BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057591
Article Type:	Protocol
Date Submitted by the Author:	21-Sep-2021
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Keywords:	Adult palliative care < PALLIATIVE CARE, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Study Protocol for a Randomized Trial Evaluating the Non-Inferiority of Stepped Palliative Care versus Early Integrated Palliative Care for Patients with Advanced Lung Cancer

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Funding: National Cancer Institute of the National Institutes of Health, R01CA215188 (PI: Temel)

Protocol Version 11, 5/27/21

Word Count: 3,998

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Abstract

Introduction

Integrating palliative care (PC) early in the illness course for patients with serious cancers improves their outcomes and is recommended by national organizations such as the American Society of Clinical Oncology. However, monthly visits with PC clinicians from the time of diagnosis can be challenging to implement due to the lack of specialty-trained PC clinicians and resources. Therefore, we developed a stepped care model to triage PC service based upon patients' needs.

Methods and Analysis

We are conducting a non-blinded, randomized trial to evaluate the non-inferiority of a stepped PC model compared with an early integrated PC model for improving patients' quality of life (QOL) at 24 weeks (primary outcome). Patients assigned to early integrated PC meet with PC every four weeks throughout their illness. Patients assigned to stepped PC have PC visits only at clinically significant points in their illness (e.g., cancer progression) unless their QOL decreases at which time they are "stepped up" and meet with PC every four weeks throughout the remainder of their illness. Secondary aims include assessing whether stepped PC is non-inferior to early integrated PC regarding patient-clinician communication about EOL care and length of stay on hospice as well as comparing resource utilization. Patients are recruited from the Massachusetts General Hospital Cancer Center, Boston, MA; Duke Cancer Center, Durham, NC; and University of Pennsylvania Abramson Cancer Center, Philadelphia, PA. The target sample size is 510 patients.

Ethics and Dissemination

The study is funded by the National Cancer Institute, approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board, and will be reported in accordance with the Consolidated Standards of Reporting Trials statement. We will disseminate results through professional society meetings, peer-reviewed publications, and presentations to patient organizations.

Trial Registration

NCT03337399; Pre-results.

Keywords: palliative care, stepped care, quality of life, advanced lung cancer, randomized trial

ARTICLE SUMMARY

Strengths and Limitations

- This study utilizes a patient-centered, evidence-based, early integrated palliative care model to improve patient-reported outcomes in those newly diagnosed with advanced lung cancer.
- This study employs a randomized controlled design as well as rigorous intervention fidelity measures to ensure consistent study procedures and intervention delivery across study sites.
- Given the limited availability of PC clinicians and clinic resources to implement an early integrated palliative care model in all care settings, this study includes a stepped care arm which has the potential to be less resource intensive and allow for intervention dissemination.
- The sample is homogenous with respect to patients' cancer type and oncology care at urban academic cancer centers, limiting the ability to generalize the study findings to other populations and care settings.

INTRODUCTION

Integrating palliative care (PC) and oncology care early in the course of disease for patients with advanced cancer improves their quality of life (QOL), depression symptoms, prognostic understanding, and quality of care at the end of life (EOL) as demonstrated by numerous trials over the past decade.[1–8] These findings were the basis for the 2017 American Society of Clinical Oncology Practice Guidelines which recommended that patients with advanced cancer in both the inpatient and outpatient settings are offered PC early in the disease trajectory and in conjunction with cancer therapy.[9] The National Comprehensive Cancer Network also endorses screening all oncology patients for their PC needs at their initial oncology consultation as well as at critical time points along their cancer care continuum.[10]

Despite the benefits of integrating palliative and oncology care, adequate numbers of specialty-trained PC clinicians as well as PC infrastructure and resources are lacking to care for all patients diagnosed with advanced cancer.[11,12] Thus, healthcare systems are generally unable to implement this evidence-based, early integrated palliative and oncology care model for their patients in a longitudinal fashion. Studies are needed to examine the potential benefits of alternative approaches to longitudinal PC delivery, such as a stepped PC model in which patients are "stepped up" to more frequent PC contact based upon their clinical need. Specifically, in a stepped care model, all patients receive care for their condition with a minimum level of required contact with a clinician, and patients are periodically monitored and stepped up to more intensive treatment if the minimal level of engagement with clinicians does not achieve a sufficient health benefit. Stepped care models, which have been successfully used to manage depression,[13] addiction,[14] obesity,[15] hypertension,[16] chronic pain[17] and distress in patients with cancer,[18–20] have the potential to achieve similar outcomes, and be more cost-effective, feasible, and generalizable than traditional models of care.[15,21,22] Additionally, a stepped PC model is aligned with the shift towards personalized cancer care in that the frequency of PC visits reflects the patients' individual needs throughout their disease course.

The current report outlines the details of an ongoing multisite, randomized controlled trial (RCT) comparing a stepped PC model to an early integrated PC model (entailing monthly contact with a PC clinician) in patients with advanced lung cancer. We seek to demonstrate the non-inferiority of a stepped PC model to the more resource-intensive early integrated PC model, thus establishing a role for this more accessible, adaptable, and patient-centered approach to PC.

The primary objective of this study is to determine if stepped PC is non-inferior to early integrated PC in improving patients' QOL at 24 weeks as measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L).[23] The secondary aims are to: 1) 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 (LOS) on hospice, 2) compare the superiority of stepped PC versus early integrated PC with respect to resource utilization, and 3) determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL longitudinally up to 48 weeks.

METHODS AND ANALYSIS

Study Design

This is a multisite RCT comparing stepped PC to early integrated PC in 510 patients with advanced lung cancer at the Massachusetts General Hospital (MGH), Duke Cancer Center, and University of Pennsylvania Abramson Cancer Center. The Consolidated Standards of Reporting Trials flow diagram is illustrated in Figure 1. The Dana Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board approved the study prior to initiation.

Patient and Public Involvement

We involved patients and the public in the design and conduct of this trial by initially presenting the study design and procedures to the MGH Cancer Outcomes Research & Education Program (CORE) Patient and Family Advisory Council prior to finalizing the study protocol. Additionally, at the conclusion of the trial, we will review the study findings with the CORE Advisory Council as well as disseminate the results through presentations to community organizations, academic institutions, and professional societies.

Participant Selection

Eligible patients are ≥18 years old, diagnosed with advanced non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), or mesothelioma; treated with non-curative intent; and informed of advanced disease within the prior 12 weeks (see Figure 2). Patients must also have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, be able to read and respond to questions in English or Spanish, and receive their cancer care at a participating site. Patients are excluded if they are already receiving outpatient PC or hospice services since diagnosis of advanced NSCLC, SCLC, or mesothelioma. Finally, patients who have cognitive or psychiatric conditions prohibiting study consent or participation, as determined by the treating oncologist, are not eligible for the study.

Study Procedures

Recruitment

Trained study staff screen the electronic health records (EHR) of all patients presenting to the outpatient thoracic oncology clinic to identify potentially eligible for enrollment. Study staff then request permission from the patients' oncology clinicians to approach potentially eligible patients for study participation. Either study staff or an oncology clinician can review with patients the study details, offer study participation, and obtain informed consent in person, via telephone, or using video conferencing. For patients who speak Spanish, an interpreter or a Spanish-speaking study staff member verbally explains all study procedures and information regarding risks and benefits.

Enrollment and Randomization

Within two weeks of providing informed consent, patients complete baseline demographic and study questionnaires. Once baseline measures are completed, patients are randomized in a 1:1 fashion, stratified by study site (MGH vs. Duke vs. Penn) and cancer diagnosis (NSCLC vs. SCLC and mesothelioma) using a computer-generated randomization schema.

Intervention Delivery

Early Integrated PC: Patients randomized to early integrated PC are scheduled to meet with a PC clinician within four weeks of enrollment and at least every four weeks throughout their disease course. PC visits occur in person or via secure videoconference. If a patient misses a scheduled visit or is unable to be scheduled within four weeks of their last PC visit, a PC clinician attempts to call them by telephone to maintain contact at least every four weeks and re-schedules the visit as soon as possible. The inpatient PC team follows patients who are admitted to a study site hospital.

Stepped PC: Patients randomized to stepped PC are scheduled for an initial visit with a PC clinician within four weeks of enrollment. During step 1, further visits with a PC clinician are scheduled at clinically significant points in the patient's illness, including within four weeks of (1) a change in cancer treatment (due to either progression or toxicity) or (2) hospital discharge. PC visits occur in person or via secure videoconference. After each visit, the PC clinician communicates with the oncology clinician(s) either by telephone, email, or in person. If a patient misses a scheduled visit or is unable to be scheduled for a PC visit, the PC clinician attempts to contact them by telephone and re-schedules the visit as soon as possible. Patients assigned to stepped PC complete the FACT-L every six weeks during the first 18 months of study participation (see Table 1). Those whose scores decrease by ≥10 points from baseline are "stepped up" to step 2 and follow the same protocol as those randomized to the early integrated PC arm. Specifically, they meet with a PC clinician at least every four weeks for the remainder of their illness and if they are hospitalized.

All study participants in both groups surviving greater than 18 months from enrollment are permitted to decrease the frequency of PC visits as per their preference and the discretion of their PC and oncology clinicians.

Table 1. Study 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 up to 18 months from enrollment

Study Questionnaires

Table 1 lists the self-report questionnaires and the time points at which they are administered.

- At baseline, participants self-report their gender, ethnicity, race, smoking history, with whom they reside as well as the travel time, distance, and mode of transportation to the cancer center. We assess medical comorbidity at baseline with the Self-Administered Comorbidity Questionnaire.[24]
- To measure QOL, patients complete the FACT-L. The FACT-L is a well-validated 36-item tool that assesses five QOL domains including physical wellbeing, social/family wellbeing, emotional wellbeing, and functional well-being, as well as a lung cancer specific subscale[23] using a 5-point Likert scale ranging from 0 "not at all" to 4 "very much."
- We assess EOL care preferences via the Prognosis and Treatment Perceptions Questionnaire (PTPQ). The PTPQ is a 9-item tool that assesses patients' illness understanding, communication about prognosis and goals of care, as well as discussions and preferences regarding EOL care.[25]
- To assess coping strategies, we administer the Brief Cope, a 28-item questionnaire that assesses methods of coping (e.g., active, acceptance, denial) using a 4-point Likert scale ranging from 1 "not at all" to 4 "a lot."[26,27] We limit our evaluation to eight coping strategies (16-items) of the Brief Cope deemed most relevant for the study (i.e., emotional support, positive reframing, active coping, acceptance, self-blame, denial, spiritual coping, and behavioral disengagement).
- We evaluate patient depression symptoms via the Patient Health Questionnaire-9 (PHQ-9), a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*.[28]
- We use the EuroQol-5 Dimension (EQ-5D) to measure five dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression according to three levels of severity.[29,30] The EQ-5D also asks patients to rate their health status on a 1-100 visual analog scale. This tool has been shown to be sensitive to QOL changes in patients with lung cancer.[31]
- At the week 24 primary endpoint, patients also report their utilization of any mental health services since diagnosis.

Study staff administer study questionnaires at baseline prior to randomization and then again at weeks 12, 24, 36, and 48 (with a +/- two-week window). As noted above, step 1 patients complete the FACT-L every six weeks. Patients may complete questionnaires either in the clinic, on paper at home, via telephone, by secure videoconference, or electronically via Research Electronic Data Capture (REDCap),[32] a Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based survey tool.

EHR Data

We are collecting the following information from the EHR: date of birth; cancer type (and genotype if applicable); previous diagnosis of early-stage disease; date of diagnosis of advanced lung cancer; smoking pack years; ECOG Performance Status; documentation of advance care directives status; referrals to and LOS on hospice; and date and location of death. We are also collecting dates of outpatient and inpatient PC visits; cancer treatment regimens (e.g., chemotherapy, immunotherapy, targeted therapy, radiation); and emergency department, hospital, and intensive care unit admissions.

Intervention Fidelity

We are ensuring the fidelity of intervention delivery through consistent training of PC clinicians and reviewing the content of PC visits.

Training: We standardized the training procedures for site principal investigators (PI) and study staff including the development of a PC intervention guide and study standard operating procedures. The lead study site (MGH) completed a full day in-person training with the site PIs prior to the study start. The site PIs then trained the participating PC clinicians at their respective institutions using the information they learned during the in-person training. All participating PC clinicians also reviewed the PC intervention guide and watched training videos developed by the MGH investigative team regarding the intervention delivery and study procedures.

Intervention Delivery: PC clinicians complete an electronic survey after each intervention visit to record the topics addressed during the encounter. Two study staff review these electronic surveys quarterly to ensure intervention fidelity and consistency between sites in addressing the domains and topics as specified by the intervention manual. Finally, trained study staff review PC notes in the EHR to ensure adherence to the intervention guide content and provide feedback to clinicians on a quarterly basis. All the site PIs and study staff meet monthly to review intervention delivery and fidelity data.

Outcomes

Primary outcome

- To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL, as measured by the FACT-L at week 24

Secondary outcomes

- To assess the non-inferiority of stepped PC versus early integrated PC with respect to patient-clinician communication about EOL care preferences via the PTPQ at week 48 or the final assessment prior to death
- To assess whether stepped PC is non-inferior to early integrated PC with respect to hospice LOS

- To compare the superiority of stepped PC versus early integrated PC with respect to resource utilization
- To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL longitudinally up to 48 weeks as measured by the FACT-L

Exploratory outcomes

- To compare the superiority of stepped PC versus early integrated PC with respect to cost-effectiveness
- To compare coping strategies in patients assigned to stepped PC versus early integrated PC as measured by the Brief Cope at week 24
- To compare prognostic understanding in patients assigned to stepped PC versus early integrated PC by analyzing relevant items from the PTPQ at week 24
- To compare depression symptoms in patients assigned to stepped PC versus early integrated PC as measured by the HADS-Depression scale at week 24

Safety and Adverse Events

Study staff review the PHQ-9 upon completion to evaluate for suicidal ideation. If a patient endorses suicidal ideation, the site PI and/or a member of the patient's PC or oncology team are notified and contact the patient to conduct a safety assessment.

Given that this study is a supportive oncology PC intervention trial, we do not anticipate any study-related serious adverse events. We report summaries of study-related non-serious adverse events to the IRB at the continuing reviews. These summaries include types of events, severity, and treatment phase. Additionally, the study staff review reasons for study withdrawal by treatment group at weekly meetings.

Data Collection and Management

The primary study PI and site PIs oversee all aspects of data collection and management. MGH developed and trained all study staff in the standard operating procedures for data collection, quality control, and data extraction. The study staff enter all data abstracted from the EHR as well as all survey data collected from participants in REDCap. Each site maintains a list of patient names and study IDs saved in a secure file, and participants are identified on study assessments only by study ID to protect confidentiality. Study source documents, including signed informed consent forms, completed eligibility checklists, and participant questionnaires, are scanned and stored on secure study site computers.

As this supportive care study has a low risk of study-related serious adverse events, we formed a data safety and monitoring committee comprised of MGH investigators to provide additional oversight of data quality and completeness.

Statistical Analysis

We will use intention-to-treat analyses for all randomized subjects. All non-inferiority comparisons will be based on 0.05-level one-sided tests and all superiority comparisons will be based on 0.05-level two-sided tests.

The primary endpoint is to demonstrate the non-inferiority of stepped PC versus early integrated PC in improving patients' QOL at 24 weeks, as measured by the FACT-L. The primary endpoint will be analyzed between the study groups using a linear regression model controlling for baseline values and demographic and clinical factors and a non-inferiority margin of 4.5 points (SD = 17.5). We will also evaluate the frequency of PC visits between study arms to determine if the stepped PC model leads to a reduction in PC visits. We will employ linear mixed models of longitudinal data to control for demographic and clinical factors and to account for dependency among means over time when evaluating change in QOL between groups across multiple time points.

The secondary endpoints of this RCT are to assess whether stepped PC is non-inferior to early integrated PC with respect to communication about EOL care and LOS in hospice. Specifically, we will use the following item from the PTPQ to examine patient reports of discussing EOL care preferences with their clinicians: "Have you and your doctors discussed any particular wishes you have about the care you would want to receive if you were dying?" We will use either the week 48 assessment or the final assessment before death for this analysis, whichever comes first. We will evaluate differences in patients reporting "yes" to this item using a Fisher's exact test, and a non-inferiority margin of 10%. If there are important imbalances between groups at baseline, we will use a logistic regression model controlling for any demographic and clinical factors that are imbalanced to assess differences between groups.

We will assess the non-inferiority of hospice LOS between stepped PC and early integrated PC. We will use linear regression modeling controlling for selected clinical and demographic factors, and a non-inferiority margin of 7 days.

We will compare PC resource utilization and cost effectiveness between study groups. Costs considered in this analysis will include PC visits, other outpatient care, emergency department use, inpatient care, and pharmaceuticals (chemotherapeutics and other pharmaceuticals evaluated separately).[33,34] To collect outpatient and inpatient hospital costs, we will query the hospital cost accounting system at study sites.[35] To compare the superiority of stepped PC versus early integrated PC with respect to PC resource utilization, we will collect the number and duration of outpatient PC visits from our REDCap database as well as data on the inpatient and telephone PC encounters from the EHR. Both total cost as well as category specific costs (such as inpatient care, emergency department use, and pharmaceuticals) will be evaluated to determine how resource utilization differs between stepped PC and early integrated PC. Direct health care costs and indirect costs (such as time) incurred by patients throughout their life spans while enrolled in this study will be included in this analysis.[36] We will compare the mean number of outpatient and inpatient PC visits between the two groups using a two-sample t-test. We will assess the cost effectiveness of early integrated PC as compared to stepped PC from a societal perspective using the average cost and quality adjusted life years (QALY) accrued under each study arm. As such, a $50,000 QALY will be considered cost effective.[37]

To examine prognostic understanding for non-inferiority between stepped PC and early integrated PC at week 24, we will analyze select items from the PTPQ using the appropriate test (e.g., Fisher's exact test). Additionally, we will examine coping strategies (Brief Cope) and depression symptoms (PHQ-9) at week 24 between groups using linear regression models controlling for baseline values and selected demographic and clinical factors. Linear mixed models will also be used as described above to examine changes in these outcomes between groups across multiple time points.

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 regression and linear mixed models to examine whether differences in outcomes are moderated by patient factors (age, gender, and race) or study site.

Finally, we will employ multiple imputation methods when data can reasonably be assumed to be missing at random. In settings where data are likely missing *not* at random (e.g., due to progressive illness), we will employ pattern mixture modeling or terminal decline joint modeling to address missing data.

Sample Size

For the primary outcome in our previous trials of early integrated PC, we assessed the change in QOL, as measured by the FACT-L from baseline to week 12.[6,38] However, for this trial, we chose to focus on week 24 as life expectancy for patients with advanced lung cancer has improved in recent years.[39,40] With 188 patients per group, we will have 80% power to demonstrate the non-inferiority of stepped PC versus early integrated PC in improving patient-reported QOL as measured by the FACT-L, and a non-inferiority margin of 4.5 points (SD = 17.5). To account for potential missing data and ensure adequate power to assess for non-inferiority, we increased our sample size to 255 per group for a total sample size of 510 participants.

Limitations

The current trial has several potential limitations. First, we are only enrolling patients with advanced lung cancer receiving care at three large academic medical centers, limiting generalization of the results to patients with different cancer types or stages of disease as well as those receiving treatment in other oncology care settings. However, existing data support early integrated PC in patients with advanced lung cancer,[6,19,38] making this an ideal population in which to compare different PC models. Second, we are only enrolling English and Spanish speaking patients due to the availability of study questionnaires in these languages. In future studies, investigators could consider study procedures to enroll patients who speak languages other than English or Spanish. Third, both the participating study clinicians and patients are aware of the study group assignments, potentially introducing bias. However, the frequency and timing of intervention visits precluded blinding PC clinicians or patients to the study group assignments. Finally, we do not prevent patients in the stepped PC group from having additional appointments with their PC clinicians if requested by either the patient or the clinician, which could also influence study findings. However, denying PC services for patients with advanced cancer would neither be feasible nor acceptable.

ETHICS and DISSEMINATION

This trial was approved by the DF/HCC IRB and is being conducted in compliance with the approved protocol. We are obtaining informed consent either in person, verbally via telephone, or via secure videoconferencing technology. Patients who provide informed consent verbally receive a copy of the written consent form. All documents relating to study participants are confidential. Participant data are deidentified and stored in a HIPAA-compliant manner. All significant modifications to the study protocol have and will be submitted to the DF/HCC IRB for approval and communicated to study staff at all sites as well as to patients as indicated.

We will present the study findings through multiple outlets including national conferences, peer-reviewed publications, social media, and community organizations. A study description and summary of the results will also be available on ClinicalTrials.gov. Only the study staff have access to the study database, however, access can be considered via a data usage agreement with the DF/HCC IRB. There are no plans for professional writers for the final manuscript. If a study patient expresses an interest in the study findings, the study staff will provide an abstract of study findings once data collection is complete.

Current trial status

We began recruitment of participants on February 12, 2018. As of September 10, 2021, 384 patients have enrolled. We placed the study on a temporary recruitment pause in March of 2020 due to the COVID-19 pandemic and resumed recruitment in July, 2020.

Funding

This study is supported by a R01 grant from the National Cancer Institute of the National Institutes of Health (R01CA215188; Temel).

Competing Interest Statement

All of the authors declare that they have no conflicts of interest to report.

Author Statement

JT, JG, and VJ contributed to the study conception and design. The protocol was developed and written by JT, JG, and VJ. KP, LH, ME, SG, JH, FF, AJ, provided substantial contributions to the acquisition of data for the study. The first draft of the manuscript was written by KP and LH. JT, JG, AK, PK, ME, SG, JH, CT, RP, CV, and DR contributed critically important revisions on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the study patients for their time and dedication to this research study.

Figure Legends

Figure 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; QOL, Quality of Life.

Figure 2. Eligibility criteria

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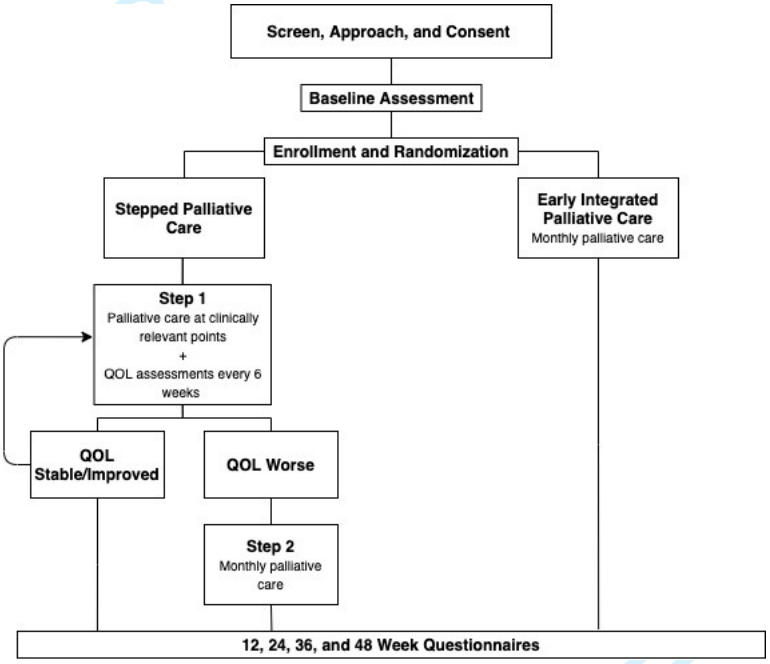
Screen, Approach, and Consent
Baseline Assessment
Enrollment and Randomization
Stepped Palliative Care
Early Integrated Palliative Care
Monthly palliative care
Step 1
Palliative care at clinically relevant points
+
QOL assessments every 6 weeks
QOL Stable/Improved
QOL Worse
Step 2
Monthly palliative care
12, 24, 36, and 48 Week Questionnaires

Inclusion Criteria:

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 ≤ 2.
3. Ability to read and respond to questions in English or Spanish
4. Primary cancer care at one of the three participating sites.
5. Age ≥ 18 years.

Exclusion Criteria:

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

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	10

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8, 10

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	10

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12-13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12-13

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 12-13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

Study Protocol for a Randomized Trial Evaluating the Non-Inferiority of Stepped Palliative Care versus Early Integrated Palliative Care for Patients with Advanced Lung Cancer

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057591.R1
Article Type:	Protocol
Date Submitted by the Author:	02-Nov-2021
Complete List of Authors:	Post, Kathryn; Massachusetts General Hospital, Cancer Center Heuer, Lauren; Massachusetts General Hospital, Kamal, Arif; Duke University School of Medicine, Oncology Kumar, Pallavi; University of Pennsylvania Elyze, Madeleine; Massachusetts General Hospital Griffith, Sarah; Massachusetts General Hospital Han, Jacqueline; Massachusetts General Hospital Friedman, Fred; Duke University Jackson, Ashley; University of Pennsylvania Trotter, Chardria; Massachusetts General Hospital Plotke, Rachel; Massachusetts General Hospital Vyas, Charu; Massachusetts General Hospital Jackson, Vicki; Massachusetts General Hospital Rabideau, Dustin; Massachusetts General Hospital Greer, Joseph; Massachusetts General Hospital Department of Psychiatry, Temel, Jennifer; Massachusetts General Hospital Cancer Center, Medicine
Primary Subject Heading:	Palliative care
Secondary Subject Heading:	Oncology, Patient-centred medicine, Research methods
Keywords:	Adult palliative care < PALLIATIVE CARE, Adult oncology < ONCOLOGY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Respiratory tract tumours < ONCOLOGY

Study Protocol for a Randomized Trial Evaluating the Non-Inferiority of Stepped Palliative Care versus Early Integrated Palliative Care for Patients with Advanced Lung Cancer

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Funding: National Cancer Institute of the National Institutes of Health, R01CA215188 (PI: Temel)

Protocol Version 11, 5/27/21

Word Count: 4,013

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Abstract

Introduction

Integrating palliative care (PC) early in the illness course for patients with serious cancers improves their outcomes and is recommended by national organizations such as the American Society of Clinical Oncology. However, monthly visits with PC clinicians from the time of diagnosis can be challenging to implement due to the lack of specialty-trained PC clinicians and resources. Therefore, we developed a stepped care model to triage PC service based upon patients' needs.

Methods and Analysis

We are conducting a non-blinded, randomized trial to evaluate the non-inferiority of a stepped PC model compared with an early integrated PC model for improving patients' quality of life (QOL) at 24 weeks (primary outcome). Patients assigned to early integrated PC meet with PC every four weeks throughout their illness. Patients assigned to stepped PC have PC visits only at clinically significant points in their illness (e.g., cancer progression) unless their QOL decreases at which time they are "stepped up" and meet with PC every four weeks throughout the remainder of their illness. Secondary aims include assessing whether stepped PC is non-inferior to early integrated PC regarding patient-clinician communication about EOL care and length of stay on hospice as well as comparing resource utilization. Patients are recruited from the Massachusetts General Hospital Cancer Center, Boston, MA; Duke Cancer Center, Durham, NC; and University of Pennsylvania Abramson Cancer Center, Philadelphia, PA. The target sample size is 510 patients.

Ethics and Dissemination

The study is funded by the National Cancer Institute, approved by the Dana-Farber/Harvard Cancer Center Institutional Review Board, and will be reported in accordance with the Consolidated Standards of Reporting Trials statement. We will disseminate results through professional society meetings, peer-reviewed publications, and presentations to patient organizations.

Trial Registration

NCT03337399; Pre-results.

Keywords: palliative care, stepped care, quality of life, advanced lung cancer, randomized trial

ARTICLE SUMMARY

Strengths and Limitations

- This study utilizes a patient-centered, evidence-based, early integrated palliative care model to improve patient-reported outcomes in those newly diagnosed with advanced lung cancer.
- This study employs a randomized controlled design as well as rigorous intervention fidelity measures to ensure consistent study procedures and intervention delivery across study sites.
- Given the limited availability of PC clinicians and clinic resources to implement an early integrated palliative care model in all care settings, this study includes a stepped care arm which has the potential to be less resource intensive and allow for intervention dissemination.
- The sample is homogenous with respect to patients' cancer type and oncology care at urban academic cancer centers, limiting the ability to generalize the study findings to other populations and care settings.

INTRODUCTION

Integrating palliative care (PC) and oncology care early in the course of disease for patients with advanced cancer improves their quality of life (QOL), depression symptoms, prognostic understanding, and quality of care at the end of life (EOL) as demonstrated by numerous trials over the past decade.[1–8] These findings were the basis for the 2017 American Society of Clinical Oncology Practice Guidelines which recommended that patients with advanced cancer in both the inpatient and outpatient settings are offered PC early in the disease trajectory and in conjunction with cancer therapy.[9] The National Comprehensive Cancer Network also endorses screening all oncology patients for their PC needs at their initial oncology consultation as well as at critical time points along their cancer care continuum.[10]

Despite the benefits of integrating palliative and oncology care, adequate numbers of specialty-trained PC clinicians as well as PC infrastructure and resources are lacking to care for all patients diagnosed with advanced cancer.[11,12] Thus, healthcare systems are generally unable to implement this evidence-based, early integrated palliative and oncology care model for their patients in a longitudinal fashion. Studies are needed to examine the potential benefits of alternative approaches to longitudinal PC delivery, such as a stepped PC model in which patients are "stepped up" to more frequent PC contact based upon their clinical need. Specifically, in a stepped care model, all patients receive care for their condition with a minimum level of required contact with a clinician, and patients are periodically monitored and stepped up to more intensive treatment if the minimal level of engagement with clinicians does not achieve a sufficient health benefit. Stepped care models, which have been successfully used to manage depression,[13] addiction,[14] obesity,[15] hypertension,[16] chronic pain[17] and distress in patients with cancer,[18–20] have the potential to achieve similar outcomes, and be more cost-effective, feasible, and generalizable than traditional models of care.[15,21,22] Additionally, a stepped PC model is aligned with the shift towards personalized cancer care in that the frequency of PC visits reflects the patients' individual needs throughout their disease course.

The current report outlines the details of an ongoing multisite, randomized controlled trial (RCT) comparing a stepped PC model to an early integrated PC model (entailing monthly contact with a PC clinician) in patients with advanced lung cancer. We seek to demonstrate the non-inferiority of a stepped PC model to the more resource-intensive early integrated PC model, thus establishing a role for this more accessible, adaptable, and patient-centered approach to PC.

The primary objective of this study is to determine if stepped PC is non-inferior to early integrated PC in improving patients' QOL at 24 weeks as measured by the Functional Assessment of Cancer Therapy-Lung (FACT-L).[23] The secondary aims are to: 1) 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 (LOS) on hospice, 2) compare the superiority of stepped PC versus early integrated PC with respect to resource utilization, and 3) determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL longitudinally up to 48 weeks.

METHODS AND ANALYSIS

Study Design

This is a multisite RCT comparing stepped PC to early integrated PC in 510 patients with advanced lung cancer at the Massachusetts General Hospital (MGH), Duke Cancer Center, and University of Pennsylvania Abramson Cancer Center. The start date of the trial was February 1, 2018 and the estimated completion date is December 31, 2023. The Consolidated Standards of Reporting Trials flow diagram is illustrated in Figure 1. The Dana Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board approved the study prior to initiation.

Patient and Public Involvement

We involved patients and the public in the design and conduct of this trial by initially presenting the study design and procedures to the MGH Cancer Outcomes Research & Education Program (CORE) Patient and Family Advisory Council prior to finalizing the study protocol. Additionally, at the conclusion of the trial, we will review the study findings with the CORE Advisory Council as well as disseminate the results through presentations to community organizations, academic institutions, and professional societies.

Participant Selection

Eligible patients are ≥18 years old, diagnosed with advanced non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), or mesothelioma; treated with non-curative intent; and informed of advanced disease within the prior 12 weeks (see Figure 2). Patients must also have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, be able to read and respond to questions in English or Spanish, and receive their cancer care at a participating site. Patients are excluded if they are already receiving outpatient PC or hospice services since diagnosis of advanced NSCLC, SCLC, or mesothelioma. Finally, patients who have cognitive or psychiatric conditions prohibiting study consent or participation, as determined by the treating oncologist, are not eligible for the study.

Study Procedures

Recruitment

Trained study staff screen the electronic health records (EHR) of all patients presenting to the outpatient thoracic oncology clinic to identify potentially eligible for enrollment. Study staff then request permission from the patients' oncology clinicians to approach potentially eligible patients for study participation. Either study staff or an oncology clinician can review with patients the study details, offer study participation, and obtain informed consent in person, via telephone, or using video conferencing. For

patients who speak Spanish, an interpreter or a Spanish-speaking study staff member verbally explains all study procedures and information regarding risks and benefits.

Enrollment and Randomization

Within two weeks of providing informed consent, patients complete baseline demographic and study questionnaires. Once baseline measures are completed, patients are randomized in a 1:1 fashion, stratified by study site (MGH vs. Duke vs. Penn) and cancer diagnosis (NSCLC vs. SCLC and mesothelioma) using a computer-generated randomization schema.

Intervention Delivery

Early Integrated PC: Patients randomized to early integrated PC are scheduled to meet with a PC clinician within four weeks of enrollment and at least every four weeks throughout their disease course. PC visits occur in person or via secure videoconference. If a patient misses a scheduled visit or is unable to be scheduled within four weeks of their last PC visit, a PC clinician attempts to call them by telephone to maintain contact at least every four weeks and re-schedules the visit as soon as possible. The inpatient PC team follows patients who are admitted to a study site hospital.

Stepped PC: Patients randomized to stepped PC are scheduled for an initial visit with a PC clinician within four weeks of enrollment. During step 1, further visits with a PC clinician are scheduled at clinically significant points in the patient's illness, including within four weeks of (1) a change in cancer treatment (due to either progression or toxicity) or (2) hospital discharge. PC visits occur in person or via secure videoconference. After each visit, the PC clinician communicates with the oncology clinician(s) either by telephone, email, or in person. If a patient misses a scheduled visit or is unable to be scheduled for a PC visit, the PC clinician attempts to contact them by telephone and re-schedules the visit as soon as possible. Patients assigned to stepped PC complete the FACT-L every six weeks during the first 18 months of study participation (see Table 1). Those whose scores decrease by ≥10 points from baseline are "stepped up" to step 2 and follow the same protocol as those randomized to the early integrated PC arm. Specifically, they meet with a PC clinician at least every four weeks for the remainder of their illness and if they are hospitalized.

All study participants in both groups surviving greater than 18 months from enrollment are permitted to decrease the frequency of PC visits as per their preference and the discretion of their PC and oncology clinicians.

Table 1. Study 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 up to 18 months from enrollment

Study Questionnaires

Table 1 lists the self-report questionnaires and the time points at which they are administered.

- At baseline, participants self-report their gender, ethnicity, race, smoking history, with whom they reside as well as the travel time, distance, and mode of transportation to the cancer center. We assess medical comorbidity at baseline with the Self-Administered Comorbidity Questionnaire.[24]
- To measure QOL, patients complete the FACT-L. The FACT-L is a well-validated 36-item tool that assesses five QOL domains including physical wellbeing, social/family wellbeing, emotional wellbeing, and functional well-being, as well as a lung cancer specific subscale[23] using a 5-point Likert scale ranging from 0 "not at all" to 4 "very much."
- We assess EOL care preferences via the Prognosis and Treatment Perceptions Questionnaire (PTPQ). The PTPQ is a 9-item tool that assesses patients' illness understanding, communication about prognosis and goals of care, as well as discussions and preferences regarding EOL care.[25]
- To assess coping strategies, we administer the Brief Cope, a 28-item questionnaire that assesses methods of coping (e.g., active, acceptance, denial) using a 4-point Likert scale ranging from 1 "not at all" to 4 "a lot."[26,27] We limit our evaluation to eight coping strategies (16-items) of the Brief Cope deemed most relevant for the study (i.e., emotional support, positive reframing, active coping, acceptance, self-blame, denial, spiritual coping, and behavioral disengagement).
- We evaluate patient depression symptoms via the Patient Health Questionnaire-9 (PHQ-9), a nine-item measure that evaluates symptoms of major depressive disorder according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*.[28]
- We use the EuroQol-5 Dimension (EQ-5D) to measure five dimensions of health including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression according to three levels of severity.[29,30] The EQ-5D also asks patients to rate their health status on a 1-100 visual analog scale. This tool has been shown to be sensitive to QOL changes in patients with lung cancer.[31]
- At the week 24 primary endpoint, patients also report their utilization of any mental health services since diagnosis.

Study staff administer study questionnaires at baseline prior to randomization and then again at weeks 12, 24, 36, and 48 (with a +/- two-week window). As noted above, step 1 patients complete the FACT-L every six weeks. Patients may complete questionnaires either in the clinic, on paper at home, via telephone, by secure videoconference, or electronically via Research Electronic Data Capture (REDCap),[32] a Health Insurance Portability and Accountability Act (HIPAA) compliant, web-based survey tool.

EHR Data

We are collecting the following information from the EHR: date of birth; cancer type (and genotype if applicable); previous diagnosis of early-stage disease; date of diagnosis of advanced lung cancer; smoking pack years; ECOG Performance Status; documentation of advance care directives status; referrals to and LOS on hospice; and date and location of death. We are also collecting dates of outpatient and inpatient PC visits; cancer treatment regimens (e.g., chemotherapy, immunotherapy, targeted therapy, radiation); and emergency department, hospital, and intensive care unit admissions.

Intervention Fidelity

We are ensuring the fidelity of intervention delivery through consistent training of PC clinicians and reviewing the content of PC visits.

Training: We standardized the training procedures for site principal investigators (PI) and study staff including the development of a PC intervention guide and study standard operating procedures. The lead study site (MGH) completed a full day in-person training with the site PIs prior to the study start. The site PIs then trained the participating PC clinicians at their respective institutions using the information they learned during the in-person training. All participating PC clinicians also reviewed the PC intervention guide and watched training videos developed by the MGH investigative team regarding the intervention delivery and study procedures.

Intervention Delivery: PC clinicians complete an electronic survey after each intervention visit to record the topics addressed during the encounter. Two study staff review these electronic surveys quarterly to ensure intervention fidelity and consistency between sites in addressing the domains and topics as specified by the intervention manual. Finally, trained study staff review PC notes in the EHR to ensure adherence to the intervention guide content and provide feedback to clinicians on a quarterly basis. All the site PIs and study staff meet monthly to review intervention delivery and fidelity data.

Outcomes

Primary outcome

- To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL, as measured by the FACT-L at week 24

Secondary outcomes

- To assess the non-inferiority of stepped PC versus early integrated PC with respect to patient-clinician communication about EOL care preferences via the PTPQ at week 48 or the final assessment prior to death

- To assess whether stepped PC is non-inferior to early integrated PC with respect to hospice LOS
- To compare the superiority of stepped PC versus early integrated PC with respect to resource utilization
- To determine whether stepped PC is non-inferior to early integrated PC in improving patients' QOL longitudinally up to 48 weeks as measured by the FACT-L

Exploratory outcomes

- To compare the superiority of stepped PC versus early integrated PC with respect to cost-effectiveness
- To compare coping strategies in patients assigned to stepped PC versus early integrated PC as measured by the Brief Cope at week 24
- To compare prognostic understanding in patients assigned to stepped PC versus early integrated PC by analyzing relevant items from the PTPQ at week 24
- To compare depression symptoms in patients assigned to stepped PC versus early integrated PC as measured by the HADS-Depression scale at week 24

Safety and Adverse Events

Study staff review the PHQ-9 upon completion to evaluate for suicidal ideation. If a patient endorses suicidal ideation, the site PI and/or a member of the patient's PC or oncology team are notified and contact the patient to conduct a safety assessment.

Given that this study is a supportive oncology PC intervention trial, we do not anticipate any study-related serious adverse events. We report summaries of study-related non-serious adverse events to the IRB at the continuing reviews. These summaries include types of events, severity, and treatment phase. Additionally, the study staff review reasons for study withdrawal by treatment group at weekly meetings.

Data Collection and Management

The primary study PI and site PIs oversee all aspects of data collection and management. MGH developed and trained all study staff in the standard operating procedures for data collection, quality control, and data extraction. The study staff enter all data abstracted from the EHR as well as all survey data collected from participants in REDCap. Each site maintains a list of patient names and study IDs saved in a secure file, and participants are identified on study assessments only by study ID to protect confidentiality. Study source documents, including signed informed consent forms, completed eligibility checklists, and participant questionnaires, are scanned and stored on secure study site computers.

As this supportive care study has a low risk of study-related serious adverse events, we formed a data safety and monitoring committee comprised of MGH investigators to provide additional oversight of data quality and completeness.

Statistical Analysis

We will use intention-to-treat analyses for all randomized subjects. All non-inferiority comparisons will be based on 0.05-level one-sided tests and all superiority comparisons will be based on 0.05-level two-sided tests.

The primary endpoint is to demonstrate the non-inferiority of stepped PC versus early integrated PC in improving patients' QOL at 24 weeks, as measured by the FACT-L. The primary endpoint will be analyzed between the study groups using a linear regression model controlling for baseline values and demographic and clinical factors and a non-inferiority margin of 4.5 points (SD = 17.5). We will also evaluate the frequency of PC visits between study arms to determine if the stepped PC model leads to a reduction in PC visits. We will employ linear mixed models of longitudinal data to control for demographic and clinical factors and to account for dependency among means over time when evaluating change in QOL between groups across multiple time points.

The secondary endpoints of this RCT are to assess whether stepped PC is non-inferior to early integrated PC with respect to communication about EOL care and LOS in hospice. Specifically, we will use the following item from the PTPQ to examine patient reports of discussing EOL care preferences with their clinicians: "Have you and your doctors discussed any particular wishes you have about the care you would want to receive if you were dying?" We will use either the week 48 assessment or the final assessment before death for this analysis, whichever comes first. We will evaluate differences in patients reporting "yes" to this item using a Fisher's exact test, and a non-inferiority margin of 10%. If there are important imbalances between groups at baseline, we will use a logistic regression model controlling for any demographic and clinical factors that are imbalanced to assess differences between groups.

We will assess the non-inferiority of hospice LOS between stepped PC and early integrated PC. We will use linear regression modeling controlling for selected clinical and demographic factors, and a non-inferiority margin of 7 days.

We will compare PC resource utilization and cost effectiveness between study groups. Costs considered in this analysis will include PC visits, other outpatient care, emergency department use, inpatient care, and pharmaceuticals (chemotherapeutics and other pharmaceuticals evaluated separately).[33,34] To collect outpatient and inpatient hospital costs, we will query the hospital cost accounting system at study sites.[35] To compare the superiority of stepped PC versus early integrated PC with respect to PC resource utilization, we will collect the number and duration of outpatient PC visits from our REDCap database as well as data on the inpatient and telephone PC encounters from the EHR. Both total cost as well as category specific costs (such as inpatient care, emergency department use, and pharmaceuticals) will be evaluated to determine how resource utilization differs between stepped PC and early integrated PC. Direct health care costs and indirect costs (such as time) incurred by patients throughout their life spans while enrolled in this study will be included in this analysis.[36] We will compare the mean number of outpatient and inpatient PC visits between the two groups using a two-sample t-test. We will assess the cost effectiveness of early integrated PC as compared to stepped PC from a societal perspective using the average cost and quality adjusted life years (QALY) accrued under each study arm. As such, a $50,000 QALY will be considered cost effective.[37]

To examine prognostic understanding for non-inferiority between stepped PC and early integrated PC at week 24, we will analyze select items from the PTPQ using the appropriate test (e.g., Fisher's exact test). Additionally, we will examine coping strategies (Brief Cope) and depression symptoms (PHQ-9) at week 24 between groups using linear regression models controlling for baseline values and selected demographic and clinical factors. Linear mixed models will also be used as described above to examine changes in these outcomes between groups across multiple time points.

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 regression and linear mixed models to examine whether differences in outcomes are moderated by patient factors (age, gender, and race) or study site.

Finally, we will employ multiple imputation methods when data can reasonably be assumed to be missing at random. In settings where data are likely missing *not* at random (e.g., due to progressive illness), we will employ pattern mixture modeling or terminal decline joint modeling to address missing data.

Sample Size

For the primary outcome in our previous trials of early integrated PC, we assessed the change in QOL, as measured by the FACT-L from baseline to week 12.[6,38] However, for this trial, we chose to focus on week 24 as life expectancy for patients with advanced lung cancer has improved in recent years.[39,40] With 188 patients per group, we will have 80% power to demonstrate the non-inferiority of stepped PC versus early integrated PC in improving patient-reported QOL as measured by the FACT-L, and a non-inferiority margin of 4.5 points (SD = 17.5). To account for potential missing data and ensure adequate power to assess for non-inferiority, we increased our sample size to 255 per group for a total sample size of 510 participants.

Limitations

The current trial has several potential limitations. First, we are only enrolling patients with advanced lung cancer receiving care at three large academic medical centers, limiting generalization of the results to patients with different cancer types or stages of disease as well as those receiving treatment in other oncology care settings. However, existing data support early integrated PC in patients with advanced lung cancer,[6,19,38] making this an ideal population in which to compare different PC models. Second, we are only enrolling English and Spanish speaking patients due to the availability of study questionnaires in these languages. In future studies, investigators could consider study procedures to enroll patients who speak languages other than English or Spanish. Third, both the participating study clinicians and patients are aware of the study group assignments, potentially introducing bias. However, the frequency and timing of intervention visits precluded blinding PC clinicians or patients to the study group assignments. Finally, we do not prevent patients in the stepped PC group from having additional appointments with their PC clinicians if requested by either the patient or the clinician, which could also influence study findings. However, denying PC services for patients with advanced cancer would neither be feasible nor acceptable.

ETHICS and DISSEMINATION

This trial was approved by the DF/HCC IRB and is being conducted in compliance with the approved protocol. We are obtaining informed consent either in person, verbally via telephone, or via secure videoconferencing technology. Patients who provide informed consent verbally receive a copy of the written consent form. All documents relating to study participants are confidential. Participant data are deidentified and stored in a HIPAA-compliant manner. All significant modifications to the study protocol have and will be submitted to the DF/HCC IRB for approval and communicated to study staff at all sites as well as to patients as indicated.

We will present the study findings through multiple outlets including national conferences, peer-reviewed publications, social media, and community organizations. A study description and summary of the results will also be available on ClinicalTrials.gov. Only the study staff have access to the study database, however, access can be considered via a data usage agreement with the DF/HCC IRB. There are no plans for professional writers for the final manuscript. If a study patient expresses an interest in the study findings, the study staff will provide an abstract of study findings once data collection is complete.

Current trial status

We began recruitment of participants on February 12, 2018. As of September 10, 2021, 384 patients have enrolled. We placed the study on a temporary recruitment pause in March of 2020 due to the COVID-19 pandemic and resumed recruitment in July, 2020.

Funding

This study is supported by a R01 grant from the National Cancer Institute of the National Institutes of Health (R01CA215188; Temel).

Competing Interest Statement

All of the authors declare that they have no conflicts of interest to report.

Author Statement

JT, JG, and VJ contributed to the study conception and design. The protocol was developed and written by JT, JG, and VJ. KP, LH, ME, SG, JH, FF, AJ, provided substantial contributions to the acquisition of data for the study. The first draft of the manuscript was written by KP and LH. JT, JG, AK, PK, ME, SG, JH, CT, RP, CV, and DR contributed critically important revisions on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank the study patients for their time and dedication to this research study.

Figure Legends

Figure 1. CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials; QOL, Quality of Life.

Figure 2. Eligibility criteria

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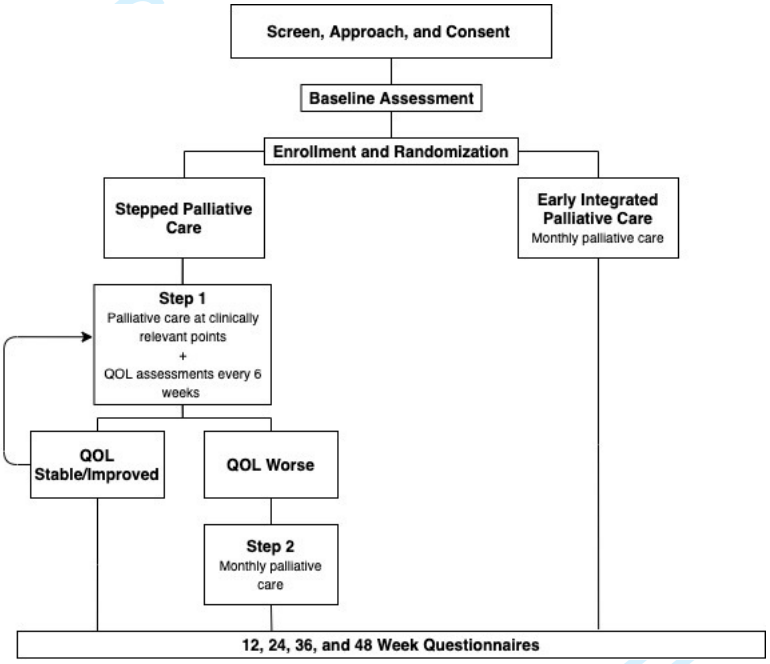
Screen, Approach, and Consent
Baseline Assessment
Enrollment and Randomization
Stepped Palliative Care
Early Integrated Palliative Care
Monthly palliative care
Step 1
Palliative care at clinically relevant points
+
QOL assessments every 6 weeks
QOL Stable/Improved
QOL Worse
Step 2
Monthly palliative care
12, 24, 36, and 48 Week Questionnaires

Inclusion Criteria:

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 ≤ 2.
3. Ability to read and respond to questions in English or Spanish
4. Primary cancer care at one of the three participating sites.
5. Age ≥ 18 years.

Exclusion Criteria:

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

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1

Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	1
Protocol version	#3	Date and version identifier	1
Funding	#4	Sources and types of financial, material, and other support	1
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and	10

		other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	5
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10

Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque,	7

		sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-8, 10

Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10-11
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10-12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10-12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and	10

		competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	10
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	12-13
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12-13

Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10, 12-13
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13

Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	13
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	appendix
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A