**FINAL PROTOCOL**

# Comparative Effectiveness of Early Integrated Telehealth versus In-Person Palliative Care for Patients with Advanced Lung Cancer

DF/HCC SOCIAL-BEHAVIORAL RESEARCH PROTOCOL

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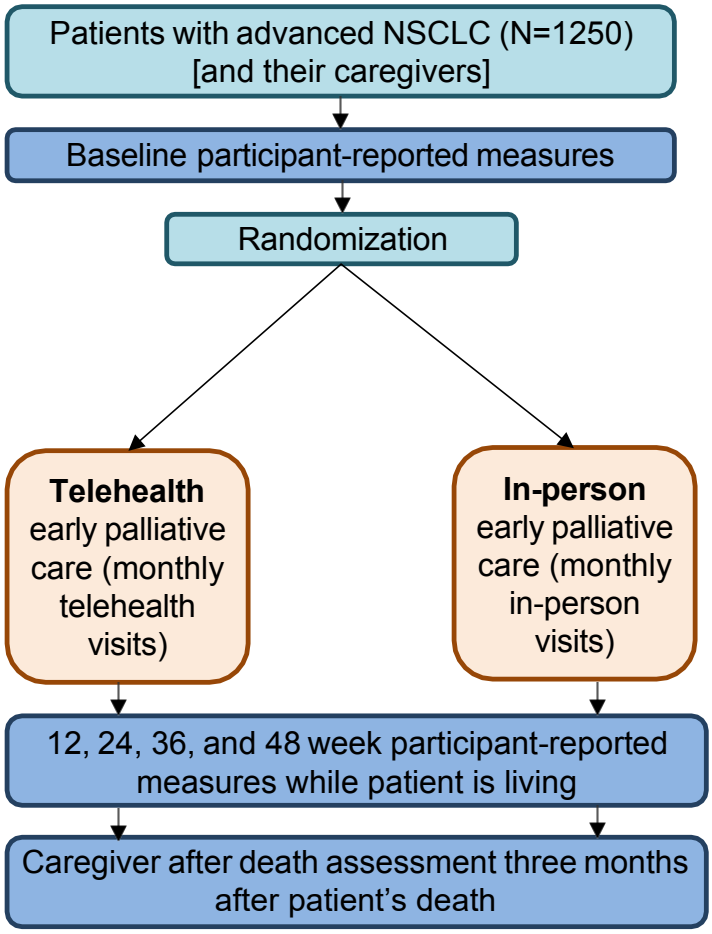
Section 1: Protocol Schema



Section 2: Body of Protocol

# Contents

# 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. Telehealth (i.e., the use of information and communication technology in health care delivery) is an effective strategy to increase patients' access to health care services when the numbers of specialty-trained clinicians are limited.[1] We seek to perform a multi-site comparative effectiveness trial of early integrated telehealth versus in-person PC in patients with advanced lung cancer. By demonstrating the equivalence of the telehealth delivery modality, 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.[2-9] 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.[3] 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.[6] 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.[7] 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.[10] 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.[11] 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.

**Early Integrated PC also Improves Outcomes in Caregivers of Patients with Advanced Cancer**

The practice of PC encompasses the psychosocial, emotional, and spiritual care needs of both patients and their caregivers. In our recent trial of early integrated PC in patients with advanced lung and gastrointestinal cancers, we invited caregivers of enrolled patients to participate in a secondary study evaluating the impact of this care model on caregiver-reported outcomes. The results showed that the caregivers of patients assigned to early PC had improvements in several QOL domains and lower depression.[12]

Moreover, even in the months closer to the patient's death, the caregivers of patients receiving early PC reported lower depression and anxiety compared to those receiving usual care.[12] Thus, early integrated PC improves the experience and outcomes of not only patients with advanced cancer but also their caregivers.

**Most Cancer Care Settings Lack Capacity to Provide Guideline-Concordant, Patient-Centered Early Integrated PC**

Based largely on the data described above, the American Society of Clinical Oncology (ASCO) published an Opinion Statement in 2012 recommending early PC for any patient with advanced cancer.[13] Similarly, the Institute of Medicine and the National Comprehensive Cancer Network recommend consideration of early PC for patients with advanced cancers.[14,15] By recognizing the value of PC for patients with advanced cancer, these recommendations represent significant progress in the delivery of comprehensive cancer care. However, the early integrated PC model studied to date included at least monthly visits with a PC clinician. Currently, most cancer care settings have insufficient outpatient PC services to provide this level of care to all patients with advanced cancer. Additionally, many individuals receiving cancer care in remote, resource-poor, and rural settings have no access to PC services.[16] Therefore, to provide guideline-concordant care, further research is critically needed to evaluate novel PC delivery models that increase patients' access to PC services in a patient-centered fashion.[17]

Patients with advanced cancer and their caregivers are burdened by frequent visits for oncology care, chemotherapy and radiation treatment, and radiographic studies. To address this, patients receiving early integrated PC typically meet with both their oncology and PC clinicians on the same day to help minimize additional trips to the cancer clinic. Yet, few institutions have sufficient numbers of PC clinicians, outpatient clinic space or support staff to provide such care in accordance with recommended guidelines.[17,18] If PC is to be delivered in a patient-centered fashion, novel models of service delivery are needed to reduce the burden of additional clinic visits, given transportation costs and disruptions to home and work schedules of both patients and their caregivers. While home-based PC models are being developed as an alternative to in-person clinical services, home care requires an even greater number of clinicians and is generally not feasible for remote areas where travel time would be prohibitive.[19] Therefore, the study of innovative service delivery models has the potential to increase access and efficient utilization of limited PC resources in a patient-centered fashion.

**Telehealth Increases Access and Efficiency with Limited Health Care Clinicians and Resources**

Telehealth (i.e., the use of information and communication technology in health care delivery) is an effective strategy to increase patients' access to health care services when the numbers of specialty-trained clinicians are limited.[1] Initially developed as a means to provide specialized care to patients with acute conditions such as stroke, telehealth services are expanding to the care of patients with chronic health conditions, especially given the growing interest among health care stakeholders such as physician organizations, health care systems, and insurance providers.[20,21] To date, telehealth for patients with chronic conditions has focused predominantly on asynchronous monitoring,

such as collecting vital signs of patients with congestive heart failure in the home setting and transmitting the information to clinicians.[22] However, health care stakeholders now recognize the need for the practice of medical care by clinicians through *telehealth* as a means to provide patient-centered care for patients in their homes.[23] A recent Cochrane review concluded that further research is needed to evaluate the effectiveness, efficiency and appropriateness of telemedicine.[24]

Telehealth enables clinicians to perform virtual house calls to provide patients "the care they need, the convenience that they desire, and the comfort they want."[25] Studies of telemedicine using video house calls with clinicians for patients with chronic health conditions, such as Parkinson's disease and diabetes, have demonstrated the feasibility, acceptability and preliminary efficacy of this delivery model.[26,27] While the use of video house calls has yet to be studied in the context of PC, Bakitas and colleagues evaluated telephone-based, psycho-educational interventions, delivered by PC-trained advanced practice nurses, for patients with advanced cancer and their caregivers.[3-5] The investigators observed an improvement in QOL and lower depression among patients with newly diagnosed poor prognosis cancers as well as lower depression in caregivers; however, the intervention did not increase rates of advance care planning or utilization of PC and hospice services.[3] Although these studies demonstrate the feasibility of providing such services via telehealth, the intervention failed to improve salient PC outcomes, including communication about EOL care preferences or the delivery of high quality EOL care. In contrast, the in-person early integrated PC model, which could be efficiently adapted to a video telehealth platform, is associated with improved patient-clinician communication and EOL care outcomes.

**Lung Cancer is an Ideal Population in which to Study Early PC Models**

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.[7,28] However, treatment paradigms for patients with advanced lung cancer are changing rapidly.[29] 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.[30-35] 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.[36] Moreover, these patients often experience a high symptom burden and poor QOL at diagnosis, which intensifies throughout their illness course.[37]

**Scientific Premise of the Project**

We propose to transform the delivery modality of our proven efficacious in-person early integrated PC model to a telehealth platform, thereby enabling PC clinicians to provide virtual house calls and increase access to services in a patient-centered manner. If the proposed study demonstrates that telehealth is as effective as (or superior to) in-person PC, such findings would address a major evidence gap between the data supporting early integrated PC and lack of data regarding how to disseminate this care model most efficiently, equitably, and effectively. The 2016 ASCO Clinical Practice Guideline

Update on the integration of palliative and oncology care highlights this evidence gap by not only making a strong recommendation for early PC for patients with advanced cancer, but also acknowledging that PC resources are currently lacking to provide this essential care.[38]

## 2.0 Objectives

### 2.1 Primary Aim

To determine whether telehealth PC is equivalent to in-person PC for improving patients' QOL.

Hypothesis: Patients assigned to telehealth PC will report QOL that is equivalent to patients receiving in-person early integrated PC, with an equivalence margin of 4.0 points on the Functional Assessment of Cancer Therapy-Lung (FACT-L).

### 2.2 Secondary Aims

2.2.1 To determine whether telehealth PC is equivalent to in-person PC with respect to patient-clinician communication about EOL care preferences and length of stay in hospice.

Hypothesis 1: Telehealth will be equivalent to in-person PC in the rate by which patients communicate their EOL care preferences to their clinicians, with an equivalence margin of 8%.

Hypothesis 2: Telehealth PC will be equivalent to in-person PC with respect to patients' length of stay in hospice, with an equivalence margin of 6 days.

2.2.2 To compare the effect of telehealth versus in-person PC on caregiver participation in PC visits.

Hypothesis 1: Compared to caregivers receiving in-person PC, those receiving telehealth PC will participate in a higher percentage of visits with the PC clinician.

2.2.3 To compare patient and caregiver satisfaction with telehealth versus in-person PC.

Hypothesis: Patients and caregivers will be more satisfied with telehealth PC compared to in-person early integrated PC.

### 2.3 Exploratory Aims

2.3.1 To compare coping strategies in patients assigned to telehealth versus in-person PC.

2.3.2 To compare prognostic understanding in patients and caregivers assigned to telehealth.

2.3.3 To compare the effect of telehealth versus in person PC on caregivers'

outcomes, including QOL and mood.

2.3.4 To compare the effect of telehealth versus in-person PC on patients' mood.

## 3.0 Research Subject Selection

We will recruit 1250 patients with advanced NSCLC and up to 1250 of their caregivers (2500 total) receiving their care at Massachusetts General Hospital and Palliative Care Research Cooperative (PCRC) designated institutions to participate in a multi-site comparative effectiveness trial of early integrated telehealth versus in-person PC in patients with advanced lung cancer. Patients without willing or available caregivers are still eligible to participate in the study. Patients will be randomized using blocked randomization and stratified by site.

### 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 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 3 (symptomatic and in bed >50% of the day)
3. The ability to read and respond to questions in English or Spanish
4. Receiving primary cancer care at one of the participating sites
5. Age $\geq$ 18 years

Exclusion Criteria:

Patients will be excluded if:

1. They are already receiving outpatient PC or hospice services
2. They have cognitive or psychiatric conditions as determined by the treating oncologist to prohibit study consent or participation

### 3.2 Caregiver Eligibility Criteria

Inclusion Criteria:

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

1. Relative or friend who is identified by the patient participant and lives with the patient or has contact with them at least twice per week.
2. The ability to read and respond to questions in English or Spanish
3. Age $\geq$ 18 years

Exclusion Criteria:

1. 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 participating sites, the research team 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 research team will identify all patients with advanced NSCLC 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 or health record, as some patients with locally advanced disease cannot be treated for cure and some patients with metastatic disease are treated with curative intent. If the determination about treatment intent cannot be determined based upon the chemotherapy plan or documentation in the health record, the research team will confer with the oncology team about the goals of cancer treatment. We will institute the same patient screening procedures in all participating thoracic oncology clinics.

We are requesting a HIPAA Waiver of Authorization to Review Preparatory to Research from the Institutional Review Board (IRB). This waiver is being requested to allow the research team to screen the thoracic oncology clinic schedules and identify potential study participants from a minimal chart review. In accordance with the DF/HCC policy, this Waiver: (1) is being sought solely to review Protected Health Information as necessary to prepare a research protocol; (2) will not include removing Protected Health Information from the Covered Entity by the researcher, and (3) the Protected Health Information for which we are requesting access is necessary for research purposes.

**4.2** Participant Recruitment and Enrollment

We will use the same recruitment and enrollment procedures used in our previous and ongoing trials.[7,28] Prior to the study start, site investigators will meet with their respective thoracic oncology teams to review recruitment and enrollment procedures. Specifically, the research team 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, the research team will document the reason.

**4.3** Informed Consent Process

Either research team member 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 research team member 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 by a Spanish-speaking research team member or via the use of an interpreter as a first preference, or family member as a second preference. Spanish speaking participants may be given the institutional 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 research team 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 research team member 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 research team member or an oncology clinician may contact eligible, English speaking patients via telephone to obtain verbal consent using the HIPAA-compliant verbal consent form. Verbal consent procedures will not apply to Spanish speaking patients. If the patient does not answer the telephone, the clinician or research team member may leave a voicemail (see appendix).

**4.4** Baseline Completion and Registration

Patients will be asked to complete baseline demographic and study questionnaires in person, online, or over the telephone with a research team member on the day of consent. Patients will be registered for the study and randomized once the baseline demographic and study questionnaires are completed. If patients do not complete the baseline demographic and study questionnaires (either on paper in the clinic or at home, via email, or via telephone) within two weeks of signing informed consent or completing the verbal consent process, they will not be permitted to be enrolled on the study.

The research team will collect data from each patient who enrolls about whether they have a person who would fit the criteria to be an enrolled caregiver, and this data will be recorded for all enrolled participants. As caregivers are often not present at every clinic appointment, they will be eligible to consent, either in person or via telephone, for the study on the day that the patient is registered for the study and for four weeks thereafter. Caregivers will be asked to complete the baseline demographic and study questionnaires on the day of consent. If caregivers do not complete the baseline demographic and study questionnaires (either on paper in the clinic or at home, via email, or via telephone) within two weeks of signing informed consent or completing the verbal consent process, they will not be permitted to be enrolled on the study. However, patients may remain on study even if their caregiver is not eligible or does not remain on study. The research team may share the one-page study information sheet (see appendix) with the patient or caregiver to learn about the study as they decide to participate.

If the patient or caregiver requests additional information about palliative care, the

clinician or research team member may provide a brochure about palliative care, such as institutionally approved materials, 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"*. This additional information is meant to be a resource for potential study participants who are interested in learning more about palliative care.

If either the patient requests that we do not approach or contact the caregiver to participate in the study or if the caregiver defers study participation, the research team will document the reason. The clinician or research team member will also review the study procedures and consent form with caregivers and obtain written informed consent or verbal consent.

DF/HCC institutions will register eligible participants from all sites 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 or assessments.

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

Patients from other participating sites will be entered on the study centrally by the MGH research team. The research team from the participating institution will confirm eligibility criteria and fax or email the following documents to the research team at MGH: deidentified signed consent form/s or deidentified verbal consent form/s, copy of baseline assessment, and a completed eligibility checklist. The MGH research team 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 research team (independent from research team member who recruit, enroll and administer assessments to participants) will perform randomization procedures using on a computer-generated randomization schema, stratified by study site. The MGH research team will fax or e-mail the information about randomization to the research team at the participating site. The MGH research team may also call the research team at the participating site to verbally confirm registration and randomization.

Study participants will not be compensated for their participation in the research study.

## 5.0 Study Design and Methods

### 5.1 Study Design

We will conduct a randomized comparative effectiveness trial of early integrated telehealth versus in-person PC in patients with advanced lung cancer and their caregivers.

### 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. The research team will administer study assessments at baseline and multiple follow-up time points from the date that the baseline surveys were completed (with a +/- two-week window) to accommodate patient schedules (see table of Self Report Measures). 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, Prognosis and Treatment Perceptions Questionnaire, Caregiver Oncology QOL Questionnaire, Satisfaction with Care Delivery Questionnaire, and After Death Assessment, which we translated (forward and backward) into Spanish with a native Spanish speaking clinician.

Patient Measures:
Demographic Questionnaire: Participants will self-report their gender, race/ethnicity, marital status, religion, education level, employment status, tobacco use, computer experience, 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.[39] 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.[40] 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.[7,11]

Hospital Anxiety and Depression Scale (HADS): The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week. [41]

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.[42]

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."[43] The psychometric properties of the Brief Cope have been demonstrated in studies of patients with serious illness and cancer.[43,44] 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).

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 receive mental health services external to the hospital or access services which are not routinely documented in the electronic health record (EHR).

Prognosis and Treatment Perceptions Questionnaire (PTPQ): The PTPQ is a tool that assesses patients' (and their caregivers') illness understanding, communication about prognosis and goals of care, as well as discussions and preferences regarding EOL care.[45] 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 patients with cancer.[46]

The Satisfaction and Care Delivery Questionnaire: is a 13-item satisfaction questionnaire which assesses patients' satisfaction with their PC visits. This questionnaire is adapted from the Visit-Specific Satisfaction Instrument (VSQ-9).[47] Each response item is given a score of 0-4 and items are summed together to obtain a composite satisfaction score. This will be given starting at week 12.

Caregiver Measures:
Demographic Questionnaire: Caregivers will report their age, gender, race/ethnicity, marital status, religion, education level, relationship to the patient and travel time to the cancer center.

Caregiver Oncology QOL Questionnaire (CARGOQOL): The CARGOQOL is a 29-item, well-validated instrument to measure caregiver QOL in multiple domains.[48]

HADS: The HADS is a 14-item questionnaire that contains two 7-item subscales assessing depression and anxiety symptoms during the past week. [41]

PTPQ: The caregiver PTPQ is a tool that assesses caregivers' perceptions of their loved ones' illness and prognosis and their communication with their doctors about their prognosis and EOL care preferences.[45]

The Satisfaction and Care Delivery Questionnaire (for caregivers): is a 12-item satisfaction questionnaire which assesses caregivers' satisfaction with the PC visits. This questionnaire is adapted from the Visit-Specific Satisfaction Instrument (VSQ-9).[47] Each response item is given a score of 0-4 and items are summed together to obtain a composite satisfaction score. This will be given starting at week 12.

After Death Assessment: We will ask family caregivers to rate care in the last week of life using a 10-point scale for (1) quality of patient's death (ranging from "worse possible" to "best possible); (2) physical distress (ranging from "none" to "extremely distressed"); and (3) psychological distress (ranging from "none" to "extremely upset").[46]

**5.3** Description of Intervention

5.3.1 Multi-site research team training

To ensure vigorous recruitment and enrollment, all study lead PC investigators and research team members will participate in a one-day in-person training session in Boston. The MGH-based investigative team has conducted seven prior and ongoing PC trials in oncology. Thus, we have considerable experience training research teams to: (1) identify potentially eligible patients via chart review, (2) track potentially eligible patients until their cancer diagnosis is documented, (3) communicate with oncology clinicians about patient eligibility, (4) obtain written informed consent or verbal consent from patients and caregivers, (5) monitor patients and caregivers longitudinally to administer study questionnaires, (6) collect data from the health record, and (7) enter all study data into the study specific database. The MGH investigators developed a training program for the site investigators and research teams on how to collaborate with oncology clinicians to implement this trial successfully.

We will draw on these experiences to conduct a one-day training session with the lead research team members (led by our MGH PC Research Project Manager Chardria Trotter) and site investigators (led by Drs. Temel, Jackson and Greer). The MGH TeleHealth Program will also participate in this one-day in-person session to educate the lead investigators on utilizing telehealth for virtual home visits and the research teams on training patients and clinicians to use the technology.

Finally, we will facilitate quarterly teleconference calls with the site investigators and monthly calls with research team members to ensure vigorous recruitment and address any implementation challenges. Ms. Trotter will lead the teleconference calls with the research teams to address any difficulties with patient identification, recruitment, enrollment, and data collection. The MGH based study investigators will lead the teleconference calls with the site investigators to address any issues with study implementation as well as perform site visits as necessary to provide more direct assistance with study issues. The PCRC has extensive experience overseeing multi-site trials and will also support participating institutions through email communication, teleconference calls, and site visits throughout the study. To conduct this study with established research principles, site visits may be conducted during the study to evaluate study conduct. Sites will be monitored by the PCRC for patient enrollment, compliance with protocol procedures, completeness and accuracy of data entered, and the occurrence and reporting of any study related challenges.

5.3.2 Telehealth Arm

The research team will contact patients randomized to telehealth within three business days of enrollment to inquire if they have video capacity (camera and sufficient internet connection) for telehealth visits. Patients who do not have video capacity will be sent a

tablet with cellular service, which will be programmed for secure videoconferencing only. Upon request, patients may receive an instructional guide on how to operate the tablet device and currently approved telehealth software. The research team will contact patients (and caregivers who wish to participate in the telehealth visits from a separate location) to conduct a videoconference test call prior to the first telehealth PC visit. Any patients whose equipment is not sufficient for the videoconference platform will be sent the study iPad with cellular service. Caregivers at other locations from the patient wishing to join telehealth visits will be required to use their own video and cellular service.

Video visits will be conducted using any HIPAA-compliant vendor that is licensed for clinical use and meets institutional informational security regulations. Sites will practice in accordance with their institutional policies for practicing medicine via telehealth across state lines. Sites will be encouraged, but not required to use the video visit platform supported by MGH. If sites chose to utilize a non-MGH supported video visit platform, they must obtain approval from the MGH study team.

The first visit with the PC clinician will be conducted in person in the oncology clinic within four weeks of enrollment to enable the patient and clinician to establish rapport. All subsequent visits will take place in patients' homes (or the setting of their choice) via telehealth at least every four weeks until death. Patients admitted to rehabilitation or skilled nursing facilities should continue to have contact with PC via telehealth at least every four weeks if possible. PC can continue to perform at least monthly telehealth visits with patients receiving hospice services, at their discretion. PC clinicians may see patients more frequently than every four weeks at their discretion. Patients scheduled to meet with PC clinicians who do not speak their native language will be seen in conjunction with an interpreter service used by the hospital or with a family member or friend who speaks the language. As PC and oncology clinicians will not be meeting patients in the same location, the PC clinician should make every effort to communicate with the oncology clinicians via email or telephone or in person after each patient encounter.

If technical problems occur with the telehealth technology during a patient's scheduled virtual visit, then the PC clinician should immediately switch to calling the patient and conducting the visit via telephone. The PC clinician should notify the research team to address the technical issue prior to the patient's next scheduled telehealth appointment.

Patients may be scheduled to meet with the PC clinician in the clinic if requested by the patient or a clinician. If a patient has an in-person visit with the PC clinician, they will still be scheduled for their telehealth visits every four weeks.

If a patient defers telehealth visits but is still participating in the study, they should continue to have in-person or telephone contact with the PC clinician at least every four weeks. The patient should be encouraged to reinitiate telehealth visits by the PC clinician or research team when possible.

Participating sites are not required or prohibited from submitting claims for telehealth visits. Submitting claims for telehealth visits will be at the discretion of the participating institution and should comply with state and federal laws and regulations that govern the practice of medicine. However, sites that choose to submit claims must ensure that patients are not charged in excess of their insurance copayment. Participating sites are required to ascertain their state laws and regulations that govern the practice of medicine, as this is not the responsibility of the funding agency (PCORI) or lead study site (MGH).

5.3.3 In-Person Arm

Patients randomized to in-person PC will be scheduled for their first PC visit within four weeks of enrollment and then at least every four weeks thereafter until the patient is no longer coming into the clinic (i.e. due to enrollment in hospice) or death. PC visits will be scheduled on the same day as oncology visits unless the patient is agreeable to scheduling the PC visit on a different day. Joint visits with PC and oncology (with both clinicians seeing the patient together in one visit) are recommended but not required. PC clinicians may see patients more frequently than every four weeks at their discretion. If patients do not have a scheduled visit to the cancer center the PC clinician will contact them via telephone within four weeks of their prior appointment to conduct the visit. Patients admitted to rehabilitation or skilled nursing facilities who are still coming into the cancer clinic for oncology visits should continue to meet with PC at least every four weeks. Patients who are receiving hospice services but still coming into the cancer clinic for oncology visits should continue to meet with PC at least every four weeks. Patients scheduled to meet with PC clinicians who do not speak their native language will be seen in conjunction with an interpreter service used by the hospital or with a family member or friend who speaks the language. In-person PC visits will require a standard co-payment as per the patients' insurance requirements, and PC will bill for the services.

5.3.4 Both Study Arms

PC clinicians will document all patient encounters (in-person, telehealth, or telephone) in the patient's medical records. They will also complete an electronic survey after each clinical encounter to note the topics addressed during each study visit and whether any caregiver was present (see Data Collection).

If participants on either arm miss their scheduled visit and it cannot be rescheduled within four weeks of their prior visit, the PC clinician will attempt to contact them via telephone within seven days from the missed visit to conduct a visit via telephone. The PC clinician will document the telephone calls in the health record. If the patient is unable to be reached by telephone, the PC clinician will document in the health record 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. Patients 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.

While the study protocol entails every four-week patient 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. We will document missed contact as a minor violation 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.

If the standard practice of the participating PC service is to have the inpatient PC team follow patients who receive outpatient PC if they are admitted to a hospital, the inpatient PC team will follow this practice and see the patient during their hospitalization.
If patients are admitted to the hospital and miss a scheduled PC visit, they will have four weeks from the date of discharge for their next in-person or telehealth visit.

**5.4** Data Collection

The research team will administer study assessments at baseline, and every 12 weeks (from the date patient baseline was completed) up to 48 weeks with a two-week window to accommodate patient schedules and will collect measures during regularly scheduled visits when possible. We have utilized similar data collection strategies in our prior trials. We will ask participants to provide their email address to allow us to send study assessments using a secure electronic system when patients do not have a scheduled, in-person appointment within the follow-up time points. Patients who opt out of using secure email may either receive paper copies of the survey by mail or complete the questionnaires verbally over the telephone. The assessment battery takes approximately 15 minutes to complete. Patients who are receiving hospice services will not be asked to complete study assessments. Table 1 depicts the assessments, measurements, and time points for the data collection.

We will contact caregivers approximately 3 months after the patient's death to complete the After Death Assessment either via email, telephone, or paper. If they are unable or unwilling to complete the questionnaires, the research team will attempt to contact the caregiver again in one month. For caregivers who refuse participation at any time, we will document their refusal and make no further attempts at data collection. Caregivers who do not object to being contacted at a future time will receive monthly reminders via telephone, mail or email until six months after the patient's death.

*Table 1. Self-report instruments and time-points for administration.*

| Measures | Baseline | Week 12 | Week 24 | Week 36 | Week 48 | 3-6 Months After Death |
|---|---|---|---|---|---|---|
| **Patient Measures** | | | | | | |
| Demographic Questionnaire | X | | | | | |
| Functional Assessment of Cancer Therapy – Lung (FACT-L), Patient Health Questionnaire – 9 (PHQ-9), Hospital Anxiety and Depression Scale (HADS), Brief Cope, Prognosis and Treatment Perceptions Questionnaire (PTPQ) | X | X | X | X | X | |
| Satisfaction and Care Delivery Questionnaire | | X | X | X | X | |
| Self-Administered Comorbidity Questionnaire (SCQ) | X | | | | | |
| **Caregiver Measures** | | | | | | |
| Demographic Questionnaire | X | | | | | |
| Caregiver Oncology QOL (CAROQOL), HADS, PTPQ | X | X | X | X | X | |
| Satisfaction and Care Delivery Questionnaire | | X | X | X | X | |
| After Death Assessment | | | | | | X |

5.4.1 Data from Electronic Health Record:

Clinical information regarding tumor type, 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 18-months from the date the last patient enrolled on the study. We will collect data on: (1) outpatient (in-person and telehealth) 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 Data on PC Visits and Resource Utilization:

1. PC clinicians will enter data on the topics addressed during the study visit after each patient encounter, using a Research Electronic Data Capture (REDCap) survey. The domains included in the REDCap survey correspond to the those in the Early PC Treatment Guide to allow the PC clinician to document the content areas addressed during the visit, any referrals or medications prescribed, and whether a caregiver was present.[50] The PC clinician will also document the type of visit (in-person, telehealth, or telephone) and the approximate duration of the visit. In our recent MGH trial, all PC clinicians completed REDCap entries after their clinical interactions with study patients for over 99% of their encounters. We will use the identical successful study procedures to

ensure documentation of all PC clinical interactions in this proposed trial. Prior to the study start, we will train the lead investigators from each site on the use of the REDCap survey and importance of entering these data. The site lead investigators will then train their participating PC clinicians on completing the REDCap survey during the study period. On the morning of each patient encounter, a research team member will send a secure email with the patient's 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 email reminders until the end of the 28-day window. We will not accept REDCap entries more than 28 days 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.

#### 5.4.3 Data Storage:

Patient data will be collected at each institution using REDCap. Each site will maintain their own separate list of participant names and study IDs. Participants will be identified on study forms and in the REDCap database by participant number only. To further prevent the loss of confidentiality, all electronic information stored on the main database within MGH is password protected, and is protected by anti-virus software. Only the research team will have access to the study data on shared file areas. We are requesting a partial HIPAA waiver of authorization to identify potential study participants.

Data abstracted from the health record in Section 5.4.1will be maintained in REDCap, which is a free, secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group.

## **5.5** Description of Study Processes

### 5.5.1 Instrument Administration

The research team will administer study assessments at baseline and multiple follow-up time points (see table of Self-Report Measures) with a +/- two-week window to accommodate patient schedules. The assessment battery takes approximately 15 minutes to complete. The baseline assessments and follow-up measures may be completed either in the clinic, online via REDCap email, on paper at home, or via telephone (see cover letters for mailed and emailed surveys in appendix). We will attempt to collect follow-up self-reported measures in person at scheduled visits to the outpatient clinic whenever possible. 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.

Spanish speaking participants will have the option of completing follow-up assessments in -person as a first preference or otherwise via mail. Spanish version questionnaires will not be administered over the telephone (due to the fact that research assistants may not speak Spanish) nor via email as the REDCap assessments cannot be in multiple languages.

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.

5.5.2 PC Intervention Administration

Drs. Greer and Jackson developed the Early PC Treatment Guide based upon our prior studies that details the elements of PC in the outpatient care setting.[50-52] This guide does not determine the timing of addressing each of the content areas, as the relevance of the topics (e.g., symptom management and advance care planning) depends on the patient's course of illness and experience with cancer. However, it does provide guidance for PC clinicians about addressing each content area, when appropriate in the patient's course of illness. We also developed a series of training videos to illustrate the techniques included in the manual. Both the intervention guide and training videos are being used in our ongoing NCI Alliance for Clinical Trials multisite PC trial. For the proposed study, all participating PC clinicians will undergo training to ensure that the provision of services is consistent across study sites. We will utilize a "train-the-trainer" approach by having the study site lead PC clinicians participate in a one-day training session in Boston to educate them on the key components of the intervention, to standardize and troubleshoot the delivery of the intervention in each setting, and to prepare them to train their respective clinical staff to deliver the intervention. Prior to the study start, all participating PC clinicians will watch the PC and telehealth training videos, review the intervention guide, and read several required papers on the early PC model.

The practice of early integrated PC includes six domains: (1) Developing and maintaining the **therapeutic relationship** with patients and caregivers; (2) Assessing and treating **patient symptoms;** (3) Providing support and reinforcement of **coping with advanced cancer** in patients and caregivers; (4) Assessing and enhancing **prognostic awareness and illness understanding** in patients and caregivers; (5) Assisting with **treatment decision-making**; and (6) Planning for **EOL care**. Although the content domains of early PC often occur across multiple sessions or several may occur within a single consultation, the Early PC Treatment Guide presents the information according to the types of PC interventions that occur most prominently during the following time frames: initial visits at the initiation of treatment; visits throughout the entire course of disease; visits at clinical turning points (e.g., changing to a new regimen of chemotherapy or after being discharged from the hospital); and visits upon the conclusion of ambulatory treatment and/or transition to hospice services. A summary of the treatment guide is included in Table 2 below:

*Table 2. Summary of palliative care treatment*

| Timing | Domain | Elements | Key Points |
|---|---|---|---|
| Initial Visits | Therapeutic Relationship | • Introducing PC<br>• Understanding the Patient and Caregiver Experience<br>• Building Trust with the Patient and Caregiver | • Develop a strong therapeutic relationship with patients and caregivers<br>• Learn about the values, life goals, and experiences of patients and their caregivers both prior to and after the cancer diagnosis<br>• Develop trust and credibility with patients and caregivers by providing reassurance and outlining parameters of communication |
| All visits | Patient Symptoms | • Preparing for Symptoms<br>• Assessing & Treating Symptoms<br>• Coordinating Symptom Management with Oncology<br>• Providing Referral for Symptom Management | • Clarify the symptoms the patient will likely experience and offer reassurance about the methods for reporting and treating symptoms<br>• At every visit, elicit existing and new symptom concerns<br>• Maintain ongoing, effective communication with oncologists to define mutual collaboration and work within their preferred practice patterns<br>• 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<br>• Discussing & Advocating for Different Methods of Coping<br>• Supporting Caregiver Coping<br>• Providing Referral for Additional Support | • Recognize that patients and caregivers bring their own expertise in coping to the current circumstance based on prior experiences<br>• Introduce strategies to help improve adjustment and meaning in life (e.g., behavioral, cognitive, and spiritual approaches; social support)<br>• Bolster caregiver coping by assessing burden, enhancing their communication with patients, and recommending additional support<br>• 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<br>• Exploring Goals & Values<br>• Assessing & Informing Patient Expectation of Prognosis<br>• Conducting Separate Conversations with Caregivers | • Consult with the oncologist to ensure the care team is consistent with their understanding of the patient's prognosis<br>• Assess patient's hopes and expectations for treatment and future to clarify the patient's level of prognostic awareness<br>• Recognize that illness understanding often vacillates between more & less realistic expectations and work to improve prognostic awareness<br>• Include both patients and caregivers in conversations about prognosis and illness understanding when possible |

| | | | |
|---|---|---|---|
| | Treatment Decision-making | • Assessing Patient Values in Treatment Decision-Making<br>• Discussing Treatment Considerations<br>• Supporting Treatment Decisions | • Elicit information from patients and caregivers regarding their decision-making style, quality versus quantity of life concerns, and life goals<br>• Provide support for patients and caregivers to understand the efficacy, and risks and benefits associated with cancer treatment<br>• Clarify any misunderstanding about treatment, support patient decision-making and freedom to change course |
| Visits Near EOL | EOL Care | • Discussing EOL Care Options<br>• 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<br>• 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. The table below depicts the steps we will take to ensure the fidelity of our study design and intervention training and delivery.

*Table 3. Summary of methods for treatment fidelity*

| Types of Fidelity | Procedures to Ensure Fidelity | Fidelity Assessment |
|---|---|---|
| Study Design | • Intervention development based on a well-defined conceptual model and systematic review of literature<br>• Standardization of intervention dose with clear feasibility data based on prior work<br>• Minimization of cross contamination effects given both groups will receive PC | • Utilize evidence-based PC intervention guide developed through multiple prior trials<br>• Measure number of PC intervention visits and visit duration using electronic PC clinician encounter survey<br>• Measure number of in-person PC visits in the telehealth group and telephone visits in the in-person group |

| | | |
|---|---|---|
| Training | • Development of PC intervention guide and videos<br>• Initial in-person training of lead site investigators on PC intervention and use of telehealth<br>• Initial in-person training of site research team members on study procedures and use of telehealth<br>• Onsite training at each participating site with all PC clinicians providing care to study patients<br>• Quarterly conference calls (led by Drs. Temel & Jackson) with site investigators to address study issues<br>• Monthly conference calls (led by Chardria Trotter) with the research team to address study procedures<br>• Annual retraining seminar via video conferencing with lead site investigators | • Complete review of PC intervention guide and training videos<br>• Complete training of all site investigators in protocol administration, intervention delivery, and standardized material<br>• Complete training of research team members on study procedures, protocol and use of technology<br>• Assess pre- and post-knowledge that PC clinicians and research team members acquired during training<br>• Send meeting minutes from conference calls to all lead site investigators<br>• Send meeting minutes from conference calls to all site research team members<br>• Assess pre- and post-knowledge that lead site investigators acquired during retraining |
| Intervention Delivery by PC Clinicians | • Utilization of PC intervention guide with standardized content areas<br>• Completion of electronic survey after each study encounter to record the content and topics that the PC clinician addressed<br>• Documentation of clinical encounters in site medical record | • Conduct ongoing training of any new staff in standardized PC intervention guide and videos<br>• Review PC electronic surveys quarterly to ensure adherence to content (by Dr. Greer). These findings will be discussed during quarterly meetings with lead site investigators<br>• Review a random sample of PC visit notes quarterly to ensure adherence to content (by trained research team member) |

5.5.4 Special Concerns
The study investigators will 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 overall 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 PCRC designated participating sites.

**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 health record. In such circumstances, the PIs and investigative team will follow the following procedures:

Serious Adverse Events: Given that this study is 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 symptom burden, 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 adverse events in our supportive care studies. Examples of potential non-serious adverse events are participants' discomfort with the study assessments or with their assignment group.

5.6.2 Anticipated Reactions
As this is a behavioral study, there are no ingested medications, and no biomedical procedures. Thus, participants will not be at any risk for physical harm due to their 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.

5.6.3 Reaction Management
A detailed consent form will be signed by each participant following the explanations by the research team member or 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 research team members 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 research team 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 site PI and the primary oncology clinician will be notified. Should several participants express distress over an individual item, the research team 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 research team member has a formal obligation to inform the site PI and/or patient's PC or oncology team. These clinicians will determine the need to involve psychiatry and take further action as deemed necessary. The research team 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 patients PC or oncology team.

## 6.0 Ethical and Legal Issues

### 6.1 Confidentiality

Patient data will be collected at each participating institution using REDCap. Each site will maintain their own separate list of patient names and study ID's, which will be saved in password protected 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 shared between the PCRC and MGH using a secure data transfer.

Participants' responses to survey questions will remain confidential unless there is active suicidal ideation confirmed by the research team. Under these circumstances, as clearly stated in the patient consent form, participants will be informed that the research team has a formal obligation to inform the site PI and/or a member of the patient's PC or oncology team. These clinicians will then determine the need to involve psychiatry and/or take further action as deemed necessary.

## 7.0 Statistical Analysis

### 7.1 Primary Endpoint

To determine whether telehealth PC is equivalent to in-person PC for improving patients' QOL.

### 7.2 Secondary Endpoints

7.2.1 To determine whether telehealth PC is equivalent to in-person PC with respect to patient-clinician communication about EOL preferences.

7.2.2 To determine whether telehealth PC is equivalent to in-person PC with respect to length of stay in hospice.

7.2.3 To assess the superiority of telehealth versus in-person PC on caregiver

participation in PC visits.

7.2.4 To assess the superiority of telehealth versus in-person PC on patient satisfaction.

7.2.5 To assess the superiority of telehealth versus in-person PC on caregiver satisfaction.

**7.3** Exploratory Endpoints

7.3.1 To compare coping strategies in patients assigned to telehealth versus in-person PC.

7.3.2 To compare prognostic understanding in patients and caregivers assigned to telehealth.

7.3.3 To compare the effect of telehealth versus in person PC on caregivers' outcomes, including QOL and mood.

7.3.4 To compare the effect of telehealth versus in-person PC on patients' mood.

**7.4** Sample Size and Power Calculation

The primary endpoint of the study is to establish that telehealth PC is equivalent to in-person PC in patient-reported QOL at week-24, as measured by the FACT-L. 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 increased over the last few years. In our most recent randomized trial of early integrated PC versus standard oncology care, we observed a 7.5 (SD = 17.0) point difference in the FACT-L at week-24 favoring the early integrated PC group. Thus, we chose a conservative equivalence margin of 4 points, which is slightly more 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 equivalence margin would not reach the threshold of clinically meaningful difference in QOL between telehealth PC and in-person PC.[53] With 469 patients per group, we would have 95% power to establish the equivalence of telehealth PC compared to in-person PC on the FACT-L, with a two-sided alpha of 0.05, and an equivalence margin of 4 points. In our recent trial, we observed 25% missing data at 24 weeks. Therefore, we increased our sample size to 625 per group (total sample size = 1250 patients) to ensure we have adequate power to assess the equivalence of telehealth PC compared to in-person PC. Importantly, we chose to be conservative in estimating the sample size of this trial given the proposed testing of equivalence of telehealth PC to in- person PC on secondary outcomes as well as the planned subgroup analyses.

The proposed study will also have adequate power to assess for equivalence of telehealth PC compared to in-person PC in EOL communication and hospice length-of-stay. With a sample size of 1250, we will have 89% power, with a two-sided alpha of 0.05, to assess the equivalence of telehealth to in-person PC on patient-reported EOL communication with an equivalence margin of 8%, assuming the rate of EOL communication in the in-person PC group is 30% (based on our recent trial). With this sample size, we will also have 94% power to establish the equivalence of telehealth PC compared to in-person PC in hospice length-of-stay, with a two-sided alpha of 0.05, and an equivalence margin of 6

days (SD = 30.0). Given that this is an equivalence trial, we were conservative with the power estimations by using the highest observed standard deviation for all outcomes from our prior studies.

**7.5** Analysis Plan

Aim 1: To determine whether telehealth PC is equivalent to in-person PC for improving patients' QOL

We will begin with descriptive and graphical summaries of the endpoints to evaluate whether normality assumption is reasonable or if transformation is necessary. As the goal of the proposed study is to establish that patient-reported QOL with telehealth PC is equivalent to in-person PC, statistical testing for equivalence of the primary outcome will be two-sided with an alpha level of 0.05. We will use analysis of covariance (ANCOVA) models controlling for baseline values, and demographic and clinical factors (as necessary for any imbalances in baseline variables) to assess the effect of telehealth PC compared to in- person PC on QOL at 24 weeks. 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 (as necessary for any imbalances in baseline variables) when examining change between groups in QOL across multiple time points (i.e., baseline, week-12, week-24, week-36, and week-48). Lastly, we will test Heterogeneity of Treatment Effect (HTE) based on age, gender, race, computer experience, and enrollment of caregivers using interaction terms in the linear mixed models (see HTE analysis plan).

We will use ANCOVA models controlling for baseline values, and demographic and clinical factors as necessary to assess the effect of telehealth PC compared to in-person PC on patient mood (HADS, PHQ-9), and coping strategies (Brief Cope subscales) at 24 weeks. We will then utilize linear mixed models of the longitudinal data as described above to examine change in depression and coping between groups across multiple time points. Lastly, we will also compare illness understanding as measured by the PTPQ between the two groups through week-24, analyzing items using linear or logistic regression as appropriate and adjusting for demographic and clinical factors as necessary. The patient's final post-baseline PTPQ assessment within 24 weeks will be used.

Aim 2: To determine whether telehealth PC is equivalent to in-person 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?" (Yes/No). Although patients will complete this measure repeatedly during the study, we will use the final assessment for this analysis. We will assess differences between study groups in the rate of patients reporting "Yes" to this item using a Fisher's exact test with a two-sided alpha of 0.05 (equivalence margin=8%). We will then use a logistic regression model adjusting for any demographic and clinical factors that are imbalanced to assess differences in this dichotomous outcome between the two groups.

Additionally, we will assess the equivalence of hospice length-of-stay between telehealth PC and in-person PC with an equivalence margin of 6 days. We will use linear regression models adjusting for demographic and clinical factors as necessary to compare hospice length-of-stay between telehealth PC and in-person PC. Although hospice length-of-stay is not normally distributed, based on a sample size of 1250, the means would have a normal distribution (central limit theorem). Nonetheless, we will also perform poisson regression or Wilcoxon rank sum test to compare our results to those obtained with linear regression.

Aim 3: To compare the effect of telehealth versus in-person PC on caregiver participation in PC visits and outcomes

We hypothesize that caregivers receiving telehealth PC will participate in a higher proportion of their loved ones' PC visits during the study and that the participating caregiver will report better QOL at 24 weeks compared to those randomized to in-person PC (superiority aim). We will compare rates of caregivers' participation in PC visits between the two groups using mixed logistic models in to account for correlation between multiple PC visits for each caregiver (controlling for any imbalances in demographic and clinical factors). In addition, we will compare caregiver QOL (CARGOQOL) at week-24 between the study groups using ANCOVA adjusting for baseline values and any imbalances in clinical and demographic factors. We will also use linear mixed models of the longitudinal data to account for dependency among means over time and to control for demographic and clinical factors (as necessary for any baseline imbalances) when examining change between groups in QOL across multiple time points (i.e., baseline, week-12, week-24, week-36, and week-48).

We will compare caregiver mood on the HADS at week-24 between groups using ANCOVA models as described previously. We will then evaluate linear mixed models of the longitudinal data as described above to examine change in caregiver depression and anxiety symptoms between groups across multiple time points. To compare caregiver illness understanding (as measured by the PTPQ) within 24 weeks between groups, we will analyze items using linear or logistic regression analyses as appropriate to adjust for clinical and demographic variables. The caregiver's final post-baseline PTPQ assessment within 24 weeks will be used. Lastly, we will compare caregivers' perception of quality of care at the EOL (per the After Death Assessment) between the two groups using ANCOVA as described previously.

Specific Aim 4: To compare patient and caregiver satisfaction with telehealth PC versus in-person PC

We will measure patient and caregiver satisfaction with the intervention using The Satisfaction and Care Delivery Questionnaire. Although patients and caregivers will complete this measure repeatedly during the study, we will use the final assessment for this analysis. We will compare scores between the telehealth PC and the in-person PC using ANCOVA adjusting for study site and any imbalances between the two groups.

**Tests for Heterogeneity**. We will analyze Heterogeneity of Treatment Effect (HTE) by testing for interaction effects between the intervention group and the following variables: patient age (>65, ≤65), gender (male vs. female), race/ethnicity (White vs. Black; White

vs. Asian; Non-Hispanic White vs. Hispanic/Latino), computer experience (yes vs. no), and enrollment of caregiver (yes vs. no). The interaction terms will be tested in the linear mixed effects models examining patient QOL, depression, hospice length-of-stay as well as in a logistic regression model examining EOL communication. Observing an interaction effect ($P < 0.15$), [54] we will conduct separate subgroup analyses to assess for HTE of the telehealth intervention compared to in-person PC. Since this trial is testing the modality of delivery of PC (telehealth vs. in-person), all HTE analyses are considered exploratory and hypothesis-generating.

Prior studies have found that age, gender, and race can moderate the impact of PC in patients with cancer.[55,56] However, it remains unclear whether these factors would contribute to HTE of the telehealth intervention versus in-person PC. While studies utilizing mobile and computer technology have not shown that computer experience moderates the effect of interventions with adequate training,[57,58] we will specifically assess HTE based on computer experience to ensure generalizability of our findings. Lastly, since the use of telehealth may facilitate the presence of a caregiver during the appointments, we will also examine whether the enrollment of a caregiver contributes to the HTE of the telehealth PC compared to in-person PC.

Multiple testing: For all significance tests of secondary outcomes, we will use the false discovery rate (FDR) control method to address the issue of multiple tests. 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.

7.3.1 Stratification Factors and Intervention Allocation Plan for Randomized Studies.
Patients will be randomized between study groups using block randomization with stratification by study site.

7.3.2 Stratification Factors and Their Impact on Design
Stratification factors do not impact the design of the study but will be considered during the data analysis to compare baseline statistics and outcomes based on initial eligibility criteria to participate in the study.

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

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

**7.6** Handling of Missing Data
As in our prior PC trials, we will utilize rigorous methodology in reporting reasons for dropout and missing data during the study period. Specifically, we will report the following reasons for missing data: 1) patient death, 2) inability to complete the study

due to illness (too ill, hospitalized, hospice), 3) transfer of care, 4) withdrawal of consent, and 5) unable to contact for follow up. During the quarterly meetings with the lead site investigators, led by Drs. Temel and Jackson, the investigative team will review missing data rates for all participating sites to address any discrepancies in missing data compared to prior studies and to ensure rigorous retention and follow-up procedures.

The analyses will initially focus on the study completers to compare telehealth PC with in-person PC in patients who completed the protocol as intended without imposing assumptions about missing data. We will also use the intention-to-treat (ITT) 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 the study because of disease worsening, suggesting that data are not missing at random, we will employ terminal decline joint modeling approach, under the direction of the study statistician. The advantage of the terminal decline approach is that it models the trend in participant-reported outcomes backward from the time of the patient's death rather than prospectively from the time of enrollment. Thus, this approach controls for the known relationship between patient and caregiver QOL deterioration as the patient's death approaches. Notably, the terminal decline approach also accounts for missing outcome data. It utilizes a mixed-effects model for the longitudinal outcomes to provide valid and efficient estimates for missing outcome data. We will analyze the terminal decline and survival distributions with semiparametric models applied to both groups. Based on the fitted models, we will compare participant-reported outcomes at specified times before death (one, three, and six months prior to the patient's death). All models will adjust for baseline criterion scores, and any potential imbalances between the two groups. The terminal decline joint modeling approach has been utilized in multiple prior PC studies given its ability to account for deterioration in outcomes closer to death.[59]

## 8.0 Disseminating the Study Results

Expanding the application of telemedicine to the care of patients with chronic illness and establishing the effectiveness of a novel delivery model to increase access to PC for diverse patients in community settings are two questions of significant importance to patients and caregivers, PC clinicians, as well as health care institutions, insurers and organizations. Thus, our dissemination and implementation plan will address these key stakeholders. First, we will work closely with the MGH Public Affairs office to disseminate study findings to patients and caregivers through news outlets, such as newspapers (e.g., USA Today), social media (e.g., Twitter and Facebook), and news shows (e.g., NPR). We will also work with our lead site investigator and health care organization stakeholders to work with their respective media and public affairs offices to disseminate study findings throughout the country. Second, we will disseminate study results to the oncology and PC community through manuscripts in high-profile peer review publications, national meetings (such as ASCO and the American Association of Hospital and Palliative Medicine), and advocacy organizations (such as the Center to Advance PC [CAPC)]). Our study co-investigator and stakeholder, Dr. Lee Schwamm, has published key manuscripts about implementing telehealth technology, including "Telehealth: seven strategies to successfully implement disruptive technology and

transform health care" in *Health Affairs*.32 Thus, as a third strategy to disseminate and implement study findings, we will collaborate with Dr. Schwamm to publish the study findings in journals, such as Health Affairs, which influence policy makers and leaders of health care institutions. We will also present study findings throughout Partners HealthCare and strongly encourage our site lead investigators to present the results at their institutions. Our stakeholder engagement plan includes members from five key health care insurers, and so as a fourth strategy, we will engage our MGH and Partners HealthCare colleagues and stakeholders to assist us in meeting with these insurers to develop a plan to implement telemedicine PC (specifically developing reimbursement models). Fifth, we have engaged multiple key health care organizations and advocates, including ASCO, ACS, and CAPC to help us disseminate study findings through their organizations and to advocate for health care policy changes to increase the number of trained PC clinicians and reimbursement for telemedicine. Sixth, we will publish and present our methodology for training staff, clinicians, patients and caregivers on the use of the telemedicine video platform to enable the dissemination of this care model.

We will disseminate all study results to patients and caregivers who participated in this study through both email (which we collect as part of our study procedures) and direct mailings. We will also engage our study patient and caregiver stakeholders, which includes two individuals at each of the participating sites to communicate study results to local hospital and advocacy organizations, including their cancer clinics' patient and advisory councils.

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