Randomized Trial of Stepped Palliative Care versus Early Integrated Palliative Care in Patients with Advanced Lung Cancer
DF/HCC SOCIAL-BEHAVIORAL RESEARCH PROTOCOL

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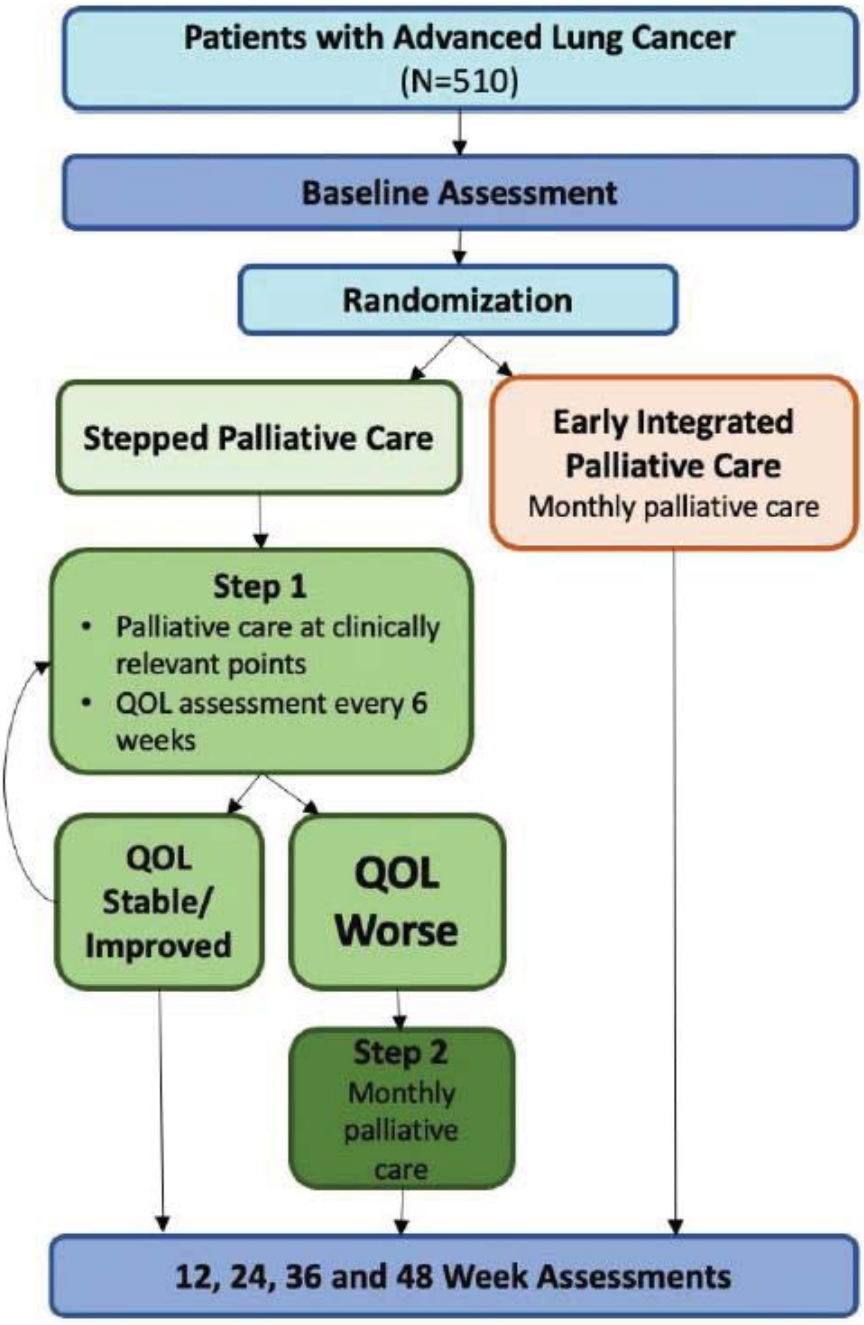
Section 1: Protocol Schema



Section 2: Body of Protocol

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1.0. Introduction

1.1. Overview

Early and longitudinal involvement of palliative care (PC) in the outpatient management of patients with advanced cancer improves patient-reported and end of life (EOL) care outcomes. While recommended by national organizations as the standard of care, this early integrated care model utilizes substantial PC resources, which has limited its dissemination across care settings. We seek to perform a multi-site randomized trial of stepped PC versus early integrated PC in patients with advanced lung cancer. By demonstrating the non-inferiority of a stepped PC model to early integrated PC, we seek to define a role for this more accessible, scalable and patient-centered approach to PC.

1.2. Background and Rationale

Early Integrated PC Improves Patient-Reported and End-of-Life Care Outcomes

Over the past decade, a growing body of evidence has supported a new role for PC clinicians in the outpatient management of patients with advanced cancer.[1-8] For example, Bakitas conducted a randomized trial comparing a telephone-administered PC psycho-educational intervention with usual care in patients with newly diagnosed poor prognosis cancers, which demonstrated improvements in quality of life (QOL) and mood.[2] In two additional trials, investigators evaluated in-person interventions administered by PC-trained clinicians. Specifically, Zimmermann evaluated a four-month intervention involving monthly outpatient PC visits in patients with poor prognosis cancers, demonstrating improvements in QOL, symptom burden and satisfaction, compared with usual care.[5] Similarly, in our trial of patients with newly diagnosed advanced non-small cell lung cancer (NSCLC), monthly visits with PC throughout the course of illness ("early integrated PC") improved patient-reported QOL and depression, compared with usual care.[6] Notably, this study also demonstrated improvements in the delivery of EOL care with early integrated PC including greater documentation of EOL care preferences, longer length of stay in hospice, and less chemotherapy administration near death.[9] More recently, we completed a larger efficacy trial of the early integrated PC model in patients with advanced cancers, which confirmed prior findings and also demonstrated that the intervention led to an increase in patient-clinician communication about EOL care preferences.[10] While both telephone-based and brief duration in-person PC interventions improve patient-reported outcomes, only early integrated PC enhances communication and decision-making about EOL care.

Few Cancer Care Settings Can Deliver Guideline-Concordant Early Integrated PC

Based largely on the data described above, in 2012 and 2016 the American Society of Clinical Oncology (ASCO) published Clinical Oncology Practice Guidelines recommending early PC for any patient with advanced cancer.[11,12] Similarly, the Institute of Medicine and the National Comprehensive Cancer Network recommend consideration of early PC for patients with advanced cancers.[13,14] By recognizing the value of PC in the care of patients with advanced cancer, these recommendations represent a significant advance in the field of oncology. However, few institutions have sufficient numbers of PC clinicians to provide care in accordance with these guidelines.[15] Despite a recent growth in the number of PC clinicians, data suggest that the current workforce would need to be at least tripled to meet the growing demand for their services.[16] Moreover, it is

unlikely that there will ever be a sufficient number of trained PC clinicians to see all patients with advanced cancer from the time of diagnosis and throughout the course of illness.[17,18] Thus, we must develop and evaluate health care delivery models that increase access to care and efficient utilization of PC services.

Stepped Care Increases Access with Limited Health Care Clinicians and Resources
Stepped care was initially developed as a health care delivery model to increase access to and efficiency of psychological therapy due to limited numbers of trained mental health clinicians.[19] In stepped care, all patients receive care for their condition, but with a minimum of required contact with the specialty trained clinician.[20] More intensive treatment with the clinician is reserved for those who do not benefit sufficiently from the less intensive treatments. A key element of this model is that patients must be monitored systematically and "stepped up" to more intensive treatment if the minimal level of exposure to the clinician does not achieve sufficient health gain. Stepped care models have been shown to be effective in managing psychological illnesses such as depression, bulimia, and addiction as well as physical conditions including obesity, hypertension, and back pain.[21-24] Moreover, studies support the use of stepped care models to address psychological distress in patients with cancer.[25-27] When compared with proven strategies of more intensive specialist-delivered treatment, stepped care can achieve similar outcomes using fewer resources and at a lower cost.[22,28,29]

Stepped Care as a Strategy to Deliver Accessible and Patient-Centered PC
Stepped care is an appealing approach for PC delivery as it would enable all patients with advanced cancer to have some exposure to PC clinicians, thus representing guideline-concordant care. Importantly, stepped care is patient-centered in tailoring the delivery of PC services to patients' clinical needs. Such a patient-centered approach to integrating palliative and oncology care is quite timely as cancer therapies are becoming more personalized and effective with fewer side effects. For example, patients treated with targeted oral chemotherapies often remain on treatment for years and may see their oncologist only every few months.[30,31] While these patients may have challenges with the physical and psychological burdens of their cancer, many are unlikely to require monthly visits with a specialized PC clinician.[32,33] Thus, in the modern era of cancer therapeutics, a stepped care model, in which low intensity PC is delivered to all patients at clinically relevant points when they are likely to have symptoms or concerns about their cancer while reserving a higher level of PC involvement when patients' health worsens, may be more accessible, efficient, and patient-centered.

Lung Cancer is an Ideal Population in which to Study Patient-Centered PC
The strongest evidence base supporting early integrated PC is among patients with advanced lung cancer, with two randomized trials demonstrating significant improvements in QOL, mood, and EOL care.[6,34] However, treatment paradigms for patients with advanced lung cancer are changing rapidly.[35] Approximately one-third of patients with metastatic lung cancer have gene mutations or fusions that predict responses to targeted oral therapies or express PDL1 and have tumor shrinkage with immune checkpoint inhibitors, both of which can portend a prognosis of several years.[36-41] Despite these advances, the majority of patients with advanced lung cancer do not respond to

novel therapies and have a median survival of approximately one year.[42] Moreover, these patients often experience a high symptom burden and poor QOL at diagnosis, which intensifies throughout their illness course.[43] With the myriad of medical and psychosocial concerns that patients with advanced lung cancer experience, a one-size-fits-all approach to PC is unlikely to be optimal for this population. Rather, a PC delivery model personalized to each patient's disease course and care needs represents a more patient-centered approach for those with advanced lung cancer.

Scientific Premise of the Project

Early integrated PC has been shown to be an effective care model but is resource intensive, which has limited its dissemination in the outpatient oncology setting. Similarly, an insufficient number of trained clinicians has been a longstanding challenge in psychiatry, which led to the development of stepped care models to tailor treatment to the individual patient, ensure access to care, and increase efficiency. Although stepped care has not been specifically tested as a model for delivering PC, it has been used successfully in addressing the psychosocial needs of patients with cancer.[25-27,44] In addition to increasing access to PC, a stepped care model is a more patient-centered approach by personalizing care to the patients' illness trajectory and needs. Importantly, a limitation of prior research regarding stepped care models is the inclusion of usual care as the control arm in clinical trials. To ensure a stepped care intervention is *as effective* as more resource intensive standard of care interventions requires a non-inferiority study design.[19] Thus, we propose to perform a multi-site randomized trial of stepped PC versus early integrated PC in patients with advanced lung cancer. By demonstrating the non-inferiority of a stepped PC model to early integrated PC, we seek to define a role for this more accessible, scalable and patient-centered approach to PC.

2.0. Objectives

2.1. Primary Aim

To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL at 24 weeks

Hypothesis: Patients assigned to stepped PC will report QOL that is non-inferior to patients receiving early integrated PC at 24 weeks.

2.2. Secondary Aims

A. To assess whether stepped PC is non-inferior to early integrated PC with respect to patient-clinician communication about EOL care preferences and length of stay in hospice.

   Hypothesis: Stepped PC will be non-inferior to early integrated PC in the rate by which patients communicate their EOL care preferences to their clinicians and with respect to patients' length of stay in hospice.

B. To compare the superiority of stepped PC versus early integrated PC with respect to resource utilization.

   Hypothesis: Stepped PC will utilize fewer PC resources than early integrated PC.

3.0. Research Subject Selection

We will recruit 510 patients with advanced lung cancer receiving their care at Massachusetts General Hospital, Duke Cancer Center, or University of Pennsylvania Abramson Cancer Center to participate in a multi-center, non-inferiority randomized trial of stepped PC versus early integrated PC. Patients will be randomized in 1:1 fashion and stratified by site (MGH vs. Duke vs. Penn) and underlying diagnosis (NSCLC vs. small cell lung cancer and mesothelioma). As patients with NSCLC have a significantly better prognosis than those with small cell lung cancer or mesothelioma, we will stratify by the underlying diagnosis to ensure adequate and balanced representation between the two study groups.

3.1. Patient Eligibility Criteria

Inclusion Criteria:

The patient eligibility criteria will mirror those of our prior early PC studies in this patient population.

1. Diagnosed with advanced NSCLC, small cell lung cancer, or mesothelioma, being treated with non-curative intent, and informed of advanced disease within the prior twelve weeks
2. Eastern Cooperative Oncology Group (ECOG) Performance Status from 0 (asymptomatic) to 2 (symptomatic and in bed <50% of the day)
3. The ability to read and respond to questions in English or Spanish
4. Primary cancer care at one of the three participating sites
5. Age $\geq$ 18 years

Exclusion Criteria:

Patients will be excluded if:

1. They are already receiving outpatient PC or hospice services since diagnosis of advanced NSCLC, small cell lung cancer, or mesothelioma
2. They have cognitive or psychiatric conditions as determined by the treating oncologist to prohibit study consent or participation

4.0. Research Subject Entry

4.1. Patient Screening

At all three sites, the study staff will screen all patients presenting to the outpatient thoracic oncology clinic for study participation. By reviewing the electronic scheduling system and health record to determine cancer stage and treatment goals, the study staff will identify all patients with advanced lung cancer who are not being treated with curative intent. This determination will be made based upon stage of disease and the designated treatment goal in the chemotherapy treatment plan as some patients with locally advanced disease cannot be treated for cure and some patients with metastatic disease are treated with curative intent. We will complete a privacy waiver with our protocol submissions to the Institutional Review Board (IRB) to allow study staff to screen the thoracic oncology clinic schedules and identify patients for study participation. We will institute the same patient screening procedures in all three of the participating thoracic oncology clinics.

4.2. Patient Recruitment

We will use the same recruitment and enrollment procedures used in our previous and ongoing trials.[6,34] Prior to the study start, site investigators will meet with their respective thoracic oncology teams to review recruitment and enrollment procedures. Specifically, the study staff will send an email (see appendix) to the oncology clinicians to notify them when their patients appear to be eligible for study participation. If an oncology clinician reports that the patient is being treated with curative intent or otherwise does not meet eligibility criteria, study staff will document the reason.

4.3. Informed Consent Process

Either study staff or the oncology clinician can review the study details, offer study participation, and obtain informed consent in-person or verbally. Both the written and the verbal consent forms describe all study procedures, information about potential risks and benefits of participation, and information regarding who they can contact for further questions. The forms also state that participation is voluntary, that participants can refuse to answer any questions, that they can withdraw from the study at any time, and that study participation is in no way related to their medical care. Study participants who do not provide consent will be asked the reason why they prefer to not participate in the study.

4.3.1. In-Person Informed Consent Process

Willing participants will be presented with a detailed, HIPAA-compliant consent form and given the opportunity to sign written informed consent either with the study staff or their oncology clinician.

Patients who speak Spanish will have all study procedures and information regarding risks, benefits and study contacts explained to them verbally via the use of an interpreter or a Spanish-speaking study staff member as a first preference, or a family member as a second preference. Spanish speaking participants will be given the DF/HCC Spanish consent short form for signing, as well as a copy of the full English consent form for their own reference. The Spanish consent short form will be signed by the participant and by a witness. The witness will be either an interpreter, a Spanish-speaking study staff member or a family member. Spanish speaking participants will be provided with Spanish-version baseline demographic and study questionnaires.

4.3.2. Verbal Informed Consent Process

We are requesting a Waiver of Written Documentation of Consent. This study meets the requirements for a waiver as it is a Minimal Risk study and all study procedures can be communicated verbally. This Waiver will allow study staff to recruit participants remotely to address barriers to study enrollment including infrequent in-person visits, lack of space in clinic, and patients' time constraints. All patients who provide verbal consent will receive an unsigned copy of the written informed consent.

The study staff or an oncology clinician may contact eligible, English speaking patients to obtain verbal consent using the HIPAA-compliant verbal consent form. The verbal

consent process may be offered to patients via telephone or during a scheduled oncology video visit via institution-approved video technology. Verbal consent procedures will not apply to Spanish speaking patients. If the patient does not answer the phone, the clinician or study staff may leave a voicemail (see appendix 9.2 for suggested language for the voicemail).

4.4. Baseline Completion and Registration

Patients will be asked to complete baseline demographic and study questionnaires in-person, over the phone, or via institution-approved video technology with a study staff member at the time of consent, or alternatively via email, telephone, institution-approved video, or mail within two weeks of signing consent. Once baseline measures are complete, patients will be registered for study randomization.

If additional information about palliative care is requested by the patient, the study staff member or clinician may provide any of the following brochures about palliative care: an institutionally approved palliative care brochure produced by the site; the National Institute of Nursing Research brochure "*Palliative Care: The Relief You Need When You Have a Serious Illness*"; or the Center to Advance Palliative Care brochure "*Palliative Care: What You Should Know"*. These brochures are intended to provide additional information for potential study participants who are interested in learning more about palliative care.

DF/HCC institutions will register eligible participants in the Clinical Trials Management System (CTMS) Oncore as required by DF/HCC SOP REGIST-101. Registration must occur prior to the initiation of protocol-specific procedures.

For registration of patients from DF/HCC institutions, study staff will complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. Study staff will confirm that the participant meets all inclusion criteria as described in this protocol and the criteria on the eligibility checklist.

Patients from other investigative sites will be entered on the study centrally by MGH study staff. Study staff from the participating institution will confirm eligibility criteria and fax or email the following documents to study staff at MGH: deidentified signed consent form/s, copy of baseline assessment, and a completed eligibility checklist. MGH study staff will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. Once the patient has been registered, a member of the MGH study staff (independent from study staff who recruit, enroll and administer assessments to participants) will perform randomization procedures using a computer-generated randomization schema, stratified by study site. MGH study staff will fax or e-mail the information about randomization to the study staff at the participating site. MGH study staff may also call the study staff at the participating site to verbally confirm registration and randomization.

5.0. Study Design and Methods

5.1. Study Design

We will conduct a randomized trial of stepped PC versus early integrated PC in patients with advanced lung cancer. We have chosen three specific aims focused on demonstrating the non-inferiority of the more accessible and patient-centered stepped care model.

5.2. Selection of Instruments

We selected instruments based on our prior studies and the theoretical framework of our intervention, which seeks to improve patients' QOL, illness understanding, use of adaptive coping strategies and ultimately communication and delivery of EOL care. Study staff will administer study assessments at baseline and multiple follow-up time points (with a +/- two-week window) to accommodate patient schedules (see Table 1). The selected self-report measures have strong psychometric properties and have been well validated in previous studies. All study measures are available in both English and Spanish, except the Self-Administered Comorbidity Questionnaire and the Prognosis and Treatment Perceptions Questionnaire, which were translated (forward and backward) into Spanish with a native Spanish speaking clinician.

Measures:

Demographic Questionnaire: Participants will self-report their gender, race/ethnicity, marital status, religion, education level, employment status, tobacco use, travel time and transportation mode to the cancer center, and health insurance co-payment charge.

Self-Administered Comorbidity Questionnaire (SCQ): Medical comorbidity will be assessed at baseline with the Self-Administered Comorbidity Questionnaire.[45] Patients will report on the presence of twelve comorbidities such as heart disease, lung disease, diabetes and arthritis. They will also have the option of reporting up to three further unlisted comorbidities and will be assigned a comorbidity score ranging from 0-45.

Functional Assessment of Cancer Therapy-Lung (FACT-L): The FACT-L is a 35-item QOL tool that assesses physical, social/family, emotional, and functional well-being, as well as lung cancer specific symptoms over the past 7 days.[46] We have used this measure in three prior PC trials in patients with lung cancer, demonstrating that early involvement of PC improves FACT-L scores.[6,10]

EuroQol-5 Dimension (EQ-5D): The EQ-5D measures five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with three levels of severity and self-rated health status on a 0-100 visual analog scale[47,48] and is sensitive to QOL changes in patients with lung cancer.[47,49]

Patient Health Questionnaire-9 (PHQ-9): The PHQ-9 is a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, which can be scored continuously or categorically.[50] In our previous trials, early involvement of PC has improved PHQ-9 scores.[6,10]

Brief Cope: The Brief Cope is a 28-item questionnaire that assesses methods of coping (e.g., active, acceptance, denial) using a 4-point Likert scale ranging from 1 "a lot" to 4 "never."[51] The psychometric properties of the Brief Cope have been demonstrated in studies of patients with serious illness and cancer.[51,52] For our prior study, to minimize questionnaire burden, we solicited feedback from our research and PC teams about the coping strategies most likely to be influenced by our early PC intervention. We chose to exclude items such as self-distraction, substance use, and venting. We will limit our evaluation to eight coping strategies (16-items) deemed most relevant for the study (i.e., emotional support, positive reframing, active coping, acceptance, self-blame, denial, spiritual coping and behavioral disengagement). In our prior study, early involvement of PC increased use of active coping and decreased use of poor coping. We will administer 16-items in the current trial.

Support Service Utilization: At the 24-week primary endpoint, patients will be administered a single item assessing mental healthcare utilization since diagnosis. This item is designed to capture information which is routinely missing from the health record, as patients often either see mental health services external to the hospital, or access services which do not routinely document encounters in the electronic health record (EHR).

Prognosis and Treatment Perceptions Questionnaire (PTPQ): The PTPQ is a tool that assesses patients' illness understanding, communication about prognosis and goals of care, as well as discussions and preferences regarding EOL care.[53] The PTPQ includes the item: "Have you discussed any particular wishes you have about the care you would want to receive if you were dying?" (Yes/No). This item has been previously used to assess EOL communication in patient with cancer.[54]

5.3. Description of Intervention

5.3.1. Stepped PC Arm

Patients who have been randomized to the stepped PC arm will be scheduled for an initial visit with the PC clinician either in person or via secure video visit within four weeks of enrollment. During step 1, additional visits with the PC clinician will be scheduled at clinically relevant points in the patients' illness. In our recent study, we observed that over 80% of clinic visits that the PC clinicians recorded as "significant interactions" occurred after patients' cancer progressed or a recent hospitalization. Therefore, during step 1, patients will be scheduled to meet with the outpatient PC clinician either in person or via secure video visit within four weeks after a change in cancer treatment (including radiation), or within four weeks of discharge from an inpatient admission. 'Change in treatment' for this study is defined as:

i. A change in cancer treatment due to either progression or toxicity
ii. A discontinuation of cancer treatment

Furthermore, if a step 1 patient is hospitalized within the first four weeks of enrollment, or if an inpatient admission occurs at any time, step 1 patients will default to the

procedure for hospitalizations and a PC appointment will be scheduled within four weeks of discharge. While hospitalized, step 1 patients may have inpatient PC appointments at the discretion of their oncology team, and such appointments will otherwise have no impact on study procedures.

In our recent study, the early integrated PC intervention group had a median of seven PC visits per patient by week 24. Examining rates of cancer progression and hospitalizations from this study, we estimate that stepped care patients on step 1 of the intervention will have a median of three PC visits per patient by week 24, representing an approximate 60% reduction in PC resource utilization. If a patient is unable to be scheduled in person or via secure video visit within four weeks of the change in treatment or hospitalization, the PC clinician will attempt to contact them by telephone within the four weeks, document the call in the EHR, and the visit will be scheduled as soon as possible. If patients miss any scheduled PC visits during step 1, and the visit cannot be rescheduled within four weeks of the change in treatment or hospitalization, the PC clinician will attempt to contact the patient by telephone within seven days from the missed visit, document the call in the EHR, and the visit will be rescheduled as soon as possible. If the patient is unable to be reached by phone, the PC clinician will document the attempted contact or voicemail in the EHR. If the PC clinician does not speak Spanish, visits for Spanish-speaking patients will be conducted with the assistance of an interpreter or family member. During step 1, PC clinicians will attempt to communicate with oncology regarding what occurred in each visit, either by phone, email, personalized electronic communication, or in person.

Step 1 patients will complete the FACT-L every six weeks for a minimum of 12 months and up to 18 months from enrollment. FACT-L scores will be used to determine which step 1 patients need to step up to PC visits every four weeks. A 10-point change in the FACT-L is considered the upper range of a clinically meaningful difference and correlates with outcomes such as disease progression.[55] Therefore, we will use a $\geq$10-point decrease in the FACT-L from baseline at any follow-up time point to transition patients to step 2 of the intervention. In our recently completed trial of early integrated PC, 30% of patients receiving usual oncology care alone experienced a $\geq$10-point decrease in the FACT-L from baseline to week 12 with an additional 11% experiencing a $\geq$10-point decrease at week 24. For this trial, given that patients in step 1 will have intermittent visits with PC clinicians to help with symptoms and QOL, we anticipate that substantially fewer than 40% will have a $\geq$10-point decrease on the FACT-L by week 24, necessitating transition to step 2 of the intervention.

Patients who transition to step 2 will then meet with the PC clinician either in person or via secure video visit at least every four weeks for the remainder of their illness and be seen by the inpatient PC team if they are hospitalized. If a patient is unable to be scheduled within four weeks from the last contact, the PC clinician will attempt to contact them by telephone (and document the call in the EHR) to maintain contact at least every four weeks. If patients miss a scheduled PC visit, and the visit cannot be rescheduled within four weeks of their previous contact, the PC clinician will attempt to contact them via telephone within seven days from the missed visit and document the call

in the EHR. If the patient is unable to be reached by phone, the PC clinician will document the attempted contact or voicemail in the EHR. If the PC clinician does not speak Spanish, visits for Spanish-speaking patients will be conducted with the assistance of an interpreter or family member. For some short or weekend admissions or brief admissions for a planned medical procedure, it may not be feasible for PC to see the patient; if we are aware of a planned admission for a medical procedure or of a planned brief admission we will attempt to consult with the patient's outpatient PC provider to see if it would be beneficial for them to see PC during the brief admission.

A study staff member will score the FACT-L within 5 business days of receiving the surveys. Step 1 patients whose FACT-L scores are found to decrease by ≥10-points from baseline at any time during the study will be transitioned to Step 2 for the remainder of their illness. As outpatient PC is an available service at participating institutions, we will not deny patient or oncologist requests for additional PC visits for patients assigned to step 1. However, these visits will only be scheduled upon request and they will not trigger regularly scheduled visits every four weeks. In our prior study, only one-third of patients randomized to standard oncology care received a PC consultation based on request from the oncologist or the patient, with a median of 2 visits by 24 weeks. As step 1 patients will have PC visits at clinically relevant points in their illness, we anticipate few requests for additional PC visits for patients on step 1 of the stepped care intervention. For patients who are still on step 1 at 18 months from enrollment, PC scheduling will be at the discretion of their PC and oncology teams. Patients on Step 2 surviving greater than 18 months will be permitted to decrease the frequency of PC visits as per the discretion of their PC and oncology teams. Once patients are on hospice study visits will end, and further PC care will be per standard practice.

5.3.2. Early Integrated PC Arm

Patients assigned to early integrated PC will follow the identical study procedures used in our previous and ongoing trials.[6,34] Specifically, patients will meet with the PC clinician either in person or via secure video visit within four weeks of enrollment and at least every four weeks throughout their course of illness. If a patient is unable to be scheduled in clinic within four weeks from the last contact, the PC clinician will attempt to contact them via telephone (and document the call in the EHR) to maintain contact at least every four weeks. If patients miss a scheduled PC visit, and the visit cannot be rescheduled within four weeks of their previous contact, the PC clinician will attempt to contact them by telephone within seven days from the missed visit and document the call in the EHR. If the patient is unable to be reached by phone, the PC clinician will document in the EHR that the PC team has attempted to contact the patient or they have left a voicemail asking for a return call if there are issues needing to be addressed. If the PC clinician does not speak Spanish, visits for Spanish-speaking patients will be conducted with the assistance of an interpreter or family member. The inpatient PC team will follow patients assigned to early integrated PC when they are hospitalized. For some short weekend admissions or brief admissions for a planned medical procedure it may not be feasible for PC to see the patient; if we are aware of a planned admission for a medical procedure we will consult with the patient's outpatient PC provider to see if it would be beneficial for them to see PC during the brief admission. Patients on the early integrated PC arm

surviving greater than 18 months will be permitted to decrease the frequency of PC visits as per the discretion of their PC and oncology teams. Once patients are on hospice study visits will end, and further PC care will be per standard practice.

5.3.3. Palliative Care Intervention Delivery

While the study protocol details the frequency of contact with a PC clinician, a variety of uncontrollable factors may impact intervention delivery. Patient factors include a change in their cancer treatment schedule, cancellation of cancer treatment, or fatigue that prohibits participation in a visit. Clinician factors include clinic delays leading to missed patient appointments and insufficient staffing, especially due to meetings and vacations. To reduce patient and clinician burden, we will conduct PC visits either in-person or via an institution-approved secure video platform. If an in-person or video visit cannot be scheduled, PC visits may be conducted via telephone. We will document missed contacts as minor violations and institute a corrective action plan if more than 15% of all planned patient contact with PC does not take place per study protocol at a study site.

5.4. Data Collection

Table 1 depicts the assessments, measurements, and time points for the data collection. We will administer patient-reported measures for 48 weeks from enrollment. We selected a longer administration period in the current study as the median survival for patients with lung cancer is now approximately one year. The study assessment battery takes approximately 20 minutes to complete.

Table 1. Summary of data collection instruments and time-points.

Self-Report Measure	Baseline	Every 6 weeks*	Week 12	Week 24	Week 36	Week 48
Demographic Questionnaire	X					
Self-Administered Comorbidity Questionnaire (SCQ)	X					
Functional Assessment of Cancer Therapy-Lung (FACT-L)*	X	X*	X	X	X	X
Patient Health Questionnaire-9 (PHQ-9)	X		X	X	X	X
Prognosis and Treatment Perceptions Questionnaire (PTPQ)	X		X	X	X	X
Brief Cope	X		X	X	X	X
EuroQol – 5 Dimension (EQ-5D)	X		X	X	X	X
Support Service Utilization Item				X		

*Step 1 patients will complete the FACT-L every 6 weeks for a minimum of 12 months and up to 18 months from enrollment

5.4.1. Data from Electronic Health Record:

Clinical information regarding tumor type (NSCLC, small cell lung cancer, and mesothelioma), current treatment regimen, date of diagnosis of incurable disease,

previous diagnosis of early stage disease, tumor genotype, and ECOG Performance Status will be collected at baseline.

Health care utilization data will be collected after death or at 12-months from the date the last patient enrolled on the study. We will collect data on: (1) outpatient and inpatient PC visits; (2) chemotherapy and radiation therapy administration; and (3) emergency department, hospital and intensive care unit admissions. EOL care measures will include referrals to and length of stay on hospice and location of death.

5.4.2. PC Cost and Resource Utilization Data:
To collect information on PC costs and resource utilization we will use the same data collection procedures as in our prior randomized trial of early integrated PC.[56] Specifically, we will collect data on the inpatient, and telephone PC encounters from the EHR and on number of outpatient, the duration of the PC visits from the Research Electronic Data Capture (REDCap) database. To collect outpatient and inpatient hospital costs, we will query Eclipsys Sunrise (EPSI^{TM}), which is the hospital cost accounting system used by all participating institutions and includes site specific software that provides Ambulatory Patient Classification (APC) codes for these encounters.[57] Although we are unable to capture health care costs incurred at non-study institutions, patients receiving care at the participating sites most often utilize their institutions' hospital. EPSI^{TM} has embedded reporting and analysis features that use the following data sources: budgeting and planning, cost accounting, patient financial and clinical analysis, and productivity. Actual total costs represent the total of direct costs (such as supplies, labor, laboratories, and procedures) and indirect costs (such as overhead and building management for the patient encounter). The data abstracted from EPSI ^{TM} represent the opportunity or resource use cost of care at the institution, rather than the amount charged to the patient's insurance or the amount the hospital is reimbursed for patients' care. We will utilize APC codes to normalize costs to those of the Center for Medicare and Medicaid Services (CMS). We will track medications prescribed in the EHR and determine their costs using standard methods.[58] Chemotherapy drugs which are administered as part of a clinical trial will be assigned costs based on costs of similar FDA-approved medications. We will assign the cost of home and inpatient hospice days based on the CMS payment per day for the year of the patient's hospice use. We will assess patient costs using survey data incorporated into our demographic questionnaire (travel time, transportation mode, co-payments), clinical data (number of clinic visits), and national wage data (value of patient time). All outpatient visits will incur 20% co-insurance rate based on the Medicare Part B rate. We will also use Medicare Part A co-insurance rates to estimate co-insurance costs for inpatient stays.

5.4.3. Data on PC Visits:
PC clinicians will report which domains they addressed during the study visit and the duration of the visit after each patient encounter, using REDCap. In our MGH trial, all PC clinicians completed REDCap entries after their clinical interactions for over 99% of their encounters.[59] We will use the identical successful study procedures to ensure documentation of all PC clinical interactions in this trial. Specifically, prior to the study start all participating PC clinicians will be trained on the use of the REDCap survey and

the importance of entering this data. For each study patient encounter, the study staff will send a secure email with the patients' name and a link to the REDCap system. PC clinicians will receive an email after the visit to remind them to complete the data entry. If the PC clinician does not complete the REDCap entry, they will continue to receive periodic reminders until the end of the 4-week window. We will not accept REDCap entries more than four weeks later than the appointment date. While we have trained study sites to complete these surveys after each patient encounter, it is not feasible for them to complete 100% of this documentation. As such, we will not consider missed REDCap surveys from the PC clinicians to be protocol violations.

5.4.4. Data Storage:

All patient information and study source documents, including but not limited to signed informed consent forms, completed eligibility checklists, and participant questionnaires, will remain confidential and be scanned and stored on secure Partners computers and in REDCap. Since these records necessarily contain patient identifiers, only study staff will have access to them. Study staff will scan completed source documents, which may include identifiers such as participant names, upon their completion. Location, time, and date of the scanning of the document will be recorded. After the source document is scanned and the corresponding electronic document is confirmed to be legible, it will be collected and destroyed immediately. Study staff will destroy the original copy of the source document by following MGH procedures of destroying documents with Personal Health Information (PHI). Data abstracted from the EHR in Section 5.4.2 will be maintained in REDCap. REDCap is a free, secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data collection projects rely on a study-specific data dictionary defined by members of the study staff with planning assistance from Harvard Catalyst and The Harvard Clinical and Translational Science Center EDC Support Staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides flexible features that can be used for a variety of research projects and provides an intuitive interface to enter data with real time validation (automated data type and range checks). The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

5.5. Description of Study Processes

5.5.1. Instrument Administration

A study staff member will administer study assessments at baseline and multiple follow-up time points (see Table 1) within a +/- 2-week window to accommodate patient schedules. The assessment battery takes approximately 20 minutes to complete. Patients may complete assessments either in the clinic, online via REDCap email, on paper at home, via telephone, or via institution-approved video technology. As a first preference, we will attempt to collect questionnaires in-person at scheduled visits to the outpatient

clinic. We will ask patients to provide their email address to allow us to email study measures using a secure electronic system when patients do not have a clinic appointment within the follow-up time points. For patients who opt out of using email, we will either send them paper copies of the survey or ask them to complete them verbally over the telephone or via institution-approved video technology. Surveys that are completed on paper at home will be labeled only with a case number and no identifying information; we will also add a note reminding participants to please not add their name or identifying information to the survey. We will provide a pre-paid, stamped envelope for participants who want to return questionnaires by mail.

Spanish speaking participants will have the option of completing follow-up assessments in-person as a first preference, or otherwise via mail. Study staff who are fluent in Spanish may administer questionnaires via telephone or via institution-approved video technology. Spanish questionnaires will not be administered via email as this is not possible with REDCap.

We will administer patient-reported measures for 48 weeks from enrollment. We selected a longer administration period in the current study as the median survival for patients with lung cancer is now approximately one year. The selected self-report measures have strong psychometric properties and have been well validated in previous studies. All study measures are available in both English and Spanish, except the Prognosis and Treatment Perceptions Questionnaire, which were translated (forward and backward) into Spanish with a native Spanish speaking clinician.

5.5.2. PC Intervention Administration

All participating PC clinicians will undergo training to ensure that the provision of PC services is consistent across study sites. Drs. Greer and Jackson developed a PC intervention guide based upon our prior studies that details the elements of PC in the outpatient care setting.[60-62] The intervention guide outlines the domains that the PC clinicians will address at the initial visits (e.g., establishing a therapeutic relationship), visits throughout the disease course (e.g., symptom management and coping), and visits at the EOL (e.g., EOL care options), highlighting the essential elements and key points of each care domain. The delivery of PC in both study arms will follow the intervention guide, with only the frequency and timing in which patients engage with PC differing by study arm. We also developed a series of training videos to illustrate the techniques included in the guide. Both the intervention guide and training videos are being used in our ongoing Alliance for Clinical Trials multi-site PC trial. Prior to the study start, all participating PC clinicians will watch the training videos. They will then attend a four-hour training using video conferencing to review the intervention guide (the site PIs will complete this during their in-person or virtual training), led by the MGH study staff. They will also lead monthly supervision calls with the participating PC clinicians throughout the trial and ensure that new PC clinicians will receive training. Table 2 below summarizes the domains, elements, and key points of the PC intervention visits.

Table 2. Palliative care visit summary

Timing	Domain	Elements	Key Points

Initial Visits	Therapeutic Relationship	• Introducing PC • Understanding the Patient and Caregiver Experience • Building Trust with the Patient and Caregiver	• Develop a strong therapeutic relationship with patients and caregivers • Learn about the values, life goals, and experiences of patients and their caregivers both prior to and after the cancer diagnosis • Develop trust and credibility with patients and caregivers by providing reassurance and outlining parameters of communication
All visits	Patient Symptoms	• Preparing for Symptoms • Assessing & Treating Symptoms • Coordinating Symptom Management with Oncology • Providing Referral for Symptom Management	• Clarify the symptoms the patient will likely experience and offer reassurance about the methods for reporting and treating symptoms • At every visit, elicit existing and new symptom concerns • Maintain ongoing, effective communication with oncologists to define mutual collaboration and work within their preferred practice patterns • Emphasize team approach to care by referring to specialty care, mental health, alternative medicine, and spiritual support as needed
	Coping with Advanced Cancer	• Reviewing & Validating Prior Coping Efforts • Discussing & Advocating for Different Methods of Coping • Supporting Caregiver Coping • Providing Referral for Additional Support	• Recognize that patients and caregivers bring their own expertise in coping to the current circumstance based on prior experiences • Introduce strategies to help improve adjustment and meaning in life (e.g., behavioral, cognitive, and spiritual approaches; social support) • Bolster caregiver coping by assessing burden, enhancing their communication with patients, and recommending additional support • Involve other members of the team for patients and caregivers who may be experiencing severe distress (e.g., social work, psychology)
	Prognostic Awareness & Illness Understanding	• Communicating with Oncology • Exploring Goals & Values • Assessing & Informing Patient Expectation of Prognosis • Conducting Separate Conversations with Caregivers	• Consult with the oncologist to ensure the care team is consistent with their understanding of the patient's prognosis • Assess patient's hopes and expectations for treatment and future to clarify the patient's level of prognostic awareness • Recognize that illness understanding often vacillates between more & less realistic expectations and work to improve prognostic awareness • Include both patients and caregivers in conversations about prognosis and illness understanding when possible
	Treatment Decision-making	• Assessing Patient Values in Treatment Decision-Making • Discussing Treatment Considerations • Supporting Treatment Decisions	• Elicit information from patients and caregivers regarding their decision-making style, quality versus quantity of life concerns, and life goals • Provide support for patients and caregivers to understand the efficacy, and risks and benefits associated with cancer treatment • Clarify any misunderstanding about treatment, support patient decision-making and freedom to change course
Visits Near EOL	EOL Care	• Discussing EOL Care Options • Supporting Caregivers in EOL Care Coordination & Bereavement	• Discuss/review selection of healthcare proxy, determination of resuscitation preferences, transition to hospice care, and location of death • Determine available resources for EOL care and whether it is appropriate for patients to receive care in the home or other settings; and provide resources and counseling for bereavement for caregivers

5.5.3. Ensuring Fidelity of Study Design, Training, and Intervention

We will take several steps to ensure the fidelity of our study design, training, and intervention delivery. Specifically, for the study design, we will utilize an evidence-based PC intervention guide, measure the number and duration of PC visits, and monitor the proportion of stepped care patients who transition to step 2 of the intervention. Also, we will employ rigorous training procedures for site PIs and study staff; use of video to illustrate delivery of the PC intervention; video-conferencing for training site PC clinicians and training for new PC clinicians; and monthly calls with the PC clinicians (led by Dr. Jackson) and the study staff (led by the MGH Project Manager). To ensure the

fidelity of intervention delivery, we will review PC documentation, and provide feedback to PC clinicians. As noted previously, the participating PC clinicians will complete an electronic survey after each clinical encounter to record the topics addressed during each visit. Two study staff will independently review the electronic surveys every 3 months to ensure intervention fidelity and conformity between sites in addressing the domains and topics as specified by the guide, allowing assessment of inter-rater agreement. Coder disagreement will be resolved via consensus discussion with Dr. Temel. Based on this review, Dr. Jackson will provide constructive feedback as needed to individual clinicians to confirm fidelity to the PC intervention. Trained study staff will also review PC notes in the health record to ensure adherence to the intervention guide content and provide feedback to clinicians at the site research meetings.

5.5.4. Special Concerns

Study staff at MGH, Duke, and Penn will all meet on a weekly basis to discuss any issues or concerns with study procedures. If it is decided that the protocol needs to be amended or modified, the lead site PI will make the necessary changes and submit an amendment to the DF/HCC IRB for approval. Once the amendment has been approved by the DF/HCC IRB, then the amendment will be submitted to the Duke IRB and the Penn IRB.

5.6. Adverse Reactions and their Management

5.6.1. Reporting Adverse or Unanticipated Events

Identification of adverse events may come through notification from the study participant, caregiver, clinician, or from review of the EHR. In such circumstances, the PIs and investigative team will follow the following procedures:

Serious Adverse Events: Given that this study is a PC intervention, we do not anticipate any study-related events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). This study population is comprised of individuals diagnosed with advanced lung cancer who frequently experience disease worsening, high rate of symptoms, and hospitalizations from the underlying disease and/or side effects of treatment. Therefore, as advanced lung cancer is a chronic-type terminal illness, regular fluctuations in cancer-related symptoms, disease worsening, hospitalizations, emergency department visits, and deaths are to be expected throughout the study, and we will not consider or report such events as SAEs in this trial.

Non-Serious Adverse Events: The IRB will be provided with unblinded summaries of study related non-serious adverse events by treatment group at the continuing reviews. These reports will include types of events, severity, and treatment phase. To date, we have had very few non-serious events in our supportive care studies.

5.6.2. Anticipated Reactions

As this is a behavioral study, there are no ingested medications, and no biomedical procedures. It is unlikely that participants will be at any risk for physical harm as a result of study participation.

Participants may find some of the questions asked in the questionnaire to be emotionally upsetting and may experience some fatigue from the length of the assessment battery. As this is a study targeting symptoms that are debilitating and interfere with QOL, it is possible that some participants will experience depression.

5.6.3. Reaction Management

A detailed consent form will be signed by each participant following the explanations by the study staff or oncology clinician. The consent form will include all study procedures, information about potential risks and benefits of participation, and information regarding whom the participant can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their medical care. All study staff will complete the required human subjects training before working on any human subject aspects of the study.

Should a participant exhibit or express distress, they will be reassured by the study staff that they need not answer any questions they find upsetting. They will also be reminded that study participation is voluntary. If participants remain distressed, both the PI and the primary oncology clinician will be notified. Should several participants express distress over an individual item, the study staff will review the questionnaire and contact the IRB to consider removing it from the study.

If a participant reports severe distress or suicidal ideation during the study conduct, the study staff member has an obligation to inform the site PI and/or a member of the patient's PC or oncology team. These clinicians will determine the need to involve psychiatry and take further action as deemed necessary. The study staff will review sensitive items regarding suicidal ideation within 120 hours (5 business days) of receipt of completed surveys and will report any suicidal ideation to the site PI and/or a member of the patient's PC or oncology team promptly.

6.0. Ethical and Legal Issues

6.1. Confidentiality

Patient data will be collected at each institution (MGH, Duke, and Penn) using REDCap. Each site will maintain their own separate list of patient names and study ID's, which will be saved in secure electronic files. Participants will be identified on study forms by case number only to protect confidentiality. Identifiers such as name will only be used during the initial data retrieval process and can be destroyed once all data records have been obtained and data analysis has been completed as discussed previously. At the completion of the study, de-identified data files will be transferred from Duke and Penn to the MGH using a secure data transfer.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the study staff. Under these circumstances, as clearly stated in the patient consent form, the study staff member will inform the patient's site PI and/or a member of the patient's PC or oncology team. These clinicians will then

determine the need to involve social work, psychiatry and/or take further action as deemed necessary.

7.0. Statistical Analysis

7.1. Primary Endpoint

To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL at 24 weeks.

7.2. Secondary Endpoints

7.2.1. To assess whether stepped PC is non-inferior to early integrated PC with respect to patient-clinician communication about EOL care preferences.

7.2.2. To assess whether stepped PC is non-inferior to early integrated PC with respect to length of stay in hospice.

7.2.3. To compare the superiority of stepped PC versus early integrated PC with respect to resource utilization.

7.3. Exploratory Endpoints

7.3.1. To compare the longitudinal patterns in QOL in patients assigned to stepped PC versus early integrated PC, as measured by repeated assessments of FACT-L.

7.3.2. To compare the superiority of stepped PC versus early integrated PC with respect to cost-effectiveness.

7.3.3. To compare coping strategies in patients assigned to stepped PC versus early integrated PC.

7.3.4. To compare prognostic understanding in patients assigned to stepped PC versus early integrated PC.

7.3.5. To compare depression in patients assigned to stepped PC versus early integrated PC.

7.3.6. To compare health care utilization at the end of life (i.e., emergency department visits, hospitalizations, and chemotherapy administration) in patients assigned to stepped PC versus early integrated PC.

7.4. Sample Size and Power Calculation

The primary endpoint of the study is to establish that stepped PC is non-inferior to early integrated PC in the change in QOL, as measured by the FACT-L at week-24. Although the primary endpoints in our previous studies assessed the change in FACT-L from baseline to week-12, we chose to focus on QOL at 24 weeks as the life-expectancy of patients with advanced lung cancer has improved over the last few years. Thus, examining QOL at 12 weeks may overlook important differences between groups as the disease progresses. In our most recent trial of early integrated PC versus standard oncology care, we observed a 7.5-point difference in the FACT-L at week-24 favoring the integrated PC group. Thus, we chose a conservative non-inferiority margin of 4.5 points, which is slightly less than 50% of the previously observed advantage with early integrated PC compared to oncology care alone. As a 6-point difference in FACT-L score is considered the lowest range of a clinically meaningful difference, our non-inferiority margin would not reach the threshold of clinically meaningful difference in QOL.[55] With

188 patients per group, we will have >80% power to establish the non-inferiority of stepped PC compared to early integrated PC on the FACT-L with a one-sided alpha of 0.05, and a non-inferiority margin of 4.5 points. We are currently observing 35% missing data across sites at 24 weeks, primarily due to progressive illness or death. Therefore, we increased our sample size to 255 per group to ensure we have adequate power to assess for non-inferiority of stepped PC.

Our study also has adequate power to assess for non-inferiority of stepped PC compared to early integrated PC in EOL communication and hospice length-of-stay. With a sample size of 510, we will have >80% power, with a one-sided alpha of 0.05, to reject the hypothesis that patient-reported EOL communication with stepped PC would be 10% lower than early integrated PC, assuming that the rate of EOL communication in the early integrated PC group is 30% (based on our recent trial). With this sample size, we will also have >80% power to establish the non-inferiority of stepped PC compared to early integrated PC in hospice length-of-stay with a one-sided alpha of 0.05, and a non-inferiority margin of 7 days. We were conservative with our power estimations by using the highest observed standard deviation for all outcomes from prior studies.

Multiple testing: Testing of secondary outcomes will be one-sided for outcomes being tested for non-inferiority and two-sided for outcomes being tested for superiority. The Benjamini-Hochberg false discovery rate (FDR) control approach will be used to interpret results of significance tests of secondary outcomes with an FDR of 0.15. We selected an FDR of 0.15, which denotes the acceptable percentage of results that potentially represent false positives. Analyses of exploratory outcomes will not be adjusted for multiple comparisons, and presented results will emphasize estimates and confidence intervals.

7.5. Analysis Plan

The primary endpoint of the study is to establish that stepped PC is non-inferior to early integrated PC in QOL, as measured by the FACT-L at week-24. We will begin with descriptive and graphical summaries of the endpoints to evaluate whether the normality assumption is reasonable or if transformation is necessary. Based upon our prior study demonstrating statistical and clinically meaningful between group differences in the FACT-L at 24-weeks, the primary endpoint to compare patient FACT-L scores at week-24 between the study groups using a linear regression model controlling for randomization stratification factors, baseline values, and demographic and clinical factors (as necessary for any imbalances in baseline variables). We will also use linear mixed models of the longitudinal data, allowing us to account for dependency among means over time and to control for demographic and clinical factors when examining change between groups in QOL across multiple time points. We will also compare the number of PC visits between the two groups to ensure that the stepped PC model led to a reduction in PC visits.

We will compare depression (PHQ-9) and coping strategies (Brief Cope, including higher-order factors of the Brief Cope in our sample[52]: active coping & avoidant coping) at week-24 between groups using linear regression models controlling for randomization

stratification factors, baseline values and selected demographic and clinical factors. We will then evaluate linear mixed models of the longitudinal data, as described above, to examine changes in these outcomes between groups across multiple time points.

To compare illness understanding as measured by the PTPQ between the two groups at week-24, we will analyze appropriate items using the appropriate model for the outcome of interest (e.g., linear regression or generalized linear models with an identity link function and binary response probability distribution) with adjustment for randomization stratification factors and any demographic and clinical factors that are imbalanced to assess differences between groups.

We recently found that improvements in QOL and depression with PC are mediated through use of adaptive coping skills, and prior studies have shown that age, gender, and race can moderate the impact of PC in patients with cancer.[63,64] Therefore, we will conduct bootstrapped tests of mediation to determine whether group differences in the FACT-L are mediated by improved coping or other potential mediators such as psychological distress. Additionally, we will explore potential moderators of the interventions to ensure generalizability and identify whether certain groups benefit more from one of the two PC models. We will create interaction terms for the linear regression and linear mixed models to examine whether differences in FACT-L are moderated by patient factors (e.g., age, gender, race, baseline distress), disease or treatment factors, or study site.

The secondary aim of the study is to assess whether stepped PC is non-inferior to early integrated PC with respect to patient-clinician communication about EOL care preferences and length of stay in hospice. We will examine patient report of discussing EOL care preference with their clinicians using the following item: “Have you and your doctors discussed any particular wishes you have about the care you would want to receive if you were dying?” Although patients will complete this measure repeatedly during the course of the study, we will use the patient’s final assessment for this analysis. We will assess differences between study arms in the rate of patients reporting “yes” to this item using a one-sided alpha of 0.05 and a non-inferiority margin of 10%. The difference in rates between study arms will be assessed using a generalized linear regression model specified with an identity link function and binomial response probability distribution with adjustment for the randomization stratification factors and any demographic and clinical variables that are imbalanced between groups.

We will assess the non-inferiority of hospice length-of-stay between stepped PC and early integrated PC using linear regression model controlling for randomization stratification factors, as well as demographic and clinical factors that are imbalanced at baseline, with a one-sided alpha of 0.05 and a non-inferiority margin of 7 days. Although hospice length-of-stay is not normally distributed, based on a sample size of 510, the means would have a normal distribution (central limit theorem). We will also perform the Wilcoxon rank sum test to compare our results to those obtained with linear regression. We will also test whether differences in EOL outcomes are mediated by prognostic

awareness or moderated by patient factors (e.g., age, gender, race), disease or treatment factors, or study site as described in aim 1.

We will also compare PC resource utilization and cost effectiveness of stepped PC versus early integrated PC. We will assess the superiority of stepped PC compared to early integrated PC with respect to PC resource utilization and cost. Total as well as category-specific utilization and costs including PC, other outpatient care, emergency department use, inpatient care, and pharmaceuticals (chemotherapeutics and other pharmaceuticals evaluated separately) will be assessed to determine how resource use shifts for stepped versus early integrated PC. We will first compare the mean number of outpatient PC visits between the two groups using a linear regression model with adjustment for randomization stratification factors.. Although most utilization and cost outcomes are not normally distributed, based on a sample size of 510, the means would have a normal distribution (central limit theorem). We will also perform the Wilcoxon rank sum test to compare our results to those obtained with the linear regression model.

We will assess the incremental cost-effectiveness of the early integrated PC arm relative to the stepped PC arm from the societal perspective using the average costs and quality adjusted life years (QALYs) accrued under each study arm and as follows: $(\text{Cost}_{\text{early integrated PC}} - \text{Cost}_{\text{stepped PC}})/(\text{QALYs}_{\text{early integrated PC}} - \text{QALYs}_{\text{stepped PC}})$.[65] A $50,000 per quality-adjusted life-year gained will be considered cost effective.[66] Costs will include all direct health care costs and indirect (time) costs incurred by patients over their life spans while enrolled in the trial.[67] The EQ-5D will be used to apply utility weights (quality adjustment) to patients' life spans. Both costs and QALYs will be discounted at a rate of 3%. Based on our prior trials, we expect that few patients will survive past the end of the study period.[9] Cost and QALY data beyond the end of follow-up for those who are alive will be treated as missing data and estimated using multiple imputation methods. If we find that stepped care is non-inferior to early integrated PC in terms of both QALYs accrued and FACT-L scores, we will ignore QALY data and perform only a cost comparison between the study arms. We will use Monte Carlo methods using 10,000 simulations to incorporate uncertainty in parameter estimates and develop confidence bounds on the estimated cost-effectiveness ratio or the cost difference. Following standard methods of economic evaluation as we have done in other studies, we will also perform parameter-specific sensitivity analyses in which individual parameters are varied singly and in combination, through plausible ranges to assess the relative impact different elements of the program have on overall cost-effectiveness.[68,69]

7.5.1. Stratification Factors and Intervention Allocation Plan
Patients will be randomized in 1:1 fashion and stratified by site (MGH vs. Duke vs. Penn) and underlying diagnosis (NSCLC vs. small cell lung cancer and mesothelioma). As patients with NSCLC have a significantly better prognosis than those with small cell lung cancer or mesothelioma, we will stratify by the underlying diagnosis to ensure adequate and balanced representation between the two study groups.

7.5.2. Stratification Factors and Their Impact on Design
Stratification factors do not impact the design of the study but will be considered during data analysis to compare baseline statistics and outcomes based on initial eligibility criteria to participate in the study. Post-hoc comparisons between patients with NSCLC and those with small cell lung cancer and mesothelioma will determine if different outcomes existed between these two groups.

7.5.3. Early Stopping Rules
Not applicable. Participants will be included in the study as long as they continue seeking care at the study sites. Death or discontinuation of clinic visits are the only reasons for participants to not be included in the full intervention.

7.5.4. Definition of and Allowance in Design for Unevaluable/Ineligible Participants
No unevaluable and/or ineligible participants will be included in this study.

7.5.5. Handling of Missing Data
The analyses will initially focus on patients who completed the 24-week assessment to compare stepped PC with early integrated PC without imposing assumptions about missing data. We will also use the intention-to-treat principle with all randomized subjects, conducting sensitivity analyses to explore how various assumptions about missing data and differences between completers and non-completers affect the estimated outcomes. If data appear to be missing at random, we will employ multiple imputation methods. However, if we find that participants do not complete assessments due to progressive illness, suggesting missing data are not random, we will employ pattern mixture modeling or terminal decline joint modeling approach to address missing data.

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9.0. Appendices

9.1. Suggested Template for Emailing Clinicians: Permission to Approach Patient

Dear **[MD/NP]**,

We are screening patients for the randomized study of stepped palliative care versus early integrated palliative care in patients with advanced lung cancer. As a reminder, ALL study patients will receive longitudinal, concurrent care from a palliative care clinician but the timing in which the visits are scheduled will vary by study group.

We plan to approach/contact **[patient] [MRN]** at one of their upcoming appointments to offer enrollment in this study. /We plan to contact **[patient] [MRN]** via telephone to offer enrollment in this study.

Please respond to this email if you prefer to approach the patient for study participation yourself or if you prefer that we do not approach this patient (and please indicate the reason why).

Thank you for your support,
[Study Principal Investigator]

9.2. Suggested Voicemail Script for Contacting Patients to Offer Enrollment

Hello, my name is **[study staff member]** and I am contacting **[patient]** from **[institution]** on behalf of **[oncologist]** to offer participation in a research study. If you are interested in learning more about this opportunity, please contact our study staff at **[staff phone number]** at your convenience. Thank you for your time.

9.3. Suggested Template for Emailing Oncology Clinicians: Notification about Step 1 Patients Following Enrollment

Dear **[MD/NP]**,

Thank you for allowing me to meet with **[patient]** to introduce the Stepped Palliative Care study. After reviewing the details of the study and the consent form, [patient] signed consent and completed baseline measures. **[Patient]** will begin the study on Step 1 and will see palliative care at a reduced frequency following the initial visit. They will see palliative care again only following hospitalization or progression. Please plan to manage this patient's prescriptions, since they will not see PC regularly.

Thank you for your continued support of our study,
[Study Staff Member]

9.4. Suggested Template for Emailing Oncology Clinicians: Notification about Step 1 Patients on the Day of their First Oncology Appointment since Enrollment

Good morning,

You have an appointment with a Stepped Palliative Care [**protocol number**] study patient today.

[Last name, first name] (MRN) is on Step 1 of the study and **[will see/is seeing]** palliative care at a reduced frequency following the initial visit. They will see palliative care again only following hospitalization or progression. As a reminder, we will follow [**patient name**] closely and if their quality of life decreases, the palliative care visit frequency will increase to monthly. Please plan to manage this patient's prescriptions, since they will not see palliative care regularly.

Thank you for your continued support of our study,
[Study Staff Member]

9.5. Suggested Verbal Script for Questionnaire Administration

Hello—is **[name of patient]** there? Hi, my name is **[research coordinator's name]**; I work at the **[institution name]**, and I am calling about the palliative care research study in which you are participating. Is now a good time to talk briefly?

If yes →*Move on to next section.*
If no → "Is there a better time at which I could call back?"

As part of the study procedures, we would like to ask you to complete a questionnaire over the phone. Do you have about 15 minutes to complete it with me now?

If yes →"Great, thank you." *Proceed to administering the questionnaire.*
If no → "Is there a better time at which I can call back so that we could complete the questionnaire together?"

9.6. Suggested Paper Cover Letter when Mailing the Baseline Questionnaire to Participants

Dear **[name of patient]**,

We are writing from **[institution name]** to see if you would be willing to take a questionnaire to complete your enrollment in the Stepped Palliative Care study that you discussed with our study staff [over the phone/at MGH] on **[DATE]**. The questionnaire should take about 15 minutes to complete. We have included a postage paid envelope for return of the questionnaire at no cost. If you prefer to do this electronically or by phone, please contact us at the phone number below.

We greatly appreciate the time you have taken to participate in this study and for completing this questionnaire. Our study staff will contact you upon receipt of this questionnaire to confirm your enrollment and share the details about your first palliative care appointment.

Thank you very much,
[study staff name and contact information]

Estimado/a **[name of patient],**

Le estamos escribiendo de parte de **[institution name]** para ver si usted estaría dispuesto a tomar una encuesta y completar la registración en el estudio de cuidados paliativos que usted discutió con nuestro equipo de investigación por teléfono el **[FECHA]**. La encuesta debe tomar 15 minutos en completar. Hemos incluido un sobre prepago para la devolución de la encuesta sin costo. Si usted

preferiría completarla electrónicamente o por el teléfono, por favor contáctenos al **[número de teléfono].**

Agradecemos mucho el tiempo que ha tomado para participar en este estudio y por completar esta encuesta. Nuestro equipo de investigación se comunicará con usted al recibir la encuesta para confirmar su registración y compartir los detalles de su primera cita con cuidados paliativos.

Muchas gracias,
[study staff name and contact information]

9.7. Suggested Paper Cover Letter when Mailing the Questionnaires to Participants

Dear **[name of patient]**,

We are writing from **[institution name]** to see if you would be willing to take a questionnaire that is part of the Stepped Palliative Care study that you are participating in with **[oncology clinician name]**. The questionnaire should take about 15 minutes to complete. We have included a postage paid envelope for return of the questionnaire at no cost.

We greatly appreciate the time you have taken to participate in this study and for completing this questionnaire.

Thanks very much,
[study staff name and contact information]

Distinguido **[name of patient],**

Estamos escribiendo de **[institution name]** para ver si usted estaría dispuesto a tomar una encuesta que es parte del estudio de cuidados paliativos que estás participando en con **[oncology clinician name]**. La encuesta tomará 15 minutos para completar. Hemos incluido un sobre de franqueo pagado para la devolución de la encuesta sin costo.

Agradecemos mucho el tiempo que ha tomado para participar en este estudio y para completar esta encuesta.

Muchas gracias,
[study staff name and contact information]

9.8. Suggested Email Cover Letter when Emailing the Baseline Questionnaire to Prospective Participants

Dear **[patient first name]**,

I hope you are doing well. We are writing from **[institution name]** to see if you would be willing to take a questionnaire to complete your enrollment in the Stepped Palliative Care study that you discussed with our study staff on **[DATE]**.

We are hoping that you can complete this questionnaire as a part of your participation. It would be great if you could try to complete it in the next few days.

Please feel free to reach out to me with any questions or concerns.

Thank you,
[Name and contact details of study staff member]

9.9. Suggested Email Cover Letter when Emailing the Questionnaires to Participants

Dear **[patient first name]**,

I hope you are doing well. As a reminder, I am the research coordinator for the study you are enrolled in at **[institution]**.

We are hoping that you can complete this questionnaire as a part of your participation. It would be great if you could try to complete it in the next few days.

Please feel free to reach out to me with any questions or concerns.

Thanks,
[Name and contact details of study staff member]

9.10. Suggested Email Template when Sending Consent Form Copy to Participants via Email

Dear **[patient first name]**,

I hope you are doing well. We are writing from MGH to share a copy of the consent form for the Stepped Palliative Care study that you discussed with our study staff on **[MONTH + DAY, YEAR]**. I will reach out shortly with a baseline questionnaire.

Please feel free to reach out to me with any questions or concerns.

Thank you,
[Name and contact details of study staff member]

9.11. Suggested Email Template when Scheduling PC Visits with Participants via Email

Hi **[patient first name]**,

I hope you are doing well. As a reminder, I am the research coordinator for the study you are enrolled in at **[institution]**. I am reaching out to schedule a follow up appointment with **[PC PROVIDER]**.

Do you have any availability on **[WEEKDAY, MONTH + DAY]**? **[PC PROVIDER]** is available [at for any 30 minute session beginning at xx:yy-yy:xx./the following times:]

Thank you so much,
[Name and contact details of study staff member]

9.12. Data Safety Monitoring Plan

The following procedures will be followed, in compliance with the Policy of the NCI for Data and Safety Monitoring of Clinical Trials.

A. Responsibility for Data Safety and Monitoring
As a supportive care efficacy trial with low risk to participants, the study will have a data safety monitoring plan and committee. Specifically, participation in this trial carries no risk of a Serious Adverse Event (SAE) and therefore the NCI does not require monitoring by a Data Safety Monitoring Board (DSMB). Members of the MGH-based study staff (Temel, Greer, and Jackson) will serve as the data safety and monitoring committee (SMC). The study PI will be responsible for submitting necessary reports to the sponsor institutional regulatory board, as well as the NCI. The study PI will collaborate with the two site-PIs to submit reports to their institutional regulatory board.

B. Procedures for Monitoring Safety, Minimizing Research-Associated Risk, & Protecting Confidentiality.
The SMC will meet weekly in person to review randomization data, as well as adverse events, across all three study sites. These adverse events are tracked for IRB submission as well. Per our IRB, study related adverse events are reported in real time, and study unrelated adverse events are reported with the continuing review. Safety information for this study will be reviewed by the SMC in an unblinded manner. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the committee. Unblinded data will not be released to the investigators unless necessary for safety reasons.

a. Protocol Fidelity and Investigator Compliance. To ensure protocol fidelity and investigator compliance, the SMC will audit and review a random selection of 5 participant cases from each study site each year. This process will include a review of study procedures for conforming with informed consent requirements and investigative team compliance with all study activities, as outlined in the protocol.
b. Minimizing Research-Related Risks. The study PI/project manager will oversee weekly meetings with the participating institutions' research staff members to discuss study operations and ensure consistent and safe implementation of study procedures, address problems or challenges with study procedures, and review general training issues. During this meeting, the study PI/project manager will review study procedures and address issues related to participant recruitment and enrollment, and data collection, management and analysis. The study PI/project manager will also provide continuous training to address any issues with study operations and ensure ongoing review of the protocol and assessment procedures. The PI will review and address any participant risks and human subject issues. In addition, to ensure appropriate implementation of the study intervention and guard against any risk to participants, the primary and site PIs (i.e., Drs. Temel, Kumar, and Kamal) will ensure a rigorous training and supervision process for the study staff.
c. Protection of Participant Confidentiality. Confidentiality will be assured by study procedures to ensure that participants will be identified on all study materials only by participant number, visit number, and date of visit. By recording the study data in this manner, the information can be considered 'de-identified,' and therefore compliant with the Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule") of the Health Insurance Portability Act of 1996 ("HIPAA"). All study research staff will be trained in standard procedures to ensure that no participant names are directly associated with any data forms, but rather use designated ID codes to protect participant confidentiality. The study staff will present reports to the SMC on any breach to participant confidentiality, reasons for the breach, and a proposed plan for corrective action.
d. Ensuring Data Validity and Security. The study PI had coordinated research initiatives over the past ten years that have established procedures and technologies for data collection, management, and security. Dr. Temel will oversee that aspect of the study, and the study staff

will have operational responsibility for data collection, de-identification, and management. Specifically, the study staff will develop a study specific data management protocol and standard operating procedures for the creation and testing of all study forms, data collection, quality control, and data extraction. We will provide ongoing oversight of data management throughout the study, and will be responsible for generating reports and datasets for quality control and data analysis. All data management activities will utilize REDCap, a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. REDCap (Research Electronic Data Capture) data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the study staff with planning assistance from Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. REDCap provides secure, HIPAA compliant, web-based applications with an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry.

e. Monitoring of Data Quality by the SMC. The SMC will review data quality and completeness from each of the participating sites twice yearly. They will review the progress of participant intake and retention; summary reports describing participant adherence with visits and evaluations as described in the protocol; and a summary of the completeness and quality of key data elements needed to characterize participants, their protocol adherence, and their primary and secondary outcomes. These reports will be used to evaluate the capacity of the data capture and processing to support scientifically valid analyses. For ease of understanding, reports will be done graphically, similarly to the CONSORT diagrams.

A. Procedures for Review and Reporting of Adverse Events and Unanticipated Problems.
Identification of adverse events may come through notification from the study participant, clinician, or from review of the electronic health record. In such circumstances, the PIs and investigative team will follow the following procedures:

a. Serious Adverse Events. Given that this study is a randomized trial comparing two delivery modalities of an evidence-based supportive care intervention, we do not anticipate any study-related events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). The proposed study population is comprised of individuals diagnosed with advanced lung cancer who frequently experience disease worsening, high rate of symptoms, and hospitalizations from the underlying disease and/or side effects of treatment. Therefore, as advanced lung cancer is a chronic-type terminal illness, regular fluctuations in cancer-related symptoms, disease worsening, hospitalizations, emergency department visits, and deaths are to be expected throughout the study, and we will not consider or report such events as SAEs in this trial.

b. Non-Serious Adverse Events. At yearly intervals during the course of the study and then again at its completion, the SMC will review unblinded summaries of the numbers and rates of non-serious adverse events by treatment group. To date, the majority of non-serious adverse events in our prior supportive care studies have been due to patient discomfort with the study questionnaires.

c. Other Safety-Related Reports. At yearly intervals throughout the course of the study, the SMC will also review unblinded summary reports of treatment retention and reasons for dropout, by treatment group.

d. Study Stopping Rules. If at any time during the course of the study, the SMC judges that risk to participants outweighs the potential benefits, the SMC shall have the discretion and responsibility to recommend that the study be terminated. We do not, however, have a pre-specified stopping rule given the low risk of this behavioral study to participants.

B. Multisite Study Data Safety and Monitoring.

The procedures for data safety monitoring and reporting will be the same for the three participating study sites. Throughout the course of the study, the primary PI will have monthly meetings with the site PIs to ensure consistent implementation of procedures for data safety monitoring and reporting. The SMC will review reports that include all relevant data stratified by study site.

C. External Factors That May Impact Safety of Participants or Ethics of the Study.
The PI will conduct a literature review every six months to ensure that no new developments have emerged that may affect the study or participants.

D. Advance Plans for Interim and/or Futility Analyses.
This study will not include interim and/or futility analyses.

E. Timely Reporting to the NCI.
The PI will report to the NCI within 7 days of occurrence of any unanticipated problems or unexpected adverse events that may be related to the study protocol; IRB-approved revisions to the study protocol that indicate a change in risk for participants; a summary of recommendations made by the SMC and the action plan for response; or notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

9.13. Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

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1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

***DF/HCC Multi-Center Protocol**: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.*

***Lead Institution:** One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.*

***DF/HCC Sponsor:** The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies. The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions.*

***Participating Institution:** An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.*

***Coordinating Center:** The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.*

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Jennifer Temel, will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- *Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.*
- *Ensure that the investigators, study staff members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.*
- *Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.*
- *Ensure all Participating Institutions are using the correct version of the protocol.*
- *Ensure that each participating investigator and study staff member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.*
- *Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).*
- *Maintain documentation of Adverse Event (AE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.*
- *Monitor progress and overall conduct of the study at all Participating Institutions.*
- *Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. NIH) reporting requirements are met.*
- *Review data and maintain timely submission of data for study analysis.*
- *Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.*
- *Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.*
- *Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.*
- *Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.*

2.2 Coordinating Center

The general responsibilities of the Coordinating Center, which will synonymous with the DF/HCC sponsor for this protocol, may include but are not limited to:

- *Assist in protocol development.*
- *Maintain NIH correspondence, as applicable.*
- *Distribute protocol and informed consent document updates to Participating Institutions as needed.*

- *Oversee the data collection process from Participating Institutions.*
- *Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.*
- *Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.*
- *Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federal wide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites*
- *Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.*

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- *Document the delegation of research specific activities to study personnel.*
- *Commit to the accrual of participants to the protocol.*
- *Submit protocol and/or amendments to their local IRB.*
- *Maintain regulatory files as per sponsor requirements.*
- *Provide the Coordinating Center with regulatory documents or source documents as requested.*
- *Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e., teleconferences).*
- *Update Coordinating Center with research staff changes on a timely basis.*
- *Register participants through the Coordinating Center prior to beginning research related activities.*
- *Submit AE reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.*
- *Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.*
- *Have office space, office equipment, and internet access that meet HIPAA standards.*
- *Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.*
- *Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.*

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- ***Non life-threatening revisions:*** *Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.*

- ***Revisions for life-threatening causes:*** *Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.*

- ***Protocol closures and temporary holds:*** *Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.*

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study staff who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- *Initial approval letter of the Participating Institution's IRB.*
- *Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.*
- *Participating Institution's IRB approval for all amendments.*
- *Annual approval letters by the Participating Institution's IRB.*

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPAA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB\, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e., Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

To register a participant, the following documents should be completed by the Participating Institution and e-mailed to the Lead Institution ***[***mghsteppc@partners.org***]***:

- *Signed de-identified informed consent document*
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Lead Institution will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Lead Institution will:

- *Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).*
- *Upon receiving confirmation of registration, the Coordinating Center will inform the Participating Institution and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.*

Protocol-specific interventions may not begin without confirmation from the Coordinating Center that the participant has been registered.

Randomization can only occur during normal business hours, Monday through Friday from 8:00 AM to 5:00 PM Eastern Standard Time.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of protocol-specific interventions. Protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Lead Institution, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the DF/HCC sponsor in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.9 Safety Assessments and Toxicity Monitoring

The study staff at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 5.6. As a supportive care trial entailing scheduled interactions with a palliative care clinician, this trial is of low risk to study participants. Specifically, participation in this trial carries no risk of a Serious Adverse Event (SAE).
Participating Institutions must report the AEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The DF/HCC Sponsor will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.10 Data Management

The DF/HCC Sponsor will develop case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

Participating institutions will participate in monthly conference calls to review the study progress and address any challenges with the study conduct The Coordinating Center will also send monthly emails to the Participating Sites to update them on the study progress.

4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. All Participating Institutions agreed to enroll a minimum of 160 patients per year.

5. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

5.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

5.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

5.4 Participating Institution Performance

The DF/HCC Sponsor, Coordinating Center, and the DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.