The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Benefits of Early vs. Delayed Palliative Care to Informal Family Caregivers of Persons with Advanced Cancer: Outcomes from the ENABLE III Randomized Controlled Trial

Dionne-Odom, et al

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Early vs. Later Palliative Cancer Care: Clinical and Biobehavioral Outcomes

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Abstract

Background:
In 2008, cancer claimed more than 565,000 American lives -1,500 people a day. Palliative care strives to improve quality of life (QOL) and to prevent "bad deaths" by providing expert, interdisciplinary care to manage the effects of disease and treatment. Effective end-of-life (EOL) care depends upon proactive, patient-centered interventions to prepare patients and families for the challenges of terminal illness. We were able to demonstrate the feasibility and efficacy of a concurrent oncology palliative care (COPC) intervention in improving quality of life and mood; however, a number of gaps in our knowledge remain. The proposed study is a logical extension of that work.

Specific Aims/Study Design
The **primary aims** of this randomized controlled clinical trial are to determine whether a COPC intervention (introduced immediately or 12 weeks after diagnosis) can improve clinical outcomes (survival, quality of life, mood, symptom intensity) and end-of-life (EOL) care (as judged through chart review and proxy after death interview) for patients with advanced cancer and their caregivers (as measured by caregiver burden, quality of life, and grief outcomes). We will also examine potential mechanisms, mediators, and moderators whereby the intervention has its effects.

Exploratory aims will investigate the feasibility of recruiting patients from a community-based practice and those with less common solid tumors and hematological malignancies from all sites, the patterns of stress and immune biomarkers, and the biomarkers' relationship to QOL, mood, symptoms, and survival.

Methods
Patients will be randomized to begin the intervention either immediately or 12 weeks after a new diagnosis of advanced or recurrent . **This phone-based intervention consists of:** 1) an Advanced Practice Palliative Care Nurse Interventionist instituting 1a) a 6-session manualized patient curriculum- Charting Your Course, 1b) a 3-session manualized, caregiver curriculum- the COPE program, and 1c) on-going patient and caregiver follow up; and 2) Palliative Care Team Comprehensive Assessment & Management.

Patients will complete baseline questionnaires about QOL, depression, and symptoms. Caregivers will complete questionnaires on personality traits, depression, caregiver burden, quality of life, and grief. Questionnaires will be completed by patients and caregivers at 6, 12, 18, and 24 weeks, and every 12 weeks thereafter until the patients' death or study completion. Patient, caregiver, and provider satisfaction with the intervention will be evaluated at the community-based practice. For participants' who die in hospital or with hospice or home care, a chart review will be conducted to document the circumstances around the participants' death, including location of death. Two-three months after a participant's death, caregivers will be asked to complete an after death questionnaire about the quality of care the patient received while dying. Saliva and blood samples will be collected at baseline and 12 and 24 weeks from patients who choose to participate in the sub-study to examine biomarkers of stress and immune function. Quantitative and qualitative analyses will be performed to determine clinical, biological, and caregiver outcomes of this early vs. later entry palliative care intervention. This study will also provide pilot feasibility data regarding recruitment of community-based oncology practice patients in preparation for submission of a larger community-based palliative care intervention study.

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1.0 INTRODUCTION

In 2008, cancer claimed more than 565,000 American lives -1,500 people a day.[1] As most cancers are not immediately fatal, patients will experience months to years of life-limiting illness with a relatively brief period of decline prior to death.[2-5] Two Institute of Medicine (IOM) reports detailed unnecessary suffering resulting from inadequacies of the current health care system in providing end of life (EOL) care.[6, 7] Although it is imperative to improve patients' care at EOL, *preventing* the use of unwanted, aggressive interventions may have a greater overall impact on the quality of EOL care. As a result**,** international oncology and palliative care expert panels [7, 15-17] have recommended early introduction of **concurrent oncology palliative care (COPC)** to improve patients' quality of life and EOL care. The central thrust of COPC is to ensure that patient values, preferences, and treatment goals guide care through the EOL. Few NCI-designated cancer centers have systematically developed an empirically-based COPC intervention, especially one that is tailored to an ambulatory, rural population. Our clinical and research interdisciplinary teams represent diverse disciplines and we are poised to address these questions via a scientifically rigorous **Early vs. Later entry RCT** with ***3 primary specific aims, 1 secondary aim, and 3 exploratory aims***:

2.0 OBJECTIVES

OBJECTIVE 1) PRIMARY SPECIFIC AIMS

Compare Early (at diagnosis) vs. Later (12 weeks post-enrollment) entry COPC in persons with any newly-diagnosed or recurrent terminal cancer with respect to:

2.1) Patients' quality of living and dying.

a. Quality of living assessments will include quality of life (QOL), mood, and symptom intensity measures.

-We hypothesize that Early entry patients will report higher QOL and mood and lower symptom intensity at assessments 12, 24, and 36 weeks after enrollment and the assessments prior to death compared with Later entry patients.

b. Quality of dying assessments include EOL care chart review and proxy report.

-*We hypothesize that Early entry patients will have better EOL care compared with Later entry patients.*

2.2) Caregiver burden, QOL and grief outcomes.

-We hypothesize that Early entry caregivers will report reduced burden and higher QOL during the illness trajectory and a lower incidence of "complicated grief" during bereavement compared with Later entry caregivers.

2.3) Patients' survival.

-We hypothesize that Early entry patients will have longer overall survival compared with Later entry patients.

OBJECTIVE 2: SECONDARY AIMS

2.4) Explore mediating mechanisms and moderators of the COPC intervention.

-We hypothesize that participant-reported COPC intervention components (the "5As" as measured by Patient Assessment of Chronic Illness Care [PACIC] survey) 12 weeks post-intervention will mediate COPC intervention effect on study outcomes (QOL, mood, symptom intensity, and survival).

-We hypothesize that selected psychosocial and demographic factors will moderate intervention effectiveness.

OBJECTIVE 3.EXPLORATORY AIMS

Based on our previous study demonstrating COPC intervention feasibility in 4 common advanced cancers we will:

2.5) Determine the feasibility of enrolling patients with less common "poor prognosis" solid tumors (e.g. brain) and hematologic malignancies and their caregivers.

-We hypothesize that patients with less common "poor prognosis" solid tumors (e.g. brain) and hematologic malignancies and their caregivers will participate in the COPC intervention.

Based on a putative biobehavioral paradigm whereby psychosocial interventions may affect solid tumor patients' cancer-associated chronic stress components of the psychoneuroimmune (PNI) axis, we will:

2.6) Explore patterns of stress (diurnal salivary and plasma cortisol) and immune biomarkers (lymphocyte subsets and cytokines) biomarkers at baseline, 12, and 24 weeks after intervention.

-We hypothesize that stabilized or improved biomarkers of stress and immune function will be evident after Early and Later entry intervention participation.

2.7) Examine the relations among QOL, mood, symptoms, survival, stress and immune biomarkers.

-We hypothesize that higher QOL and mood, lower symptom intensity, and longer survival will be associated with stable or improved stress and immune biomarkers (e.g. normal plasma cortisol and diurnal salivary cortisol variability, lymphocyte subsets and cytokines)

2.8) Determine the feasibility of enrolling patients with newly diagnosed, advanced stage cancer and a caregiver who receive their care from a community-based private oncology practice into a COPC intevention.

-We hypothesize that at least 50%of community practice patients with newlydiagnosed, advanced stage cancer and a caregiver will enroll and complete the study.)

3.0 ELIGIBILITIY CRITERIA

3. 1 Patient Inclusion Criteria

1) Able to speak and understand English
2) Over age 18
3) NEW diagnosis, recurrence, or progression of an advanced stage cancer within approximately -60 days of the date the patient was informed of the diagnosis by his/her oncology clinician
4) Estimated survival of 2 years or less.
5) Diagnosed with an advanced stage solid tumor such as one of the following:
    - Lung Cancer: Stage IIIB or IV non-small cell, or extensive stage small cell
    - Breast Cancer: Stage IV with poor prognostic indicators including by not limited to:
        - a) > 2 cytotoxic regimens for MBC,
        - ,
        - b) Diagnosis of MBC less than or equal to 12 months since completion of adjuvant or neo-adjuvant treatment
        - c) Triple negative disease (ER/PR and HER -)
        - d) Parenchymal brain mets and/or carcinomatous meningitis
    - Gastrointestinal Cancers: Unresectable stage III or IV
    - Genitourinary Cancers: Stage IV (for prostate cancer inclusion is limited to persons with hormone refractory prostate cancer)
    - Brain Cancer: Unresectable; Grade IV
    - Melanoma, Stage IV
    - Hematologic Malignancies

        -Leukemia (e.g. AML, ALL, CML, CLL) –
        advanced stage, treatment refractory, poor prognosis cell type or chromosomal abnormalities, “older age”

        -Lymphoma-
        Stage IV or treatment refractory Hodgkin’s disease or non-Hodgkin’s lymphoma

        -Multiple Myeloma –
        elevated β_2-microglobulin, albumin <3.5, PCLI >1%, CRP >6µg/mL, elevated LDH, plasmablastic morphology, abnormal. chromosome 13.

3.2 Patient Exclusion Criteria

1) Dementia or significant confusion (Impaired cognitive status as indicated by a score of 3 or less on the Callahan six-item cognitive screening tool [18])
2) Axis I psychiatric diagnosis of severe mental illness (DSM-IV) (e.g. schizophrenia, bipolar disorder, or active substance use disorder)
3) Patients will not be excluded if they do not identify a caregiver
4) Prior involvement with palliative care service within the last year.
5) Minimum predicted survival of less than 12 weeks (3 months)

BIOMARKER SUB-STUDY

Inclusion:

1) Only patients with lung, breast, GI, GU are eligible

Exclusion:

1) Receiving chronic steroid hormones or unable to schedule specimen collection distant from chemotherapy from steroid pre-medications
2) Unable to come to NCCC for specimen collection times.

3.3 Caregiver Inclusion Criteria

1) Able to read and understand English
2) Anyone identified by the patient as "a person who knows you well & is involved in your medical care".

3.4 Caregiver Exclusion Criteria

Caregiver Exclusion Criteria

1) Unwilling to participate in study.

4.0 REGISTRATION

4.1 Recruitment

All NCCC sites: Patients will be screened for eligibility by an RA attending/reviewing weekly disease management group (DMG) [tumor board] and through weekly contact at the 4 outreach sites (Manchester, Keene, Nashua, St. Johnsbury, VT) . All newly-diagnosed patients are presented at a DMG. On the Lebanon campus there are 10 DMGs that meet weekly or bi-weekly: thoracic (lung and esophageal cancer), gastrointestinal, genitor-urinary, breast, melanoma, neuro-oncology, head and neck, gynecological, lymphoma, and hematology. Clinical research assistants attend these groups or review patient presentation lists to identify patients to screen for eligibility.

Eligible newly recurrent disease patients may not be presented at a DMG, therefore recruitment is done by reviewing providers' weekly schedules for eligible patients. If so, personal contact is made with the clinician or a brightly colored trial informational sheet is provided with the clinical paperwork that the clinician normally reviews prior to seeing the patient. This reminds them to mention the option of a clinical trial. Research assistants may also be present during 'high volume' clinics of potentially eligible patients so that they may see the patient during their clinic visit. If this is not possible then the clinician will provide written information on the study and ask the patient if the research assistant can contact them by phone to discuss the study. Study specific brochures are also placed in all examination rooms and waiting areas of the respective clinics. Also all of the cancer center clinics' web-sites actively advertise available clinical trials and patients can self refer.

VAMC: The VA-based research coordinator screens all VA oncology clinic (including chemotherapy clinic) appointments (for the next working day), and all inpatient admissions on a daily basis. Screening consists of medical record review for eligibility for any open clinical trials. After record review, the coordinator meets with the VAMC study PI (Dr. Lambert) to review patient appointment lists/admissions and to confirm which patients should be approached for study consideration. After patients are identified, either the PI or the study coordinator approaches the patient to present information about the study. The consent discussion takes place with the PI or coordinator (or both).

All recruitment procedures and materials are IRB-approved and HIPPA compliant.

Mountainview Medical Center: The site-based staff will review clinician schedules weekly for patients that may be eligible for the trial. Based on our prior trials we anticipate 50% accrual for the target of 50 patients and their caregivers per year, or 100 patients/caregivers over the course of the 2 year study.

St. Joseph Hospital, Nashua, New Hampshire. The site-based staff will review clinician schedules weekly for patients that may be eligible for the trial as per the study subsite agreement.

4.2 Enrollment

At NCCC patients who are interested in learning more about the study will be contacted either in person or by phone by a study RA who will describe the study, screen for exclusion criteria, and obtain signed informed consent. VAMC patients who are eligible and interested in learning more about the study will be contacted in person by the VA clinical research administrator who will describe the study in detail, screen for exclusion criteria, and obtain signed informed consent.

At the 3 NCCC outreach sites, Mountainview Medical, and St. Joseph Hospital patients who are eligible and interested in learning more about the study will be contacted in-person or by telephone by the study RA at their site. The site RA will describe the study in detail, screen for exclusion criteria, and obtain informed consent. The RA will invite the potential participant to the respective study site for this interaction but will complete the process over the telephone if travel to the respective site is impractical or inconvenient for the participant.

Patients who provide informed consent will be asked to complete the baseline measures (see Outcome Measures) and to identify a person who knows them well and would be willing to participate in the Caregiver component of the intervention. Caregivers will then have the study explained in detail and a separate informed consent will be obtained using the same procedures as described above.

Patients must complete the baseline interview within 21 days of signing the consent or they will be considered a screen failure. Patients who complete the baseline interview will be randomized to Early or Later-entry-palliative care.

Patients who screen fail or who withdraw from the study after baseline, will receive a letter thanking them for their interest and offering them the option to allow access to their medical record for collection of data on their health status and treatments during the course of the study. Two copies of a PHI consent (one for patient/one to sign and return) and a postage-paid return envelope will be included in the mailing. Patients will only receive one mailing and only patients who return a signed PHI consent within 21 days of the date mailed will have their charts abstracted.

Patients and caregivers will then be asked to complete questionnaires at 6, 12, 18, and 24 weeks and every 12 weeks thereafter. Caregivers will also be asked to complete the After Death Interview and the Inventory of Complicated Grief (ICG) if the patient should die during the course of the study. Patient is still eligible if no caregiver is identified or if the caregiver fails the mental status test.

Chart Audit Study: If a patient chooses not to enroll in the study (i.e., does not want to participate in the intervention) then we will ask the patient if he or she would allow us to periodically audit his or her medical record to obtain information on treatment

and survival status. If agreeable, we will ask the patient to sign a form granting permission to access his or her protected health information (Authorization to Collect Protected Health Information) and will conduct the chart audit upon the same schedule as all other participants (see section 8 for specifics on information collected from the medical record).

5.0 TREATMENT PLAN

5.1 Intervention Protocol and Procedures

The Intervention will include <u>two major components:</u>

1) Advanced Practice Palliative Care Nurse Interventionist instituting a phone-based: a) Charting Your Course-Patient Curriculum (6-session manualized); b) COPE Caregiver Curriculum (3 session manualized) and c) ongoing contact as determined by the Palliative Care Team assessment/plan; and

2) Comprehensive Palliative Care Team Assessment & Management Plan.

5.1.a: Advanced Practice Palliative Nurse Interventionist & <u>Patient/Caregiver Curriculums</u>.

The primary goal is for the Nurse Interventionist to be the consistent person who interacts with the patient and caregiver over time and across settings (home, clinic, hospital, hospice, etc). The Nurse Interventionist will begin by interacting with patients and caregivers using: a) Charting Your Course-Patient Curriculum (6-session manualized); b) COPE Caregiver Curriculum (3-session manualized) and 3) on-going coordination of a palliative care plan in the cancer center and the patients' community. The CYC Patient Manual and the "Home Care Guide for Advanced Cancer" Caregiver guidebook will be mailed to the patient/caregiver home(s) prior to initiating the calls. The patient/caregiver will be asked to review components of these manuals to prepare for each session**.**

In delivering this content the Nurse Interventionist uses the counseling approach of the CCM '5As' (ask, advise, agree, assist, and arrange). Sessions begin with 'Ask/Assessing' patients current situation using the Distress Thermometer developed by Holland (See Appendix),[19] 'advising' or providing patient counseling in areas of need; 'agreeing' entails collaborative agreement about setting realistic goals; 'assisting' or coaching the patient regarding lifestyle changes, and 'arranging' for follow up or accessing other resources. The goal of this approach is to enhance: patient activation, decision support, goal setting, problem-solving, and coordination.

The Nurse Interventionist will begin each patient session by evaluating and documenting the participants level of distress using the Distress Thermometer which asks patients to rate their level of distress on a 0 (no distress) to 10 (extreme distress) scale and to identify their sources of distress in 5 areas: 1) Practical Problems (e.g., work/school); 2) Family Problems; 3) Emotional Problems; 4) Spiritual / Religious Concerns; and 5) Physical Problems.

CYC Module 1: This module focuses on patient activation, problem solving (PS) skills and goal setting.[20] It also includes the problem-solving attitude COPE (described in CG Curriculum below). PS teaches the person how to break down problems and identify barriers to overcoming a problem, and uses a systematic approach to develop novel

solutions proceeding in a six-step sequence. [20, 21],.[22],.[23 24] Goal setting, developing an action plan and making a commitment to follow through, is a process called Behavioral Activation. Behavioral Activation interventions (BA) do not necessarily require problem solving in order to be effective. However, if there are barriers to achieving a goal then PS may complement this approach; thus combined BA with PS (BAPS).

CYC Module 2: Module 2 focuses on care coordination and education about symptom self-care management. We will encourage the use of a worksheet to record their symptoms, strategies for relief and strategies to effectively communicate about these issues with clinicians. Information about many symptoms (e.g., pain, nausea, etc.) is provided through an accompanying handbook called, "Caring for the Patient with Cancer at Home" (published by the American Cancer Society). The module also includes information on healthy behaviors such as smoking cessation, exercise, and nutrition.

CYC Module 3: This Module builds on the problem solving session with a specific focus on decision support and communication skills. The content includes taking care of one's self, building a support network, talking with clinicians, and basics of effective communication. This module also introduces the use of evidence-based patient decision aids (ptDA): a) the Ottawa Personal Decision Guide (OPDG) [25, 26] a 2-page decision aid that helps people to assess their decision making needs, plan the next steps, and track their progress in decision making and b) "Looking Ahead: Choices for Medical Care When You Are Seriously Ill" DVD. This 45 minute shared decision-making program (produced by Health Dialog), focuses on palliative care issues and making treatment choices and advance care planning. Participants will be encouraged to view the DVD following this session and we will solicit feedback about the DVD to begin session 4. During this session the patient will be coached though an actual decision they are facing or might face using the OPDG to any decisions they may be facing in their medical care. Advance care planning content will also be discussed during this session if the participant is not familiar with this content.

CYC Modules 4, 5, 6: The last 3 weekly sessions will cover the Outlook intervention.[27] This is a manualized, 3-session psychosocial intervention that enhances palliative care for patients with advanced disease by promoting discussion and supportive counseling of issues pertinent to life completion.[28] Pilot testing has shown improvements in functional status, anxiety, depression, and preparation for end of life. Each session is approximately 45 minutes in length. In the first session patients engage in life review. In the second, patients are invited to speak about issues such as regret, forgiveness and things left undone. In the final session, patients are asked to explore issues of heritage and legacy.

Patient Curriculum - Charting Your Course (CYC)
Module 1 (week 1) Behavioral Activation/Problem Solving
Module 2 (week 2) Symptom Management
Module 3 (week 3) Decision-making, Communication & Support
Module 4 (week 4) Life Accomplishments & Goals and Life Review
Module 5 (week 5) Accomplishments and Future Goals/Forgiveness
Module 6 (week 6) Unfinished Business/Leaving a Legacy
Monthly follow up

COPE-Caregiver Curriculum

Using McMillan's COPE model,[29, 30] (Table 2) all caregivers will participate in a 3-session problem-solvingintervention concurrent with the patient.. As the ENABLE II patient intervention focused on improving problem-solving, the addition of a caregiver component with similar goals is ideal. Caregivers will be taught the problem-solving tools necessary to deal with problems faced when caring for a person with serious illness. This approach gives caregivers an opportunity to build skills and discuss individualized solutions to common problems that can arise at EOL. The COPE acronym reflects the essential intervention components: Creativity, Optimism, Planning, and Expert Information. Similar to CYC, caregivers receive a workbook entitled "Home Care Guide for Advanced Cancer" that covers the program content

Caregiver Curriculum - COPE
Module 1 (week 1) Problem Solving & Self Care (COPE principles)
Module 2 (week 2) Review progress with last week's problem Identify next problem (Focus on **Symptom Management**) Apply COPE principles to problem
Module 3 (week 3) Review progress with last week's problem Identify next problem (Focus on **Decision-Making**) Apply COPE principles to problem Engage in closure
Monthly follow up
Bereavement Follow Up & Interview 8-12 weeks after patient's death

On-going Patient/Caregiver Follow Up

The Nurse Interventionist will be responsible for coordinating on-going palliative within the cancer/medical center and within the patients' community. This will be determined following the PCT Assessment (described below) This may include referrals for psychological or spiritual counseling, social work consultation, financial guidance, home health, palliative care or hospice services, and bereavement counseling for the family. The goal is to ensure continuity of care as the patient interacts with different providers / systems. Therefore, the Nurse Interventionist will be a vital link between these services and the oncology treatment team.

5.2 Palliative Care Team Comprehensive Assessment & Plan. As soon as feasible the patients in the Early-entry group will be scheduled for an outpatient consultation visit with the Palliative Care Team Clinician. Patients randomized to the Later-entry group will have this appointment scheduled 12 weeks from enrollment. This initial assessment is conducted by the PCT Advanced Registered Nurse Practitioner (ARNP). The ARNP scope of practice allows for the diagnosis and management of common symptoms of patients with advanced illness. The ARNP has a DEA number and per NH law may prescribe Schedule II opioids as well as other medications according to an exclusionary formulary developed and maintained by the State Board of Nursing. The ARNP assessment includes chart review of existing medical records, patient interview using a standardized consultation format, and physical exam as indicated. If the patient wishes, their caregiver is invited to participate in this initial assessment. A plan of care including follow up for any problems that have been identified is then developed with the patient, appropriate prescriptions for medications may be provided, and further psychosocial care may be recommended. The plan of care is documented in the electronic medical record and e-mailed in real time to the Nurse Interventionist and other clinicians as appropriate. The PCT secretary will schedule follow up appointments with the PCT as determined by the patient and PCT clinician. Each week the ARNP formally presents new patients to the full palliative care interdisciplinary team (IDT). Each member of the team provides input into the plan of care. Individual appointments or contacts with individual IDT members may be planned. The attending Palliative Medicine physician is available at all times to the ARNP for assistance. The Attending MD is on-call 24 hours/day, 7 days per week to respond to patient issues. The

PCT is automatically notified if any patient on whom they have consulted is admitted to the DHMC hospital. PCT members will make contact with the patient's admitting physician and patient to determine if the patient would be served by inpatient PCT consultation and follow up. Arrangements will be made with local palliative care resources for patients to have their initial PCT Assessment visit.

All study participants will continue to utilize all oncology services (routine visits with their oncologists and oncology team) .Throughout this time the PCT complements oncology services with added attention to symptom assessment and surveillance, shared decision making and clarifying goals of care, advance care planning, crisis prevention and early crisis management, emotional, social and spiritual aspects of adjustment to illness, including issues of life completion.

5.3. General Procedures of the Intervention

The Nurse Interventionist will contact the patient and caregiver (if enrolled) within a week following enrollment (for participant-caregiver dyad randomized to EARLY entry) or at week 12 (for participant-caregiver dyad randomized to LATER entry) to introduce themselves and to determine a convenient time to conduct the phone-based CYC and COPE sessions (described above). It is anticipated that patient CYC session 1 and caregiver COPE session 1 will be scheduled during the week following enrollment and the remaining sessions will be scheduled for the subsequent consecutive weeks. After the completion of these calls, phone contact will be continued at a minimum of once per month, but can be more frequent if needed.

In addition to providing the patient and caregiver sessions, the Nurse Interventionist will provide feedback to the PCT and/or patient's oncology team about issues requiring attention (e.g., unrelieved pain) or referrals to community resources (e.g., spiritual counselor). All prescriptions and other direct care medical interventions will be directed by the PCT or oncology team as is currently the practice. For example, if it has been determined that the PCT will take primary responsibility for prescribing opioids and a change in pain medication is needed then the PCT will prescribe. However if the patient's oncology team wishes to have PCT consultation only and maintain primary prescriptive authority then they will be responsible for prescribing.

Patients in the Later Entry group will be receiving their oncology care from the hematology/oncology physician / nurse practitioner team for the first 12 weeks of the study. However if at any time prior to the scheduled patient caregiver intervention entry at 12 weeks the oncology team or the patient or family member wish access to the PCT this will be arranged at the earliest possible appointment. In this case the Nurse Interventionist and Patient/ Caregiver Curriculums components of the intervention will still begin at the 12 week post baseline timeframe. These participants will not be removed from the study; however the earlier referral will be noted for purposes of data analysis.

6.0 POTENTIAL TOXICITY, DOSE MODIFICATIONS, AND MANAGEMENT

NA

7.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

NA

8.0 REQUIRED DATA, DATA COLLECTION AND RECRUITMENT

NA

8.1 Data collection

All patient and caregiver subjective questionnaire data will be collected via oral interview.

Alternatively patients and caregivers may request paper and pencil versions of the questionnaires. This data will then be entered by the RA into the main data base. We will monitor and identify which method was used and perform analyses to determine if there are systematic missing data or other issues based on method of completing data collection. Although there is some concern when multiple methods of data collection are used the need for flexibility in obtaining study-related assessments in this very ill population outweighs the small chance that data collection method could influence our results. [31]

Study Variable and Aims	Measure	Schedule	Data Source
Primary Aims			
1.a Compare Patient (PT) QOL , Mood, Symptom intensity	FACIT-pal, CES-D, QUAL-E	Baseline, 6,12,18, 24 wks & every 12 weeks till death	Phone interview
1.b. Compare quality of EOL care	EOL Care Data Form QODD	Time of death chart review 12 weeks after death	Patient medical record (MR) Caregiver phone interview
2. Determine Caregiver (CG) QOL, Burden and Grief	C-QOL, MBCBS, CES-D, FACT-Spiritual, ICG	Baseline, 6,12,18 , 24wks & every 12 weeks till death 3 months after patient death	CG phone interview
3. Survival	Vital Status	Baseline till death or study completion	PT/CG/Clinician/MR review
Secondary Aim			
1. Mediating Mechanisms (5As) Patient Activation, Decision Support, Goal Setting, Problem Solving, Coordination	PACIC	Baseline, 6,12,18, 24 wks & every 12 weeks till death	Phone interview
Moderators Decision Control & Tx Goals Self-efficacy (CBI) Optimism (LOT Revised) Coping Style (COPE) Social Support (MSPSS) **Demographics:** Age, Education, Marital Status, Income, Insurance, Religion, Rural, Smoking status, alcohol use, function (KPS) & comoribidities (Charslon score)	 Control Pref. & Tx Goals CBI Lot-R COPE MSPSS Caregivers only: Personality (BFI)	Baseline Only	Phone interview
Exploratory Aims			
1. Feasibility of enrolling poor prognosis ca (e.g. brain) & heme ca. malignancies	Enrollment figures (numerator) vs. eligible subjects (denominator)	Monthly enrollment figures	CA Registry Study Database
2. Stress biomarker	Cortisol Plasma & Salivary diurnal variation	Baseline, 12 & 24 weeks	Saliva & plasma
Immune biomarkers	CD3, CD4, CD8, CD 19, CD 16/56 IL-6, TNFalpha, IL-1beta, MCP-1, IL-10, IL-13	Baseline, 12 & 24 weeks	Plasma-flow cytometry Plasma-Luminex assay
3. QOL, Symptom, Mood, Survival, Immune, Stress Biomarker	As above	As above	FACIT-Pal, CESD, QUAL=E scores, biomarker salivary and plasma values
4. Patient, caregiver, provider satisfaction with intervention	2-item participant satisfaction survey	1-2 weeks post-intervention	Rural Breast Cancer Satisfaction Survey

8.1.1Subjective Measures

Patient and caregiver assessments will be completed at baseline, 6, 12, 18, 24 weeks after enrollment, and then every 12 weeks until death. EOL Care chart review will be completed by the RA based on site specific documentation (or if patient died at home without home health agency support we will interview a family member at time of ADI). Measures of

Moderators will be collected at baseline only The After-Death Interview and Inventory of Complicated Grief are caregiver phone surveys completed 3 months after a patients' death.

Primary Outcome Measures (Specific Aim 1a-Quality of living):

Functional Assessment of Chronic Illness Therapy-Palliative Care (FACIT-Pal): The FACIT-Pal consists of the FACIT-G, a general measure of quality of life, and the FACIT-Pal, which assesses issues specifically relevant to palliative care.[32, 33] The FACIT-G is a 28-item questionnaire which provides a total score as well as four subscale scores: physical, social/family, emotional, and functional well-being. The FACIT-Pal includes 19 additional concerns relevant to patients at EOL. Evidence supports the reliability, validity, and sensitivity of the instrument and its ability to detect change over time.[34]

Quality of Life at End of Life (QUAL-E).[35]The QUAL-E is a 21-item tool measuring quality of life in critically ill populations. Factor analysis reveals four domains of the tool: life completion, symptoms impact, relationship with healthcare provider, and preparation for end of life. Validity was supported by associations with other measures of quality of life, spirituality, social support and decision-making. Test-retest reliability was adequate at a one week interval.

Center for Epidemiological Study- Depression (CES-D). The CES-D is a 20-item measure of depressive symptoms that has been widely used in epidemiological studies of depression.[36, 37] Participants are asked to rate how frequently they have experienced each symptom on a 4 point scale ranging from "Rarely or none of the time" to "Most or all of the time." The CES-D has been widely studied and has strong validity and reliability.[38]

Distress Thermometer. (Nurse Interventionists will administer at the beginning of CYC sessions only.) The Distress Thermometer (DT) is a visual analogue scale with scores from 0 (no distress) to 10 (extreme distress) and a midpoint anchor labeled "moderate distress"[19, 39]. Scores correlate with other measures of clinically significant distress and have been shown to increase as cancer-related problems increase.[40] NCCN guidelines recommend considering a score of > 5 as being a clinically significant elevation. In addition, scores greater than 4 on the DT results in specificity and sensitivity levels of 82-84% and 61-82% for diagnosing major depressive disorder.[41, 42]

8.2 Quality of EOL Care (Specific Aim 1b)

EOL Care Data Collection Form: This form is used to collect information about the quality of EOL care and circumstances surrounding the last 48 hours of life for patients who die in hospital, nursing home, or home. It was originally developed for the Study to Understand Prognoses and Preferences of Treatment.[43] It has been modified, adapted, and found to have good interrater reliability for use in multiple research and quality improvement projects.[44, 45] A single form is used for all 3 settings (home, hospital, nursing home), however items that do not pertain to a setting are omitted if not site specific(e.g. admitting unit for a home patient. There are 14 demographic items (e.g. date of death, hospital admission/discharge data), 4 advance directives/DNR items, 14 medical interventions items (e.g. ventilator, feeding tube, etc.), 14 symptom items (e.g. pain, dyspnea, etc.), and 6 family/emotional support items (e.g. chaplain offered, family emotional needs addressed, etc.)

Quality of Dying and Death Measure (QODD).[46] The QODD is a structured interview conducted with a family member to measure the quality of a patient's last week or mpnth of

life. The interview assesses the caregiver's perception of patient symptoms, preferences, and satisfaction with care. The tool has been validated for use with adults whose family member did not suffer a sudden death. Higher scores indicate higher quality of death and dying.

8.3 Caregiver Outcome Measures (Specific Aim 2)

Quality of Life- Cancer- (QOL-C) The CQOL-C is a 35-item self-report measure of quality of life for caregivers of patients with cancer. Items measure impact of caregiving on caregiver's emotional and spiritual well-being, their relationship with their loved one, sleep, daily life, and family life. Each item is answered using a 5-point Likert-type scale (not at all; a little bit; somewhat; quite a bit; very much) and a composite score is created by summing each response. This tool has previously been used to measure the effect of a problem-solving intervention on caregivers' QOL.[30] This tool is reliable, with an internal consistency of 0.91 and a test-retest reliability of 0.95.[47] It is associated with but independent of well-validated measures of physical health, depression, and caregiver burden.[47] This tool will provide data as to whether the intervention has an impact on caregivers' QOL.

Montgomery Borgatta Caregiver Burden Scale (MBCBS). The MBCBS is a 14-item self-report measure of caregiver burden.[48, 49] The tool has three subscales, providing scores for objective burden, subjective demand burden, and subjective stress burden. Each subscale has shown strong internal reliability, averaging around 0.88, 0.75, and 0.84, respectively. The subscales also appear psychometrically valid; objective burden is positively correlated with having to provide more help to patient, whereas the subjective scales are related to demographic characteristics (i.e. factors that affect one's experience of objective burden).[49]

Center for Epidemiological Study- Depression (CES-D). The CES-D is a 20-item measure of depressive symptoms that has been widely used in epidemiological studies of depression.[36, 37] Participants are asked to rate how frequently they have experienced each symptom on a 4 point scale ranging from "Rarely or none of the time" to "Most or all of the time." The CES-D has been widely studied and has strong validity and reliability.[38]

Functional Assessment of Chronic Illness Therapy – Spiritual Module (FACIT-Sp).[50]The FACT-Sp is a 12 item measure of spiritual well-being developed for persons with chronic illness. The tool offers a total score and a score for each of two subscales: (1) sense of meaning and peace and (2) role of faith in illness (only sense of meaning and peace subscale to be sued). Adequate reliability and validity was demonstrated in samples of adults with cancer.

Prigerson Inventory of Complicated Grief-Short form (ICG-SF) The ICG-SF is a reliable and validated 18-item survey of complicated grief.[51] The scoring algorithm can be used in a dichotomous fashion to identify persons at risk of complicated grief or in a continuous fashion to indicate the degree of grief expressed by the respondent. As we did with the ENABLE RCT, we will embed the ICG-R-SF within the ADI interview to provide evidence to explore any moderating effect of grief and complicated grief on caregiver outcomes

8.4 Mediating Mechanisms and Moderating Variables (Secondary Aim)

At baseline we will collect a one time measure of the following to serve as baseline measures of potential mediators or moderators of intervention effect. Each of the potential factors has support in cancer literature

Mediators

Patient Assessment of Chronic Illness Care (PACIC) The PACIC was developed as a patient reported measure of the CCM "5As" of health counseling behaviors (ask, advise, agree, assist, and arrange).[52, 53] It consists of 20 items assessing five scale constructs: patient activation, delivery system/ decision support, goal setting/tailoring, problem solving/contextual, follow-up/ coordination. It has good psychometric properties with Cronbach alpha ranging from 0.78 to 0.90, and the test retest validity, estimated by the intracluster correlation coefficient (ICC), was at least 0.77.[54] Assuming that the PACIC-5A reflects clinicians CCM prescribed behaviors, the tool measures the patients perception of the extent to which they received care that contains the core elements of activation, support, goal setting, assistance and a frequent follow up. Content validity procedures, developed by Lynn,[55] will be used to establish validity in the palliative care setting prior to use in this study. The tool will be evaluated by a palliative care expert clinician panel and it will be pilot-tested with 5 palliative patients who are not part of the study.

Moderators

Control Preferences Scale (CPS). The CPS was developed to measure a construct that emerged from a grounded theory of how treatment decisions are made among people with life-threatening illnesses. It measures the construct "the degree of control an individual wants to assume when decisions are being made about medical treatment". [56] The original version, adapted from a 5 level to 3 level scale by Sepucha et al. [57] measures preference for sharing decisions equally with doctor, having control with input from doctor, wanting complete control or wanting doctor to have complete control.

Treatment Goals and Outcomes- This 7 item scale was developed by Sepucha et al to measure patients perceptions of the purpose of their cancer treatments, bother from treatments, and whether they are making treatment choices. Responses are measured on a 0-10 point visual analog scale, and the purpose of treatment item has 3 responses ranging from "extending life as long as possible", 'relieving pain even if it means not living as long" , and unsure. It is reported to have good content validity and reliability but psychometrics have not yet been published.[58]

Cancer Behavior Inventory (CBI) The revised Cancer Behavior Inventory (CBI) [59, 60] is a 33-item questionnaire specifically designed to assess self-efficacy in coping with cancer. It is comprised of 7 sub-components as verified by factor analysis (maintenance of activity and independence; seeking and understanding medical information; stress management; coping with treatment-related side-effects; accepting cancer/maintaining positive attitude; affective regulation; seeking support). Both the total scale and subscales have been shown to have good psychometric properties. [59, 60]

Life Orientation Test – Revised (LOT-R) Optimism-pessimism has been related to adaptation to cancer.[61-63] The Life Orientation Test – Revised (LOT-R)[64] is a 10-item measure of dispositional optimism-pessimism. Along with the earlier version of the LOT, a variety of studies have supported the psychometric properties of the scale both in terms of reliability and convergent, discriminant, and construct validity in a variety of languages (e.g., French, Japanese, Spanish, Chinese, and Portuguese). At the same time, several studies have demonstrated the utility of distinguishing optimism and pessimism subscales within the LOT and LOT-R[65, 66]and this distinction will be incorporated into the present research.

Multidimensional Scale of Perceived Social Support (MSPSS). The MSPSS is a 12-item self-report measure to assess perceived adequacy of social support using a 7-point scale from very strongly disagree to very strongly agree.[67] Item scores are averaged for a

total ranging from 1 to 7. It provides a summary score as well as three subtype scores for perceived adequacy of support from a significant other, family, and friends. Internal and test-retest reliability are high and validity has been demonstrated in cancer patients.[68]

The Brief Cope The Brief Cope has 28 items that combine to form 14 subscales of coping reactions. Items are rated on a 4-point scale (0-3) according to how much they pertain to the person. The internal consistency for each subscale is at or well above minimally acceptable levels (alpha coefficients ranging from .50-.90). It has been shown to have excellent psychometric properties among breast cancer patients undergoing treatment including reliability coefficients that were actually higher than those observed for the full scale as well as evidence of good construct, convergent and concurrent criterion validity.

The Big Five Inventory (BFI). This measure of personality will be used for caregivers only. The Big Five Inventory (BFI) is a 44-item scale measuring Neuroticism, Extraversion, Openness to New Experience, Agreeableness, and Conscientiousness.[69] The BFI is a self-administered questionnaire with a five-point Likert response format that provides a detailed assessment of normal personality. It has shown ample internal consistency, temporal stability, and convergent and divergent validity.[69-71] The BFI has been used in at least one study of cancer caregivers; Cronbach's alpha ranged from 0.63 to 0.84 across the factors.[72]

Satisfaction Measures

Participant Satisfaction – At Mountainview Medical Center, a two-item post-intervention satisfaction survey will be asked of patients, caregivers, and providers. 1. How would you rate your level of satisfaction with participating in this study? and 2. How would you rate your level of overall satisfaction with the ENABLE intervention (education materials and phone calls with the nurse)? Patients will answer on a 5 point Likert scale from “very satisfied” to “very dissatisfied”.

8.6 Objective Measures

Biomarkers of Stress and Immune Function-Blood and Saliva Samples

All participants who consent to biomarker sub-study will have blood and saliva collection at the time period as close to each of the subjective measurement time points as feasible.

Salivary cortisol. The RA who obtains consent will determine if the subject has a scheduled blood draw within the coming week. If so then the subject will be provided with pre-labeled salivettes and verbal and written instructions for proper specimen collection. Subject will be instructed not to brush teeth, smoke, eat or drink for 15 minutes prior to specimen collection. The proper timing and storage of specimens will be stressed in order to obtain high quality specimens. The subject will be instructed to collect saliva at 8:00 and 21:00 on the day preceding the blood draw. The subject will be instructed to place the salivettes in the provided bag and store the specimens in their refrigerator until coming to clinic. When they arrive in clinic they will give the specimens to the Laboratory Tech who will be drawing their blood. The lab tech will send the salivettes via pneumatic tube per laboratory standard specimen transport protocol to Dr. Lee’s lab for processing and storage. Subjects will be instructed to complete their questionnaires within 24 hours of specimen collection.

Blood specimens. Plasma cortisol, Lymphocyte subsets (CD3, CD4, CD8, CD 19, CD 16/56), Cytokines (IL-6, TNFalpha, IL-1beta, MCP-1, IL-10, IL-13). In our prior RCT 80% of patients were undergoing some type of cancer chemotherapy treatment. Therefore we will attempt to minimize the need for additional needle sticks by utilizing the blood specimens collected for standard of care blood tests. Lymphocyte subsets will be done from the same peripheral blood sample collected for complete blood count (CBC) and plasma cortisol will be

able to be done from the same specimen as it provided for routine chemistry tests. An additional tablesoon of blood will be needed for cytokine analysis. These specimens will be collected by the trained blood drawing technicians at the Hematology / Oncology Lab located adjacent to the Hematology / Oncology Clinic. We will attempt to have all blood specimens drawn between 0800 and 1000.

Demographic and Medical Data: Patients will be asked to complete a basic demographic questionnaire that assesses age, sex, marital status, race, occupation, education, smoking status, alcohol consumption, Charlson co-moribidity score and Karnofsky Performance Scale. Prior to first phone contact nurse-interventionist will review basic medical information including diagnosis, stage, , and treatment regimen through chart review and consultation with the primary oncologist.

Other: Resource Utilization. We will collect information about participants use of palliative care, hospice, and health care resources by self report and by medical chart review. We choose to use both methods as chart review alone might underestimate use as patients may choose to use local community facilities for some urgent care that may not be accessible to us by chart review alone. In our previous trial, as we predicted, patient estimates were slightly higher but the self- reported and chart derived figures were highly correlated. In this trial, these data will be used primarily for descriptive purposes. In conjunction with a nationally-recognized Dartmouth comparative effectiveness researcher, Dr. Anna Tosteson, we are currently determining the best model to analyze this same data from our prior RCT. We expect to have that analysis completed this summer and will use our experience to seek funding to do such an analysis with the data we will collect from this study.

Hospice / Palliative Care Referrals: We will record date of referral to palliative care team, date of PCT visits, date of hospice program referral and length of stay in each.

Advance Care Planning: We will ask patient about presence of an advance directive document(s) and we will also conduct a medical chart review to determine whether the documents are available to clinicians.

Days in hospital, Intensive Care Unit, Emergency Department Visits: we will track days in hospital, days in the intensive care unit, and emergency room visits. These data will be collected by patient self-report at each 3 month assessment and confirmed by medical record review.

Location of Death: for subjects who die during the study we will identify this through surviving caregiver at time of bereavement follow up call or at time of afterdeath interview or medical record review if noted

9.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

NA

10.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

NA

11.0 ADVERSE DRUG REACTION REPORTING

NA

12.0 ANCILLARY THERAPY

NA

13.0 STATISTICAL CONSIDERATIONS

13.1 Randomization

Patients will be randomized equally into the late and early treatment groups using computer-generated treatment assignments. Randomization will be blocked using random block sizes, and will be stratified by diagnosis and by center (NCCC or VA Medical Center). Only lung, GI, breast, and GU patients will be invited to participate in the biomarker sub-study, and they will be randomized accordingly. Participants from all sites other than the VA will be randomized as part of NCCC. Participants from Mountainview Medical Center will be randomized as a separate site.

13.2 Statistical Analyses

13.2a Primary Study Aims

The primary study endpoints are: FACIT-Pal-Total Score, QUAL-E-Total Score, and Mood (CES-D) as measured at 6, 12,18, 24 and 36 weeks after randomization. All three sets of variables, together with background and demographics, Karnosfky Performance Scale and Charlson co-morbidity score, will be assessed at baseline. Data analysis will begin with descriptive statistics for patient characteristics by treatment group. Distributional assumptions will be examined and transformations will be considered. The groups will be compared with respect to baseline covariates and outcomes via t-tests and chi-squared tests as appropriate. Missing data and compliance patterns will be analyzed and compared according to baseline covariates. Adjustments will be considered for baseline factors showing either imbalances or highly predictive of missing data or compliance.

The "intention to treat" philosophy will be employed for all treatment comparisons. That is, all randomized patients will be included in primary comparisons, regardless of whether the patient actually received the randomly assigned treatment. Data analyses will focus on a) primary **patient-reported outcome (PRO)** measures (QOL, Mood, Symptom Intensity scores); b) caregiver burden, QOL and grief outcomes; c) potential mediators of the impact of the intervention (PACIC); and d) theorized moderators of the effectiveness of the intervention.

1) **Patients' quality of living and dying**

   a. **Quality of living as measured by quality of life (QOL), mood, and symptom intensity.**

-We hypothesize that Early entry patients will report higher QOL and mood and lower symptom intensity at the assessments 12, 24, 36 weeks following enrollment and the assessments prior to death compared with later entry patients.

We will conduct two sets of longitudinal, intention-to-treat analyses of the primary study endpoints for all participants with baseline and one or more follow-up assessments using mixed effects modeling for repeated measures to examine (a) the relative impact of the Early and Later interventions in the year after enrollment and (b) its effects on the assessments proximal to the time to death. All calculations will be performed using SAS 9.1. Two-sided p-values less than 0.05 will be considered statistically significant.

The primary PRO variables will be compared at three points in time after baseline/enrollment: 12, 24 and 36 weeks post randomization. Initial analyses will be conducted on PRO measures within an intention-to-treat framework using linear mixed random and fixed effects models (LMM) to test the effect of the Early intervention relative to Later intervention over time. These analyses will be conducted statistically controlling for factors identified as differing between the randomized groups or being predictive of missing data or compliance. Separate analyses will be conducted to

examine the effect of the intervention at time points moving forward from baseline and, among those participants who have died, backward from time of death, as in our previously described analysis of the ENABLE II RCT.[10]

b. Quality of dying as measured by chart review and proxy report.

We hypothesize that Early entry patients will experience a better quality of death compared with Later entry patients.

For all patients who die during the study, caregiver's perception of the patients' EOL experience (QODD) and caregiver grief will be assessed 2-3 months after the patient's death. The EOL experience will be analyzed using domain 'problem' scores. The distribution of the scores will be examined, and variance stabilizing transformations will be considered. Highly skewed distributions will be subjected to a cutoff and analyzed as dichotomous data. The distributions for the outcomes will be compared on an intention-to-treat basis using t-tests or chi-squared tests depending whether they are continuous or dichotomous. Adjusted analyses will be conducted using linear or logistic regression for covariates found to be unbalanced between the treatment groups or predictive of missing data.

Other outcomes for quality of death will be extracted from chart review by the study RA, including indicators of location of death, pain, shortness of breath, and agitation. As some participants may not have caregivers willing to complete proxy interview, we will have only objective data for some subjects. Methods for dichotomous data will be used to form intent–to-treat effect estimates and adjusted analyses will be performed using binary regression models.

2) Caregiver burden, QOL and grief outcomes.

-We hypothesize that Early entry caregivers will report reduced burden and better QOL during the illness trajectory and a lower incidence of "complicated grief" during bereavement compared with Later entry caregivers.

Our primary caregiver outcomes are burden (MBCBS), care giver quality of life (CQOL-I) and grief (IGS). For each outcome, we will conduct a longitudinal, intention-to-treat analysis for all participants with baseline and one or more follow-up assessments using mixed effects modeling for repeated measures to examine (a) the impact of the intervention in the year after enrollment and (b) its effects on the assessments proximal to the time to death. This analysis will closely follow the analysis for Specific Aim 1a, with similar statistical methodology and longitudinal structure.

3) Patient survival.

-We hypothesize that early entry patients will have longer overall survival compared with later entry patients.

To examine the potential effects of the Early vs Later entry on survival, we will use a log-rank test to compare Kaplan-Meier survival curves for the two groups. We will use a Cox proportional-hazards regression modeling with an indicator of time less than one year to estimate and compare the hazard ratios (HR) for Early versus Later groups before and after one year from enrollment, corresponding to the sample median survival time.

13.3 Analysis Plan for Secondary Aim

1) Explore mediating mechanisms and moderators of the COPC intervention.

-We hypothesize that participants will report higher levels of COPC intervention behaviors (e.g. the "5As" as measured by a modified Patient Assessment of Chronic

Illness Care [PACIC] survey) at 12 weeks following the intervention and that these behaviors will mediate COPC intervention effect on study outcomes (QOL, mood, symptom intensity, and survival).
-We hypothesize that selected psychosocial and demographic factors (including Charlso Co-moribidity Index and Karnofsky Performace Scale) will moderate intervention effectiveness.

Following tests of the intervention on QOL, mood, and symptom intensity as described above, a variety of analyses will be conducted to test for potential mediators of intervention effectiveness. [73-75] As a measured by the PACIC, potential mediators of effectiveness include (a) patient involvement in care, (b) decision support and satisfaction with the care delivery system, (c) involvement in goal setting, (d) problem solving and contextual counseling, and (e) satisfaction with follow-up and coordination of care. In addition to examining mediators, we hypothesize that the effectiveness of the intervention may be moderated by individual differences previously demonstrated to be associated with well-being in cancer patients. These include Optimism, Self-efficacy, Social Support, Decision Control Preference/Treatment Goals, and Coping Style. We hypothesize that the intervention will be most effective for subjects who are relatively pessimistic, low in self-efficacy, low in social support, passive decision role, and with an Avoidant coping style.
To examine the moderating effects of such variables, they will be assessed at baseline and incorporated individually in a linear mixed model (LMM) together with and in interaction with the intervention and time indicator (measurement period). Least square means with confidence intervals will be used to summarize the moderated effects. The statistical significance of the intervention and individual moderators will be assessed in terms of the p-values associated with effects and interactions estimated within the LMM after controlling for demographic and background variables. Tests of mediation will follow recommendations in the statistical literature.[73-75]

13.4 Analyisis Plan for the Exploratory Aims

1) Determine the feasibility of enrolling patients with less common advanced cancers (e.g. brain) and hematologic malignancies and their family caregivers.

Based on the number of brain, other solid tumors, and hematologic malignancies screened and the number actually enrolled, we will consider the program feasible if we are able to recruit, randomize, and complete at least 24 weeks of observation/intervention in at least 50% of eligible subjects from each new target group.

2) Determine the feasibility of enrolling patients with newly diagnosed, advanced stage cancer and a caregiver who receive their care from a community-based oncology practice into a COPC intervention.

Based on the number of cancer patients screened and the number actually enrolled, we will consider the program feasible if we are able to recruit, randomize, and complete at least 24 weeks of observation/intervention in at least 50% of eligible subjects from the community practice. We will also tally patient, caregiver, and clinician satisfaction measures.

3) Estimate biomarkers patterns of stress.

The main outcomes of this exploratory aim will be a description of patterns of diurnal salivary and plasma cortisol concentrations, immunoassays of peripheral blood lymphocyte subsets, and plasma cytokine concentrations at baseline and at 12 and 24 weeks after enrollment. Distributions for each of these biomarkers will be examined, and normalizing transformations will be applied as necessary. Responses will be estimated for each parameter based on longitudinal mixed models, and compared according to intervention group.

Outcome	Standard deviation	Minimum detectable difference
12 weeks: 126 in each group		
FACT-Pal	17	6.0
CESD	7	2.5
ESAS	137	48.5
24 weeks: 108 in each group		
FACT-Pal	18	6.9
CESD	7	2.7
ESAS	142	54.4
36 weeks: 90 in each group		
FACT-Pal	19	8.0
CESD	8	3.4
ESAS	148	62.1

For our hypotheses to be supported, we will expect to see a decrease in absolute numbers of peripheral blood lymphocyte subsets following baseline in participants not receiving the intervention. That is at 12 weeks following baseline LATER entry subjects would have experienced the stressors of disease and treatment without the intensive phase of the intervention, and EARLY entry subjects will be at the conclusion of the intensive phase of the intervention. We would anticipate stable or lower plasma cortisol, normal salivary diurnal variation (e.g. high in am/low in pm), higher levels of lymphocyte subsets, and elevated cytokines in Early entry compared with later entry subjects.

4) Examine relationships among QOL, mood, symptoms, survival, stress, immune responses.

To assess associations with the primary outcomes, the stress and immune responses will be included in the longitudinal mixed models as time varying covariates and the associated regression coefficients and confidence intervals will be examined as measures of association. These models will include the treatment effect and baseline covariates if adjustments are deemed necessary.

For survival, the stress and immune responses will be included as time-varying covariates in Cox models including treatment and baseline covariates. Relative risk estimates will be estimated comparing hazards between quantiles of the biomarkers.

14.0 HUMAN SUBJECTS

Human Subjects Involvement and Characteristics

Participants will be 360 patients with advanced cancer and his or her designated caregiver (for a maximum total of 720 participants) who meet the following criteria:

Patient Inclusion Criteria

*1) Able to speak and understand English

*2) Over age 18

3) NEW diagnosis, recurrent, or progression of an advanced stage cancer within approximately -60 days of the date the patient was informed of the diagnosis by his/her oncology clinician.
4) Estimated survival 2 years or less
5)) Diagnosed with one of the following:

- ☐ * Lung Cancer: Stage IIIB or IV NSCLC, or extensive SCLC
- ☐ * Breast Cancer: Stage IV with poor prognostic indicators, including but not limited to :
  - a) > 2 cytotoxic regimens for MBC
  - b) Diagnosis of MBC less than or equal to 12 months since completion of adjuvant or neo-adjuvant treatment
  - c) Triple negative disease (ER/PR –and HER 2 - ,
  - d) Parenchymal brain mets and/or carcinomatous meningitis
- ☐ * Gastrointestinal Cancers: Unresectable stage III or IV
- ☐ * Genitourinary Cancers: Stage IV (for prostate cancer inclusion is limited to persons with hormone refractory prostate cancer)
- ☐ Brain Cancer: Unresectable; Grade IV
- ☐ Melanoma: Stage IV
- ☐ Hematologic Malignancies

Leukemia (e.g. AML, ALL, CML, CLL) - advanced stage, treatment refractory, poor prognosis cell type or chromosomal abnormalities, “older age”

Lymphoma- Stage IV or treatment refractory Hodgkin’s disease or non-Hodgkin’s lymphoma

Multiple Myeloma – elevated β_2-microglobulin, albumin <3.5, PCLI >1%, CRP >6µg/mL, elevated LDH, plasmablastic morphology, abnormal. chromosome 13.

Patient Exclusion Criteria

1) Dementia or significant confusion (Impaired cognitive status as indicated by a score of 3 or less on a six-item cognitive screening tool [18])
2) Axis I psychiatric disorders (DSM-IV) including schizophrenia, bipolar disorder, or active substance use disorder
3) Patients will not be excluded if they do not identify a caregiver
4) Prior involvement with palliative care service within the last year
5) Minimum predicted survival of less than 12 weeks (3 months)

*Denotes inclusion / exclusion criteria for Biomarker sub-study. In addition patients will not be eligible for sub-study if they are receiving chronic steroid hormones for any reason or if specimen collection is not able to be scheduled around standard steroid chemotherapy pre-medications, or if they are not able to come to NCCC at the time of predicted specimen collection.

BIOMARKER SUB-STUDY

Inclusion:
1) Only patients with lung, breast, GI, GU are eligible

Exclusion:
1) Receiving chronic steroid hormones or unable to schedule specimen collection distant from chemotherapy steroid pre-medications

2) Unable to come to NCCC for specimen collection times.

Caregiver Inclusion Criteria
1) Able to read and understand English
2) An eligible caregiver will be identified by the patient and defined as “a person who knows you [the patient] well and is involved in your medical care".

Caregiver Exclusion Criteria
1) Unwilling to participate in study.

Sources of Research Materials

The data will consist of a) answers to the patient and caregiver survey instruments, b) information obtained from medical record review regarding vital status (i.e., date of death), treatment (i.e., interventions and referrals), Karnofsky Performance Scale score, Charlson Co-Morbidity score weight, hospitalizations (i.e., emergency room visits, days in hospital and intensive care unit), and advance directives and c) biomarkers obtained from saliva and plasma samples. Surveys and record reviews will occur upon enrollment, six, twelve and eighteen weeks after enrollment, and then every twelve weeks thereafter until study end or participant death. Biomarkers will be obtained upon enrollment and at 12 and 24 weeks after enrollment.

Potential Risks

General Risks. There are two general risks associated with study participation. First, participants may become distressed after reflecting on their symptoms, mood and quality of life during the survey completion or the intervention. In our experience of providing palliative care interventions, this risk is quite low. The surveys and intervention also offer the opportunity to reflect upon strengths and resilience and participants often express gratitude for the chance to respond to the surveys and share their experiences. The second risk concerns a loss of confidentiality regarding the data (i.e., the chance that participant answers to surveys will be seen by people not associated with the study). Plans to minimize these risks are described below under: Procedures for Minimizing General Risks.

Risk of Blood/Saliva Collection. Blood will be collected by trained laboratory technicians. Risks associated with the drawing of blood include bruising, syncope, temporary discomfort, and rarely, infection. Plans to minimize these risks are described below.

Procedures for Minimizing General Risks

As part of the informed consent discussion, research assistants will encourage participants to discuss any distress they have with their medical providers.. Participants will also have the opportunity to discuss their distress with the nurse interventionists who have expertise in managing emotional distress as part of their palliative care training. The PI (Dr. Bakitas) will be notified immediately in the event any participant expresses suicidal ideation to the nurse interventionists or research assistants. During normal business hours the participant will be immediately referred to Dr. Byock so that he may

perform a risk assessment and develop an appropriate management plan with the participant. In the event Dr. Byock is not available the participant will be immediately referred to Palliative Care physician on call which is available 24 hours/day, 7 days/ week.

Protection from Risk Related to Loss of Confidentiality.

Regarding risks related to loss of confidentiality, all participants' contact information will be stored in password protected databases that exist within the firewalled network of NCCC. Each participant will be assigned an identification number so that survey data will not be labeled with the participant's name. All data will be stored in locked cabinets and password protected computers within the offices and laboratories at NCCC. Only study personnel will be allowed to access the data.

Protection from Risk Related to Blood Drawing

We will attempt to minimize the number of blood draws by coordinating the sample collection with a blood test conducted for another medical purpose. Blood will be drawn by trained technicians, who will minimize risk of syncope by drawing blood in a recumbent position and minimize risk of infection by following sterile technique,

Potential Benefits of the Proposed Research to Subjects and Others

This RCT will allow us to determine if the previous positive results of this intervention can be replicated and whether early versus later introduction of the intervention provides greater or lesser benefit. The greatest benefit of the study is to advance our collective understanding of how to improve palliative care for future patients with advanced disease. However, participants will have access to a modification of an intervention that was demonstrated in our previous RCT to have favorable outcomes regarding mood and quality of life. Therefore, there is the chance that participants will benefit directly from the study.

Importance of Knowledge to be Gained

This study will provide knowledge that will contribute to the evidence base for effective end of life care (e.g., provide information as to the best timing of introduction of palliative care and strategies to improve quality of life, minimize negative mood, and decrease symptom intensity and caregiver burden). Evidence for efficacy and effectiveness of palliative care interventions is sorely needed. Overall, the study has the chance to provide important knowledge with low risk to participants.

Data and Safety Monitoring Plan

Monitoring the Progress of the Study and the Safety of Participants

The data and safety of the study will be monitored annually by the Data and Safety Monitoring Board which consists of Dr. Tim Ahles, Dr. Dale Collins, and Dr. Mark Hegel. The PI and the project director will prepare a report that details progress related to enrollments, withdrawals, deaths, data collection, adverse events, and treatment fidelity. The Board will review the report and make recommendations regarding the continuation

or termination of the study. These reviews will be monitored annually by the Institutional Review Board of Dartmouth College.

Assuring Compliance with Requirements Regarding the Reporting of Adverse Events.

The PI and the project director will report any adverse events to the Data and Safety Monitoring Board and the Institutional review Board within 48 hours of occurrence. Given the low risk nature of the study, serious adverse events are unlikely to occur.

Assuring Data Accuracy and Protocol Compliance

Data Accuracy. Data will be entered via a password-protected computer by research assistants. Participant surveys will be associated only with an identification number so that data managers and analysts will not know which person provided the data (in order to protect confidentiality). Data will be transferred from the central data base and cleaned and checked once again for accuracy prior to entering it into SAS for analysis.

Fidelity Monitoring of Nurse Interventionists. During the intervention phase, all Nurse Interventionist phone sessions will be audio-taped and 25% of the tapes will be randomly scored using the checklist developed in our prior study to insure that treatment is being administered reliably over time and across Nurse-Interventionist. For each scored session, feedback will be reviewed with the nurse interventionists in order to maximize performance and expertise. A Nurse-Interventionist who exhibits a pattern of non-adherence on three consecutive ratings will be required to receive additional training and supervision. Additionally, a subset of nurse interventionists' audio-taped sessions from DHMC participants will be transcribed and content analyzed to allow us to more fully describe and understand the mechanism of the intervention.

Monitoring 10% of Palliative Care Team (PCT) Consultation Notes. We will randomly sample 10% of the PCT consultation notes and use a checklist to review the initial palliative care assessment to ensure that the essential elements of holistic care were performed and an adequate care plan was identified. These notes will be reviewed by a Palliative Medicine physician and feedback will be provided to each ARNP in order to maximize performance and expertise. An ARNP who exhibits a pattern of non-adherence on three consecutive notes will be required to receive additional training and supervision.

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16.0 APPENDIX

Instruments

I. Patient Baseline Questionnaires
   a. Patient Assessment of Chronic Illness Care (PACIC)
   b. Decision-Making Style & Treatment Goals and Outcomes (BL only)
   c. Cancer Behavior Inventory (CBI-B) (BL only)
   d. Life Orientation Test**-**Revised **(**LOT-R) (BL only)
   e. Brief Cope (BL only)
   f. Multidimensional Scale of Perceived Social Support (MSPSS) (BL only)
   g. Functional Assessment of Chronic Illness Therapy Palliative Care (FACIT-PAL)
   h. Center for Epidemiological Studies-Depression Scale (CES-D)
   i. QUAL-E Patient-Reported Resource Use Survey
   j. Patient Background Information (BL only)

II. Patient Follow Up Questionnaires
   a. Patient Assessment of Chronic Illness Care (PACIC)
   b. Functional Assessment of Chronic Illness Therapy Palliative Care (FACIT-PAL)
   c. Center for Epidemiological Studies-Depression Scale (CES-D)
   d. QUAL-E
   e. Patient-Reported Resource Use Survey

III. Caregiver Baseline
   a. Caregiver Background Information
   b. Caregiver Burden Scale
   c. The Caregiver Quality of Life Index-Cancer (CQOLC) Scale
   d. Center for Epidemiological Studies-Depression Scale (CES-D)
   e. Steinhauser – FACTsp-spiritual measure
   f. BFI (Big Five Inventory)

IV. Caregiver Follow up Questionnaires
   a. Caregiver Burden Scale
   b. The Caregiver Quality of Life Index-Cancer (CQOLC) Scale
   c. Center for Epidemiological Studies-Depression Scale (CES-D)
   d. Steinhauser – FACTsp-spiritual measure
   e. BFI (Big Five Inventory)

V. End of Life Care Assessments
   a. QODD
   b. End of Life Care Data Collection Form: Hospital Death Version
   c. Prigerson Inventory of Complicated Grief

VI. Patient, Caregiver, Provider Satisfaction Measure (Mountainview site only)
   a. Rural Breast Cancer Satisfaction Survey v1