Aim: To demonstrate the efficacy of *Massage Therapy* for decreasing pain, improving quality of life, and lessening physical and emotional symptom distress among cancer patients at the end of life.

Primary Hypothesis: Massage will decrease pain among cancer patients at the end of life.

Secondary Hypotheses:

Hypothesis a: Massage will improve quality of life among cancer patients at the end of life.

Hypothesis b: Massage will decrease physical symptom distress among cancer patients at the end of life.

Hypothesis c: Massage will decrease emotional distress among cancer patients at the end of life.

Hypothesis d: Massage will be associated with less total analgesic medication use among cancer patients at the end of life.

B. Background and Significance

Relief of physical and emotional symptoms is a key component of end-of-life care.² Terminally ill cancer patients have a significant burden of unrelieved symptoms even though many of these symptoms are treatable. Many dying patients experience serious pain, despite the availability of effective interventions. Other symptoms are less well studied, but current evidence suggests a similar pattern of inadequate symptom relief. The most common symptoms at the end of life are lack of energy (83-90%), pain (76%), anorexia (63-85%), nausea (68%), constipation (65%), drowsiness (61%), difficulty concentrating (60%), and sadness (51%).³⁻⁵ Studies of the efficacy of therapies that have potential to mediate these symptoms deserve our highest priority. The purpose of the proposed study is to examine the efficacy of massage therapy for treatment of pain, physical and emotional symptom distress, and improvement of quality of life for cancer patients at the end of life.

Massage has potential to be an efficacious and effective therapy for palliative care. Massage therapy may facilitate pain management, decrease anxiety and depression, promote relaxation and enhance quality of life in a variety of patient populations. Massage therapy may augment traditional analgesics and may enhance alertness. There are a few studies with small sample sizes that support one or more of these outcomes with patients with cancer and/or those receiving hospice care. Massage can be integrated easily into routine hospice care, and even family members can learn effective massage techniques to comfort loved ones during the last days of their lives.

Massage Therapy. Massage therapy is one of the oldest forms of treating diseases and symptoms, and is perhaps an instinctive response to relieve pain and discomfort. Massage was essential to the healing rituals of ancient Chinese, Hindu, Persian, Egyptian, Polynesian, Greek and Roman cultures. Hippocrates described the value of massage for treating a variety of ills from sprains to constipation.⁶⁻⁸ In 1812, Per Henrik Ling, a Swedish physiologist, systematized massage into the now familiar "Swedish Massage". Following World Wars I and II, therapeutic massage was widely employed in hospitals, and by the 1950's it was taught in nursing schools as an essential skill within the foundational nursing curriculum, and basic nursing texts suggest massage to "relax muscles, improve muscle tone, increase blood flow, and possibly relieve muscle spasms".⁹ Massage therapy as a specialized practice emerged in the mid-1900s as a spa treatment and for sports injuries. The American Massage Therapy Association (AMTA) has defined massage as "manual soft tissue manipulation, and includes holding, causing movement, and/or applying pressure to the body" (<http://www.amtamassage.org/about/definition.html>). In the past 25 years massage therapists have broadened their practice to include the treatment of disease-related symptoms, and many hospital-based massage therapy practices have been instituted.

Prevalence of Massage Therapy. Massage therapy is growing in acceptance among US health care consumers. A 1990 study found that 34% of adult Americans surveyed used complementary or

alternative medicine (CAM) therapies; massage was utilized by 6.9%, making it the fifth most utilized treatment.¹⁰ A 1997 study found an increase in CAM use, with 42% of those surveyed using CAM. Eleven percent used massage during the preceding 12 months, making it the third most prevalent therapy.¹¹ Use of complementary and alternative therapies is particularly common among persons with cancer. This is likely due to the critical need for relationship, communication, relief from symptoms of disease and side effects of cancer therapies, reassertion of a sense of control, stress reduction and hope.¹²⁻¹⁴ Lerner and Kennedy reported that 14.7% of cancer patients in the Rocky Mountain region used alternative therapies, the highest prevalence in the country.¹⁵ During the past decade, massage has become one of the most widely used therapies by cancer patients.¹⁶

Efficacy of Massage Therapy

A Medline search of the past ten years for randomized clinical trials using massage therapy modalities as treatment alone identified 21 studies, of which 17 showed significant positive effects for massage.¹⁷⁻³³ The **Table** below characterizes results from 11 randomized trials examining the impact of massage on physical and psychological symptoms and functioning. The results of these trials indicate effect sizes on outcomes of physical symptoms and psychological symptoms ranging from .02 to greater than 1.00, with the majority of effect sizes falling between moderate (.50 SD) to large (.75 SD). Note that only one of these trials has a study population directly relevant to the proposed study (Wilkie 2000) and that sample sizes are smaller than that for the proposed study.

Table - Randomized Controlled Trials of Massage Therapy

Author/ Year	Symptom or Illness	Total N and Randomization Scheme	Intensity and Duration	Followup	Effect Size for Selected Comparison Groups (Peak/Final)	Quality
Cherkin et al, 2001 ³⁴	Persistent low back pain	262 randomized to massage, acupuncture, and self-care	≤10 treatments of unspecified length over 10 weeks	4, 10 and 52 weeks	Massage vs. self-care Physical symptoms .53 / .32 Psychiatric symptoms NA ⁺ Functioning .50 / .08	****
Preyde, 2000 ³⁵	Sub-acute low back pain	98 randomized to massage therapy, tissue manipulation, exercise or placebo	6 treatments of 30 minutes each over 1 month	1 month and 1 month following final treatment	Massage vs. exercise Physical symptoms 1.71 / 1.21 Psychiatric symptoms 1.30 / .92 Functioning 1.06 / 1.23	****
Irnich et al, 2001 ³⁶	Chronic neck pain	177 randomized to massage, acupuncture, and sham laser	5 treatments of 30 minutes each over 3 weeks	1 week and 3 months after last treatment	Massage vs. sham laser Physical symptoms # Psychiatric symptoms NA Functioning .32 / .02	***
Field et al, 1997 ³⁷	Chronic fatigue syndrome	20 randomized to massage versus tens sham intervention	10 treatments of 30 minutes each over 5 weeks	5 weeks	Massage vs. tens sham Physical symptoms .70 / NA Psychiatric symptoms .88 / NA Functioning 1.43 / NA	***
Field et al, 1997 ²⁶	Juvenile rheumatoid arthritis	20 randomized to massage versus relaxation therapy	30 treatments of 15 minutes each over 1 month	1 month	Massage vs. relaxation Physical symptoms .83 / NA Psychiatric symptoms 1.27 / NA Functioning .78 / NA	***
Field et al, 1998 ²²	Burn injuries	28 randomized to massage versus usual care	7 treatments of 20 minutes each over 1 week	1 week	Massage vs. standard treatment Physical symptoms .73 / NA Psychiatric symptoms 1.02 / NA Functioning .50 / NA	**
Field et al, 1998 ²³	Asthma	32 randomized to massage versus relaxation therapy	30 treatments of 20 minutes each	1 month	Massage vs. relaxation Physical symptoms ## / NA Psychiatric symptoms ### / NA Functioning .93 / NA	**
Wilkie et al, 2000 (Wilkie 2000)	Cancer pain	29 randomized to massage versus usual hospice care	4 treatments of 30-45 minutes each over 2 weeks	2 weeks	Massage vs. usual hospice care Physical symptoms .30 / NA Psychiatric symptoms NA Functioning .67 / NA	**
Hernandez- Reif et al, 1999 ¹⁷	Cystic fibrosis	20 randomized to massage versus reading to child before bed	30 treatments of 20 minutes each over 1 month	1 month	Massage vs. control Physical symptoms NA psychiatric symptoms .34 / NA Functioning .47 / NA	**

Author/ Year	Symptom or Illness	Total N and Randomization Scheme	Intensity and Duration	Followup	Effect Size for Selected Comparison Groups (Peak/Final)	Quality
Field et al, 1996 ²⁸	Depression	32 randomized to massage versus relaxation therapy	10 treatments of 30 minutes each over 5 weeks	5 weeks	Massage vs. relaxation Physical symptoms 1.52 / NA Psychiatric symptoms .87 / NA Functioning .05 / NA	*
Ahles et al, 1999 ³⁸	Bone marrow transplant	34 randomized to massage versus usual care	4-9 treatments for 20 minutes each over 3 weeks	3 weeks	Massage vs. usual care Physical symptoms .44 / NA Psychiatric symptoms .50 / NA Functioning NA	*

NA = not assessed

Massage failure to improve physical symptoms reflects that most subjects had previously failed massage before entering trial. Massage significantly improves functioning.

For physical symptoms relaxation superior for children ages 6-8 (1.0); massage superior for children ages 9-16 (1.0);

For psychiatric symptoms, relaxation superior to massage for children ages 6-8 (.86); massage superior for children ages 9-16 (.70)

Massage and cancer. Studies of massage therapy for cancer patients are the most relevant to the proposed study. A review of the evidence related to the use of CAM therapies in treating symptoms at the end of life concluded that massage therapy may be efficacious in pain relief in cancer pain or in dying patients.³⁹ Studies on massage therapy have focused primarily on the outcomes of pain, anxiety and relaxation in cancer patients. Massage therapy interventions have varied from a 3-minute back massage to a 10-minute massage by a novice provider (nursing student) to 20-minute shoulder, neck, head and facial massage to two consecutive 30 minute sessions of effleurage, petrissage, and myofascial trigger point therapy. These studies, while small, overall indicate decreases in pain level, physiologic relaxation (lower blood pressure, respiratory rate and heart rate, higher skin temperature) and less symptom distress with massage therapy in a range of cancer populations.^{40 41 42 43 44 38 45}

Three studies employed variations of massage therapy. Wilkinson tested massage with aromatherapy for pain relief in a case series of 103 cancer patients. Of patients who completed the study (47%), 33% reported pain relief. There was a significant reduction in anxiety, lessening of physical and psychological symptoms and improved quality of life for those receiving the aromatherapy massage.^{46 47} Another study of aromatherapy massage supported this finding.⁴⁸ Grealish and colleagues studied the efficacy of foot massage for 10 minutes (5 minutes per foot) on perceptions of pain in 87 hospitalized cancer patients. There were significant immediate effects on pain, nausea and relaxation.⁴⁹

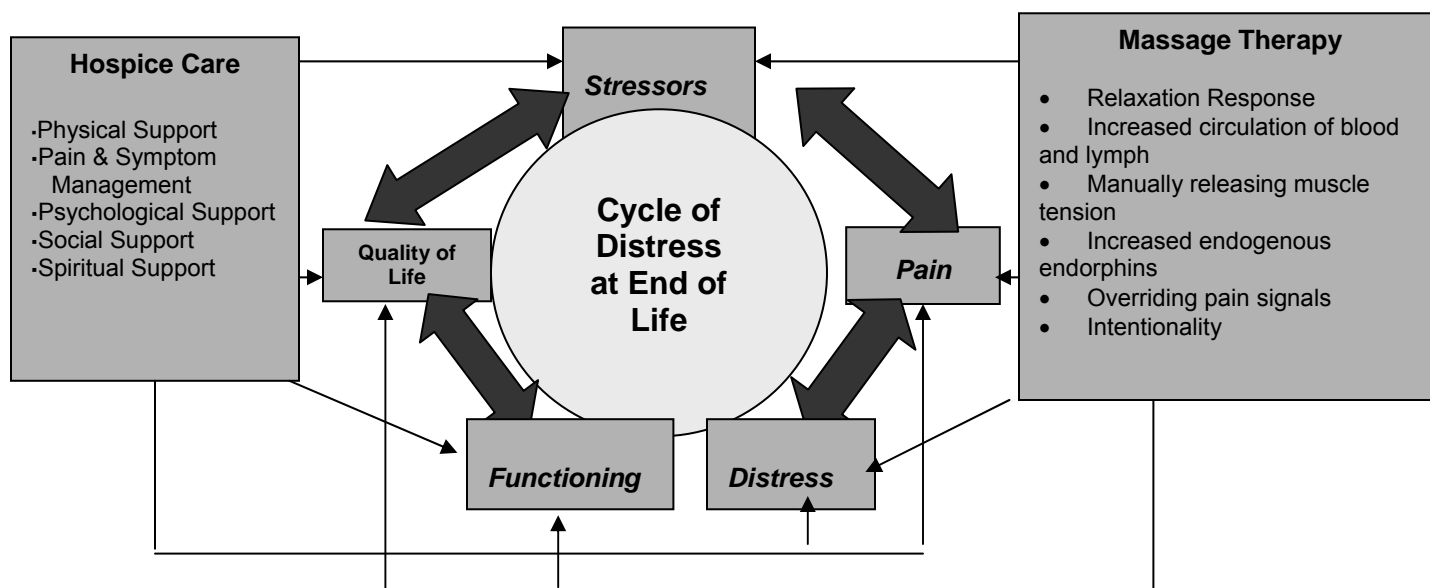
Massage and non-cancer pain reduction. Massage has been identified as a valid intervention for the treatment of pain.⁵⁰ Massage has been shown to be effective in reducing pain among acute and critical care patients and for low back pain, burn patients, chronic pain due to sickle cell disease, in the post-operative setting, and for patients with fibromyalgia, chronic headaches, and chronic neck pain.^{19;22;27;30;34-36;51-58}

Massage and arousal/relaxation, stress, and anxiety. Based on current evidence, the most consistent effect of massage is reduction of subjective levels of anxiety. Subjective ratings of anxiety may be more sensitive than objective indicators of relaxation/arousal. Eight of 10 studies reported that massage therapy significantly decreased anxiety or perception of tension. Studies of the effects of back massage on objective indicators of arousal/relaxation such as galvanic skin response, blood pressure, pulse, body temperature, pupil diameter, respirations and urinary and salivary cortisol levels have demonstrated inconsistent findings.^{51 52 51 41;59-64} Massage therapy has been associated with decreased anxiety during bone marrow transplant, among burn patients, women with premenstrual dysphoric disorder, healthy students during academic stress, sexually-abused women, hospitalized patients, critical care patients, in the setting of fibromyalgia, preoperatively, among nursing home patients and patients with multiple sclerosis.^{38;43;65-69}

Massage and Health Care Utilization. In a clinical trial in persons with HIV, subjects receiving massage therapy and stress management had significantly less health care utilization and significantly better health perceptions than those not receiving these interventions.⁷⁰ Similarly, in a trial of massage therapy, acupuncture and self-care education for people with chronic low back pain, the massage group used the least medications ($p < .05$) and had the lowest cost of care.³⁴

Conceptual Framework for Efficacy of Massage Therapy. Figure 1 depicts the cycle of distress in terminal cancer and the theorized mechanism of action for massage therapy and hospice care as interventions in disrupting this cycle.⁷¹ End stage cancer is a stressor that can precipitate pain which, when unmanaged, can result in physical and emotional distress, including anxiety and depression. This distress leads to a decrease in functional ability and a concomitant decrease in quality of life. This becomes a stressor, and the cycle continues. The two-way arrows indicate that the cycle can begin at any point. For example, emotional distress can increase pain which becomes a stressor. The goals of both hospice care and massage are related to breaking this cycle of distress. This occurs in usual hospice care through pain and symptom management using both pharmacologic and non-pharmacologic therapies, and physical, psychological, social and spiritual support. This comprehensive approach to care of the dying can interrupt the cycle at any one of the points. Massage may interrupt the cycle of distress through the following possible mechanisms: 1) inducing a relaxation response, decreasing skeletal muscle tension and its exacerbating effect on pain and inducing a calm, cognitive-affective state which can decrease distress^{61,72}; 2) increasing blood and lymphatic circulation to areas of pain, potentiating the effects of analgesics and decreasing inflammation and edema that may increase pain⁴⁴; 3) manually releasing spasms and tension in muscles⁶¹; 4) increasing release of endogenous endorphins due to the pleasure of receiving massage⁶¹; and 5) overriding pain signals through introduction of a competing sensory stimulus^{43,51}; and 6) intentionality of the therapist: presence, communication and desire to produce a therapeutic response. Massage may interrupt the cycle of distress by decreasing response to the stressor, decreasing pain and distress, increasing functioning through enabling greater mobility and decreasing use of analgesics, and increasing quality of life through the affective response to massage. Massage therapy may thus decrease pain intensity, diminish distress from both physical and emotional symptoms and can increase quality of life.

Figure 1: Disrupting the Cycle of Distress: Mechanism of Action for Massage Therapy in End of Life Care



Randomized Clinical Trials of Massage Therapy: Control Exposure Selection. Control conditions for clinical trials of bodywork therapy are required to isolate the specific effects of massage therapy from

the non-specific effects of the environment in which the therapy is practiced. The Medline search of the past ten years for randomized clinical trials using massage therapy modalities as treatment alone (**Table** above) revealed no studies that used a sham bodywork therapy regimen as a control. The control arms used in these studies varied widely but included usual care or other treatments (such as rest, spinal manipulation, and relaxation therapy). Unfortunately, because the way these studies were designed, none of them sufficiently addressed the question of whether the act of massage (the movement of muscle tissue) is what caused positive outcomes or whether these responses could be attributed to the additional time and/or personal contact between the provider and patient. Other forms of bodywork, such as acupressure⁷³ and Feldenkrais⁷⁴, have been studied using a sham bodywork control arm; one study⁷⁵ described a Reiki placebo procedure. An ongoing study (NCCAM-funded R21) has developed and is testing a sham bodywork control that would represent an important advance in the development of clinical-trial methods that examine the specific effects of massage and other bodywork therapies.¹ This “non-moving touch” protocol is being used in the proposed study.

Innovation and Significance. A key innovative and clinically important element of this study is the selection of the non-moving touch control group. For a hospice population, a non-moving touch control group answers a programmatically important question. A growing number of hospice programs now teach family members how to massage their dying loved one; however, it has never been demonstrated in a randomized trial whether massage affords a dying patient more comfort than simple physical contact. If massage proves to be no better than simple touch, then simple touch is much easier to implement than massage therapy. Conversely, if massage therapy proves to be significantly better than simple touch, then it provides the justification for integrating massage therapy into hospice programs and expending the time and energy to train family members in administering this modality. The proposed study, given its sample size and methodologic rigor, has significant potential to identify an intervention that may promote the comfort and quality of life of cancer patients receiving palliative care while advancing the state of the science for massage therapy trials.

C. Preliminary Studies

The Principal Investigator, **Dr. Jean Kutner**, has significant experience in conducting studies among terminally ill individuals in the community-based hospice setting and among cancer patients and others with advanced illness.^{3;76-80} With initial internal funding from the Hartford/Jahnigen Center of Excellence in Geriatrics and the Division of General Internal Medicine Small Grants Program at the University of Colorado Health Sciences Center and now with support from the Robert Wood Johnson Generalist Physician Faculty Scholars Program and the Paul Beeson Physician Faculty Scholars in Aging Research Award, Dr. Kutner has developed the Population-based Palliative Care Research Network (PoPCRN), a nationally recognized practice-based research network dedicated to improving end-of-life care (see “Setting” section). She has successfully demonstrated the benefits and feasibility of this model for conducting end-of-life research.

An initial PoPCRN-based study, “Symptom Burden at the End of Life: Hospice Providers’ Perspectives”, provides important background data for the proposed study. This study of 348 hospice/palliative care patients from 16 sites (median age 78 years, 55% cancer diagnosis), utilized the Memorial Symptom Assessment Scale, one of the planned instruments for the proposed study, to describe the prevalence, severity, and frequency of symptoms at the end of life, from the perspective of hospice care providers. This study identified and described a substantial unrelieved symptom burden perceived by hospice providers among terminally ill patients.³

A second PoPCRN-based study, “Psychosocial and Spiritual Issues Among Hospice Patients”, provides evidence for preservation of quality of life among terminally ill individuals receiving hospice care and demonstrates the feasibility of data collection among this patient population (manuscripts in

preparation). This study entailed one-on-one interviews of patients receiving hospice care, using two of the instruments planned for the proposed study, the McGill Quality of Life Questionnaire (MQOL) and the Karnofsky Performance Scale. Sixty-six individuals from 14 PoPCRN sites participated in this study. Fifty three percent had a cancer diagnosis. The median respondent age was 76 years. Among this older, terminally ill population receiving hospice care, whose functional level was poor (Karnofsky Performance Scale mean score < 50%) and for whom physical symptoms were troublesome, quality of life persisted, as measured by the MQOL. Quality of life was particularly preserved among patients with cancer, those who were cared for at home, and those who had better functional status.^{81;82}

Dr. Kutner is currently funded by the Robert Wood Johnson Generalist Physician Faculty Scholars Program and the Paul Beeson Physician Faculty Scholars Award for work intended to decrease distress and improve quality of life at the end of life. A series of studies is planned, first describing the time course and variation of symptom distress at the end of life, then developing and testing symptom management interventions. Dr. Kutner is currently completing final data collection for the first of these studies, "Natural History of Symptoms at the End of Life", that entails following patients from the time of hospice admission until death or discharge, collecting data from patients (when able), caregivers (when present) and hospice/palliative care nurses regarding symptom distress and quality of life, using instruments planned for the proposed study, including the Condensed Memorial Symptom Assessment Scale (MSAS), the McGill Quality of Life Questionnaire (MQOL) and the Karnofsky Performance Scale (KPS). This study will provide important data regarding the variation in symptom burden and quality of life experienced by patients at the end of life over the final months of illness. In addition, this current study will significantly contribute to the methodology of studying persons at the end of life. By specifically collecting data from three sources (patient, caregiver and nurse), Dr. Kutner expects to determine the role of surrogate responses in studies of symptoms and quality of life, a key issue in a population where a significant percentage of respondents are unable to participate due to cognitive impairment or frailty. One hundred patients have been enrolled in this study, demonstrating the willingness and ability of these patients to participate in longitudinal data collection. Preliminary analyses indicate that these patients have a significant unrelieved symptom burden in the weeks preceding death, with pain, the primary outcome for the proposed study, being both common (82% of respondents having pain) and distressful (mean pain distress score=2.2 on the 0 – 4 scale, with higher score indicating more symptom distress). Patients experienced, on average, 11 symptoms (SD 4.9, range 0 - 17). The most prevalent symptoms were also the most distressful. The 5 most common symptoms were: lack of energy (95%), pain (82%), lack of appetite (81%), difficulty concentrating (76%) and feeling drowsy (74%). MSAS mean scores (range 0 - 4; higher number=more symptom distress) indicate that these symptoms were also distressful: lack of energy=3.3, pain=2.2, lack of appetite=2.2, difficulty concentrating=2.2, feeling drowsy=2.0 and Global Distress Index=1.9. Despite this significant symptom burden and the proximity of data collection to time of death, the overall quality of life of these patients was fair, as demonstrated by mean total MQOL score=5.5 (range 0 - 10; 0=bad, 10=good).⁵

Several other less intensive studies have also been completed or are ongoing at PoPCRN sites, indicating the motivation of network members to participate in research. Through the current study of the natural history of symptoms at the end of life, as well as the previous study of psychosocial and spiritual issues among hospice patients, Dr. Kutner and her PoPCRN research team have gained significant experience in use of appropriate study instruments, as well as the logistics of conducting rigorous, quality research among diverse study sites. This experience and expertise ensure the success of the proposed project.

The **Co-Investigator, Marlaine Smith, RN, PhD, HNC** is Associate Dean for Academic Affairs and Director of the Center for Integrative Caring Practice at the UCHSC School of Nursing. **Dr. Smith will**

co-chair a group convened by the Samueli Institute to develop exemplar research protocols to study the nurse-patient healing relationship. In January 2003 she will participate in a national meeting of scientists studying the biology of healing to refine research protocols related to healing intentionality, healing energy and healing relationships.

Dr. Smith has conducted three studies related to outcomes of massage therapy for hospitalized patients. The first was a quasi-experimental, pretest-posttest, nonequivalent comparison group evaluation of a massage therapy program at an urban teaching tertiary care facility. The evaluation assessed differences in pain, sleep quality, rest, anxiety, and length of stay for patients on the solid organ transplant, orthopedic/rehabilitation, and neuroscience units of a hospital. Subjects (n=110) received 2 massages each week for 2 weeks of their hospital stay. Pain was measured by a Numerical Rating Scale; sleep quality by the Verran Snyder-Halpern Sleep Scale; rest by Smith's Rest scale, and anxiety by the STAI. Subjects in both the treatment and control groups completed the questionnaires on admission and the day after each massage; those in the control group completed them on the day after the massage would have been administered. There were no significant differences in pain, rest, anxiety or length of stay between those subjects who received massage and those who did not. There was, however, a significant improvement in quality of sleep in the treatment group ($p = .05$).⁸³ Subjects described 7 areas in which they noticed benefits associated with massage therapy: pain, sleep, muscle tension and anxiety, body awareness, physical functioning, psychological support, and enhanced healing.⁸³ The study provided an opportunity to refine a hospital-based massage therapy protocol, to develop patient inclusion criteria through therapist, physician, nurse, and risk management consensus, and to develop and assess outcome measurement tools in this acutely-ill population.

Dr. Smith's second study, conducted in collaboration with Linnea Hemphill, examined the effects of therapeutic massage on perception of pain, sleep patterns, symptom distress, and anxiety in patients who were hospitalized for the treatment of cancer.⁸⁴ The study employed a pretest-posttest comparison group design without random assignment in which twenty subjects received therapeutic massage and 21 received routine care and nurse interaction. Both interventions were given for approximately 30 minutes three times a week for a one week period. The outcome variables were measured on admission and at the end of one week with: a Visual Analogue Scale for pain intensity and Likert-type scale for distress from pain; The Verran Snyder-Halpern Sleep Scale, the McCorkle's Symptom Distress Scale, and the State-Trait Anxiety Inventory (STAI). A statistically significant improvement in pain and symptom distress occurred for subjects receiving therapeutic massage. While sleep quality remained stable for those who received massage therapy, it significantly deteriorated for those in the control group. The findings support the value of massage as a nursing therapeutic for cancer patients receiving chemotherapy.

Dr. Smith's third study, a randomized trial, investigated the effects of therapeutic touch and massage therapy on time for engraftment, complications of chemotherapy, and patient perceptions of benefits of therapy during bone marrow transplant.⁸⁵ Subjects were randomly assigned to one of three treatment groups: therapeutic touch (TT), massage therapy (MT), or a control group, the friendly visit (FV). Eighty eight subjects entered the study, stratified by type of transplant (allogeneic or autologous). Subjects received the interventions every third day during their time in the transplant program. There were no significant differences among the 3 groups with respect to time of engraftment. The score for CNS/neurological complications of chemotherapy for subjects who received massage therapy was significantly lower as compared with the control group; however, there were no differences among the 3 groups with respect to the other complications or in the total mean score for complications of chemotherapy. Patients' perceptions of benefits of therapy were

significantly higher in the group receiving MT. The findings suggest that massage therapy can be effective in altering the psychological and neurological complications associated with chemotherapy during bone marrow transplant.

Pilot Data Collection. After receiving human subjects review approval from the Colorado Multiple Institutional Review Board (COMIRB) in August 2002, we initiated pilot data collection at 2 Colorado hospices for the massage (intervention) arm of the proposed study in order to evaluate study procedures, data collection instruments and feasibility. Pilot study participants completed screening for study eligibility, informed consent, baseline data collection (pain, other symptoms, quality of life), one intervention (massage) session and peri-intervention pain assessment. This pilot data collection has led to clarification of the components of the massage intervention protocol and refinement of the study instruments (revised instruments included in Appendix; see “Instrument” section below for description of study instruments). We have data on 8 patients to date, who have a mean age of 64 years (range 49 – 81), a variety of cancer diagnoses (breast, kidney, lung, ovary, prostate, skin, bowel and brain) and are, on average, 5 years from initial diagnosis (range <1 month – 23 years). Average pain score (0 – 10 scale) at time of study enrollment is 4.6 (range 2 – 8), with worst in past week of 7 (range 4 – 10) and worst in past 24 hours of 6 (range 4 – 10). Pain interferes with function: mean BPI interference score=5.1 (range 0 – 10; higher number=more interference). As we have found in other studies, patients experience multiple symptoms in addition to pain (lack of energy 88%, feeling drowsy 75%, shortness of breath 63%, feeling nervous 63%). MSAS mean scores indicate that these symptoms were also distressing: Global Distress Index=2.8 (range 0 - 4; higher number=more symptom distress). The quality of life of these pilot patients is fair; mean MQOL global quality of life score=4.6 (range 0 - 10; 0=bad, 10=good). MPAC pre- / post- massage intervention scores preliminarily indicate responsiveness of this instrument to massage effects: mean pre-massage pain scale=38, post=11 (range 0 – 100; higher score=worse pain); mean pre-massage mood scale=61, post=80 (range 0 – 100; higher score=better mood). We will continue pilot data collection for the massage arm of the study until we have enrolled 20 subjects. We will conduct similar pilot data collection for the “non-moving touch” study arm once we have received COMIRB approval of this amended version of the study protocol and prior to implementation of the study proposed here.

D. Research Design and Methods

Study Design: The design of this study is a multi-site randomized clinical trial comparing massage therapy plus usual hospice care to “non-moving touch” plus usual hospice care. Changes in the outcome variables from baseline to follow-up will be compared between the two study arms. See Appendix for study design diagram.

Setting: This study will be conducted in the Population-based Palliative Care Research Network (PoPCRN), a research network of organizations that provide hospice/palliative care, based at the University of Colorado Health Sciences Center. PoPCRN is modeled on practice-based research networks, which have served as laboratories for the study of health events and health care delivery in real-world settings, integrating practical perspectives with accepted and innovative research methods.^{86;87} Research from primary care research networks has allowed policy makers and practitioners to address primary care issues from the perspective of data rather than unsubstantiated opinion.^{86;88-90}

Since the majority of end-of-life care is provided outside academic institutions, the practice-based research network provides an essential model for conducting population-based end-of-life research. The mission of PoPCRN is to enhance the care of persons at the end of life and their families by conducting high-quality research in and disseminating evidence-based information to settings in which palliative care is provided. To date, 171 hospice/palliative care organizations from 36 states

have expressed interest in participating in PoPCRN-based studies, and 126 (74%) hospice/palliative care organizations have collected data for 12 network-based studies. Organizational level data are routinely collected from participating sites. These organizations provide care in patient homes (59%), nursing homes (26%), and freestanding facilities (10%) in both rural and urban locales. Average census ranges from 2 to over 1500 patients, 82% of patients are age 60 or older, 45% are female and 85% are non-Hispanic white. Fifty-eight percent of patients cared for by these organizations have a cancer diagnosis. Similar characteristics are found on the national level, where 78% of hospice patients are age 65 or older, 55% are female, and 84% are non-Hispanic white.⁹¹ PoPCRN was honored in July 2002 by receipt of an American Hospital Association "Circle of Life Award for Innovation in End-of-Life Care", sponsored by the Robert Wood Johnson Foundation.

Each participating hospice/palliative care organization identifies one contact person, uses standardized data collection procedures and allows collected data to be analyzed and distributed in ways consistent with confidentiality requirements. An Advisory Committee, composed of representatives from participating sites and senior research personnel at the University of Colorado Health Sciences Center, provides guidance regarding study design, implementation, and data interpretation. A web page (www.uchsc.edu/popcrn), quarterly newsletter and listserves facilitate communication.

PoPCRN sites for this study have been selected to assure recruitment of sufficient sample size, fidelity to study methodology and intervention, and accuracy and completeness of data collection. Specifically, study sites have been selected from among current PoPCRN sites based on: performance and participation in previous PoPCRN or other research studies, availability of a dedicated on-site study coordinator who will champion the project, availability of a second on-site professional to collect study data, availability of a qualified massage therapist, availability of personnel to conduct the "non-moving touch" sessions, absence of ongoing studies that might compete for patients required by this study, enthusiasm of site personnel, and support of site administration.⁸⁴ A general solicitation that explained the study procedures and inquired regarding potential interest in participating in the proposed study was sent to all PoPCRN sites. Interested sites were asked to complete a questionnaire that addressed the site selection criteria above as well as average daily census, average number of admissions per week, percent of patients with cancer, percent of cancer patients with at least moderate pain and whether the sites had their own IRB. We selected the study sites from among respondents to this inquiry. Letters of support from the 11 potential study sites are included in the Appendix. These sites all indicated that they meet the stated site selection criteria. The average daily census of these sites is 277 (range 12 – 1300) with, on average, 26 new admissions per week (range 2 – 60), of which, on average, 59% have cancer and 61% are in at least moderate pain. Only 4 of these sites have their own IRB. IRB issues are addressed in the "Informed Consent" section below. We expect to include up to 10 PoPCRN sites in this study, with the final number of sites to be determined based on the average daily census at each of the selected sites, projected study enrollment per site and actual site availability at the time of study implementation.

Sample: Eligible patients will be English-speaking persons age ≥ 18 years with a primary hospice diagnosis of cancer who have at least moderate pain (at least a level 4 on a 0 – 10 numeric pain scale) in the week prior to study enrollment, who are receiving care from participating hospice/palliative care organizations during the study period, who have an anticipated life expectancy of at least three weeks and who consent to and are able to participate. Individuals may be enrolled at any point while they are receiving hospice care as long as they meet study eligibility criteria. Patients with all cancer diagnoses will be eligible for study participation. Since all study participants will be enrolled in hospice/palliative care, it is assumed that all participating patients will have significantly advanced disease and have selected a palliative, rather than curative course of care. The study will

be limited to patients with primary hospice diagnoses of cancer to assure some uniformity regarding mechanisms of disease and, particularly, mechanisms of pain. While it is possible that there may be some differential efficacy of massage therapy across cancer diagnoses, this hypothesis is not the primary focus of this study. We will collect data regarding type of cancer, length of time since initial diagnosis, cancer-specific treatment received and comorbid conditions, allowing for subgroup analyses if sufficient subgroup sample sizes are achieved.

This study will be limited to patients who have experienced at least moderate pain (level 4 on a 0 – 10 point pain scale) in order to maximize the likelihood of observing an effect of the proposed intervention. Study participation will not be limited to one type of pain, eg. somatic, visceral or neuropathic, for several reasons. First, in this frail, terminally ill population, it is likely that participating individuals will be experiencing several types of pain. Second, particularly in this population, delineation of the exact type of pain is usually based on clinical judgment rather than objective criteria. Exhaustive evaluation of pain type would significantly increase respondent burden. Given the broad range of potential qualitative descriptors of pain, and the acknowledged difficulty of classifying pain based on symptoms, it is unlikely that we would have sufficient sensitivity or specificity to use such a determination consistently for inclusion/exclusion criteria.⁹²⁻⁹⁴ Third, this study is intended to have a broad focus on overall pain in advanced cancer, rather than a more narrow focus on one particular type of pain. If massage therapy is found in this study to be efficacious for the treatment of pain in the setting of advanced cancer, further studies may delineate the settings or specific patients or types of pain in which massage therapy is most efficacious. We will, however, obtain sufficient information regarding the pain experienced by participating individuals to begin to understand potential differential efficacy (see Appendix for study instruments).

This study will be limited to English-speaking patients as the planned study instruments, with the exception of the Brief Pain Inventory, have been validated only in English. It is not the intent of this study to create validated study instruments in other languages. Patients will be excluded if they have had massage therapy within the month prior to study enrollment, if they are not willing to agree to the random study treatment, or if they are not competent to consent to study participation. Competence for study participation will be evaluated by potential participants' ability to explain the following to study personnel: the goals of the study, requirements of study participation, and potential risks and benefits. This study will not enroll individuals who require proxy consent, since individuals who require proxy consent would also require proxy responses to the study instruments measuring pain, symptom distress, emotional distress and quality of life, outcomes which are best assessed by the patient. In addition, patients who are receiving anticoagulant therapy, have a known platelet count below 10,000 or a known unstable spine will be excluded in order to minimize potential adverse effects of the massage therapy intervention.

Patients will be screened for presence of basic eligibility criteria (age \geq 18 years, cancer diagnosis, experienced at least moderate pain within the prior week, anticipated life expectancy of at least 3 weeks, English-speaking, agreeable to randomization) and absence of exclusion criteria (receiving anticoagulant therapy, have a known platelet count below 10,000 or a known unstable spine, received massage therapy within the previous month, not competent to consent) prior to undergoing informed consent (see Appendix for study instruments). Based on our pilot experience, we anticipate that <20% of potential enrollees who are otherwise eligible will be excluded due to inability or unwillingness to provide consent for study participation or having had massage therapy in the month prior to study enrollment.

Rapid attrition due to death or decreased functional status is expected in this study population. In order to minimize these expected effects, study participation is limited to individuals who are able to consent and who have an anticipated life expectancy of 3 weeks or more. Although the trajectory of

illness is relatively predictable among cancer patients⁹⁵, it is likely that a certain percentage of individuals who enter the study will not be able to complete it due to rapid functional decline or death. In a previously published pilot study of massage therapy in the hospice setting, 38% of subjects did not complete the study due to death or functional decline.⁴⁴ However, this study did not limit participation based on anticipated life expectancy. We expect attrition in our study to be lower. We have calculated the study sample size and planned analyses to address this inevitable aspect of conducting research in this population.

Informed Consent: The previous version of this proposal has received approval from the Colorado Multiple Institutional Review Board (COMIRB). All participants will undergo an informed consent process and must provide informed consent according to the requirements of COMIRB. Specifically, informed consent will be obtained by the on-site study coordinators. These individuals will be responsible for verbally describing all elements of the study and consent to each potential subject and reviewing the consent form with each potential subject. The on-site study coordinators will be trained by the principal investigator in the principles of informed consent, particularly for this vulnerable population, and will complete web-based IRB training (<http://cme.nci.nih.gov>). Participants will keep one copy of the consent form and give a second signed copy back to the study coordinator for signature by him/her and by the principal investigator. The Investigators will meet human subjects protection and institutional review board requirements as delineated by each participating site. Most PoPCRN sites do not have their own IRBs and have, to date, accepted COMIRB review and approval in lieu of their own process. We will seek approval from individual site IRBs, in addition to COMIRB approval, where applicable. We will obtain Federal Wide Assurances, per OHRP requirements, for sites that do not have or use local IRBs. These IRB issues will be addressed prior to enrollment of study subjects.

Randomization: Subjects will be randomly assigned to one of two groups: massage therapy plus usual hospice care or “non-moving touch” plus usual hospice care, using a randomized block design. Both groups will receive usual hospice care in addition to these treatments. Randomization blocks will be stratified by study site, and individuals will be randomized within study site. Block size will be randomly varied between 2, 4 and 6 so that the on-site study coordinator cannot predict what treatment the next patient will receive. The intervention (massage plus usual hospice care) and control (“non-moving touch” plus usual hospice care) will be equally represented within each block. This approach will be taken to assure achievement of approximately the same sample sizes within each treatment arm.⁹⁶ Randomizations will be performed centrally. Each site will contact the Principal Investigator’s office to register the patient in the trial. Study personnel will be able to learn the treatment assignment at all hours during which patients can conceivably be randomized.⁸⁴ After the patient is deemed eligible for the trial and has consented to be in the study, the random assignment will take place centrally and be communicated to the site contact. The randomization sequences will be developed by the statistician co-investigators who are experienced in the design and conduct of multi-site trials.

In order to minimize the likelihood that potential study participants will decline study enrollment due to reluctance to be randomized to the control (“non-moving touch” plus usual hospice care) arm, subjects who are assigned to the control arm will be offered a massage therapy treatment after completion of the 3-week study period.⁹⁷ All study participants (control and intervention subjects) will be offered the opportunity to receive massage therapy treatments following conclusion of the study, subject to the resources available at each study site. All subjects will receive routine hospice care in addition to the specified interventions.

Description of Treatment Groups

The control condition of non-moving touch was developed for the following reasons: 1) It controls for attention effects. Participants in both groups will receive the same amount of time and attention from the massage therapists and the volunteers administering the non-moving touch protocol. 2) It controls for placebo effect, the participants' expectation that the treatment may be beneficial. In the consent form, the study conditions will be described to the potential participants as "moving touch" (a synonym for massage therapy) or "non-moving touch". Eliminating the language of "massage therapy" will mediate the expectation of receiving a real treatment as opposed to a non-beneficial control condition. 3) The use of non-moving touch as a control condition may decrease the potential nocebo effect, the negative effects generated when participants perceive that they are being deprived of a potentially beneficial treatment or are assigned to a condition that they perceive to be of little or no value to them. This is a significant problem for research in massage therapy because of the positive perceptions of "feeling better" related to receiving the experimental treatment. In addition, any contrived control condition may be burdensome to hospice patients and their families. 4) The non-moving touch condition is planned so that the intentionality of the therapist is interrupted. The therapists' intent to be therapeutic is integral to many touch therapies. In the massage intervention, intentionality is encouraged through a process of centering or focusing prior to beginning the therapy. In the non-moving touch protocol, intentionality is interrupted through preoccupying the therapist with a mental exercise. 5) Therapeutic communication, part of the therapist-client relationship, may also influence study outcomes. To address this issue, communication will be standardized as much as possible in the two groups (see protocols below). 6) While sham massage therapy would blind participants to the intervention, we chose not to use this condition for the control. Even a sham therapy such as light moving touch applied by someone not trained in massage therapy has a greater possibility of producing some effect, thereby comparing two "types" of massage, substantially decreasing between-group differences. In addition, sham massage therapy has potential to produce irritation or discomfort in patients. Simple touch, while having the potential to produce some effects, should produce fewer such effects than sham therapy.

The Experimental Treatment: Massage Therapy

Massage therapists. Massage will be performed by Certified Massage Therapists who have at least 6 months of experience treating hospice patients. Therapists must have completed a minimum 500 hour program of study in massage therapy that is certified or recognized by their state as a vocational school. There will be one primary massage therapist and one back up massage therapist per participating site to minimize variation by therapist within study sites.

Training. Prior to implementation of the massage protocol, all study massage therapists will attend a full-day training session conducted by experienced members of the research team. The training session will be organized as follows:

- 1) The terminally-ill cancer patient (1 hour);
 - a. Common symptoms of the terminally-ill cancer patient
 - b. Principles of palliative care
 - c. Routine care and treatment of the terminally-ill cancer patient
- 2) Description of the study (30 minutes);
 - a. Overview of aims
 - b. Description of the sample criteria, study design and methods
 - c. Key personnel and their roles in the study
 - d. Introduction to the study sites
 - e. Responsibilities related to participating as a therapist in the study
- 3) Philosophy, setting and massage therapy protocol (1 hour)
 - a. General principles of massage therapy with terminally-ill cancer patients

- b. Description of massage therapy protocol and importance of adhering to the research protocol
 - c. Data collection (pulse, respiration, pain)
 - d. Institutional or in-home environment issues
 - e. Safety issues of administering massage with the terminally-ill patient
 - f. Documentation on the Massage Therapy Assessment Form and Patient Record
 - g. Procedures (Obtaining supplies, reimbursement for travel, contingency plans for a back up therapist, etc)
- 4) Practice and supervision of protocol massage (2 hours). Therapists will practice the protocol in the UCHSC-School of Nursing's Nursing Resource Center (skills lab).
 - 5) Competency evaluations (2 hours) - Participating therapists will be evaluated for their performance in following the study protocol through paper and pencil test and performance examinations. These exams will be developed during the planning phase of the study.

Both the primary and the back up massage therapists from all participating sites will attend the first training session at the UCHSC during the planning phase of the study. A training manual will be developed and the training session will be videotaped. The videotape and the training manual will be available for training additional massage therapists when attrition occurs. Competency evaluation of therapists will occur during the investigators' and consultants' site visits.

The Massage Protocol. The massage protocol is based on the following guiding principles: 1) Not harming the patient; 2) Preserving the integrity of the massage therapy session; 3) Allowing for therapist's clinical judgment and patient preferences; 4) Standardizing the protocol so that the treatment is recognizable and replicable; 5) Maximizing therapeutic benefit; and 6) Eliminating extraneous variables that may account for treatment effect, such as attention, communication and therapeutic intent. The massage therapy sessions will be approximately 30 minutes 3 times a week for two weeks. This length and frequency of treatment that has been efficacious in other studies and takes into account the short lengths of stay of hospice patients.⁴⁴ The protocol is designed to permit the massage therapists to exercise their judgment in planning the specific timing of the treatments during the week. One primary massage therapist per site will administer study massages with back up assistance available when needed.

The massage treatment will consist of effleurage, petrissage and myofascial trigger point therapy. Effleurage is defined as a stroke generally used in Swedish massage treatment. This smooth, gliding stroke is used to relax soft tissue and is applied using both hands. Petrissage (also called kneading) is squeezing, rolling and kneading the muscles and usually follows effleurage during Swedish massage. Trigger point therapy (also known as myotherapy or neuromuscular therapy) is the use of concentrated finger pressure to 'trigger points', painful, irritated areas in muscles, to break cycles of spasm and pain (<http://www.amtamassage.org/about/terms.htm>).

The following protocol, with precise operational definitions of each component, will be followed by the on-site massage therapists and recorded on the Massage Assessment Form (see Appendix):

- 1) Pre-treatment assessment - identifying particular areas of pain and discomfort, sites of wounds and tumors; recording heart and respiratory rate for 60 seconds and assessing pain intensity and emotional distress;
- 2) Preparation of the patient and environment - explaining the procedure to the patient, obtaining assent to proceed with the massage therapy session; creating a quiet and private environment conducive to therapeutic massage, and positioning and draping the patient for comfort. While the therapist will make every effort to facilitate a quiet environment conducive to privacy and relaxation, we have discovered in the pilot phase that the home and inpatient hospice environments may contain distractions (pets, family members,

background noise, etc.) that cannot be controlled. The therapist will give the patient the choice to either remove clothing to receive the massage or receive the massage wearing light clothing such as pajamas or a hospital gown. The patient will be positioned comfortably in the most neutral and functional body alignment possible respecting his/her wishes. While most patients will be lying in bed, those that wish to receive a seated massage will be accommodated. The ambient environment, clothing and patient positioning will be noted on the Massage Assessment Form (see Appendix).

- 3) Centering self - The therapist focuses attention to the patient and calms self;
- 4) Effleurage and petrissage to the back, shoulders/arms, hands, neck, scalp, face, legs and feet. - Strokes will be administered with therapists' fingers or full hand. The amount of time spent in each type of stroke will vary based on individual therapist judgement. Massage will be modified and administered with very light pressure and appropriate modifications in persons with: skin fragility; postural limitations; edema; osteoporosis; and bone metastasis and will be modified to avoid sites of inflammation/infection; hyperesthesias; injury, surgery, ports, intravenous catheters; deep vein thrombosis; and tumors.
- 5) During the treatment to the upper, middle and lower trapezius muscle regions, therapists will identify at least 2 myofascial trigger points if possible. After locating these trigger points the therapists will gradually reduce the pain through stroking the affected muscle.⁴³;
- 6) Post-treatment assessment - The therapist will note patient heart and respiratory rates. To minimize patient reporting bias, post-treatment pain intensity and emotional distress will be collected by the On-Site Data Collector after the practitioner leaves the room.
- 7) Ending- The therapist will indicate the conclusion of the treatment, provide 5 minutes of relaxation and quiet time, and will encourage the patient to drink water, if able.

For massage administered skin-to-skin, Biotone brand hypoallergenic and unscented massage lotion or creme will be used by all therapists. Universal precautions will be followed, including avoiding contact with any draining lesions. For the purposes of standardization and to mediate the presence of intervening variables, therapists will not introduce music as a supplement to massage therapy. In addition, therapists will be instructed to limit their communication with participants during the massage therapy session to providing instructions or requests, posing necessary questions related to the massage therapy or providing responses to questions or comments by the participant.

Data Collection by the Massage Therapist. The massage therapist will complete the Massage Assessment Form (See Appendix). The therapist will use standardized instructions and ask the subjects to complete a self-report of present pain intensity and emotional distress (Memorial Pain Assessment Card, described below) before the massage therapy session. In addition, the therapist will count 60-second heart and respiratory rates before and after the treatment, and will record the length of the massage, the subject's position and responses, environmental quality, and the types of massage therapy strokes applied to specific regions of the subject's body.

The Control Treatment: Non-moving touch.

The control treatment is described as non-moving touch. The non-moving touch intervention will be provided by hospice volunteers or volunteer health care students recruited specifically for the study. One primary volunteer and one backup will be trained at each of the participating sites. Volunteers will not have experience performing massage or bodywork.

Training. All volunteers delivering the non-moving touch intervention will receive a full day training session similar to the one received by the massage therapists. The training session will be organized as follows:

- 1) The terminally-ill cancer patient and 2) Description of the study: Identical to Massage Therapist training

- 3) Philosophy, setting and non-moving touch protocol (1 hour); and
 - a. General principles of touch with terminally-ill cancer patients
 - b. Description of the non-moving touch protocol and importance of adhering to the research protocol
 - c. Data collection (pulse, respiration, pain)
 - d. Institution or in-home environmental issues
 - e. Documentation on the Non-Moving Touch Assessment Form and patient record
 - f. Procedures (Obtaining supplies, reimbursement for travel, contingency plans for a back up volunteer, etc)
- 4) Practice and supervision time with the investigators (2 hours) in the UCHSC-School of Nursing's Nursing Resource Center (skills lab).
- 5) Competency evaluations (2 hours) - Participating volunteers will be evaluated for their performance in following the study protocol through paper and pencil test and performance examinations that will be developed during the planning phase.

Non-moving touch protocol. The non-moving touch intervention has been modeled from a protocol currently being used in an NCCAM-funded R21. ¹ The control protocol will be structured as follows and recorded on the "Non-moving Touch" Assessment Form (see Appendix). The non-moving touch group participants will also receive three 30-minute sessions per week for two weeks. While timing may vary, the treatments may not be administered less than 24 hours apart.

- 1) Pre-treatment assessment – Identical to massage protocol.
- 2) Preparation of the patient and environment - explaining the procedure to the patient, obtaining assent to proceed with the non-moving touch session; creating a quiet and private environment, and positioning the patient for comfort. As in the preparation for the massage therapy session, the volunteer will try to facilitate a quiet environment conducive to privacy and relaxation. The volunteer will give the patient the choice to receive the non-moving touch protocol draped and without clothes or wearing light clothing such as pajamas or a hospital gown. The patient will be positioned comfortably in the most neutral and functional body alignment respecting his/her wishes. While most patients will be lying in bed, those that wish to receive the non-moving touch in a seated position will be accommodated. The ambient environment, clothing and patient positioning will be noted on the Non-Moving Touch Assessment Form.
- 3) The volunteers will be instructed to interrupt conscious intention through mentally counting backwards from 100 by 7s. This will be done silently. This has been used in sham therapeutic touch studies to control for the role of conscious intent in the helping/healing process. ^{98,99}
- 4) The volunteer will place both hands on the participant in the following locations for 3 minutes each: Right shoulder blade; Left shoulder blade; Low back/ sacrum; Right heel; Left heel (15 minutes total). If the patient is lying he/she will turn over to face up. If seated, the volunteer will move to face the participant's front. Both hands of the volunteer will be placed in the following locations for 3 minutes each: Right patella; Left patella; Right elbow joint; Left elbow joint; Occipital ridge area of neck (15 minutes). Pressure will be light and consistent, no side-to-side movement of the volunteer's hands will occur. Throughout the session, volunteers will be asked to have no conscious intention of healing directed toward patient through using the technique described in #3 above.
- 5) Post-treatment assessment: Identical to massage protocol.
- 6) Ending: Identical to massage protocol.

A minimal amount of Biotone Massage lotion or crème (hypoallergenic and fragrance-free) will be applied to the volunteer's hands for consistency across groups. Universal precautions will be followed, including avoiding contact with any draining lesions. For the purposes of standardization and to mediate the presence of intervening variables, volunteers will not introduce music as a

supplement to the intervention. In addition, volunteers will be instructed to limit their communication with participants during the non-moving touch session to providing instructions or requests, posing necessary questions related to the non-moving touch or providing responses to questions or comments by the participant.

Data Collection by the Volunteers: Identical to massage data collection protocol; recorded on Non-moving Touch Assessment Form (see Appendix).

Assuring integrity of the study protocols. A member of the research team will visit each participating site at least twice in each year of the study. The purpose of the site visits will be to observe the massage and non-moving touch therapists administering the protocol and review study records to ensure that the sessions are being delivered as planned. An evaluation instrument will be developed during the planning phase of the study to guide the observations. Any problems with lack of fidelity will be addressed through additional training or replacing therapists and recruiting/retraining others. In addition, sessions will be audio recorded and randomly checked by the PI or project manager for compliance with standardized communication guidelines.

Usual Hospice Care: To ensure that key components of the intervention are not part of usual care, control subjects will agree to abstain from massage therapy during the course of the 3-week study period.⁸⁴ Back rubs as part of bathing or as a comfort measure offered by family members will be allowed. All study subjects will continue to receive usual hospice care throughout the study period, per protocols and procedures usually followed at each study site. The study will not intentionally alter usual hospice care. Usual hospice care includes attentive care provided by nurses, nursing assistants, social workers, therapists, chaplains, volunteers and physicians. This interaction and attention is variable based on the needs of the patient and family. Both the control and intervention groups will be expected to receive these components of usual hospice care. In order to permit comparison of “usual care” between intervention and control patients, data will be collected documenting frequency, length of time and content of all hospice care provider (nurse, nursing aid, social worker, chaplain, volunteer, physician, etc.) patient visits (see Appendix). These data have been readily available during pilot data collection.

Data Collection – Baseline, Follow-up, Instruments: For each component of this study, a designated individual at each participating hospice/palliative care site (On-site Study Coordinator), trained and supported by the research team, will determine study eligibility, solicit study participation, obtain informed consent, randomize patients to study arms in conjunction with the research team, coordinate data collection and serve as a resource for the On-Site Data Collector, On-Site Massage Therapist and On-Site Personnel conducting the “non-moving touch” sessions. The On-Site Data Collector, who will also be trained and supported by the research team, will be blinded to study group assignment. This individual will collect baseline and follow-up measurements on all participating individuals. The On-site Study Coordinator, On-Site Data Collector, On-Site Massage therapist and On-Site “non-moving touch” therapist will be required to attend a study training session, conducted by the research team, prior to initiation of subject enrollment. This training session will address the goals of the study, study eligibility criteria, informed consent procedures, randomization, intervention, data collection procedures, and confidentiality processes. The training session will emphasize the importance of standardizing the study protocol across sites. Following this meeting, all sites will pilot test the protocol for feasibility in their own sites. Open communication will be facilitated to define and resolve procedural issues rapidly. If protocol revisions are necessary, the changes will be documented in writing and communicated to all sites to ensure that standardization is maintained. Frequent communication will occur via newsletters, conference calls, and electronic mail groups.⁸⁴ In addition, research team members will make two site visits per year to participating study sites to assure fidelity to study design, encourage continued participation, and answer site-specific questions.

In the event of personnel changes at study sites (massage therapists, “non-moving touch” therapists, on-site study coordinators, on-site data collectors), additional training sessions will be conducted as needed.

Potentially eligible patients will be initially identified by primary hospice nurses, who collect pain assessment data as part of their routine hospice care, usually at least weekly. Primary hospice nurses will provide lists of potentially eligible patients to the On-site Study Coordinator, who will then contact these patients to conduct a study-specific pain and eligibility assessment (see). For patients who meet the eligibility criteria and do not have the exclusion criteria, the On-Site Study Coordinator will briefly describe the study and outline the activities involved in study participation. If potentially eligible patients express interest in study participation, the On-site Study Coordinator will arrange a visit to discuss the study and proceed with the process of informed consent. Once consent for study participation has been obtained, subjects will be randomly assigned to either the treatment or control group, as described above. On-Site Data Collector will be notified by the On-Site Study Coordinator of enrolled patients, but not study group assignment, and will then collect baseline and follow-up data per the **Tables** below. The On-Site Study Coordinator will inform On-Site Massage Therapists and On-Site “Non-moving Touch” therapists of enrolled study participants who have been assigned to the intervention and control study groups, respectively. Initial data collection will occur within 72 hours of study enrollment. The first intervention (massage therapy) or control (non-moving touch) session will occur within 48 hours of the baseline data collection. The intervention or control sessions will consist of 3 sessions per week for two weeks. Final data collection will occur 1 week following the final intervention or control session (3 weeks following study entry). See Appendix for study design diagram. The **Tables** below delineates timing of, person responsible for collecting and source for each data element.

Study subjects will be followed from the time of study enrollment, through 2 weeks of intervention (or control) treatment, and 1 week following conclusion of the treatment course, for a total commitment of 3 weeks of participation per study subject. All but 3 hospice staff members will be blind to subject group assignment: the On-site Study Coordinator and the massage or non-moving touch therapists. Patients and family members will be instructed to not communicate their group assignment to hospice staff or to the On-Site Data Collector.

We will collect data on: individual characteristics, disease, prior disease treatment, pain characteristics, symptom distress, quality of life, and other concurrent interventions (pharmacologic and non-pharmacologic). Study variables, data collection and measurement are described in **Tables 1 and 2** below. These study variables were selected to address components of the “Disrupting Cycles of Distress” conceptual model discussed in the “Background” section above. Data will be collected at study entry (baseline data) and then weekly (every 7 days) throughout the 3 week study period for all study participants. All study subjects will also complete a brief pain assessment immediately preceding and following each intervention (massage therapy) or control (non-moving touch) session. A regular schedule for study enrollment, intervention, and data collection will be established for and confirmed with each participating site, based on the schedules of the on-site massage therapist, non-moving touch therapist, study coordinator and data collector.

Study processes, procedures and instruments are currently undergoing pilot testing for feasibility, respondent burden, and content validity prior to implementing full study enrollment. Two Colorado PoPCRN study sites are participating in this pilot testing. To date, 8 (of 20 planned) patients have participated in pilot data collection (see “Previous Studies” section). We expect to complete initial pilot data collection by the end of December 2002. The study procedures and instruments will be revised as necessary based on the pilot testing prior to full study implementation.

Table 1: Study Variables

Construct	Variables/ Measurement
PRIMARY OUTCOME	
Pain	Brief Pain Inventory (BPI), pain intensity scale from Memorial Pain Assessment Card (MPAC), Neuropathy Pain Scale (NPS)
SECONDARY OUTCOMES	
Quality of Life	McGill Quality of Life Questionnaire (MQOL)
Symptom Distress	Condensed Memorial Symptom Assessment Scale (MSAS)
Emotional Distress	Mood scale from MPAC, psychological symptom subscales from MQOL and MSAS
Relaxation Response	Heart and respiratory rates
Use of pharmacologic interventions	Medication name, dose, route, frequency (with opiate dosages converted to parenteral morphine equivalents). ^{100;101}
Use of non-pharmacologic interventions	Type of intervention (e.g. patient/family education, acupuncture, relaxation therapy, pet therapy); length of intervention (continuous, hours); provided by whom (e.g. volunteers, hospice/palliative staff, informal caregivers)
PRIMARY PREDICTOR	
Massage therapy intervention	Random assignment to Massage plus usual hospice care vs. Non-moving touch plus usual hospice care study group; compliance with treatment protocol
SECONDARY PREDICTORS (COVARIATES)	
Functional status	Karnofsky Performance Scale
Cancer type/metastases	Bony metastases vs. not
Age	Years
Location of care	Home vs. institutional
Gender	Male vs. female
Prior cancer treatment	Chemotherapy vs. radiation vs. surgery
Comorbidities	Number and types of concurrent diseases

Table 2: Data Collection and Measurement

Time of Collection	Data source/ Data collector	Domain Measured	Instrument/ Data Items
Prior to study entry	Patient / On-site Study Coordinator		Determine study eligibility Informed consent
Study entry	Chart, administrative data, patient/ On-Site Data Collector	Individual characteristics Disease Comorbidities	Patient demographics Cancer diagnosis, stage and treatment Comorbid conditions Randomization
Study entry Week 1, Week 2, Week 3	Patient/ On-Site Data Collector	Functional level	Karnofsky Performance Status Scale ^{102;103}
Study entry	Patient/ On-site Data Collector	Pain - descriptors	Neuropathy Pain Scale (NPS) ⁹⁴
Study entry Week 1, Week 2, Week 3	Patient/ On-site Data Collector	Pain – past week	Brief Pain Inventory (BPI) ¹⁰⁴
Immediately preceding and following each intervention (massage therapy) or control (non-moving touch) session	Patient/ Massage therapist or Non-moving touch therapist (prior) and On-Site Data Collectors (following)	Pain - current	Memorial Pain Assessment Card (MPAC) - pain intensity scale ¹⁰⁵ , Body outline
Immediately preceding and following each intervention (massage therapy) or control (non-	Patient/ Massage therapist or Non-moving touch therapist (prior) and	Emotional distress - current	Memorial Pain Assessment Card (MPAC) - mood scale ¹⁰⁵

moving touch) session	On-Site Data Collectors (following)		
Study entry Week 1, Week 2, Week 3	Patient/ On-site Data Collector	Physical and Emotional Symptom distress, incidence, change	Condensed Memorial Symptom Assessment Scale (MSAS) ^{106;107}
Study entry Week 1, Week 2, Week 3	Patient/ On-site Data Collector	Quality of life	McGill Quality of Life Questionnaire (MQOL) ¹⁰⁸
Study entry Week 1, Week 2, Week 3	Chart/ On-site Data Collector	Pharmacologic interventions	Medication name, dose, route, frequency. Includes oxygen and radiation therapy.
Study entry Week 1, Week 2, Week 3	Chart/ On-site Data Collector	Non-pharmacologic interventions	Intervention; length of intervention; provided by whom

Instruments

The clinically significant differences for each of the proposed scales are presented in **Table 3** below (“Statistical Issues” section, under “Power Analyses”). These clinically significant differences are derived from the previously-published studies cited below.

Study Eligibility

The On-Site Study Coordinator and On-Site Data Collector will use Study Eligibility Screening and Study Entry forms (see Appendix) to determine whether potential subjects meet criteria for study enrollment. The pain assessment portion of the form has been modified from commonly used pain assessment forms. The remainder of the “Study Entry” questions reflect study eligibility criteria or data elements necessary to characterize the study population or secondary predictors of the primary study outcomes. The Short Portable Mental Status Questionnaire (SPMSQ), an instrument that we have used in all previous PoPCRN-based studies requiring patient consent, will be used to screen for cognitive ability to consent to study participation.^{109;110} Reason(s) for ineligibility will be recorded for all ineligible patients.

Pain

Unidimensional scales of intensity or relief of pain have been the traditional focus of pain measurement. However, in clinical trials it is useful to separately measure three related dimensions: pain intensity, pain relief, and psychological distress. Although these dimensions are not usually distinguished spontaneously by patients as aspects of their global pain experience, they are independent subjective judgments that interact in complex ways to determine the experience and expression of cancer pain.¹⁰⁵

The **Memorial Pain Assessment Card (MPAC)** was developed as a simple, efficient, and valid assessment instrument that can provide rapid evaluation of the major aspects of pain *currently* experienced by cancer patients. The MPAC has been found repeatedly to be a valid, reliable, efficient and sensitive measure. The MPAC is a brief, self-administered, measure that uses visual analogue scores to characterize pain intensity, pain relief and mood.¹⁰⁵ It was designed to provide a manageable means of measuring both pain intensity and pain relief. The construct validity of the MPAC is supported by correlations among subscales that are consistent with expected relationships among pain intensity, pain relief, and mood.¹⁰⁵ Although this instrument provides limited information, its brevity, simplicity, and reliability are attractive, particularly for repeated assessments. In previous studies, experienced patients have been able to complete the MPAC ratings in less than 20 seconds with minimal effort.¹⁰⁵ The MPAC has been used in multiple studies of cancer patients, especially as part of quality of life assessments in clinical trials.¹¹¹⁻¹¹⁴ Study participants will complete the intensity and mood MPAC scales immediately prior to and following each of the 6 massage therapy or non-

moving touch sessions as a means of quantifying immediate response to the sessions (see Appendix). We will not use the “pain relief” MPAC scale due to respondents’ expressed difficulty understanding this scale during pilot data collection.

Multidimensional instruments which provide a more comprehensive evaluation of pain and its impact have also been developed and extensively validated in the cancer population.¹¹⁵ One such instrument, the **Brief Pain Inventory (BPI)** is a self-administered, easily understood measure that provides information about pain history, intensity, location and quality. Numeric scales (range one to ten) indicate the intensity of pain in general, at its worst, at its least, and currently. Each scale for Worst Pain, Least Pain, Pain on the Average, and Pain Right Now is bounded by 0 = no pain and 10 = pain as bad as you can imagine. A percentage scale quantifies relief from current therapies. Seven questions evaluate the degree to which pain interferes with function, mood, and enjoyment of life. Patients are asked to separately rate how their pain interferes with their Enjoyment of Life, Activity, Walking, Mood, Sleep, Work, and Relations with Others. These scales are bounded by 0 = does not interfere and 10 = interferes completely. The BPI takes approximately 15 minutes to complete.^{104;116} The BPI has been used in a number of studies of cancer pain, including patients receiving palliative care.^{111;112;116-118} It has also been used in validation studies of other symptom scales.^{119;120} All study participants will complete the BPI at study entry and weekly throughout the three week study period in order to assess changes in pain over the short term (see Appendix).

The **Neuropathy Pain Scale (NPS)** was developed to address the need for a measure that is sensitive to the variety of pain qualities most common to neuropathic pain syndromes.⁹⁴ This scale has shown validity in normal volunteers and in response to treatment.⁹² While it is acknowledged that terminology with regards to neuropathic pain “is still a mess”⁹³ and that it remains to be seen whether the NPS can distinguish neuropathic pain patients from other chronic pain patients⁹², we have included this scale as means of describing the pain experienced by study participants. All study participants will complete the NPS at study entry (see Appendix).

Quality of Life

The **McGill Quality of Life Questionnaire (MQOL)** was developed specifically to measure quality of life among advanced cancer patients receiving palliative care. The instrument consists of 17 items that are scored on a 0 – 10 scale, so that a score of 0 always indicates the least desirable and 10 the most desirable situation. In addition to a single item scale (SIS) measuring overall quality of life (QOL), the MQOL consists of a total score and scores on 4 subscales: physical symptoms, psychological symptoms, existential well-being, and support. The reported Cronbach’s α indicate that the internal consistency (reliability) of the MQOL subscales and the complete scale are good (total MQOL, $\alpha=0.83$; physical symptoms, $\alpha=0.62$; psychological symptoms, $\alpha=0.81$; existential well-being, $\alpha=0.79$; support, $\alpha=0.74$). That the MQOL total score predicts the SIS score serves as an indication of the validity of the MQOL.¹⁰⁸ The MQOL has been used in two PoPCRN-based studies and in other hospice-based research, both as a single assessment and multiple assessments over time.¹²¹ In these studies, participants were able to complete the 17-item scale with a minimum of effort. In our experience, the MQOL takes approximately 10 minutes to complete in this study population. All study participants will complete the MQOL at study entry and weekly throughout the three week study period (see Appendix).

Symptom Distress

The **Memorial Symptom Assessment Scale (MSAS)** is a patient-rated, multidimensional instrument that evaluates the intensity, frequency, and distress associated with symptoms. It was developed and validated among advanced cancer patients. Internal consistency (reliability) is high (Cronbach α 0.83 – 0.88). High correlations with clinical status and quality of life measures support the validity of the

MSAS. Scoring of the MSAS yields several validated subscale scores, including a Global Distress Index (GDI), a Physical Symptom subscale score (MSAS-PHYS), and a Psychological Symptom subscale score (MSAS-PSYCH).^{107;122-124} The MSAS-SF, an abbreviated version of the MSAS, measures each of 32 symptoms with respect to distress or frequency alone. A physical symptom subscale, psychological symptom subscale, and global distress index can be derived from the MSAS-SF. The Cronbach α coefficients for the MSAS-SF range from 0.76 to 0.87). The MSAS-SF subscales show convergent validity with performance status, quality of life, and extent of disease.¹²⁴ The MSAS-SF has been used in a number of studies of symptoms, quality and life, and outcomes among cancer patients.^{123;124} For the proposed study, we will use the Condensed MSAS, which is an adaptation of the MSAS-SF focusing on the most prevalent symptoms among cancer patients at the end of life. This version of the MSAS permits calculation of the GDI, MSAS-PHYS, and MSAS-PSYCH. The Condensed MSAS is currently in validation studies (*personal communication, V. Chang, 2001*) and is the instrument being completed weekly by patients participating in the current PoPCRN-based study of the natural history of symptoms and quality of life at the end of life. All study participants will complete the Condensed MSAS at study entry and weekly throughout the three week study period (see Appendix).

Emotional Distress

Emotional distress will be measured by the mood and psychological subscales of the MPAC, MQOL, and MSAS. Specifically, we will use the following items: 1) From the MPAC, the 100 mm visual analog scale anchored by “worst mood” and “best mood” on which patients are asked to rate their current feeling, from worst to best¹⁰⁵; 2) The psychological symptom subscale of the MQOL, which includes 4 items, each rated on a 0 – 10 scale, addressing current depression, feeling nervous or worried, time feeling sad, and fear of the future. The internal consistency of this MQOL subscale is good (Cronbach $\alpha=0.81$)¹⁰⁸; and 3) The psychological symptom subscale score of the MSAS (MSAS-PSYCH), which is the average of the frequency associated with 5 prevalent psychological symptoms: worrying, feeling sad, feeling nervous, feeling irritable, and difficulty concentrating. The MSAS-PSYCH subscale has been interpreted as a measure of global psychological distress.¹²² These scales will be used to measure emotional distress, rather than additional unique emotional distress scales, to minimize the respondent burden associated with study participation. As with their parent scales, these scales will be completed by all study participants at study entry and weekly throughout the three week study period (see Appendix).

Functional Status

The **Karnofsky Performance Status Scale** (KPS) is commonly used in many hospice/palliative care settings, including PoPCRN sites, and was used in validation studies of the MSAS. The KPS has been used as a prognostic guide for cancer patients and has been found to be associated with components of quality of life.¹²³ The KPS consists of a 0 – 100 scale, with a score of 0 representing death and 100 representing “Normal; no complaints; no evidence of disease”.^{102;107} A KPS will be completed for each study participant at study entry and weekly throughout the three week study period (see Appendix).

Pharmacologic Interventions

Given that usual hospice care is attentive to patient symptoms and that we would expect use of pharmacologic interventions for symptom management to decrease if massage therapy is, indeed, efficacious, the On-Site Data Collectors will keep track of all medications given for symptom management for each study patient during the course of the patient’s 3-week study enrollment (see Appendix). Opioid doses will be converted to parenteral morphine equivalents for analysis.^{100;101}

Non-pharmacologic interventions

Usual hospice care is, by definition, interdisciplinary. A number of non-pharmacologic interventions are utilized to address troublesome symptoms. In order to address potential confounding of therapeutic efficacy due to these components of usual hospice care, the On-Site Data Collector will record, at study entry and on a weekly basis throughout the three week study period, all non-pharmacologic strategies used to decrease study patients' symptom distress as well as the discipline, amount of time and content of all hospice-related visits (see Appendix).

Massage Therapy and Non-Moving Touch Assessment Forms

The On-Site Massage Therapists and Volunteers will complete Assessment Forms (see Appendix) for each study visit. This form provides a means for documenting the circumstances and content of each of the massage therapy and control exposure sessions.

Data Management: Case report forms **have been** developed to record the study data. A manual of operations will be written to describe in detail how each patient will be managed through the study and how the data will be collected. Completed data will be sent by each site weekly to the Principal Investigator's office. The data forms will be logged in and checked for major identifiers and completeness and accuracy of entry. Data will be entered into a computer readable form and verified (double data entry). A computer program will be written to edit the data, checking for missing values, invalid characters, out of range values, and inconsistencies between fields. Query reports will be generated and sent to the sites for correction of possible errors in the data. Corrected data will then be run again through the data editing program. An accurate master file of the data will be the final result of this process.

Statistical progress reports will be generated from the cleaned master file. These will include monthly status reports by site of number of screened patients, randomized patients, completed patients, patients currently in follow-up, drop outs, and forms completion rates. Semi-annual statistical progress reports will present additional data on patient characteristics, treatments received and outcomes if requested by the Data and Safety Monitoring Board (DSMB). All participating investigators will remain blinded to the outcomes by treatment arm until the end of the study to avoid potential biases related to entry and management of patients and the data collection process. An independent DSMB, composed of several physicians and nurses who are experts in the area of the study, a biostatistician and an ethicist, will be appointed to periodically review the progress of the study and the study outcomes. At each meeting the DSMB will make a recommendation as to whether or not the study should continue, based upon the study's progress and the outcome data. All of these measures will ensure good quality data and the ethical and adequate conduct of the trial.

Confidentiality. Both computer and paper records will be kept confidential. Paper records, including consent forms and completed study instruments, will be kept in a locked file cabinet in a locked office. Only the principal investigator and the UCHSC study coordinator will have access to the locked file cabinet. Computer records will be kept in password-protected computer files. Only the principal investigator, UCHSC study coordinator, and data analyst will have access to these computer files.

Statistical Issues: The initial phase of the analysis will identify characteristics of the participants for each study group. The second phase of the analysis will conduct longitudinal analyses to determine the impact of the intervention. The third phase of the analysis will be an exploratory analysis to examine the relationship of potential explanatory variables with the outcomes. Prior to any data analysis, the data will be verified and cleaned. Each variable will be examined to identify outliers or suspicious values. Transformations will be made for continuous variables as needed to meet the requirement for normality assumption or non-parametric techniques will be used. All analyses will be

based on an intention-to-treat principle. The level of statistical significance will be set at an alpha of 0.05, two-tailed test.

- (a) *Descriptive Analysis*: Descriptive statistics at baseline will be generated for both study groups for study outcomes, demographic characteristics, length of time between diagnosis and death and potential explanatory factors for outcome measures. The balance of these key variables between control and intervention groups at baseline will be examined using appropriate statistical methods (two sample t-tests for normally distributed continuous variables, Wilcoxon Rank Sum Test for non-normal continuous variables, Chi-square tests and Fisher's Exact tests for dichotomous data and Mantel-Haenszel method for categorical data). Similar analyses will also be carried out to compare study sites (or therapists). The pattern of loss of follow-up due to death will be evaluated by study groups, study sites and type of cancers using the Kaplan-Meier approach.¹²⁵
- (b) *Longitudinal Analysis*: Multiple assessments of the outcome measures will be collected over three weeks on each subject, assuming that he or she completes the study. These observations are correlated because they are measured on a single subject over time. Linear mixed models will be used to handle the correlation between observations within a subject.^{126;127} Different error structures (e.g., compound symmetry, first order auto-regression) will be compared using Akaike's Information Criterion.¹²⁸ We will use the error structure of compound symmetry to handle therapist-related clustering effects. A mixed model approach also handles the problem of missing data by assuming that data are missing at random (MAR). When data are not missing at random (MNAR), outcome measures and dropout process will be jointly modeled with either selection or pattern mixture models whichever is appropriate.^{129;130} Multiple imputation methods will also be used to explore the sensitivity of the results to dropout and estimate the effect of intervention on outcomes.¹³¹
- (c) *Power Analyses*: Approximately 440 individuals with advanced cancer will participate in this study. Based on the Principal Investigator's previous experience and that of other investigators working with the hospice population, a loss of follow-up rate of about 30% is expected in the study. (*Susan McMillan, PhD, personal communication, February 2002*). Two hundred and twenty will be assigned to the massage intervention, and 220 to the non-moving touch control group. This number should readily be attained if the number of participating hospices is 10, the number of admissions/hospice/week averages 25, the percentage of hospice patients with cancer is 60%, the percentage of these patients with the target symptom of at least moderate pain is 60%, expected study enrollment is 40%, and the planned data collection period is 18 months (estimates of average admissions/week, percent cancer patients and percent with at least moderate pain come from responses from a survey of PoPCRN study sites that meet study participation criteria). These estimates lead to an eligible patient pool of 10 sites x 25 admissions per week x 72 weeks x 0.6 with cancer x 0.6 with at least moderate pain = 6480 eligible patients, of whom 440 (7%) need to consent to study enrollment and be randomized.

The clinical difference and estimated effect size for previous studies with no treatment control groups are listed in **Table 3** below; the majority of effect sizes are within a moderate range of 0.4-0.6 S.D. If we assume that our active control has an effect that corresponds to 20% of this difference relative to a no treatment control, then our expected difference between the control and massage intervention will be in the range of 0.32-0.50 times the S.D. Assuming that 440 individuals are enrolled and a 30% loss to follow-up rate, and a correlation of 0.5 among assessments over time, we have sufficient power ($\geq 80\%$) to detect clinically meaningful difference in the change from baseline to 3 weeks for all study outcomes except BPI Worst Pain score. For example, with a sample size of 440 and a 30% loss of follow-up rate, we will be able to detect an 8 point difference in Pain (0-100 scale) as measured by the MPAC pain intensity scale, with a power of 80% and two-tailed $\alpha=0.05$. The power will be greater for 1 and 2 week assessment or if the correlation is greater than 0.5. Note that these

calculations assume that a single final analysis will be performed and that no adjustments will be necessary due to the interim analyses.

Table 3: Effect sizes corresponding to a clinically significant difference (CSD)

Outcomes	Scale Validation Studies*		No Treatment Control	Active Control		
	Mean	Standard Deviation (S.D.)	CSD	Effect Size	Effect Size	Minimum Power
MPAC Intensity	32	25	10	0.40	0.32	0.80
MPAC Relief	64	25	10	0.40	0.32	0.80
BPI Worst Pain	5.6	3.3	1	0.30	0.24	0.56
BPI Average Pain	4.0	2.2	1	0.45	0.36	0.88
BPI Activities	24.8	6.3	6	0.95	0.76	0.99
MQOL Total	6.1	1.4	1	0.71	0.57	0.99
MSAS Global	1.3	0.8	0.5	0.62	0.50	0.99
MSAS Physical	0.9	0.8	0.5	0.62	0.50	0.99
MPAC Mood	56	25	10	0.40	0.32	0.80
MQOL-Psychological	5.9	2.4	1	0.42	0.34	0.85
MSAS- Psychological	1.1	0.8	0.5	0.62	0.50	0.99

*105-108;112-114;116-118;122;123;132-134

(d) Interim Statistical Monitoring Rules

Interim statistical monitoring is often done in a clinical trial to permit the trial to be stopped early if a large treatment effect emerges or if there is no treatment effect. The monitoring plan is specified before the trial begins and permits the alpha error to be kept at .05 even though there are multiple looks at the data as the trial progresses. Interim statistical monitoring is particularly applicable in trials evaluating interventions that are expected to affect mortality or major morbidity. In this trial, interim statistical monitoring is perhaps less compelling because the major outcomes are pain, symptom distress and quality of life. The issue of interim statistical monitoring will be raised with the Data and Safety Monitoring Board at their first meeting before the start of the trial and will be implemented if desired by the Board.

Limitations

The strengths of this study are generalizability and the experimental design. 1) Generalizability: The external validity of the study findings is maximized due to this multisite randomized clinical trial being conducted in diverse settings. The inclusion of a number of hospice/palliative care organizations, from different geographic locations across the United States and with different care delivery structures, strengthens the generalizability of findings from this study. 2) Experimental design: Since many variables may shape an individual's response to particular symptoms and therapies, randomization is essential to assure that the study truly evaluates the association between the intervention and outcomes of interest. The randomized design of this study will maximize the internal validity of the study findings.

The proposed study does have several limitations. 1) Measurement or reporting bias is possible, as most measures will be by self-report. Measurement relies on the validity and reliability of the scales used, as well as the responsiveness of the measures to actual change. The instrument design process addresses these issues by using previously developed scales with established reliability, validity and sensitivity to change as well as pilot testing the instruments; 2) Selection bias: Participants may not be representative of all terminally ill cancer patients. By design, this study will only include English-speaking individuals age 18 years or older who are able and willing to participate, who have an estimated life expectancy of 3 weeks or greater, and who are receiving hospice care. Individuals with advanced cancer who participate in this study may be systematically different from those who do not meet study eligibility criteria. However, there is no theoretical reason

to believe that massage therapy effectiveness would differ between these groups; and 3) Incomplete follow-up: Given the nature of this study population, we expect a significant drop out rate due to death or disability. We have attempted to lessen the impact of potential incomplete follow up via the eligibility criteria, sample size calculation and analysis plan.

Organization and Administration:

The multicenter clinical trial will be organized similarly to other trials sponsored by the NIH and VA. A chairman's office and data center will be established at the UCHSC to oversee the daily conduct of the trial. An Executive Committee (EC) will be established to make major management decisions related to the trial. The EC will be composed of the Principal Investigator as chairperson, the other study co-investigators, 2-3 representative site coordinators, and other consultants as needed. The EC will make decisions on major issues related to: 1) protocol changes; 2) site performance; and 3) publication and presentation of the study data. The EC will establish the publication policy for the trial, and will review and approve all publications and presentations emanating from the study. As described below (see "Data and Safety Monitoring Plan"), an independent Data and Safety Monitoring Board (DSMB) will be established to ensure the scientific integrity of the trial. Both the EC and DSMB will meet semiannually to review the progress of the trial. The chairperson's office and statisticians will produce statistical progress reports prior to each meeting to enable these committees to discharge their responsibilities.

Table 4: Work Plan

Task	Year 1
Finalize intervention and control protocols, training plans and study instruments Prepare study procedural materials and training manuals Convene Executive Committee	Months 1 - 3
Finalize participating sites and on-site personnel Convene Data and Safety Monitoring Board	Months 4 - 6
Conduct training for on-site personnel	Months 7 - 9
Begin study enrollment and data collection	Months 10 - 12
Data entry and cleaning	Months 10 - 12
	Year 2
Continue study enrollment and data collection	Months 13 - 24
Continue data entry and cleaning	Months 13 - 24
	Year 3
Complete study enrollment and data collection	Months 25 - 28
Complete study data entry and cleaning	Months 24 - 29
Data analysis, data interpretation, site-specific feedback, and manuscript writing	Months 30 - 36

E. Human Subjects Research

Protection of Human Subjects

1) Risks to the Subjects

Human Subjects Involvement and Characteristics: A total of 440 adults and children (age ≥ 18) who are identified through receiving care from one of the participating hospices, will participate in the study. Study participants must be English-speaking, provide informed consent according to requirements of the Colorado Multiple Institutional Review Board (COMIRB), and be willing and able to complete study instruments for the duration of the study. Health status, per se, will not be used as an inclusion/exclusion criterion. Study participants are expected to have a wide variety of health statuses. This project will not enroll any special populations.

Sources of Materials: Research material will be obtained from the referring hospices and from the participants. The data will be obtained specifically for research purposes, although participating hospices may routinely collect some of the study data as part of patient care. All research material will be survey and interview data. No specimens or records will be required.

Potential Risks: Participation is voluntary and individuals are free to choose not to participate or to withdraw from the study at any point in time. Potential risks of massage therapy include bleeding in thrombocytopenic patients or those on anticoagulant therapy; skin or soft tissue injury with inappropriate technique or when applied over calcified, atrophic, grafted skin, or acutely inflamed tissue; embolism; pain, and fracture in patients with osteoporosis or bone metastasis.^{7 135} There is no evidence that massage therapy accelerates metastasis.

2) Adequacy of Protection Against Risks

Recruitment and informed consent: A designated individual at each participating hospice will be responsible for soliciting participation. Potentially eligible subjects will be identified by the hospice during the study period and asked to consider participating. The study coordinator at each participating hospice will be responsible for verbally describing all elements of the consent to each potential subject and going through the consent form with each potential subject. The study coordinators will be trained by the principal investigator in the principles of informed consent. Participants will keep one copy of the consent form and give a second signed copy back to the study coordinator for signature by him/her and by the principal investigator. All participants will undergo informed consent. The consent form will comply with requirements of the Colorado Multiple Institutional Review Board (COMIRB). In accordance with requirements of the COMIRB, participant confidentiality will be maintained by use of unique identifying numbers on all study documents. No participant names will be used on study documents or in any resulting reports. All study documents will be maintained in a locked file. The computer with the database linking participant names to unique identifiers will be password protected and only accessible to the study coordinator, principal investigator and data analyst.

Protection Against Risk: The risks of the massage interventions will be minimized by the following procedures. Subjects with a known platelet count below 10,000 or on anticoagulant therapy will not be enrolled in the study. No deep tissue massage will be used. Only light effleurage and petrissage techniques will be used which minimizes risks of skin and soft tissue injury, pain and fracture. Massage will be modified to avoid any open wounds, tumors, sites of infection, inflammation, or hyperesthesia. If participants are adversely affected by participation in the study, medical care in accordance with the care goals and values of the participating patients will be provided. Per Colorado Multiple Institutional Review Board (COMIRB) requirements, any inquiries, allegations or investigations of scientific misconduct will be reported immediately to COMIRB and study enrollment will be halted until the issue is resolved.

3) Potential Benefits of the Proposed Research to Others

Risks to subjects will be minimal. Massage therapy is easily integrated into palliative care. If massage therapy is found to be an effective treatment, it may decrease the amount of pain medication needed, promote relaxation, alleviate symptoms of advanced cancer, and improve the quality of life for patients and their families.

4) Importance of the Knowledge to be Gained

This study has significant potential to identify interventions that may promote the comfort and quality of life of cancer patients in palliative care. Massage is a treatment that can be integrated into routine care by trained health care providers with little additional cost. It can augment and have a synergistic effect with traditional analgesics and may actually enhance alertness. If massage is an efficacious

intervention, family members can learn established massage techniques and can provide this intimate form of care more effectively to their loved ones during the last days of their lives.

Collaborating Sites

This research will be conducted at hospice/palliative care sites participating in the Population-based Palliative Care Research Network (PoPCRN). Sites that meet study selection criteria include (see Appendix for letters of support):

Community Hospice Care, Tiffin, OH
 Hope Hospice and Palliative Care, Fort Myers, FL
 Hospice and Palliative Care of Cape Code, Hyannis, MA
 Hospice and Palliative Care Center, Winston Salem, NC
 Hospice at Charlotte, Charlotte, NC
 Hospice at Grady, Delaware, OH
 Hospice Care in the Berkshires, Inc., Pittsfield, MA
 Hospice of Metro Denver, Denver, CO
 LifePath Hospice and Palliative Care, Inc., Tampa, FL
 Palliative Care Center of the North Shore, Evanston, IL
 Samaritan Hospice, Marlton, NJ

The Principal Investigator will obtain in writing and keep in file an assurance from each study site that the Protection of Human Subjects is addressed adequately at a level of attention that is at least as high as that documented at the applicant organization. Site(s) added after the award is made will also adhere to these requirements.

Women and Minority Inclusion in Clinical Research

Inclusion of Women: There will be no exclusion of the study population based on gender.

Inclusion of Minorities: There will be no exclusion of the study population based on minority status.

Eligible patients will be English-speaking adults and children (age \geq 18 years) with a cancer diagnosis who are consecutively enrolled in participating hospice/palliative care organizations during the study period who have an anticipated life expectancy of at least three weeks and who consent to and are able to participate. This study will be limited to English-speaking patients as the planned study instruments, with the exception of the Brief Pain Inventory, have been validated only in English. It is not the intent of this study to create validated study instruments in other languages. The study population will reflect the population cared for by the participating hospices. The population-based research network design has been chosen to obtain more diverse representation than would be available at one or several sites. Among PoPCRN sites, 82% of patients are age 60 or older, 45% are female and 85% are non-Hispanic white. Fifty-eight percent of patients cared for by these organizations have a cancer diagnosis. Similar characteristics are found on the national level, where 78% of hospice patients are age 65 or older, 55% are female, and 84% are non-Hispanic white.⁹¹ Recruitment of women will not require special efforts. Recruitment of minority subjects may be more problematic as fewer minority patients nationally use hospice services than might be expected based on population age and demographic distributions. To enhance our chances for minority recruitment, we will ask participating hospices to identify all minority patients. The study coordinator will then ascertain eligibility and pursue recruitment for study participation. Study enrollment will occur between months 10 and 28 of the proposed project. Assuming a start date of July 2003, study enrollment will thus occur between April 2004 and October 2005. See included "5/01 Targeted/Planned Enrollment Format Page". Data collection items on ethnicity and race will use the categories as defined in this table.

Additional Information

Based on prior studies, we do not expect to find clinically important sex/gender and/or race ethnicity differences in the intervention effect of the massage therapy. However, prior studies have reported differences in baseline pain intensity and quality of life scores based on gender.⁴⁴ There are little available data regarding race/ethnicity differences in pain intensity, quality of life, or massage therapy. As can be seen by the “5/01 Targeted/Planned Enrollment Format Page”, we will likely have sufficient sample size only to compare sex/gender differences and ethnic differences. We will not likely have sufficient sample size to compare racial differences. Given the potential for such differences to exist, we will conduct valid analyses of the intervention effect on sex/gender and racial/ethnic subgroups.

Inclusion of Children

Justification for exclusion of children younger than age 18 in this grant proposal is based on differences in cognitive and developmental stages between children and adults. The instruments planned for testing the outcomes have been developed, tested, and applied in adult populations. In addition, since < 0.5% of hospice patients nationally are 17 years of age or younger¹³⁶, we will not be missing a significant proportion of hospice patients by excluding children younger than age 18 from this study. For these reasons, we will exclude children younger than 18 years of age in the proposed study.

Data and Safety Monitoring Plan

An independent Data and Safety Monitoring Board (DSMB), composed of several physicians and nurses who are experts in the area of the study, a biostatistician and an ethicist, will be appointed to periodically review the progress of the study and the study outcomes. The DSMB will be independent from the development and day-to-day conduct of the trial. The role of the DSMB includes: 1) ensuring the scientific integrity of the trial; 2) reviewing and approving protocol changes; 3) reviewing overall progress of the study; and 4) reviewing efficacy and safety data broken down by treatment group. At each meeting the DSMB will make a recommendation as to whether or not the study should continue, based upon the study's progress and the outcome data. All of these measures will ensure good quality data and the ethical and adequate conduct of the trial. Per Colorado Multiple Institutional Review Board (COMIRB) requirements, any inquiries, allegations or investigations of scientific misconduct will be reported immediately to COMIRB and study enrollment will be halted until the issue is resolved. Robert Anderson, MD will serve as the head of the Data and Safety Monitoring Board (See Appendix for letter describing).

F. Vertebrate Animals

No activities involving vertebrate animals are planned at any time during the proposed project period.

G. Literature Cited

1. Avins A, Patterson M: *Massage Therapy for Cancer-Related Fatigue*, 2001. NCCAM-funded R21.
2. Singer PA, Martin DK, Kelner M: Quality end-of-life care: patients' perspectives. *JAMA* 1999;281:163-168.
3. Kutner JS, Kassner CT, Nowels DE: Symptom Burden at the End of Life: Hospice Providers' Perceptions. *J Pain Symptom Manage* 2001;21:473-480.
4. Bruera E: Research into symptoms other than pain, in Doyle D, Hanks GW, MacDonald N (eds): *Oxford Textbook of Palliative Medicine*. New York, Oxford University Press; 1998:

5. Kutner JS, Renfrew B, Kassner CT, Main DS, Steiner JF: Symptom Distress and Quality of Life in the Last Days of Life. *Journal of Palliative Care* 2002;18:236(Abstract)
6. Krusen F, Kottke F, Ellwood P: *Handbook of physical medicine and rehabilitation*, Philadelphia, Saunders; 1966:
7. Messi C: Perspective: Massage Therapist. *Rehabilitation Nursing* 1989;4:137-138.
8. White JA: Touching with intent. *Holistic Nursing Practice* 1988;2:63-67.
9. Luckmann J, Sorenson K: *Medical-surgical nursing: A psychophysiologic approach*, Philadelphia, Saunders; 1987:
10. Eisenberg DM, Kessler R, Foster C, Norlock E, Calkins MD, Delbanco TL: Unconventional medicine in the United States: Prevalence, costs, and patterns of use. *N Engl J Med* 1993;328:252
11. Eisenberg DM, Davis RB, Ettner SL, et al: Trends in alternative medicine use in the United States, 1990-1997. *JAMA* 1998;280:1569-1575.
12. Cassileth BR, Chapman CC: Alternative and complementary cancer therapies. *Cancer* 1996;77:1026-1034.
13. Donley R: The alternative health care revolution. *Nursing Economics* 1998;16:298-301.
14. Frybeck PB, Reinhert BR: Alternative therapies and control for health in cancer and AIDS. *Clinical Nurse Specialist* 1997;11:64-69.
15. Lerner KJ, Kennedy BJ: The prevalence of questionable methods of cancer treatment in the United States. *Cancer Journal Clinics* 1992;42:181-191.
16. Decker G: An overview of complementary and alternative therapies. *Clinical Journal of Oncology Nursing* 2000;4:49-52.
17. Hernandez-Reif M, Field T, Krasnegor J, Martinez E, Schwartzman M, Mavunda K: Children with cystic fibrosis benefit from massage therapy. *J Pediatric Psychology* 1999;24:175-181.
18. Patiano O, Novick C, Merlo A, Benaim F: Massage in hypertrophic scars. *J Burn & Rehab* 1999;20:268-271.
19. Field T, Hernandez-Reif M, Hart S, Theakston H, Schanberg S, Kuhn C: Pregnant women benefit from massage therapy. *J Psychosomatic Obstetrics and Gynecology* 1999;20:31-38.
20. Hernandez-Reif M, Field T, Hart S: Smoking cravings are reduced by self-massage. *Preventive Medicine* 1999;28:28-32.
21. Field T, Schanberg S, Kuhn C, et al: Bulimic adolescents benefit from massage therapy. *Adolescence* 1998;33:555-563.
22. Field T, Peck M, Krugman S, et al: Burn injuries benefit from massage therapy. *J Burn & Rehab* 1998;19:241-244.

23. Field T, Henteleff T, Hernandez-Reif M, et al: Children with asthma have improved pulmonary function after massage therapy. *J Pediatrics* 1998;132:854-858.
24. Field TM, Quintino O, Hernandez-Reif M, Koslovsky G: Adolescents with attention deficit hyperactivity disorder benefit from massage therapy. *Adolescence* 1998;33:103-108.
25. Field T, Hernandez-Reif M, Taylor S, et al: Labor pain is reduced by massage therapy. *J Psychosomatic Obstetrics and Gynecology* 1997;18:286-291.
26. Field T, Hernandez-Reif M, Seligman S, et al: Juvenile rheumatoid arthritis: Benefits from massage therapy. *J Pediatric Psychology* 1997;22:607-617.
27. Nixon N, Teschendorff J, Finney J, Karnilowicz W: Expanding the nursing repertory: The effectiveness of massage in post-operative pain. *Australian J Advanced Nursing* 1997;14:21-26.
28. Field T, Grizzle N, Scafidi F, Schanberg S: Massage and relaxation therapies' effects on depressed adolescent mothers. *Adolescence* 1996;31:903-911.
29. Scafidi F, Field T: Massage therapy improves behavior in neonates born to HIV-positive mothers. *J Pediatric Psychology* 1996;21:889-897.
30. Hulme J, Waterman H, Hillie VF: The effect of foot massage on patients' perceptions of care following laparoscopic sterilization as day case patients. *J Advanced Nursing* 1999;30:460-468.
31. Wheeden A, Scafidi F, Field T, Ironson G, Valdeon C, Bandestra E: Massage effects on cocaine-exposed preterm neonates. *J Developmental and Behavioral Pediatrics* 1993;14:318-322.
32. Scafidi F, Field T, Schanberg S: Factors that predict which preterm infants benefit most from massage therapy. *J Developmental and Behavioral Pediatrics* 1993;14:176-180.
33. Smith LL, Keating MN, Holbert D, et al: The effects of athletic massage on delayed onset muscle soreness, creatinine kinase, and neutrophil count: a preliminary report. *J Orthopedic and Sports Physical Therapy* 1994;19:93-99.
34. Cherkin DC, Eisenberg DM, Sherman KJ, et al: Randomized Trial Comparing Traditional Chinese Medical Acupuncture, Therapeutic Massage, and Self-care Education for Chronic Low Back Pain. *Arch Intern Med* 2001;161:1081-1088.
35. Preyde M: Effectiveness of massage therapy for subacute low-back pain: a randomized controlled trial. *Can Med Assoc J* 2000;162:1815-1820.
36. Irnich D, Behrens N, Molzen H, et al: Randomised trial of acupuncture compared with conventional massage and "sham" laser acupuncture for treatment of chronic neck pain. *BMJ* 2001;322:1578
37. Field TM, Sunshine W, Hernandez-Reif M, et al: Massage therapy effects on depression and somatic symptoms in chronic fatigue syndrome. *J Chronic Fatigue Syndrome* 1997;3:43-51.

38. Ahles TA, Tope DM, Pinkson B, et al: Massage therapy for patients undergoing autologous bone marrow transplant. *J Pain Symptom Manage* 1999;18:157-163.
39. Pan CX, Morrison RS, Ness J, Fugh-Berman A, Leipzig RM: Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life: a systematic review. *J Pain Symptom Manage* 2000;20:374-387.
40. Weinrich SP, Weinrich MC: The effect of massage on pain in cancer patients. *Nursing Research* 1990;3:140-145.
41. Meek SS: Effects of slow stroke back massage on relaxation in hospice clients. *IMAGE: J of Nursing Scholarship* 1993;25:17-21.
42. Sims S: Slow stroke back massage for cancer patients. *Nursing Times* 1986;83:49
43. Ferrell-Torry AT, Glick OJ: The use of therapeutic massage as a nursing intervention to modify anxiety and the perception of cancer pain. *Cancer Nursing* 1993;16:93-101.
44. Wilkie DJ, Kampbell J, Cutshall S, et al: Effects of massage therapy on pain intensity, analgesics and quality of life in patients with cancer pain: A pilot study of a randomized controlled trial conducted within hospice care delivery. *Hospice Journal* 2000;15:31-35.
45. King, P. Use of massage on cancer pain and anxiety. American Massage Therapy Association Foundation Research Grant Recipients 1996-2001. 1996. (GENERIC)
Ref Type: Electronic Citation
46. Wilkinson S, Aldridge J, Salmon I, Cain E, Wilson B: An evaluation of aromatherapy massage in palliative care. *Palliative Medicine* 1999;13:409-417.
47. Wilkinson S: Aromatherapy and massage in palliative care. *International J Palliative Nursing* 1995;
48. Corner JCN, Hildebrand S: An evaluation of the use of massage and essential oils in the well-being of cancer patients. *International J Palliative Nursing* 1995;67-73.
49. Grealish L, Lomasney A, Whiteman B: A nursing intervention to modify distressing symptoms of pain and nausea in patients hospitalized with cancer. *Cancer Nursing* 2000;23:237-243.
50. Herr KA, Mobily PR: Interventions related to pain. *Nursing Clinics of North America* 1992;27:347-369.
51. Field T: Massage therapy effects. *American Psychologist* 1998;53:1270-1281.
52. Richards K, Gibson R, Overton-McCoy AL: Effects of massage in acute and critical care. *Complementary and Alternative Therapies* 2000;11:77-96.
53. Ernst E: Massage therapy for low back pain: A systematic review. *J Pain Symptom Manage* 1999;17:65-69.
54. Farrell JP, Twomey LT: Acute low back pain: Comparison of two conservative treatment approaches. *Medical Journal of Australia* 1982;1:160-164.

55. Field T, Hernandez-Reif M, Krugman S, Burman I, Ozment-Schenk C: Post-burn itching, pain and psychological symptoms are reduced with massage therapy. *J Burn & Rehab* 2000;21:189-193.
56. Myers DD, Robinson ME, Guthrie TH, Limp SP, Lattenberg R: Adjunctive approaches for sickle cell chronic pain. *Alternative Health Practitioner* 1999;5:203-212.
57. Puustjarvi K, Airaksinan O, Pontinen PJ: The effects of massage in patients with chronic tension headache. *Acupuncture and Electro-therapeutics Research International Journal* 1990;15:159-162.
58. Hernandez-Reif M, Field MJ, Krasnegor J, Theakston H: Lower back pain is reduced and range of motion increased after massage therapy. *International Journal of Neuroscience* 2001;106:131-145.
59. Hernandez-Reif M, Field T, Theakston H: Multiple sclerosis patients benefit from massage therapy. *Journal of Body Work and Movement Therapies* 1998;2:168-174.
60. Barr JS, Taslitz N: The influence of back massage on autonomic functions. *Physical Therapy* 1970;50:1679-1691.
61. Longworth JC: Psychophysiological effects of slow stroke back massage in normotensive females. *Advances in Nursing Science* 1982;4:44-61.
62. Hayes JA, Cox C: Immediate effects of a 5 minute foot massage in critical care. *Complementary Therapies in Nursing and Midwifery* 2000;6:9-13.
63. Richards M: Quality of life: the main outcome measure of palliative care. *Palliative Medicine* 1997;11:89-92.
64. Hernandez-Reif M, Field T, Krasnegor J, Theakston H, Hossain Z, Burman I: High blood pressure and associated symptoms were reduced by massage therapy. *J Bodywork & Movement Therapies* 2000;4:31-8.
65. Hernandez-Reif M, Martinez A, Field T, Quintero O, Hart S, Burman I: Premenstrual symptoms are relieved by massage therapy. *J Psychosomatic Obstetrics and Gynecology* 2000;21:9-15.
66. Zeitlin D, Keller S, Shiflett S, Schleifer S, Bartlett J: Immunological effects of massage therapy during academic stress. *Psychosomatic Medicine* 2000;62:83-86.
67. Field T, Hernandez-Reif M, Hart S, et al: Effects of sexual abuse are lessened by massage therapy. *J Bodywork & Movement Therapies* 1997;1:65-69.
68. vanderReit P: Effects of therapeutic massage on pre-operative anxiety in a rural hospital, Part I. *Australian J Rural Health* 1993;1:11-16.
69. Fraser J, Kerr JR: Psychophysiological effects of back massage on elderly institutionalized patients. *J Advanced Nursing* 1993;18:238-245.
70. Birk TJ, McGrady A, MacArthur RD, Khuder S: The effects of massage therapy alone and in combination with other complementary therapies on immune system measures and quality of life in human immunodeficiency virus. *J Alt Compl Med* 2000;6:405-414.

71. Smith MC: *Disrupting the cycle of distress conceptual framework*, 2002:(UnPub)
72. Owens MK, Ehrenreich D: Literature review of nonpharmacologic methods for the treatment of chronic pain. *Holistic Nursing Practice* 1991;6:24-31.
73. Chen ML, Lin LC, et al: The effectiveness of acupressure in improving the quality of sleep of institutionalized residents. *Journals of Gerontology* 1999;54:M389-M394
74. Johnson SK, Frederick J, et al: A controlled investigation of bodywork in multiple sclerosis. *J Alt Compl Med* 1999;5:237-243.
75. Mansour AA, Beuche M, et al: A study to test the effectiveness of placebo Reiki standardization procedures developed for a planned Reiki efficacy study. *J Alt Compl Med* 1999;5:153-164.
76. Kutner JS, Foehner K, Steiner JF: Evaluation of a Pre-Visit Questionnaire for Addressing Cancer Patients' Information Needs. *Journal of Cancer Education* 1999;14:248-253.
77. Kutner JS, Steiner JF, Corbett KK, Jahnigen DW, Bartrop RW: Information Needs in Terminal Illness. *Social Science Medicine* 1999;48:1341-1352.
78. Kutner JS, Vu KO, Prindiville SA, Byers TE: Patient Age and Cancer Treatment Decisions. *Cancer Practice* 2000;8:114-119.
79. Wolsko P, Ware L, Kutner JS, et al: Alternative/Complementary Medicine: Wider Usage Than Generally Appreciated. *J Alt Compl Med* 2000;6:321-326.
80. Bryant LL, Corbett KK, Kutner JS: In their own words: a model of healthy aging. *Soc Sci Med* 2001;53:927-941.
81. Kutner JS, Nowels DE, Kassner CT, Bryant LL: Quality of Life Persists at the End of Life. *J Gen Intern Med* 2001;16:149.
82. Kutner JS, Nowels DE, Kassner CT, Reiquam W: Psychosocial and Spiritual issues at the End of Life. *J Am Geriatr Soc* 2001;49:P471.
83. Smith MC, Stallings MA, Mariner S, Burrall M: Benefits of massage therapy for hospitalized patients: A descriptive and qualitative evaluation. *Alternative Therapies in Health and Medicine* 1999;5:64-71.
84. Weinberger M, Oddone EZ, Henderson WG, et al: Multisite Randomized Controlled Trials in Health Services Research: Scientific Challenges and Operational Issues. *Med Care* 2001;39:627-634.
85. Smith MC, Reeder F, Daniel L, Baramée J, Hagman J: Outcomes of Touch Therapies During Bone Marrow Transplant. *Alternate Therapies in Health and Medicine* 2002;(In Press).
86. Nutting PA: Practice-based research networks: building the infrastructure of primary care research. *Journal of Family Practice* 1996;42:199-203.
87. Stange KC: Primary care research: barriers and opportunities. *Journal of Family Practice* 1996;42:192-198.

88. Stange KC: Practice-Based Research Networks: Their current level of validity, generalizability, and potential for wider application. *Archives of Family Medicine* 1993;2:921-923.
89. Iverson DC, Calonge BN, Miller RS, Niebauer LJ, Reed FM: The Development and Management of a Primary Care Research Network, 1978-87. *Family Medicine* 1988;20:177-181.
90. Green LA, Miller RS, Reed FM, Iverson DC, Barley GE: How representative of typical practice are practice-based research networks? A report from the Ambulatory Sentinel Practice Network Inc (ASPN) [see comments]. *Archives of Family Medicine* 1993;2:939-949.
91. Haupt BJ: An Overview of Home Health and Hospice Care Patients: 1996 National Home and Hospice Care Survey. *Advance Data NCHS* 1998;297:1-13.
92. Jensen TS, Gottrup H, Sindrup SH, Bach FW: The clinical picture of neuropathic pain. *European Journal of Pharmacology* 2001;429:1-11.
93. Max MB: Clarifying the definition of neuropathic pain. *Pain* 2002;96:406-407.
94. Galer BS, Jensen MP: Development and preliminary validation of a pain measure specific to neuropathic pain: The Neuropathic Pain Scale. *Neurology* 1997;48:332-338.
95. Lynn J, Ely EW, Zhong Z, et al: Living and Dying with Chronic Obstructive Pulmonary Disease. *JAGS* 2000;48:S91-S100.
96. Altman DG, Bland JM: How to randomise. *BMJ* 1999;319:703-704.
97. Mulrow CD, Aguilar C, Endicott JE, et al: Quality-of-Life Changes and Hearing Impairment: A Randomized Trial. *Ann Intern Med.* 1990;113:188-194.
98. Quinn JF: Therapeutic touch as energy exchange: Testing the theory. *Advances in Nursing Science* 1984;6:42-49.
99. Keller H, Bzdek VM: Effects of therapeutic touch on tension headache pain. *Nursing Research* 1986;35:101-106.
100. Fainsinger R, Miller MJ, Bruera E, Hanson J, Maceachern T: Symptom control during the last week of life on a palliative care unit. *Journal of Palliative Care* 1991;7:5-11.
101. Jenkins CA, Taube AW, Turner K, Hanson J, Bruera E: Initial demographic, symptom, and medication profiles in patients admitted to continuing palliative care units. *Journal of Pain & Symptom Management* 1998;16:163-170.
102. Evans C, McCarthy M: The dying patient. *The Lancet* 1985;1:1204-1206.
103. Schonwetter RS, Teasdale TA, Storey P, Luchi RJ: Estimation of survival time in terminal cancer patients: An impedance to hospice admissions? *Hospice Journal* 1990;6:65-79.
104. Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med* 1994;23:129-138.

105. Fishman B, Pasternak S, Wallenstein SL, Houde RW, Holland JC, Foley KM: The Memorial Pain Assessment Card. A valid instrument for the evaluation of cancer pain. *Cancer* 1987;60:1151-1158.
106. Chang VT, Hwang SS, Feuerman M, Kasimis B, Thaler HT: The Memorial Symptom Assessment Scale Short Form (MSAS-SF). *Cancer* 2000;89:1162-1171.
107. Portenoy RK, Thaler HT, Kornblith AB, et al: The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *European Journal of Cancer* 1994;30A:1326-1336.
108. Cohen SR, Mount BM, Bruera E, Provost M, Rowe J, Tong K: Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain. *Palliative Medicine* 1997;11:3-20.
109. Pfeiffer E: A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *Journal of the American Geriatrics Society* 1975;23:433-441.
110. Fillenbaum GG, Landerman LR, Simonsick EM: Equivalence of two screens of cognitive functioning: The Short Portable Mental Status Questionnaire and the Orientation-Memory-Concentration Test. *Journal of the American Geriatrics Society* 1998;46:Dec-1518.
111. McMillan S, Weitzner M: How problematic are various aspects of quality of life in patients with cancer at the end of life? *Oncology Nursing Forum* 2000;27:817-823.
112. Ingham J, Seidman A, Yao TJ, Lepore J, Portenoy RK: An exploratory study of frequent pain measurement in a cancer clinical trial. *Qual Life Res* 1996;5:503-507.
113. Miller MG, McCarthy N, O'Boyle CA, Kearney M: Continuous subcutaneous infusion of morphine vs. hydromorphone: a controlled trial. *J Pain Symptom Manage* 1999;18:9-16.
114. Ahmedzai S, Brooks D: Transdermal Fentanyl versus Sustained-Release Oral Morphine in Cancer Pain: Preferences, Efficacy, and Quality of Life. *J Pain Symptom Manage* 1997;13:254-261.
115. Ingham J, Portenoy RK: The Measurement of pain and other symptoms, in Doyle D, Hanks GW, MacDonald N (eds): *Oxford Textbook of Palliative Medicine*. New York, Oxford University Press; 1998.
116. Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS: When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995;61:277-284.
117. Elliott BA, Elliott TE, Murray DM, Braun BL, Johnson KM: Patients and family members: the role of knowledge and attitudes in cancer pain. *J Pain Symptom Manage* 1996;12:209-220.
118. Twycross R, Harcourt J, Bergl S: A survey of pain in patients with advanced cancer. *J Pain Symptom Manage* 1996;12:273-282.

119. Chang VT, Hwang SS, Feuerman M: Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000;88:2164-2171.
120. Philip J, Smith WB, Craft P, Lickiss N: Concurrent validity of the modified Edmonton Symptom Assessment System with the Rotterdam Symptom Checklist and the Brief Pain Inventory. *Support Care Cancer* 1998;6:539-541.
121. Tierney RM, Horton SM, Hannan TJ, Tierney WM: Relationships between symptom relief, quality of life, and satisfaction with hospice care. *Palliative Medicine* 1998;12:333-344.
122. Portenoy RK, Thaler HT, Kornblith AB, et al: Symptom prevalence, characteristics and distress in a cancer population. *Quality of Life Research* 1994;3:183-189.
123. Chang VT, Thaler HT, Polyak TA, Kornblith AB, Lepore JM, Portenoy RK: Quality of life and survival: the role of multidimensional symptom assessment. *Cancer* 1998;83:173-179.
124. Chang VT, Hwang SS, Feuerman M, Kasimis B: Symptom and Quality of Life Survey of Medical Oncology Patients at a Veterans Affairs Medical Center: A Role for Symptom Assessment. *Cancer* 2000;88:1175-1183.
125. Kaplan EL, Meier P: Nonparametric Estimation from Incomplete Observations. *J Am Statistic Assoc* 1958;53:457-481.
126. Harville DA: Maximum Likelihood Approaches to Variance Component Estimation and to Related Problems. *J Am Statistic Assoc* 1977;72:320-338.
127. Laird N, Ware JH: Random Effects Models for Longitudinal Data. *Biometrics* 1982;38:963-974.
128. Akaike H: A New Look at the Statistical Model Identification. *IEEE Trans on Automatic Control* 1974;19:716-722.
129. Little RJA: Modeling the Dropout Mechanism in Repeated-Measures Studies. *J Am Stat Assoc* 1995;90:1112-1121.
130. Diggle PJ, Kenward MG: Informative Dropout in Longitudinal Data Analysis. *Applied Statistics* 1994;43:93
131. Rubin RB, Schenker N: Multiple Imputation in Health-care Data Bases. *Statistics in Medicine* 1991;10:585-598.
132. Portenoy RK, Payne D, Jacobson P: Breakthrough pain; characteristics and impact in patients with cancer pain. *Pain* 1999;81:129-134.
133. McMillan SC, Tittle M, Hagan S, Laughlin J: Management of Pain and Pain-Related Symptoms in Hospitalized Veterans with Cancer. *Cancer Nursing* 2000;23:327-336.
134. DuPen SL, DuPen AR, Polissar N, et al: Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. *J Clin Oncol* 1999;17:361-370.
135. Geiringer SR, deLateur BJ: Physiatric therapeutics: Traction, manipulation and massage. *Arch Physical Med & Rehab* 1990;71:S264-S266

136. National Hospice and Palliative Care Organization. NHPCO Facts and Figures. NHPCO . 12-10-2001. 1-21-2.

H. Consortium/Contractual Arrangements

None

I. Consultants

See attached letters from **Carolyn Virostek, Jeannette Ezzo.**