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Project Title: Reducing Barriers to Pain and Fatigue Management

The overall purpose of this study is to test an innovative model of reducing barriers to the management of pain and fatigue in cancer patients. These two symptoms were recognized by the NIH State of the Science Conference on Symptom Management in Cancer as critical symptoms impacting QOL and as priority areas for future research ⁽¹⁾. The model, "Passport to Comfort" (or Passport) addresses patient, professional and system barriers to the relief of pain and fatigue and is based on established guidelines developed by the National Comprehensive Cancer Network (NCCN)^(2,3). The specific aims are:

Aim 1- Test the effects of the "Passport" intervention on outcomes of pain and fatigue at 1 and 3 months post intervention comparing Phase I Baseline data to the Phase II High Intensity Intervention.

Aim 2 – Test the effect of selected demographic and disease/treatment variables on outcomes of the Passport Model at 1 and 3 months post intervention.

Aim 3 – Examine the perceived satisfaction with the Passport Model by patients and health care providers.

Aim 4 – Test the effects of the "Passport" intervention by comparing the Phase II High Intensity Intervention to the Phase III Low Intensity Intervention.

The study is designed in three phases. Phase I consists of usual care/Baseline in order to describe the current status of pain and fatigue management in this population and setting. Phase II will be a High Intensity Intervention in which intensive interaction by the investigators will be implemented along with peer audit and feedback in order to address each of these categories of barriers. Phase III will be a Low Intensity Support Intervention in which the investigators will attempt to move the intervention to a more realistic model of care in clinical settings so that it can be replicated in other clinical and community settings as well as maintained in this setting after the conclusion of the project.

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A. Aims

The overall purpose of this study submitted in response to RFA-CA-05-013, is to test an innovative model of reducing barriers to the management of pain and fatigue in cancer patients. These two symptoms were recognized by the NIH State of the Science Conference on Symptom Management in Cancer as critical symptoms impacting quality of life (QOL) and as priority areas for future research⁽¹⁾. The model, “Passport to Comfort” (or Passport) addresses patient, professional and system barriers to the relief of pain and fatigue and is based on established guidelines developed by the National Comprehensive Cancer Network (NCCN)^(2,3). The specific aims are:

Aim 1- Test the effects of the “Passport” intervention at 1 and 3 months post intervention comparing Baseline data (Phase I) to the High Intensity Intervention (Phase II)

Quality of Life

- Hypothesis 1.1 – Subjects (patients) in the High Intensity “Passport” intervention will have improved pain and fatigue outcomes over 3 months time compared to those in the Baseline/Phase I receiving usual care during a 3-month time period, as measured by the Piper Fatigue Scale, the BQII, and the two single items representing pain and fatigue from the Physical subscale of the multidimensional QOL tool.
- Hypothesis 1.2 – Subjects (patients) in the High Intensity “Passport” intervention will achieve a higher quality of life over 3 months time compared to those in the Baseline/Phase I group receiving usual care during a 3-month time period, as measured by the composite QOL score.

Knowledge

- Hypothesis 1.3
 - a - Subjects (patients) in the High Intensity “Passport” intervention will have a significantly greater increase in knowledge of pain and/or fatigue assessment and management over 3 months than those in the Baseline/Phase I receiving usual care over 3 months.
 - b - Subjects (professionals) in the High Intensity “Passport” intervention will demonstrate significantly increased knowledge of pain and/or fatigue assessment and management between pre-test, 1- and 3-month knowledge tests.

Adherence

- Hypothesis 1.4 – There will be a reduction in patient, professional and system barriers to pain and fatigue management over 3 months time for subjects in the High Intensity “Passport” intervention compared to those in the Baseline/Phase I receiving usual care over 3 months, as measured by the pain and fatigue chart audit tools.

Aim 2 – Test the effect of select demographic and disease/treatment variables on outcomes of the Passport Model at 1 and 3 months post intervention compared to pre intervention.

Quality of Life

- Hypothesis 2.1 – Subject (patient) pain and fatigue outcomes will differ significantly depending upon specific demographic and disease/treatment variables (age, gender, ethnicity, education, income, number of symptoms, and disease stage), as measured by the Piper Fatigue Scale, the BQII, and the two single items representing pain and fatigue from the Physical subscale of the multidimensional QOL tool.
- Hypothesis 2.2 – Subjects’ (patients’) Quality of Life will differ significantly depending upon specific demographic and disease/treatment variables (age, gender, ethnicity, education, income, number of symptoms, and disease stage), as measured by the composite QOL score.

Knowledge

- Hypothesis 2.3 – Subjects’ (patients’) knowledge of pain and fatigue management will differ significantly depending upon specific demographic and disease/treatment variables (age, gender, ethnicity, education, income, number of symptoms, and disease stage).

Aim 3 – Examine perceived patient and professional satisfaction with the Passport Model.

- Research Question 3.1 – To what extent are patients satisfied with the format, content, and delivery methods of the Passport Model?
- Research Question 3.2 – To what extent are physicians satisfied with fatigue and pain education received in Phase II (High Intensity) and use of the Passport model with their patients?

- Research Question 3.3 – Does patient satisfaction with the Passport Model differ according to demographic and disease/treatment variables?
- Research Question 3.4 – Do patients perceive the dose of the Passport Model to be sufficient for reducing barriers to pain and fatigue management?

Aim 4 – Test the effects of the “Passport” intervention comparing High Intensity (Phase II) to Low Intensity (Phase III).

Quality of Life

- Hypothesis 4.1 – The improved pain and fatigue outcomes of the Passport Model observed in the High Intensity phase (patients) will also be achieved in the Low Intensity phase, as measured by the Piper Fatigue Scale, the BQII, and the two single items representing pain and fatigue from the Physical subscale of the multidimensional QOL tool.
- Hypothesis 4.2 – Patients in the Low Intensity Group will achieve equivalent improvements in Quality of Life as those in the High Intensity Group, as measured by the composite QOL score.

Knowledge

- Hypothesis 4.3 - Subjects (patients) in the Low Intensity “Passport” intervention will achieve equivalent increases in knowledge of pain and/or fatigue assessment and management as those in the High Intensity group.

Adherence

- Hypothesis 4.4 – Reduction in patient, professional, and system barriers to pain and fatigue management attained during the High Intensity phase will also be achieved in the Low Intensity Phase, as measured by the pain and fatigue chart audit tools.

B. Background and Significance

1. Pain

Pain is recognized as impacting all dimensions of the patient’s life including physical, psychological, social and spiritual well being ⁽¹⁾. The barriers to optimum pain relief were captured during the development of the first national clinical practice guidelines focused on cancer pain. These guidelines, also the first evidence based pain guidelines, published by the Agency of Health Care Policy and Research (AHCPR), were released in 1994 and first introduced the framework of barriers to care ⁽⁴⁾. The AHCPR guidelines identified 3 key categories of barriers to adequate pain relief including patient, professional, and system barriers. Dr. Ferrell served on the pain guideline panel that created this framework and the pain guidelines.

Patient Barriers

The literature has consistently documented that patients and their family caregivers play key roles in the undertreatment of pain ^(4,5). Patients are reluctant to report their pain for a variety of reasons including lack of skill in communicating information about their pain or its relief, the belief that professionals are too busy, as well as a tendency to avoid criticism of their healthcare providers ⁽⁶⁾. Numerous studies have documented the very significant patient barriers of fears of addiction, tolerance, and respiratory depression ⁽⁵⁻⁷⁾. Studies by the Beckman Research Institute of the City of Hope (BRICOH) investigators and others have demonstrated patient tendencies to take pain medications in much smaller doses than have been prescribed. Both patients and family members often avoid discussion of pain or its undertreatment because of their spoken or unspoken beliefs that increased pain could signify advancing disease and the possibility of death ⁽⁸⁻¹⁰⁾. Fortunately, over the past decade, several studies have demonstrated that it is possible to overcome these patient barriers ^(10,11). Model programs have emphasized patient teaching interventions including the use of pain assessment tools, strategies to dispel misconceptions, and patient coaching regarding the reporting and documenting of their symptoms. A common finding across these studies is that such interventions require attention to both knowledge and attitudes about pain ^(7,11-13).

Professional Barriers

There are also significant health care provider barriers to adequate pain relief identified by the AHCPR guidelines ⁽⁴⁾. Physicians, nurses, and other members of the interdisciplinary team often fail to adequately assess the patient’s pain or to recognize patient barriers ⁽¹⁴⁻¹⁶⁾. Professionals lack knowledge of even the most basic principles of pain relief as well as newer pharmacologic advances, side effect management, or understanding of key concepts of addiction, tolerance, dosing, and communication with patients and families about these concepts ⁽¹⁷⁻¹⁹⁾. Studies have used systematic approaches to improving care through the use of algorithms or institutional change efforts. Studies conducted by researchers in this area have included evaluation of continuing education for nurses and physicians as well as the impact of pain education on

healthcare providers through national conferences^(20,21). These studies have explored virtually all aspects of knowledge and beliefs related to pain including professional attitudes, misconceptions, pharmacologic approaches, and non-pharmacologic treatments. Most programs have been limited to standard lecture formats with few programs that include clinical application or follow up to reinforce educational efforts or evaluate outcomes and having a sustained impact on clinical practice.

System Barriers

The AHCPR pain guidelines described system barriers including legal and regulatory structures that interfere with the provision of optimum care as well as inadequate reimbursement for pain and palliative care services. System barriers can be internal, such as involving multiple providers and services of an individual patient's care, as well as external system barriers involving issues such as reimbursement and regulatory constraints⁽⁴⁾. National studies conducted by the Pain and Policy Studies Group of the University of Wisconsin⁽²²⁾ as well as the synthesis of pain literature by the Institute of Medicine and the National Cancer Institute (NCI) Policy Board have continued to document the importance of these system barriers on the ultimate outcomes of patient care⁽²³⁾.

There has been almost no formal evaluation of the impact of clinical practice guidelines on patient outcomes. One recent study did evaluate implementation of the European Pain Guidelines and documented that improved practice and adherence to the guidelines resulted from an educational program achieving 60% adherence. When education was combined with audit and feedback of actual practice, adherence to the guidelines increased to 90% compliance⁽²⁴⁾. One attempt has been cited to evaluate the NCCN Pain Guidelines in cancer centers. Weinstein reported on the NCCN Cancer Pain Management Database Project which has been implemented in five cancer centers participating in evaluation of the frequency, methods, and documentation of cancer pain assessment and management at NCCN institutions⁽²⁵⁾. The study was limited to a retrospective review of records of 209 breast cancer patients with bone metastasis and evaluated the assessment and documentation of pain with some evaluation of opioid use for moderate to severe pain. The City of Hope was one of the five NCCN cancer centers that participated in this audit and results documented weaknesses by the cancer center in both the assessment and management of pain⁽²⁵⁾.

Summary of Barriers to Pain Relief

Since publication of the Cancer Pain Guidelines in 1994, the literature has consistently supported the framework of patient, professional, and system barriers to the provision of optimum pain relief. Literally hundreds of papers have been published describing these barriers and the few studies describing interventions have been limited to short term patient education programs or traditional professional continuing education programs. Literature has strongly supported the need for approaches which integrate patient, professional, and system barriers for improved pain relief.

2. Fatigue

The symptom of fatigue has also emerged as an additional high priority concern in cancer⁽²⁶⁻²⁹⁾. In 2002, an NIH Consensus and State-of-the-Science Conference was held on symptom management in cancer and addressed pain, depression and fatigue⁽¹⁾. Recommendations for fatigue included: 1) The use of a brief assessment tool to routinely ask patients about their fatigue and to initiate evidence-based treatments; 2) Research on the definition, occurrence, assessment and treatment of fatigue through adequately funded prospective studies; and 3) All patients with cancer should have optimal symptom control from diagnosis throughout the course of the illness⁽¹⁾. While fatigue is the most common symptom of cancer, it is also the least understood. Cancer-related fatigue is reported by 60% to 99% of cancer patients and has been described as one of the most significant QOL issues in cancer care^(27,30-32). Patients with fatigue have been documented to have significantly lower QOL, cognitive function and physical performance. Similar to pain, numerous barriers to effective fatigue management have been documented. These include patient, professional, and system barriers.

Patient Barriers:

Despite its prevalence and intensity, patients are reluctant to report fatigue and have little expectation that it can be relieved^(1,32,33). A study conducted with 576 outpatients revealed that patients who experience fatigue do not report it to their doctors because they feel it is inevitable (43%), unimportant (34%) or untreatable (27%)⁽³²⁾. Patients do not regard fatigue as a valid problem about which to complain unless they are asked by a healthcare provider about fatigue^(30,31). When patients voluntarily complain of fatigue, it is generally because it is either overwhelming or severely interfering with their lives. Patients also report that they have difficulty communicating with their healthcare providers about their fatigue⁽³⁴⁾. When patients do

report their fatigue, they are often unsure about the process used to diagnose their fatigue. They are eager to discover the cause of the problem, but distressed by the amount of time, money and discomfort involved in the evaluation⁽³⁵⁾. The evaluation often leads to negative or “normal” results. This suggests to the patient that nothing can be done. Fatigue often prompts patients to interrupt treatment schedules or stop treatment altogether^(36,37), compromising the effectiveness of therapy, thereby potentially hindering the opportunity to treat the cancer^(29,38). Neither patients or their healthcare providers understand the mechanism of cancer-related fatigue or how to prevent, minimize or resolve this most pervasive and distressing of symptoms. Patients also may not always notice that they have gradually altered their everyday patterns over time to adapt to their fatigue. These patient barriers also create an imperative for professionals to take aggressive action in assessing and treating fatigue.

Professional Barriers

Fatigue is a symptom of cancer that is poorly understood by professionals^(29,39). This lack of knowledge stems from the complex nature of fatigue and the lack of agreement in the literature on the definition of fatigue, its causes, indicators, effects, or remedies. Healthcare providers place more emphasis on treating pain and nausea than fatigue, even though fatigue has a very similar effect on QOL. Fatigue is a symptom that is not routinely assessed in the clinical setting by healthcare providers⁽³³⁾. Consequently, cancer-related fatigue has been under-reported, under-diagnosed and under-treated⁽⁴⁰⁾. Even when patients report their fatigue, it may not be taken seriously by providers⁽³⁴⁾. Studies have reported that few patients ever receive treatment or advice from providers about how to manage their fatigue^(27, 32, 39,41). Providers may erroneously assume that cancer-related fatigue is the same as the fatigue that healthy persons experience in everyday living^(42, 43). Thus, providers may not appreciate the significant negative effects of cancer-related fatigue^(44,45). Providers may be unwilling to initiate discussion about fatigue with the patient, particularly if they are unaware of available treatments⁽¹⁾ or believe that there is little they can do to manage fatigue. A major barrier to fatigue management is the lack of knowledge about the underlying causes of fatigue⁽¹⁾.

System Barriers

There are institutional and system barriers related to fatigue assessment and management. Documentation of fatigue assessment and management in the medical record is not a common requirement in most healthcare institutions and is not required by JCAHO. As a consequence, assessment and management of fatigue is often not a priority. Thus, the health care provider is not reminded that fatigue should be assessed and documented routinely⁽³⁷⁻³⁹⁾. The use of physical therapy to combat deconditioning is a good example of a potentially useful intervention affected by institutional/systems barriers. A physician’s order is required for physical therapy or occupational therapy to prevent the indiscriminate use of PT/OT that could compromise care, such as in the case of PT for a patient with metastatic bone disease. Unfortunately, because it is burdensome to get a physician’s order, many patients are not referred. Healthcare reimbursement may be a barrier, affecting the availability of medications, prescription practices, or referral patterns such as for psychiatric or relational support, physical therapy, nutritional support, or erythropoietin therapy⁽⁴⁴⁾. Also interventions for fatigue are often implemented when the symptom is severe at a time when patients are least able to participate or benefit from them. There is a need for more systematic approaches to fatigue to overcome these barriers.

Summary of Barriers to Fatigue Management

The literature has documented that, similar to pain, there are significant patient, professional and system barriers to the management of fatigue. Interventions are needed to improve patient and professional assessment and communication of fatigue. Professionals require increased knowledge of fatigue management and systems are needed which provide timely, coordinated and interdisciplinary approaches to fatigue management.

3. Challenges in Integrating Symptom Management in Routine Oncology Care

The focus of this proposal is on creating a replicable model of pain and fatigue management using evidence based guidelines at an institutional level. In recent years, there have been tremendous strides in the treatment of cancer. However, these advances have progressively blurred distinctions between life-prolonging treatments and those intended to improve patient comfort and QOL⁽⁴⁶⁾. Traditionally, an unnecessary dichotomy has existed between life prolonging treatment and palliative care. This dichotomy results in a sequential rather than a simultaneous approach to oncology care, wherein palliative care is initiated only when curative treatment has been abandoned⁽⁴⁶⁾. It is only in recent years that a broad agreement advocating the

concurrent approach to care has been introduced. Currently, several new models of delivering palliative care and optimizing symptom management are emerging and being tested in various centers around the country.

One such model is titled Project Safe Conduct, a collaborative effort between Hospice of Western Reserve, and the Ireland Cancer Center at Case Western Reserve University, an NCI-designated comprehensive cancer center. The key goal of this project is to create a seamless transition of care for advanced cancer patients and their families in an ambulatory care setting by integrating palliative care principles into routine oncology care⁽⁴⁷⁾. The project was initially offered to patients with advanced lung cancer and results demonstrated improved pain and symptom management, increased hospice referrals and lengths of stay, diminished hospitalizations and decreased pharmaceutical costs⁽⁴⁷⁾.

In 1998, Project ENABLE (Educate, Nurture, Advise Before Life Ends) was conceived by the Norris Cotton Cancer Center (NCCC) Regional Palliative Care Initiative (RPCI) at Dartmouth University in New Hampshire. The program goal was to enable advanced cancer patients and their families to have access to palliative care services at the time of diagnosis⁽⁴⁸⁾. The project had three functions: 1) to provide a palliative care nurse to coordinate the care of patients and families across services; 2) to offer workshops for patients and families regarding managing their illness; and 3) to integrate palliative/hospice care into routine oncology care⁽⁴⁸⁾. This approach was implemented and tested in three sites in New Hampshire. A total of 140 historical controls and 240 intervention patients and families were enrolled. Measures of program success included improved access to hospice and palliative care services from the time of diagnosis. A randomized controlled clinical trial is currently underway to test the effect of the program on quality⁽⁴⁸⁾.

A final example, the Simultaneous Care (SCEI) Model, was developed at the University of California, Davis as a means to demonstrate that investigational therapy and palliative care can be provided simultaneously⁽⁴⁹⁾. A nonrandomized pilot study was conducted to test the feasibility and preliminary efficacy of the SCEI intervention for patients enrolled in clinical trials. Forty-four patients were entered into the intervention arm and 20 patients were entered into the usual care arm. The mean days in hospice was higher in Simultaneous Care (54 days) compared to Usual Care (37 days). Among those who died after completion of therapy, the proportion who entered hospice was greater in Simultaneous Care than in Usual Care (92% vs. 53%). Patients in Simultaneous Care received a mean of 3.8 cycles of chemotherapy, those in Usual Care received a mean of 4.5 cycles⁽⁴⁹⁾. The results suggest that palliative care can be introduced simultaneously with investigational cancer therapy without adverse events. Currently a multi-site, NCI-funded randomized controlled Phase II study of the efficacy of the Simultaneous Care is underway at UC Davis, BRICOH and Johns Hopkins (described in the preliminary studies section). Seventy-five patients have been accrued at the BRICOH site. The Simultaneous Care study uses a patient problem solving model and is limited to patients with advanced disease with no professional or systems intervention or symptom focus.

The above studies and several others have used methods by which important patient information is communicated related to symptom concerns. Latimer and colleagues have tested the idea of what they refer to as the “patient care traveling record” and compared it to traditional approaches of assessment and documentation⁽⁵⁰⁾. These authors and others conclude⁽⁵¹⁻⁵⁴⁾ that such approaches conveying patient goals, communicating symptom management plans and bridging guidelines to patient education are helpful in eliminating barriers (patient, professional and system) to symptom control and quality care⁽⁵⁰⁾. Patient education and coaching also have been recommended based on a meta-analysis of psychoeducational interventions for pain by Devine in 2003 and by Devine and Westlake in a meta-analysis of 116 studies across symptom concerns^(55,56). Evidence based symptom guidelines of the Passport model build on these model studies, but add several dimensions including a) a focus on pain and fatigue; b) application to patients across stages of diseases; c) testing of an intervention provided through the primary care providers; d) evaluation of translation across high and low dose intervention and e) targeted on patient, professional, and system barriers.

4. Summary of Background and Significance

Previous research has demonstrated that barriers to pain and fatigue management entail patient, professional, and systems barriers. After two decades of effort to advance symptom management, sources have documented that reducing these barriers requires more than publication of guidelines or staff education^(57,58). Education alone doesn't alter professional behavior and professional change does not equate to patient/family change or to system change. Allard et al.⁽⁵⁹⁾ analyzed 33 studies of educational interventions for cancer pain and found that attitudes and knowledge about cancer pain were improved but unfortunately there was minimal change in patient's pain. Ferris, von Gunten and Emanuel⁽⁶⁰⁾ recently summarized key steps to effective change by stating: “We can take the sum total of our evidence about education to improve cancer

pain management in particular, and palliative care in general, and distill it to three take-home messages for those who want to pursue education: 1) Design attitude and knowledge education that is practical, and acknowledges the multiple other demands on the time of the learner. 2) Design efforts to mentor and develop the desired skills using clinical settings and 3) Ensure that the systems are in place to facilitate and encourage the desired behaviors and outcomes". The proposed study builds on the extensive background literature which has described barriers to the relief of pain and fatigue. The study incorporates recommendations from the literature in design and implementation of an innovative yet realistic model for application to cancer care.

C. Preliminary Studies/Previous Research

This proposed development and translation of evidence based pain and fatigue management builds on a solid foundation of over 15 years of consistent research, education and publications regarding pain and fatigue by the BRICOH investigators.

1. Pain Studies

Dr. Ferrell has focused much of her research during the past two decades in the area of cancer pain management. Her research in 1984 on "Home versus Hospital Cancer Death and Bereavement Outcomes" began a 20-year program of work which has included studies of pain management for cancer patients at home⁽⁶¹⁾, measurement of QOL with cancer patients in pain⁽⁶²⁾, and the development of a QOL instrument to capture the specific QOL concerns associated with pain management. Other studies have focused on pain management in the elderly as well as studies focused on Hispanic/Latino patients and a general understanding of cultural influences in pain management^(63,64). In 1989, Dr. Ferrell and colleagues began research related to understanding the family perspective of cancer pain management^(13,65-70). Dr. Ferrell and colleagues have conducted additional studies beginning in 1990 on the evaluation of knowledge and attitudes of nurses related to pain, clinical decision-making by professionals and ethical issues, in cancer pain^(13-15,71). These studies led to professional education programs with extensive evaluation including the Pain Resource Nurse training program now in its 14th year which has been replicated by over 100 institutions nationally⁽¹⁵⁾. Drs. Ferrell and Grant have conducted extensive pain education through numerous projects funded by the National Cancer Institute (NCI) and other sources, and have extended the focus from individual professional knowledge to institutional commitment to pain management addressing system barriers⁽⁷²⁻⁷⁵⁾.

In 1996 the BRICOH investigators began work on "Patient and Public Cancer Pain Education" funded by the Californian Division of the American Cancer Society, and subsequently by the NCI for an extremely successful R25 funded project⁽⁷⁶⁾. Through this 4-year project, the investigators developed mechanisms for educating patients and the public about cancer pain management and instituted 4 national training programs reaching approximately 300 professionals from all 50 states and culminating in national training projects and materials widely disseminated. The investigators began the Pain Resource Center (PRC) in 1995 which expanded in 2000 to become the Pain and Palliative Care Resource Center (PPRC) and now includes over 450 materials accessible through the website (<http://prc.coh.org>). The PPRC serves as an model of dissemination efforts in pain management by the COH investigators. In 2003, the PPRC website received over 450,000 web hits. The COH investigators have also conducted research related to cost considerations in pain management including the costs of untreated pain^(77,78).

A continuing medical education (CME) outcomes study was conducted to evaluate the impact of pain management education on physician practice patterns. The BRICOH Continuing Medical Education department (led by Drs. Leong and Morgan, co investigators for this project), in accordance with the state mandate for pain education, designed and organized five annual pain management seminars in conjunction with the Department of Supportive Care and Palliative Medicine. This study was conducted after the implementation of the first annual seminar. Fifty-one of 81 physicians responded to post-attendance questionnaires. At four months, 67% of physicians stated that they will or have changed their practice and in the follow-up group (n=31), 90% reported having changed their practice. Results indicated that a cohort of physicians are open to changing their practice patterns in pain management and palliative care⁽⁷⁹⁾.

2. Fatigue Preliminary Studies

Fatigue studies have been conducted at BRICOH for the past 10 years. Dean, Ferrell and colleagues⁽⁸⁰⁾ conducted a descriptive study using the Piper Fatigue Scale and symptom distress in 30 patients with malignant melanoma. Patients were evaluated before treatment with subcutaneous interferon alpha treatment and every two weeks during treatment for two consecutive months. Results indicated that there was a roller coaster pattern of fatigue during two months of treatment. The most extreme fatigue scores were in the affective domain, followed by the sensory, temporal, total fatigue and fatigue severity scores. The emotional

response to fatigue was intense while the severity scores, linked to functional and social abilities, were least affected. This study was supported by a 1992 Oncology Nursing Foundation grant ⁽⁸⁰⁾ and demonstrated the impact of fatigue on QOL. Ferrell and colleagues ⁽⁸¹⁾ added to this understanding of fatigue and QOL by conducting a qualitative analysis of data from 190 patients across five data sources including a survey of cancer survivors, interviews and focus groups with breast, ovarian and thyroid cancer patients. Findings revealed that fatigue had an impact on each dimension of QOL ⁽⁸¹⁾.

Dean, Grant and colleagues ^(82,83) conducted a study to compare fatigue in women with breast cancer with healthy female controls. Salivary melatonin, body temperature and subjective fatigue were evaluated in 20 women with Stage I breast cancer (BC) and compared to 20 healthy female controls (HC). Patients were evaluated before radiotherapy, midtreatment, end of treatment and 7 weeks post treatment. Results demonstrated statistically significant differences in fatigue measures and provided evidence for continued exploration of these physiologic fatigue indicators. This study was supported by a 1995 Oncology Nursing Foundation grant ^(82,83). Dean, Sarna and Grant later explored the relationship of melatonin, body temperature and activity/sleep cycles with cancer-related fatigue in a descriptive, prospective one group (n=20), pre-post design. These clinical studies provided the BRICOH investigators with the opportunity to evaluate numerous measurement tools for fatigue ^(84, 85).

Grant and colleagues ⁽³⁴⁾ established a community-based educational model of fatigue and pain management for individuals with cancer to address patient barriers. The focus of the education was to provide general information about each symptom, assessment and management of the symptoms, and strategies for effectively communicating with their healthcare providers. Workshops were held at four Southern California sites of the Wellness Community. Participants gave immediate feedback to the information presented and reported that their symptoms were not taken seriously by health care providers. In addition, participants reported difficulty in trying to communicate with their physicians. Participants rated the program as extremely useful and reported positive outcomes ⁽³⁴⁾.

As an example of systems level interventions for fatigue, a multidisciplinary team at BRICOH was developed to assess staff knowledge and attitudes about fatigue to enhance the assessment and management of fatigue in the clinical setting ⁽⁸⁶⁾. An institutional needs assessment was conducted in 1999 which demonstrated that there was no system in place or standard of practice for fatigue management. A performance improvement project model was utilized. One major practice change that occurred as a result of this project was the inclusion of a fatigue assessment question in the Daily Patient Care Record completed by nurses in the inpatient setting ^(86,87). Dr. Grace Dean was the leading fatigue researcher at BRICOH for these studies but she relocated in 2004 to Pennsylvania to begin a post doctoral program in fatigue and sleep research. While Dr.'s Grant and Ferrell participated in these studies, they have added a senior fatigue research colleague, Dr. Barbara Piper to provide strength to this proposed intervention. Dr. Piper's key studies follow.

Piper, Lindsey, & Dodd (1989) ⁽⁸⁸⁾ conducted a pilot study in radiation therapy patients to test and evaluate the first multidimensional self-report scale to measure fatigue in cancer patients. The study results indicated that the initial version of the Piper Fatigue Scale (PFS) was indeed measuring multiple dimensions of subjective fatigue and had excellent reliability and validity estimates particularly for a new instrument. The study was supported by a 1984 grant from Sigma Theta Tau. Piper and colleagues (1998) ⁽⁸⁹⁾ subsequently conducted a mailed survey of 750 survivors of breast cancer to investigate patterns and correlates of fatigue and condense the original PFS. Four dimensions of fatigue were confirmed (affective meaning, sensory, behavioral severity, and cognitive/emotional); the total number of items scored was reduced to 22; and the PFS continued to have excellent reliability and validity. This study was one of the first to document different intensity levels of fatigue by type of treatment ⁽⁵¹⁾.

Piper and colleagues (1999) ⁽⁹⁰⁾ investigated fatigue patterns and correlates in 220 women and men with early stage breast and prostate cancers receiving chemotherapy, hormonal therapy and/or radiation therapy. This was the first international study to be conducted in cancer-related fatigue; to investigate fatigue patterns in hormonally-treated patients and to compare 3 single item fatigue intensity scales with two multidimensional fatigue scales. While strong correlations were found to exist between the three single item intensity scales and the multidimensional scales, patients universally recommended that the multidimensional scales such as the PFS be used to measure fatigue in clinical practice settings. Piper and colleagues (2003) ⁽⁹¹⁾ conducted a longitudinal pilot study to evaluate correlations and changes over time among fatigue, depression and serotonin levels in women newly diagnosed with early stage breast cancer receiving 4

consecutive cycles chemotherapy. The women with cancer had statistically significant higher fatigue and depression scores and lower serotonin levels than age and menopausally-matched healthy controls. This study was funded by Sigma Theta Tau and the University of New Mexico Clinical Research Center.

In summary, the fatigue studies conducted by Piper and colleagues⁽⁸⁸⁻⁹¹⁾ complement the previously described City of Hope studies by further documenting fatigue as a prevalent and distressing symptom in cancer patients that interferes with functional status and QOL. These studies have shown that the PFS is a reliable and valid self-report scale that measures multiple dimensions of subjective fatigue in cancer patients. Since patients can complete the PFS in less than 5 minutes, the scale's administration has not caused undue subject burden or fatigue in the measurement process, an important concern when measuring fatigue in ill populations.

3. Summary of Preliminary Studies

The BRICOH investigators have over 15 years experience of translating research into symptom management practice and into quality improvement through their extensive record of R25 funded cancer education projects. Some of these are cited within the preliminary pain studies above. Two key examples of current, extremely successful projects include the Disseminating End-of-Life Care to Cancer Centers (DELEtCC) project <http://delececc.coh.org> for which Dr. Grant is the P.I. This project is attempting to support cancer centers in improving pain, symptom management, and other aspects of palliative care within the nation's cancer centers. To date, over 140 community cancer centers and 17 NCI Cancer Centers have participated in the course sending teams of two professionals. Overall, course evaluations rate the course at 4.73 on a scale of 1= poor to 5 = excellent. There will be one additional course of the DELEtCC project reaching an additional 40 cancer centers. Most all of the cancer centers have targeted goals for improved pain and symptom management. This illustrates the experience of the BRICOH team in translating evidence-based practice to community settings. An additional extremely successful project has been the End of Life Nursing Education Consortium (ELNEC) www.aacn.nche.edu/elneec. This project funded by the Robert Wood Johnson Foundation has reached 502 undergraduate nursing programs (1 of every 3 nursing schools in the nation), over 300 CE providers, 190 pediatric settings and through support from the NCI has reached 35% of the graduate nursing programs and oncology nurses through 160 ONS chapters nation-wide. The ELNEC project includes pain as one of the nine modules as well as a symptom management module addressing fatigue. A recently concluded study of one-year follow-up of the 502 undergraduate nursing programs demonstrated that the schools had added an average of 10 hours of content to their undergraduate curriculum⁽⁹²⁾. The investigators are uniquely qualified to conduct this pain and fatigue intervention with their extensive research addressing patient, professional and system barriers. There has been strong research collaboration including the Nursing Research Department with co investigators from Medical Oncology, Surgery, Hematology and Pediatrics as well as with a broad range of Psycho-Oncology colleagues. The inclusion of Dr. Piper as a national expert in cancer fatigue is an additional strength. As co-investigator, she will share her very extensive research expertise and her experience in the development of the NCCN fatigue guidelines, which parallels Dr. Ferrell's role on the NCCN pain panel. This team's extensive research and dissemination record serves as a strong foundation for the proposed study.

D. Research Design and Methods

1. Framework

Figure 1 presents the study model. Barriers to the management of pain and fatigue are identified in the three categories of patient, professional, and system. The barriers to pain management identified in the model are taken from the Agency for Healthcare Policy and Research Clinical Practice Guidelines for cancer pain published in 1994⁽⁴⁾. The barriers to fatigue are derived from the literature. Subjects will be accrued who are medical oncology patients with pain and/or fatigue (≥ 4 on a 0-10 scale). Several demographic and disease variables are identified which may influence the process. The study is designed in three phases. Phase I consists of Usual Care/Baseline in order to describe the current status of pain and fatigue management in this population and setting. Phase II will be a High Intensity Intervention in which intensive interaction by the investigators will be implemented along with peer audit and feedback in order to address each of these categories of barriers. Phase III will be a Low Intensity Support Intervention in which the investigators will attempt to move the intervention to a more realistic model of care in clinical settings so that it can be replicated in other clinical and community settings as well as maintained at BRICOH after the conclusion. The model recognizes that there are intervening variables which may influence outcomes of care during the intervention

including disease progression, the effects of treatment and other symptoms. Outcomes will be evaluated consistent with the barriers to include patient, professional, and system factors.

2. Investigators

Dr. Betty Ferrell is P.I. for this project. She has been a Research Scientist at the BRICOH for 15 years with 27 years of experience in oncology nursing. Her research has focused on pain management, quality of life, and palliative care. Dr. Lucille Leong is Acting Director of the Department of Medical Oncology. She will serve as a co-investigator at 5% time to provide the administrative leadership for the department commitment to the project. Dr. Leong has been a staff physician at BRICOH for 19 years. Dr. Robert Morgan has been a staff physician in the Department of Medical Oncology since 1988. He is the Chairman and Director of Continuing Medical Education and the current Chief of the Medical Staff. Dr. Marianna Koczywas is a co-investigator and has committed 20% time to provide the daily involvement by Medical Oncology in this project. Dr. Marcia Grant is a co-investigator and will focus her efforts on the evaluation process. Dr. Grant has been with BRICOH for more than 25 years and is a Research Scientist and Director of Nursing Research. Shirley Otis-Green, MSW is a co-investigator contributing her psycho oncology expertise and knowledge to the study.

Jennifer Brown, MA, OTR is a physical therapist and Director of Rehabilitation Services, and will provide her expertise in exercise interventions for the fatigue protocol. Cecilia Lau, R. Ph., is a clinical pharmacist and works extensively with the Medical Oncology Department in symptom management and pharmacologic treatments related to patients on clinical trials. She will offer her expertise in the symptom management algorithms and a link to clinical pharmacy services at BRICOH. Dr. Barbara Piper is a co-investigator on this project and is the one external investigator. Dr. Piper will provide her expertise to develop the fatigue protocols, provide education to the medical staff, and participate in all phases of the research. The final co-investigator is Dr. Neal Slatkin, Director of the Department of Supportive Care and Palliative Medicine at BRICOH. He has been at BRICOH for 20 years and will provide his expertise in both pain and fatigue management.

These investigators are complemented by external consultants including Dr. Marilyn Bookbinder, Dr. Barbara Given, Dr. Charles von Gunten, and Dr. Tom Smith. Dr. Marilyn Bookbinder is the Director of Nursing for Pain Medicine and Palliative Care at Beth Israel Medical Center in New York. She is internationally recognized for her work on institutional commitment and quality improvement efforts in pain management and will offer her expertise in the integration of the pain and fatigue algorithms and in addressing system barriers. She has collaborated extensively with Drs. Ferrell and Grant over the past decade. Dr. Barbara Given is a University Distinguished Professor in the College of Nursing at Michigan State University. She will offer her consultation in intervention research for cancer prevention as well as in conducting symptom intervention studies. Dr. Given has collaborated on numerous activities with the BRICOH investigators over the past decade. Dr. Charles von Gunten and Dr. Tom Smith are nationally recognized medical oncologists who are recognized for their leadership in symptom management. Dr. von Gunten is Medical Director, Center for Palliative Studies at San Diego Hospice and Associate Clinical Medical Professor at U.C. San Diego. Dr. Tom Smith is Professor of Medicine in Health Administration as well as Division Chair at the Medical College of Virginia Hospitals/Virginia Commonwealth System and Massey Cancer Center. Dr. Smith has served in several leadership positions in the American Society of Clinical Oncology (ASCO) including serving as the program developer of their ASCO Symptom Control curriculum. He has successfully implemented symptom algorithms within the Massey Cancer Center at the University of Virginia. Drs. Smith and von Gunten will offer education to the BRICOH medical oncologists as well as expertise in the algorithms and overall project.

In addition to this strong cadre of investigators and consultants, this project is designed to include an Internal Advisory Board to ensure that the algorithms and interventions designed for this research are translatable into clinical practice and can be implemented within the usual BRICOH systems of care. The Internal Advisory Board includes: Rev. Pamela Baird, a Supportive Care and Bereavement Specialist; Peggy Mancini, R.D, MS, CNSD, CDE a Dietician whose expertise will be helpful to integrate nutritional support for fatigue; and Cindy Idell, MSN an oncology Clinical Nurse Specialist in the Department of Medical Oncology. Cindy leads a quality improvement project in progress funded by the Oncology Nursing Foundation on pain assessment and documentation. She will offer her expertise as a senior nurse clinical leader. Jill McCormick, RN, BSN, OCN is the Nursing Manager for both the inpatient and outpatient medical oncology services. She will provide her expertise in insuring aspects of continuity in both pain and fatigue management across settings of care in addressing systems and professional barriers. Annette Mercurio has been the Director/Manager of Patient, Family, and Community Education since 1993. She will offer her expertise in patient education and

will participate in Phase III to ensure that the materials and systems created for patient education become integrated into systems of care. Dr. Martin Perez is a Clinical Psychologist in the Department of Supportive Care who will provide expertise in the psychological aspects of symptom management. Virginia Sun, RN, NP is a Senior Research Specialist in the Department of Nursing Research and Education. Virginia is the Research Nurse for the Simultaneous Care Study described in the preliminary study section which provides supportive care to patients on clinical trials. She has worked for the past two years with the Medical Oncology Department addressing concerns of patients on clinical trials. Ann Tanner is the Project Director, Medical Center Operations and Director of Case Management. Elaine Goehner, RN, PhD is Director of Quality, Risk, and Regulatory Management. She will add her expertise in designing interventions that are translatable to other settings. Letters of support from all of these advisors are included in Appendix B.

In summary, this research team offers strength in both pain and fatigue research and provides an interdisciplinary approach consistent with the clinical guidelines. The inclusion of an Internal Advisory Group will strengthen the model's feasibility and will contribute to the ultimate goal of creating a model that can be widely disseminated.

3. Design

This is a prospective longitudinal comparative design using a Phase I Baseline usual care control group followed by two cohorts in experimental phases of High Intensity (Phase II) and Low Intensity (Phase III) intervention. This study demonstrates innovation by translating the evidence-based guidelines for pain and fatigue as developed by the National Comprehensive Cancer Network into practice. Dr. Ferrell serves on the pain panel and Dr. Piper serves on the fatigue panel. The BRICOH is one of the founding member institutions in the NCCN, and is represented on each of the guideline panels. This strong institutional commitment to the NCCN makes these guidelines ideal for this study. The NCCN guidelines have many strengths including their evidence-base, focus on cancer, and the fact that they are developed by and intended for implementation in cancer settings. They are updated annually based on available evidence and are accompanied by consumer versions of the guidelines. Thus, we will have consistency between patient education and professional educational materials for the study. However, the guidelines are extensive documents with fatigue guidelines encompassing 27 pages and the pain guidelines 24 pages. There is a need to operationalize the guidelines to create algorithms and tools useful in clinical practice in actual patient encounters. Algorithms for the study will be derived from the guidelines.

We have selected the symptoms of pain and fatigue for several reasons. These are symptoms of extensive previous focus by the investigators and are consistently cited as common and distressing symptoms. The literature supports the relationship between these two symptoms and it will be of interest to compare the outcomes of the interventions between them. In the case of both the pain and fatigue guidelines, the NCCN states that there is uniform expert consensus, while not consistently derived from randomized clinical trials or meta-analysis, that the recommendations are appropriate and evidenced-based. However, the guidelines have not been evaluated clinically to test feasibility in implementation. This study will provide insight into the use of NCCN guidelines and serve as a model for extending these and other guidelines into practice to eliminate serious barriers to quality cancer care.

The design and procedures as described below use peer feedback to ensure adherence with the guidelines, and include an internal advisory group to foster dissemination. The 0-10 subject criteria targets patients already experiencing pain and fatigue at four or above on the rating scale, an established point in which symptoms impact QOL^(2,3) and the rating of 4 or greater is identified in the Guidelines consistent with moderate (4-6) or severe (7-10) intensity. The focus of patient accrual and interaction will be the outpatient oncology setting as the primary site of cancer care. The procedures below emphasize both the assessment and management of symptoms since the literature has clearly documented that failure to optimally assess symptoms and patients' tendency to underreport them is the first barrier to seeking symptom relief.

As an innovative approach, we have developed the Passport Model as a unique way to facilitate patient education in pain and fatigue management and to enhance the communication of symptoms to healthcare providers. We have selected the three phase approach of first a Baseline to document usual care then Phase II as High Intensity followed by Phase III Low Intensity to create a "model intervention" in which there is significant support in "high-dose" to ensure that the algorithms are implemented and barriers are targeted. Having the third phase of a lower intensity intervention will help to translate this intervention across other clinical and community settings and to model the implementation and translation of evidence based symptom

guidelines. As a tertiary cancer center, the BRICOH has a patient population representative of those who will achieve longer term survival as well as those with more advanced disease treated on clinical trials.

4. Timeline

The investigators considered various designs and recognized that it would be impossible to randomly assign patients to a no-treatment control group versus an experimental condition as there would be broad contamination as clinicians actively engaged in the Passport Model would not be able to withhold it from a control group. Phase I of the study then, is the Baseline which will occur over the first eight months of the study simultaneously with start-up procedures and algorithm preparation to be applied in the later phases. During Baseline, we will follow patients using the same accrual criteria, and evaluate their pain and fatigue pre intervention and at 1 and 3 months post intervention using the same outcome measures as will be implemented in Phases II and III. Phase II of the study, “High Dose Passport Intervention” will occur across months 9 through 30. This high intensity phase includes intensive patient and professional education as well as the implementation of the algorithms. These interventions address the barriers to symptom management identified previously. There will be follow-up with accrued patients pre intervention and at 1 and 3 months post intervention. There will be a 4 month time during months 30-33 as we analyze the Phase II data, make any minor modifications in the procedures based on that experience and provide professional staff with feedback about the intervention and its effectiveness in addressing the barriers. We then will move into Phase III as the Low Intensity intervention (months 34-57) in which the investigators will continue to facilitate the intervention as it is implemented into existing systems and procedures within the cancer center. The final three months (58-60) are reserved for data analysis, preparation of presentations and publications. Additionally, in the final three months of the project, the BRICOH Continuing Medical Education Department, in collaboration with the investigators will host a major continuing education one-day conference targeted for community hospitals and clinics to share the results of the study and to disseminate the findings for use by other settings.

5. Procedures

a. Recruitment of Subjects across Phases

Patients recruited into this study will be under the care of the Medical Oncology service at the City of Hope.

Subject criteria include:

- Age 18 or over.
- Able to read and understand English to participate in the patient teaching.
- Estimated by the primary oncologist to have a prognosis of six months or greater. This is intended to provide adequate time to evaluate the outcome measures and to avoid burdening subjects with later stage disease that may have rapid progression.
- Reports pain and/or fatigue of four or greater on a scale of 0 = no pain/fatigue to 10 = severe pain/fatigue. This criterion is intended to target those with moderate to severe symptom intensity who would be most appropriate for the intervention.
- Diagnosed with cancer a minimum of one month prior to study entry. This criterion is intended to avoid those patients experiencing the distress of initial diagnosis.
- Diagnosed with breast, prostate, colon or lung cancer. These criteria are intended to restrict the sample to solid tumors with some degree of common treatment regimens and to decrease the heterogeneity of the population. These diagnoses account for 55% of cancers in men (30% prostate, 11% colon, 14% lung) and 55% of cancers in women (31% breast, 12% colon, 12% lung).

Table 1 presents the BRICOH program statistics for 2003. There were a total of 873 new cases of breast, prostate, colon, or lung cancer which are the diagnostic groups to be accrued to the study. The study will accrue patients across all stages of disease in order to best represent the population of patients with pain and fatigue. The race distribution of patients at BRICOH for 2003 included 65% Caucasian, 18.7% Hispanic, 4% Black, 11.7% Asian and 1% other.

Table 1: 2003 BRICOH Clinical Cancer Program Statistics

Cancer Site	New Cases 2002	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	Unk.
Breast Cancer	259	34	61	67	45	8	1
Prostate Cancer	326	1	2	234	35	14	0
Colon Cancer	136	2	10	23	22	30	2
Lung Cancer	152	0	26	6	40	46	6

Total = 873 new patients in 2003 = 72 per month

Family Caregivers

The investigators discussed extensively the inclusion of family caregivers as subjects for this study. While the literature and our own research and experience⁽⁹³⁾ has documented the important role of family caregivers in pain management, less literature is available related to fatigue. We also recognize the complexities of including family caregivers as subjects in this intervention with the associated needs to control for family caregiver relationship, evaluate their own knowledge, ensure uniform involvement of caregivers across subjects in this study, insure availability of caregivers for participation and evaluation, etc. We concluded that this study will focus on the patients as subjects and would not include family caregivers as subjects. Once the Passport model is tested and evaluated, future studies might explore the role of family caregivers using this model.

Professionals

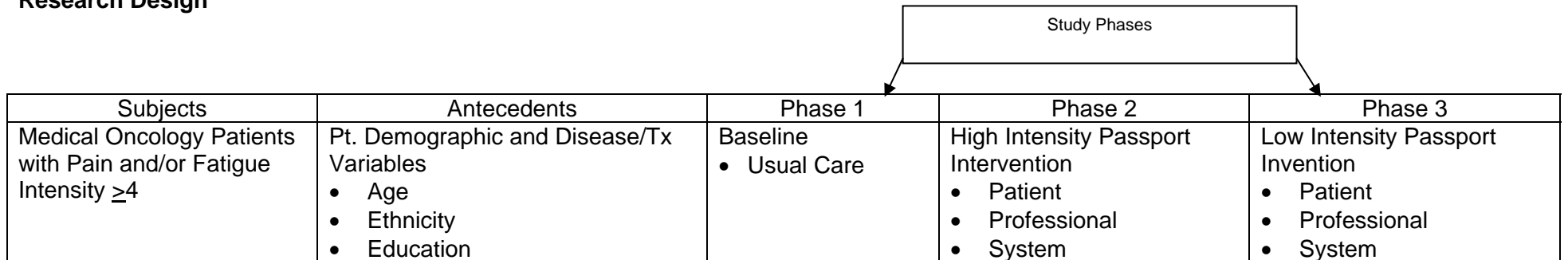
Figure 1

Passport Study Model

Barriers to Management of Pain and Fatigue

Priority Symptom	Patient / Family	Professional	System
<ul style="list-style-type: none"> • Pain 	<ul style="list-style-type: none"> • Reluctance to report pain • Concern about distracting physicians from treatment of underlying disease • Concern about not being a “good” patient • Reluctance to take pain medications • Fear of addiction or of being thought of as an addict • Worries about unmanageable side effects • Concern about becoming tolerant to pain medications 	<ul style="list-style-type: none"> • Inadequate knowledge of pain assessment and management • Poor assessment of pain • Concern about regulation of controlled substances • Fear of patient addiction • Concern about side effects of analgesics 	<ul style="list-style-type: none"> • Low priority given to cancer pain treatment • Inadequate reimbursement • Restrictive regulation of controlled substances • Problems of availability of treatment or access to it
<ul style="list-style-type: none"> • Fatigue 	<ul style="list-style-type: none"> • Reluctance to report fatigue • Belief that fatigue is less important than other symptoms • Belief that there are no treatments available for fatigue • Reluctance to participate in exercise regimens • Inability to distinguish fatigue from other physical and psychological symptoms 	<ul style="list-style-type: none"> • Inadequate knowledge of fatigue assessment and management • Belief that fatigue is inevitable and that treatments are unavailable. • Reluctance to involve patients in exercise or other aggressive treatment regimens 	<ul style="list-style-type: none"> • Low priority given to fatigue as an important symptom • Inadequate reimbursement for nutritional consults, physical therapy, and pharmacologic treatments • Lack of available treatments such as exercise programs • Lack of continuity of symptom management across settings of care

Research Design



	<ul style="list-style-type: none"> • Number symptoms • Income • Gender • Disease stage 			
--	--	--	--	--

Outcomes

Intervening Variables

- Current Treatments
- Disease Progression



Patient

Professional

System

QOL

Satisfaction
Pain Knowledge

Adherence to
Fatigue Knowledge
Pain

Adherence
Satisfaction

Adherence to algorithm

algorithm

Knowledge

Patients are cared for by a variety of professionals including physicians, nurses, nurse practitioners, oncology fellows, rehabilitation specialists, social workers, chaplains, unlicensed personnel and others. The investigators evaluated the best research design and inclusion of professionals as subjects for the study. After significant discussion, we agreed that the use of the algorithms as designed by the NCCN were focused on decisions by the physician and treatments designated for pain and fatigue. There are no NP's in the medical oncology department and the BRICOH does not have medical students or residents. There are 2 Medical Oncology Fellows in the clinical setting each year for a 1 year clinical rotation. These fellows will be included in the education but patients they see in clinic are seen in conjunction with the medical oncologist. Thus the Fellow is not considered a subject for the study. The physician is the designated professional subject in this study and we will be collecting outcome data on the physician providers. This also provides a tightly controlled design in which the physician can be directly linked to the specific patient accrued to the study as all BRICOH patients are assigned to a primary Medical Oncologist (n=12). While we recognize that nurses play a central role in the care of these patients, we also recognize the extreme difficulty of including nurses as primary subjects and to evaluate the outcomes of their interactions given a very large nursing population within medical oncology (N = ~200 total nursing staff) and the difficulty attributing aspects of care to an individual nurse. However, we believe that nurses and other professionals are central to the assessment and management of pain and fatigue. Thus, the nursing staff and all interdisciplinary colleagues working in medical oncology will be invited to attend the educational sessions provided in the professional training. Additionally, the Research Nurses who are conducting the patient teaching in Phase II will interact closely with the nursing staff and these nurses will conduct the education of the nursing staff as we move into Phase III when the usual care providers assume the responsibility for pain and fatigue management in the Passport system.

b. Accrual

The eligible patients available at study start-up will be recruited to serve as the baseline group in Phase I of the study. In Phases II and III (High and Low Intensity, respectively), eligible patients will be recruited sequentially until full accrual is reached for each phase. The sample will be balanced so that half of the subjects in each group (Phase) score at least 4 on a 0-10 pain rating scale, and half score at least 4 on a 0-10 fatigue rating scale. Because there are expected to be differences in pain and fatigue by cancer diagnosis, proportional stratification will be conducted based on cancer diagnosis, so that approximately 37% of the sample will have prostate cancer, 30% will have breast cancer, 17% will have lung cancer and 16% will have colon cancer. During recruitment of any one group, if a symptom (pain or fatigue) or a diagnosis becomes full, then only subjects meeting the selection criterion on the other symptom or other diagnoses will be recruited to participate until the intended sample size has been accrued.

c. Consent

Eligible subjects will be approached by the Research Nurse to provide informed consent. The Research Nurse will contact eligible subjects during a clinic visit. The research nurse will explain the study to invite participation, answer any questions, and verify interest in participation. If the patient agrees, written consent will be completed. Based on our experiences in this setting in conducting studies of similar burden, we estimate that 60-70% of patients approached to participate will agree. All medical oncologists will be invited to participate in this study and will provide written consent for their participation. All of the medical oncologists have provided written letters of support for the study (Section I).

d. Description of Phase I Baseline / Usual Care

This design provides a comparison of usual care with subsequent intervention phases. At present, there is no routine assessment or documentation of fatigue, and pain intensity is documented only on the nursing assistant completed form which is used only for review by the clinic nurse and for billing purposes. There is no routine documentation of pain or fatigue in the medical record. There are no pain or fatigue algorithms in routine use in the medical oncology service or elsewhere in the hospital. The BRICOH currently has one institutional policy regarding pain management which does not reference the NCCN Guidelines or treatment algorithms but rather includes only global statements about the importance of pain assessment and management. There is no institutional policy or procedure related to fatigue. There is no routine patient education for either pain or fatigue. Materials are available in the patient education center or at the Supportive Care desk in the clinic. However, it is estimated that only a very small percentage of patients seek out such information. Patients accrued in Phase I will have usual care with evaluation data collected by the Research Nurse at the time of accrual and at 1 and 3 months later. We will accrue 100 patients in each phase (see discussion of power calculations in Data Analysis Section.) Baseline data collection occurs over 3 months but

since these patients do not receive the intervention, it is possible to accrue this number of subjects. Table 2 provides a detailed comparison of care at baseline in Phase I as compared to Phases II and III.

Table 2: Comparison Across Phases

Variable	Phase I Baseline/ Usual Care	Phase II High Intensity	Phase III Low Intensity
Patient Barriers	<ul style="list-style-type: none"> • No formal patient education regarding pain or fatigue • No structured patient documentation of pain or fatigue 	<ul style="list-style-type: none"> • 4 part pain and fatigue education provided by the Research Nurse • Follow up reinforcement phone calls by the Research Nurse every 2 weeks • Patient uses “Passport” system of symptom documentation and plan 	<ul style="list-style-type: none"> • Staff assume responsibility for patient education using methods tested in Phase II
Professional Barriers	<ul style="list-style-type: none"> • No medical education routinely provided related to pain or fatigue • No algorithms used 	<ul style="list-style-type: none"> • 4 part pain and fatigue education taught by external consultants (Medical Oncologists) • Consultants reinforce/apply content in clinical rounds 	<ul style="list-style-type: none"> • Pain and fatigue continuing education provided by CME department
System Barriers	<ul style="list-style-type: none"> • Usual care with no use of algorithms addressing systems concerns. • Research nurses conduct chart audits to identify professional and system barriers but no peer review or feedback is conducted. 	<ul style="list-style-type: none"> • Algorithms based on NCCN Guidelines are developed and endorsed by Internal Advisory Board and Medical Oncologists and implemented. • Chart audit of congruence between practice and guidelines • Medical Oncologist co-investigator (Dr. Koczywas) provides peer review of pain and fatigue management audit with feedback 	<ul style="list-style-type: none"> • Algorithms and Passport Model continued by usual care staff • Chart auditing peer review continues as a department Q.I. function.

e. Development of Passport Intervention

In months one through seven, the investigators, in collaboration with our external consultants Drs. von Gunten and Smith, and our external co-investigator for fatigue, Dr. Barbara Piper, will finalize the development of the Passport system including patient education and algorithms for pain and fatigue based on the NCCN guidelines. The algorithms are intended to provide the physicians with a more operational, translated version of the evidenced-based NCCN guidelines for realistic use in clinical practice. The professional algorithms will be developed, reviewed, and revised extensively by the investigators and consultants and then presented to the Internal Advisory Committee so that we gain the interdisciplinary perspective as well as guidance by these providers throughout the institution who have the ability to view these from a system’s perspective for usual care implementation. Appendices K and L include the current version of the NCCN professional guidelines. On pages 1 – 7 of the pain guidelines and on pages 3 – 7 of the fatigue guidelines, there is content presented in an algorithm format. Our more operational algorithms will be derived from these algorithms and from the text in the remaining 20 plus pages in each guideline to design a far simpler, one to two page summary of the approach to these problems. Initial drafts of the Passport Algorithms are also included in Appendix O and P.

In addition to the algorithms, we also anticipate the development of other tools to supplement the Passport model such as perhaps laminated versions of the algorithms the physicians can carry in their lab coat pockets, wall chart revisions of pain assessment tools or algorithms to be posted in every clinic exam room and lobby and versions of the tools which can be loaded on the physicians PALM pilots. Each of these tools will be designed in collaboration with these physicians at the conclusion of the Baseline Phase (month 6) so as not to contaminate the Baseline data. Designing these in collaboration with the oncologists is seen as critical to effective systems change and to eliminate professional and system barriers.

During Phase I in months 3 - 4 the investigators will share all proposed aspects of the intervention and drafts of the algorithms, patient teaching materials and evaluation tools with our two external methods consultants, Dr. Barbara Given and Dr. Marilyn Bookbinder. Dr. Given will be asked to share her extensive research in conducting intervention studies. Dr. Bookbinder will provide her expertise in institutional change and quality improvement related to pain and fatigue. These consultations will be conducted by phone and by written correspondence.

Training of the Research Nurses

Two Research Nurses will be responsible for performing the patient teaching intervention and collecting evaluation data. Dr. Ferrell will oversee and supervise the training of the two Research Nurses. Dr. Piper will participate in presenting the fatigue content onsite in month 1. The training of the Research Nurses is detailed as follows: During month 1 we will hire the Research Nurses and begin their training in delivering the four pain and fatigue patient education sessions. The Research Nurses will use case studies and BRI/COH staff to practice teaching the four sessions. During months 6 – 7 the Research Nurses will conduct practice teaching sessions with simulated patients (COH staff) to gain experience in delivering the education. The PI and at least one co-investigator will observe all practice sessions and evaluate these teaching sessions using the Tape Monitoring Checklist (Appendix C). These mock sessions will be tape-recorded and disbursed among the investigators for feedback and critique. Beginning at month 8 until completion of accrual, the Research Nurse responsible for providing the education sessions will tape record the first education session per month in order to continually monitor and ensure the quality and consistency of the education sessions. The Principal Investigator will review all audiotaped sessions. In addition, one co-investigator will review the monthly audiotaped sessions. After listening to the audiotaped session, each investigator will complete the Tape Monitoring Checklist and provide feedback to the Research Nurses. Comments for the Research Nurses and those to be reviewed with the Research Team will also be documented using the Checklist.

f. Description of the Phase II (High Intensity) Intervention

Professional Education

Following the Baseline phase, we will prepare for Phase II, the “High Intensity Passport phase” with the intensive education of the medical oncology staff, targeted primarily for the physicians as the research subjects. All medical oncologists will be required to attend four hours of training on use of the algorithms. These four hours will parallel the four components of patient education of fatigue assessment, fatigue management, pain assessment, and pain management. The education will occur over a period of two weeks in sessions to be planned far enough in advance and in usual staff meeting designated time to ensure complete participation. Dr. Leong, Acting Chair of the department, and Dr. Morgan, as Associate Chair and Director of the Medical Oncology Department and Chief of Staff, wholeheartedly endorses this project and are co investigators. Drs. Ferrell, Leong, and Morgan have held two meetings with the medical oncology department to describe this project and have the cooperation of all the medical oncologists. Individual letters of support from each medical oncologist in the institution are included in Section I. CME’s will be provided for those classes, another significant incentive given that education in pain or palliative care is now required by California for physician license renewal in 2006 and none of the oncologists have met the renewal criteria. The sessions will also be videotaped so that if a physician misses a session, it can be viewed by the medical oncologist with the P.I.

The educational sessions will be taught by Dr. Charles von Gunten for pain management content and Dr. Tom Smith for fatigue management content. Dr. von Gunten will present pain assessment on the first day of his visit and will participate for the remainder of the day with clinical rounds with the medical oncologists. On day 2 of his visit, he will present a section on pain management and devote the rest of the day to clinical rounds and discussion with individual oncologists about patient pain problems. Both sessions will be based directly on the NCCN Pain Guidelines. The following week, Dr. Tom Smith will come to COH to provide the education on fatigue management. He will also present the first day session on fatigue assessment and the

second day on fatigue management with the remainder of the two days devoted to clinical rounds and interactions with the medical oncologists. Dr. Ferrell and Dr. Piper (by phone) will also participate in these two training sessions to reinforce the application of the guidelines to the Passport system and study design. They will also present the results of the Baseline Phase including the patient and professional knowledge and the chart audits in order to identify specific barriers to be addressed. The investigators have designed the educational sessions to be provided by the medical oncologist’s physician peers which is recognized as being most effective for medical education.

The outcome measures are described below across all phases. The data collected at Baseline will describe the usual care and document the congruence of patient care at COH related to pain and fatigue with the NCCN Guidelines. Patient data are collected at 1 and 3 months post accrual in Phase I and post intervention in Phases II and III. Chart Audits for professional and systems outcomes are collected at every encounter (see Outcomes Section). The Research Nurses will conduct the chart audits then present the audit data to Dr. Koczywas (once that subject is complete at 3 months) who will then meet with the medical oncologist to provide this peer review feedback. Dr. Morgan will provide the peer review feedback for patients cared for by Dr. Koczywas.

Patient Education

The content of the education sessions will be derived from the NCCN patient guidelines. Sessions will be limited to 30-40 minutes each and an outline of the sessions is included in Table 3 with phone call reinforcement described in Table 4. The “Passport” concept is an innovative and creative model where patients are given a “Passport to Comfort” with components such as “destination” for their goals of pain and comfort, a “flight plan” to document the suggested treatments for their symptoms “comfortable seats”, “security check” etc. The patient “traveler” is instructed to bring the Passport to each visit. A draft design of the patient Passport is included in Appendix S.

Subjects in Phase II receive 4 individual teaching visits. Session one focuses on Pain Assessment. Session two focuses on Pain Management, Session three on Fatigue Assessment and session four on Fatigue Management. The four education sessions are scheduled one time a week for four weeks based on the rationale that this will provide relatively condensed and focused time for education but will also provide time for the patient to address each aspect of symptom concerns. Appendices M and N include a copy of the NCCN Consumer Guidelines for Pain and Fatigue. These will be used as the written materials to guide the teaching. Each patient will receive a copy of these materials in their Passport folder. Appendix S also includes an outline of each of the 4 teaching sessions with references to the page numbers in the guidelines. The teaching sessions and follow up evaluation will occur at the site of the patient’s preference, either in the patient’s home or in the clinic. If at the clinic, a private and quiet room will be used. Based on our previous patient education projects we anticipate approximately 50% of sessions to occur in the clinic and 50% to occur in the home setting. The sessions are anticipated to last approximately 30-40 minutes with a breakdown described in Table 3. The variation on the length of each education session is dependent upon the complexity of the subject’s pain or fatigue. This time limit of 30-40 minutes is selected based on the investigators previous studies and in recognition of potential subject burden. We also have selected this brief time in order to create a realistic time to accommodate the constraints of clinical practice. We considered carefully the option of individual vs. group teaching but selected individual teaching for this first intervention phase in order to best capture the barriers and to best evaluate patients needs and the education. In Phase III as the patient education is transferred to the usual care staff, group education may be developed.

Table 3: Outline of Education Sessions

Each Session	<ul style="list-style-type: none"> ▪ <i>General introduction about the purpose and discuss bi-weekly telephone support.</i> ▪ <i>Elicit subject's continued willingness to participate in teaching and evaluation.</i> ▪ <i>Subjects are encouraged to use their Passport and carry it to future clinical encounters and to contact the Research Nurse with any further questions.</i> ▪ <i>Schedule next session with subject.</i>
Session #1	<ul style="list-style-type: none"> ▪ <i>Verify completion of and collect baseline questionnaires prior to teaching.</i> ▪ <i>Give copy of the Passport and teaching materials.</i> ▪ <i>Provide teaching about <u>pain assessment</u>.</i> ▪ <i>Subjects are guided through discussing barriers to <u>pain assessment and communication</u>.</i> ▪ <i>Subjects are guided to develop a plan of action for the identified barriers to pain assessment and record in their Passport.</i>

Session #2	<ul style="list-style-type: none"> Provide teaching about <u>pain management</u>. Subjects are guided through discussing barriers to <u>pain relief</u>. Subjects are guided to develop a plan of action for the identified barriers to <u>pain management</u> and record in their Passport.
Session #3	<ul style="list-style-type: none"> Provide teaching about <u>fatigue assessment</u>. Subjects are guided through discussing barriers to <u>fatigue assessment and communication</u>. Subjects are guided to develop a plan of action for the identified barriers to <u>fatigue assessment</u> and record in their Passport.
Session #4	<ul style="list-style-type: none"> Provide teaching about <u>fatigue management</u>. Subjects are guided through discussing barriers to <u>fatigue management</u>. Subjects are guided to develop a plan of action for the identified barriers to <u>fatigue management</u> and record in their Passport.

After the teaching which occurs in the first four weeks, subjects will receive a phone call from the Research Nurse throughout the remaining 3 months of Phase II every other week, except in those weeks that a evaluation session is scheduled (see study schema in Table 4). These calls are intended primarily to maintain the patient’s interest and participation in the study and to decrease attrition. Table 5 provides details of the follow-up phone support.

Table 4: Outline of Follow-Up Phone Support

Bi-Weekly telephone support for Subjects	<ul style="list-style-type: none"> The Research Nurse will contact each subject bi-weekly to reinforce the Passport model and follow-up on further concerns/problems. The Research Nurse will reinforce the focus on eliminating barriers to pain and fatigue assessment and management. If during the follow-up calls there is an indication the Passport is not being used, the nurse will attempt to discover why, and develop an appropriate plan to increase the subject involvement.
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Table 5: Study Schema by Week

Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Activity	-Accrual - Pre-Pain Evaluation Assessment Teaching	-Pain Management Teaching	-Fatigue Assessment Teaching	-Fatigue Management Teaching		Call		1 mo. post eval.		Call		Call		Call

The research team will meet every other week to include all of the investigators as described above. Dr. Ferrell will lead these meetings. During these meetings, the Research Nurses will briefly review each patient accrued to provide an opportunity for input from the interdisciplinary investigators regarding the teaching sessions. Dr. Piper will participate in these meetings by conference call.

Accrual for Phases II and III.

100 subjects are to be accrued in Phases II and III over 16 months in each phase. This requires 6.25 patients accrued per month. The BRICOH has 72 new patients each month with the diagnosis specific for this study as well as even greater numbers of current patients. Each patient in these phases require 7 visits (1 accrual and pre-evaluation, 4 teaching, 2 follow-up evaluations) thus 700 patient visits (43 per month during the accrual months).

g. Description of Phase III Low Intensity Passport Intervention

Phase III is designed to provide a more realistic implementation of the Passport model and interventions to reduce barriers to pain and fatigue management that could be disseminated to other cancer care settings. Table 2 identifies the key components of this phase. In the Low Intensity phase, the investigators are involved with the provision of less direct professional education, patient education, and system intervention, but rather in this phase the investigators are transferring the continuation of the Passport model and reducing barriers into the usual care system to sustain improved pain and fatigue management.

In months 33-34, the investigators will conduct education of all medical oncology staff (medical, nursing, rehabilitation, dietary, social work, psycho oncology) to share the experience of Phase II and to disseminate the findings into their usual care. The involvement and support of the Internal Advisory Group

which includes representation across these departments will be beneficial in this process. The Internal Advisory Group will meet every other month, co-led by Dr. Ferrell and Dr. Koczywas.

6. Outcomes and Evaluations

Data are collected for all subjects at the time of accrual prior to delivering the education and then at 1 and 3 months post intervention. The 3 month follow up time period and the evaluation points are based on review of other intervention studies as well as our own experiences with breast cancer, bone marrow transplant, and the “Simultaneous Care” study. The first data collection time point (month 1) is designed to capture immediate effects and outcomes of the intervention. The second data collection time point (month 3) is intended to capture the full effect of the education as it is anticipated that many outcomes such as referral to a dietician or rehabilitation specialist, joining a support group, etc. may not be captured in the immediate one-month follow-up. This time point also will capture the longer lasting effects of the education as well as retention of the information and continued use of the Passport model. The teaching contacts will be provided consistently by one Research Nurse and the three follow up evaluation visits will be conducted by the other Research Nurse to diminish potential subject bias in reporting evaluation data.

a. Patient Outcomes The patient self report instruments have been carefully selected to provide data for answering the study aims and minimizing respondent burden in this population. It takes approximately 30-40 minutes to complete the questionnaires. If the patient is too fatigued or is experiencing pain and can't complete the set of questions, arrangements will be made to divide the evaluation into 2 separate sessions.

i) Demographic and Treatment Data (Appendix D)--This form has evolved over the past 6 years of studies by the investigators as described above. The form is designed to capture key disease and treatment variables of importance in describing the population and for analysis of influencing variables. The form is completed by the subject and items regarding stage, pathology and treatment are verified in the medical record by the Research Nurse. The tool will be administered to subjects at accrual and the Research Nurse will reassess the status of subjects' most current treatments, medications, and other supportive care services at the follow up evaluation visits.

ii) QOL—Patient Tool (Appendix E) is a 45-item multidimensional tool encompassing four domains of Physical, Psychological, Social, and Spiritual Well Being based on the QOL conceptual model developed by the investigators^(94,95). Internal consistency reliability is .77- .89 for the four sub scales and .93 overall. Measures of validity of the generic patient version include content validity with the FACT instrument ($r = .78$), and factor analysis. The instrument has demonstrated construct validity by discriminating between known groups. There were significant differences in overall QOL and subscale scores with regard to years of survival and with regard to disease status. Patients who were recently diagnosed or experiencing recurrence had significantly lower QOL than those with no evidence of disease. The 45 QOL items were factor analyzed using principal axis factoring with a varimax rotation. A four factor solution was identified, confirming the multidimensional QOL model theorized by the investigators. The QOL tool is extremely valuable as a comprehensive, multidimensional tool which significantly limits subject burden. The QOL tool assesses multiple symptoms including fatigue, appetite, pain, sleep change, constipation, nausea, anxiety and depression. Psychological issues such as depression are known to influence physical symptoms such as pain and fatigue. Thus the single item measures of related symptoms can be used for analyzing these relationships as described in the analysis section⁽⁴¹⁾.

iii) Audit Tool (Appendix Q) Audit tools have been drafted to compare the care recommended in the NCCN Pain and Fatigue guidelines with the actual care provided. The audit tools will be pilot tested and refined in month 1. The audit tools capture adherence with the guidelines as well as the ability to overcome barriers consistent with the study model. The audits will be conducted by the Research Nurses with results provided to Dr. Koczywas who will share the findings with the primary oncologist caring for the patient during Phase II. During Phase I, the audits are conducted by the Research Nurse but no peer review or feedback occurs during this Baseline phase.

iv) Barriers Questionnaire (BQ II) (Appendix F)

The BQ was developed by Ward and colleagues⁽⁹⁶⁾ to measure the extent to which individuals with cancer reported barriers to pain management. The tool addresses eight important concerns: (1) fear of addiction, (2) concerns about tolerance, (3) concerns about side effects, (4) fatalism about experiencing uncontrolled cancer pain, (5) desire to be a “good” patient, (6) fear of distracting one's physician from treating the disease, (7) concern that pain meant disease progression, and (8) fear of injections. More recently, Gunnarsdottir and colleagues⁽⁹⁷⁾ revised the BQ to reflect changes in pain management practices and input from patients in

studies using the BQ. The revision dropped two subscales: (1) concern that pain meant disease progression, and (2) fear of injections, and added two new subscales: (1) fear that the analgesics impair the immune system, and (2) concern that analgesics may block ability to monitor illness symptoms. Significant ($t=-2.16$, $p<0.05$) construct validity and a factor analysis revealed four factors: (1) physiologic effects, (2) fatalism, (3) communication and (4) harmful effect. The BQ-II total had an internal consistency reliability coefficient alpha of 0.89 ($n=134$), and a range of 0.75-0.85 for the subscales. The mean score for the total scale was 1.53 ($SD=0.73$).

v) Piper Fatigue Scale (Appendix G) The revised Piper Fatigue Scale (PFS) is a 22-item, self-report scale that measures four dimensions of subjective fatigue (behavioral/severity [6-items], sensory [5-items], cognitive/mood [6-items], and affective meaning [5-items]) confirmed by principal axes factor analysis with oblique rotation. Evidence for moderate to strong concurrent and discriminant validity estimates also exist. Internal consistency (Cronbach's alpha) reliabilities remain strong (0.83-0.97) for the PFS and its subscales across various cultural samples, languages, and diagnostic groups. Each item is measured on a 0-10 numeric rating scale with opposing word anchors such as "not at all" to "a great deal." Items are summed and divided by the total number of scale items to keep scores on the 0-10 scaling. Higher scores indicate more fatigue. Mild (1-3), moderate (4-6) and severe (7-10) levels have been validated with declines in physical functioning (MOS-SF-36 Physical Functioning subscale & PFS-Total scores). Five additional items, not included in the scale's scoring, assess perceived causes, relief measures, additional fatigue descriptors, presence of other symptoms, and duration of fatigue. It takes patients 3-5 minutes to complete the scale ^(89,90,98).

vi) Pain and Fatigue Knowledge Tools (Appendix H)

The primary outcome of the study is increased knowledge and attitudes by patients about pain and fatigue management. The teaching materials are the NCCN Patient version of the guidelines, thus the investigators have drafted knowledge tools that are derived from the guidelines ^(2,3) and these will be used as an assessment of the patient's knowledge and beliefs at baseline, and then at one and three-months following accrual. The version in the Appendix includes a key identifying the correct answer and also cross-references the page number in the guidelines that corresponds with the content in the text. These tools have been drafted to be at a low literacy level and to be a low-burden instrument.

vii) Patient Satisfaction Tool (Appendix T)

A brief tool has been developed to measure patient satisfaction with the Passport Model and to address study aims and research questions. It is completed at the final evaluation (month 3) in Phases II and III.

b. Professional (Physician) Outcomes

i) A Demographic Data Tool (Appendix I) includes characteristics of the physician including, age, education, length of time in oncology, etc.

ii) Pain and Fatigue Knowledge Tools (Appendix J). The investigators have created drafts of knowledge tools based on the NCCN pain and fatigue algorithms to parallel the tools described above for patients. These tools are also included in Appendix J and include a key of the correct answers as well as the page of the guidelines containing this content.

iii) Chart Audit Tool. A major outcome of professional and system barriers will also be reassessment of the congruence between the patient's actual care as compared to the NCCN Guidelines for pain and fatigue. Appendices K & L include copies of the professional guidelines for pain and fatigue. Appendices O & P include drafts of simplified algorithms and Appendix Q includes from attached page the chart audit forms which will be used to assess the guidelines describing evidenced based care with actual care. The audit form is used as an outcome measure across each of the three phases, but is also used as a method of providing peer feedback by Dr. Koczywas as co investigator with her medical oncology colleagues in Phase II and continued in Phase III.

iv) Provider Satisfaction. Physician satisfaction with the Passport Model/intervention will be assessed at the conclusion of Phase II, and Phase III. This evaluation will be conducted through staff focus groups conducted by Drs. Ferrell and Koczywas using a guide similar to the Patient Satisfaction Tool.

c. System Outcomes

Chart audits will identify system outcomes. Audit tools will be completed on each encounter with the patient in the clinic setting over their 4 months duration in the study. As there will be variability in the frequency of visits, analysis of the chart data will be averaged (see analysis section). Also, if the patient is seen in urgent care or is admitted to the inpatient areas, the chart audit tool will be completed in order to determine if the pain and fatigue management is continued. This aspect of continuing care is established as an important system

barrier. The COH investigators have extensive experience in chart audits and monitoring patient encounters across settings, having conducted similar monitoring with over 300 surgical oncology patients in their ongoing palliative surgery research⁽¹⁰⁰⁾. Appendix Q includes the chart audit draft tools.

d. Dissemination of Outcomes

In addition to usual dissemination by presentations and publications, the investigators will host in the final month (60) a CME conference on Reducing Barriers to Pain and Fatigue. The conference will be conducted by the CME Department (which Dr. Morgan directs) in collaboration with the investigators. The target audience will be community oncology programs with direct mailing to the list maintained by the CME department. A modest registration fee will be charged to cover materials and meals. The conference will include usual post course evaluation required for CME.

7. Data Analysis/Treatment and Monitoring

a. Sample Size Calculation and Power Analysis

SPSS Sample Power and the PASS power calculation software were used to estimate sample size for this study. There are 11 hypotheses to be tested in this study that require adequate power for detection of significant differences. The study will only be powered for the patient outcomes, because the number of physicians is small and finite, and there is only one system. In Aim 1, the pain and fatigue items from the QOL tool, the Piper Fatigue Scale score, and the BQII (H1.1) will be tested using a 3x2 multivariate repeated measures analysis of variance (MANOVA), in which the between groups variables are the four scores at pre, 1-, and 3-months, and the within groups variable is group (Baseline vs High Intensity). Sample size needs were based upon means and standard deviations available in Dr. Ferrell’s and Dr. Piper’s studies, as well as upon discriminating group difference scores for the BQII⁽⁹⁷⁾. Table 6 shows sample sizes required to detect significance in the interaction effect of this statistical design at a power of approximately .80, with a two-tailed alpha of .05 at various effect sizes, assuming a correlation of 0.7 between repeated measures.

H1.2 regarding QOL, will be tested using a 3x2 repeated measures ANOVA. Power analysis was based on findings of the PI’s previous studies. Table 6 shows sample sizes required to detect significance in the interaction effect of this statistical design at a power of approximately .80, with a two-tailed alpha of .05 at various effect sizes.

Table 6. Sample size for Aim 1

Effect Size—>	.2	.3	.4	.5
H1.1 & H4.1 Pain and Fatigue items, BQII, & Piper Fatigue Scale	160 (80 per group)	100 (50 per group)	80 (40 per group)	70 (35 per group)
H1.2 & &4.2 QOL	110 (55 per group)	100 (50 per group)	60 (30 per group)	30 (15 per group)
H1.3a & H4.3 Knowledge	160 (80 per group)	90 (45 per group)	60 (30 per group)	50 (25 per group)
H1.4 & H4.4 Adherence (Pain &/or Fatigue Chart Audit)	140 (70 per group)	110 (55 per group)	84 (42 per group)	40 (20 per group)

H1.3a will be tested using two McNemar tests of change over time (pre to 1-month and pre to 3-months) for categorical variables, one for each group (Baseline and High Intensity). Patients’ knowledge will be classified as mastery (80% correct or above) or non-mastery (less than 80% correct) at each measurement period. Assuming that at 3 months, approximately 30% of Baseline subjects will exhibit mastery, as compared to 60% of High Intensity subjects, Table 6 shows the number of subjects per group required to detect significance of this statistical design at a power of approximately .80, with a two-tailed alpha of .025 (controlling for inflation of experimentwise error).

H1.4 will be tested using a hierarchical multivariate 3x2 repeated measures ANOVA. One dependent variable will be the pain audit score and the other will be the fatigue audit score. Scores will be a percent of possible clinical management recorded. For example, the highest possible score for the pain audit is 40, but the denominator will be adjusted for each patient to include only those clinical behaviors that are appropriate for that patient according to NCCN guidelines. Using a numerator of clinical behaviors actually recorded (coded “Yes”), a percent of appropriate behaviors will be computed. It was roughly estimated that about 30%

of clinical behaviors would be observed in the records of the baseline group, and about 60% in the records of patients in the High Intensity intervention. Table 6 shows sample sizes required to detect significance in the interaction effect of this statistical design at a power of approximately .80, with a two-tailed alpha of .05. The sample sizes estimated for hypotheses in Aim 1 will apply to Aim 4 hypotheses, which are analogous null hypotheses (hypotheses of no difference between High Intensity and Low Intensity groups).

Aim 2: The power analysis for Aim 2 was conducted using regression analysis as the statistical design, controlling for depression as a possible confounding variable⁽⁹¹⁾, and then regressing each dependent variable on the five demographic variables, three clinical variables, and group membership (Baseline vs. High Intensity) in three additional blocks. For H2.1, the alpha was set at .01 because of the four dependent variables, and thus it demanded the largest sample size. Assuming that 5% of the variance will be accounted for by depression, 10% of the variance by pre and 1-month scores, 12% by demographic and intervening variables, and 5% by group membership, 96 subjects will be required to achieve 80% power.

In summary, 100 subjects will be recruited for each of the three study groups, with the expectation of retaining 80% or a total of 80 subjects per group, stratified in equal proportions for pain or fatigue exceeding a score 3 on a 0-10 scale. This sample size should be ample to test all hypotheses in the study.

b. Handling missing data and analysis

Patterns of missing data will be reported to the investigator and study coordinator so that data collection procedures can be improved, if necessary. Subjects with missing scale or subscale scores will be compared with subjects having non-missing scores to determine whether there is any bias underlying the missing data (i.e., whether missing data are random or can be accounted for by other variables). For data that are missing completely at random (MCAR) or missing at random (MAR), the EM (estimation-maximization) method of imputation will be used to replace missing values (Musil, Warner, Yobas, and Jones, 2002), using the SPSS Replace Missing Values procedure.

Data management is a key issue in any prospective study in which accrual of subjects is incremental, especially when there are multiple instruments. The study coordinator, who will review each instrument for completeness and correct any errors, as well as supervise data collectors regarding methods of achieving complete data, will conduct initial data management. Subjects will be numbered according with a unique ID number and group number. The study coordinator will keep the list of subject names and ID numbers in a locked file cabinet. Each completed instrument will be numbered appropriately, copied, and the copies filed in a locked cabinet, while originals are transferred to the statistician for data analysis. Instrument scores and sub-scale scores will be computed according to authors' instructions. Preliminary analyses will include tabulation of standard summary statistics of demographic characteristics, disease/treatment characteristics, and all scores at each time period. Distributions of quantitative variables will be evaluated for normality, and normalizing transformations will be computed if necessary. Internal consistency reliability analysis will be performed on these subjects' scores for the QOL, BQII, Piper Fatigue Scale, knowledge tests, and chart audit scores using Cronbach's alpha.

c. Handling missing encounters

The four education sessions are essential to the intervention, and patients will be rescheduled if any sessions are missed. Educational session attendance during the High Intensity phase will be monitored and an intention to treat analysis will be conducted regardless of attendance. CME attendance, and patient teaching about assessment and management of pain and fatigue, as well as continued use of the Passport Model will be monitored during the Low Intensity phase, but again, intention to treat analyses are planned.

d. Dose of intervention and variation

This study includes three intervention dosages: no dose (Phase I, baseline), high dose (Phase II) and low dose (Phase III). Three different groups of subjects will each receive one of the dosages. Two different dose comparisons (Baseline vs. High Intensity, and High Intensity vs. Low Intensity) are of interest, and are presented, therefore, as different Aims. As described in Section C above, attendance or participation in various levels and types of education, and use of the Passport Model will be monitored, particularly so that a test a group differences on participation can be conducted as one method of confirming fidelity of the intervention dosages.

e. Analysis written by study aim

For study Aim 1, H1.1, the correlation among the four dependent variables will be examined to determine whether a 3x2 repeated measures MANOVA or multiple ANOVAs will be performed. The within

subjects variables are the pre, 1- and 3-month measures of pain, fatigue, Piper Fatigue Scale score and the BQII. The between subject measure is the group (Baseline or High Intensity).

H1.2 will be a 3x2 repeated measures ANOVA using the composite QOL score at pre, 1- and 3-months as the within subjects variables and group as the between subjects variable.

H1.3a will be analyzed by first calculating percent correct for each knowledge test, and then classifying knowledge as mastery (80% or higher) or non-mastery (less than 80% correct). This will be done both at pre, 1-month and at 3-months, and a McNemar test of differences will be conducted for both the Baseline and the High Intensity groups (comparing pre classification to 1-month and then to 3-month classifications). A p-value of $\leq .025$ for each test will be considered significant to control for inflation of experimentwise error.

H1.3b will involve two McNemar tests (pre vs. 1 month and pre vs. 3 months) for the professionals during the High Intensity phase, after classifying the knowledge data as mastery or non-mastery. For H1.4, a ratio score representing the percent of behaviors that the patient and physician exhibited of those that were appropriate under NCCN guidelines will be computed for pain assessment and management, and for fatigue assessment and management. H1.3 will be analyzed as a 3x2 hierarchical MANOVA if the pain and fatigue chart audit scores are moderately to highly correlated. If correlations are low, two separate ANOVAs will be used. Type I sums of squares will be used to control for the variance of physician before examining the time by group interaction. If the main effect for physician is significant, an exploratory analysis of scores aggregated by physicians will be conducted.

For study Aim 2, preliminary analyses will consist of two-way repeated measures ANOVAs for each dependent variable (PFS, BQII, QOL pain item, QOL fatigue item, composite QOL score, patient knowledge of pain, and patient knowledge of fatigue), by each demographic and clinical variable. For this study aim, knowledge data will be computed as a ratio variable of percent correct behaviors (Yes responses divided by the total appropriate behaviors for each patient). The significant demographic and clinical variables will then be used as predictors of the 3-month dependent variables using either hierarchical regression analysis (described below), or structural equation modeling of time dependent latent variables (QOL and Knowledge) using AMOS software (if sample size is adequate). In the case of regression analysis, for each hypothesis, one or more hierarchical linear regression analyses will be conducted using the Bonferroni procedure to control experimentwise error. Each 3-month dependent variable will be regressed on depression (a single item in the QOL tool), then on pre scores, 1-month scores, and demographic and clinical variables found to be significant in preliminary analyses, and finally on group (comparing Baseline with the High Intensity group, dummy coded).

The study Aim 3 analysis will be made up of descriptive statistics of data collected in patients' intervention evaluation forms. In addition, Research Question 3.3 will be answered by conducting one-way ANOVAs on Passport Model satisfaction by each of the nine demographic and clinical variables. All analyses for Study Aim 4 will parallel analyses for Study Aim 1, except that the two groups being compared will be the High Intensity and the Low Intensity groups.

E. Human Subjects

1. Protection of Human Subjects

- a. **Sources of Research Materials** - All data collection is limited to written surveys used widely in cancer research and selected to minimize subject burden.
- b. **Potential Risks** – All contacts with the patient will be arranged at the patient's convenience and in the setting preferred (clinic or home visit). The only potential risk involved is emotional distress in discussing sensitive QOL concerns. The time required for data collection is approximately 30-40 minutes and for the four teaching sessions is 30-40 minutes. Teaching and data collection will be done by two oncology nurses who will be closely supported by the P.I. The nurses will be trained in assessing and responding to any subject distress. The nurses will be trained by the P.I. and will meet weekly with her. The first teaching session each month will be tape recorded and reviewed by the P.I. for each nurse.
- c. **Characteristics, Inclusion of Women, Minorities and Children** - The sample will include 300 subjects. Subjects in Phase I receive usual care and in Phases II and III an intervention of the Passport education, written materials and reinforcement phone calls. Subjects in the study are men and women and we anticipate 35% ethnic minorities with the major group being Hispanic. Additional effort will be made to recruit minorities by the Research Nurses in review of available subjects. The previous QOL studies by the investigators have demonstrated significant inclusion of underrepresented groups. Children are not included as the study is limited to patients 18 years and older cared for by adult medical oncology service.

2. Adequacy of Protection Against Risks

- a. Recruitment and Informed Consent – Patients will be identified through review of the patient schedule in the clinic. The Research Nurse will verify eligibility with the physician and contact the patient in the clinic or by phone. If the patient agrees to know more about the study, the Research Nurse will make an appointment with the patient to explain the study, provide opportunity for questions and obtain written informed consent.
- b. Protection Against Risks – Participation in the study is voluntary and all data are kept anonymous and confidential. Subject's names are not included on data instruments and all data are maintained in the PI's locked files.

3. Potential Benefits of the Proposed Research to the Subjects and Others

Subjects are hypothesized to benefit from the Passport intervention. Benefits may include improved pain and fatigue management, recognition of other QOL concerns, enhanced communication of these concerns and benefits rendered from the educational materials and teaching sessions. Privacy will be provided for all teaching and data collection.

4. Importance Of The Knowledge To Be Gained – Knowledge to be gained from this study may potentially benefit present and future cancer survivors by addressing symptoms and QOL concerns. Previous research has documented the significant need for attention to pain and fatigue. The knowledge from this study will also likely be applicable to other symptoms in cancer patients.

Data and Safety Monitoring Plan--This protocol is approved by the City of Hope Cancer Protocol Research Monitoring Committee and the Institutional Review Board. Institutional procedures for quality control, data management and analysis are followed. Appendix C includes the Teaching Monitoring Checklist adapted from previous City of Hope studies that will be used in this project.

Vital Research will be concerned with protecting the integrity of the sampling frame database, and of the process and outcome data for this study. We will password protect the database containing the sampling frame of potentially eligible subjects from both sites. Only one researcher at Vital Research, Dr. Gwen Uman, will have access to the sampling database. At the end of the accrual period, the sampling database will be provided on CD-ROM to the P.I. and will be removed from the Vital Research hard drive and all back-up tapes. Vital Research will receive copies of data from the P.I., coded with identification number, group number, and devoid of subject names. The outcome data, process data, and quality control data will be stored in a locked cabinet, and returned to the P.I. after entry and data auditing. The statistician will analyze quality control data and provide ongoing feedback to the P.I. to ensure intervention quality.

The external consultants for the proposed study, and Dr. Ferrell will review the protocol quarterly to determine whether application of the model is causing increased psychological distress or decreased QOL among subjects in Phases II and III. If psychological distress increases significantly from one quarter to the next, the Research Nurses will be debriefed to assess possible causes. This will allow for early stopping of the study, if indicated. A certificate of Human Subjects Protection Education for all COH investigators and a certificate for Dr. Piper are on the following pages.

F. Vertebrate Animals

(N/A)

G. Literature Cited

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