Brief Behavioral Intervention for Dyspnea in Patients with Advanced Lung Cancer
DF/HCC SOCIAL-BEHAVIORAL RESEARCH PROTOCOL
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ClinicalTrials.Gov: NCT03089125
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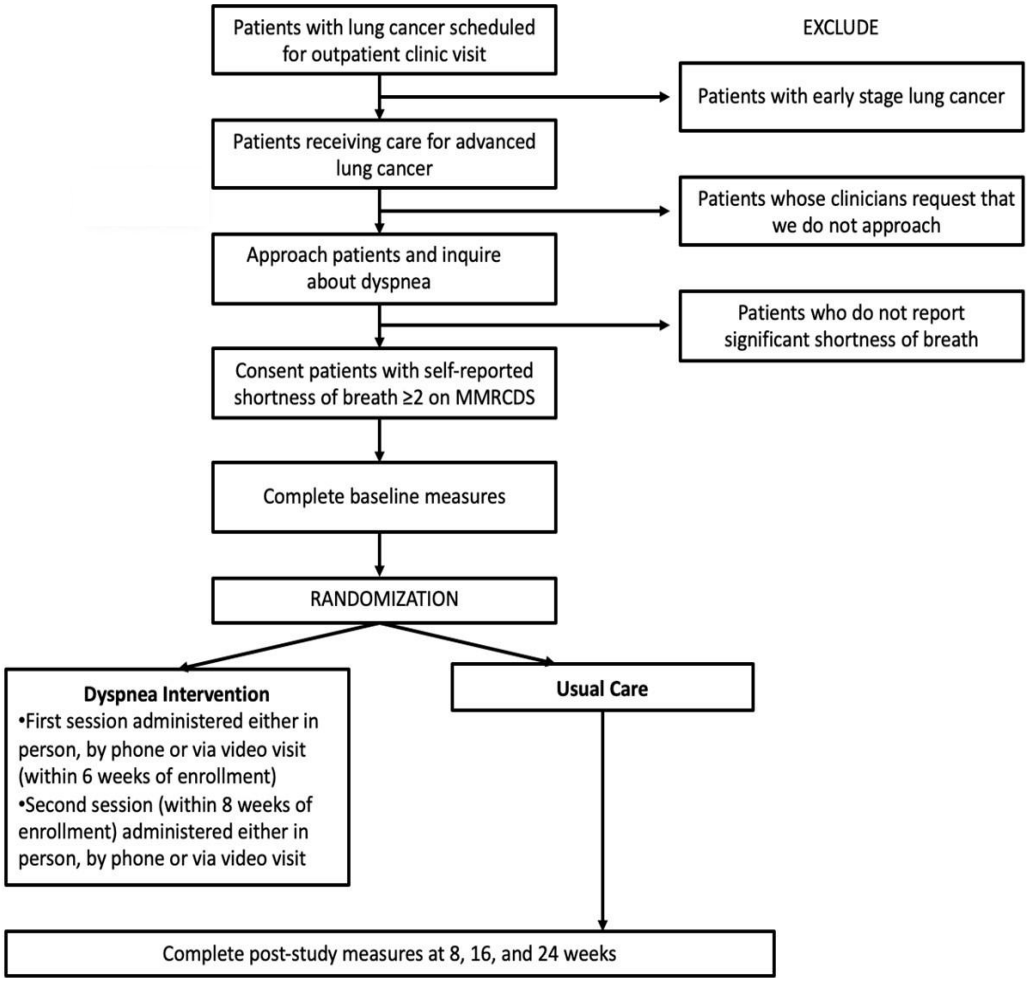
Section 1: Protocol Schema



Section 2: Body of Protocol

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1.0 INTRODUCTION

1.1 Overview.

At least 50% of patients with advanced lung cancer experience debilitating dyspnea that is associated with worse medical and psychosocial outcomes. The purpose of the present investigation is to test a brief behavioral intervention for dyspnea, delivered by oncology nurses within the outpatient cancer clinic or virtually via telephone or secure video visit. Through this study, we seek to increase access to much needed symptom management for those diagnosed with advanced lung cancers and ideally improve patients' overall quality of life.

The proposed project is being funded by the National Institutes of Health/National Institute of Nursing Research.

1.2 Background and Rationale.

Dyspnea is Debilitating and Highly Prevalent among Patients with Advanced Lung Cancer

Lung cancer remains the most commonly diagnosed cancer and leading cause of cancer death worldwide.[24] Dyspnea, a primary symptom of lung cancer, reflects a subjective experience of distress or discomfort related to the sensation of breathlessness.[25] The presentation of the symptom may vary, with patients describing dyspnea as episodic in nature, triggered suddenly upon exertion, or as continuous, occurring even at rest.[26] Among patients with advanced lung cancer, approximately half report experiencing clinically significant dyspnea that interferes with daily life activities.[1,2,10] Moreover, the symptom tends to worsen in frequency and severity as patients approach the end of life.[3-5] Several studies have shown a strong association between the severity of dyspnea and worse quality of life, with impairments in physical functioning and emotional wellbeing.[9-11,27]

Dyspnea is Associated with Significant Symptom Burden and Psychological Distress

In addition to poor quality of life, dyspnea is linked to increased pain, anxiety, and mood disturbance among patients with cancer. In a cohort of 120 patients with early and late-stage lung cancers, approximately 87% reported experiencing dyspnea, and those with more severe symptoms also had worse pain and anxiety.[27] For some individuals, dyspnea is associated with feelings of panic and impending death.[8] We found in our own investigation of patients with lung cancer that those with dyspnea were twice as likely to have panic attacks compared to those without respiratory symptoms.[28] Furthermore, investigators have observed that dyspnea is related to depression, anxiety, fatigue, cough, and decreased coping capacity in patients with cancer receiving palliative care services.[29] These studies underscore that the experience of dyspnea is multifaceted, involving physical and psychological factors, and requires comprehensive symptom assessment and management.

Dyspnea is Associated with Increased Service Utilization

Compounding the suffering experienced by patients and families, dyspnea is a major cause of healthcare utilization among individuals with cancer. Specifically, respiratory distress accounted for the greatest number of emergency department (ED) visits in patients with lung cancer (32% of visits) in one study of cancer-related ED utilization. Many of these patients were subsequently admitted to the hospital after ED evaluation.[13] This trend persists throughout the course of disease, as dyspnea is the second most common reason for visits to the ED in the final two weeks of life for patients with cancer.[12] Data suggest that the median survival for patients with lung cancer who present to the ED with dyspnea is only four weeks.[30] In the ambulatory care setting, one study showed that over half of patients with lung cancer (57%) utilized many services across disciplines, such as pulmonary rehabilitation and physical therapy, given their high symptom burden.[31] Thus, the Quality Oncology Practice Initiative of

the American Society of Clinical Oncology has identified the assessment and management of dyspnea as a key measure of quality cancer care.[14]

Novel Treatment Approaches for Dyspnea Are Greatly Needed

Despite the significant burden dyspnea represents, data are lacking to support effective treatments in patients with cancer.[16,17] Opioids have the strongest evidence base, though the medications tend to have modest benefit and carry serious risks and side effects.[32] Systematic reviews show no improvement in cancer-related dyspnea from either supplemental oxygen or benzodiazepines.[18,33,34] Although our research team found improvements in quality of life and mood among patients with metastatic lung cancer by the early integration of palliative care services, this model of care did not affect anxiety symptoms or dyspnea.[19] Non-pharmacological approaches for dyspnea have included supportive counseling, breathing control, muscle relaxation, coping strategies, energy conservation, and acupuncture.[17] Few clinical trials of these methods exist, and the resulting data appear to be mixed across techniques. Yet, interventions that include behavioral elements, such as breathing retraining combined with psychoeducation, have shown some promise and warrant further study.[20-22]

The management of dyspnea due to advanced lung cancer may be ideally accomplished by a multidisciplinary team, given the complex interplay of biomedical and psychosocial factors.[35] In fact, the National Health Service in the United Kingdom has recently developed an approach for managing dyspnea across multiple disease states that includes diverse caregivers: physicians, clinical nurse specialists, physical therapists, respiratory therapists, occupational therapists and social workers.[36] Although a well-designed randomized controlled trial of the comprehensive program yielded significant improvements in breathlessness mastery and survival, the approach involved numerous clinic visits with multiple specialists.[37] In the U.S., the lack of professionals trained in behavioral and palliative medicine severely limits the dissemination of such complex, comprehensive services.[38,39] Novel models of care that address the medical and psychosocial aspects of dyspnea in a feasible, acceptable, and seamless manner within outpatient settings may prove more beneficial and scalable.

MGH Cancer Center Sites/DFCI Are Ideal Clinical Settings for Collaborative and Cross-Disciplinary Research

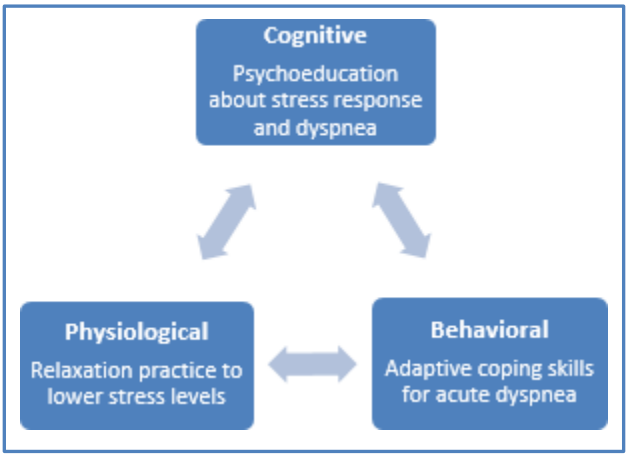
At the Massachusetts General Hospital (MGH) Cancer Center, we have gained considerable experience in multidisciplinary research in the oncology setting. Our Cancer Outcomes Research Program consists of oncologists, nurses, palliative care physicians, psychiatrists, and psychologists who share their respective expertise to inform the development of state-of-the-art clinical interventions to improve comprehensive cancer care, symptom management, and quality of life for patients with cancer. In addition to establishing highly successful methods for recruiting and retaining patient participants, we have capitalized on our cross-disciplinary collaborations to overcome barriers in communication, coordination, and integration of supportive care services into the outpatient oncology setting. With external funding from federal and nonprofit organizations, we have conducted numerous studies demonstrating improved patient and provider outcomes with interventions such as: early palliative care services;[19] clinician-directed prompts for discussing end-of-life care preferences;[40] the adaptation of cognitive-behavioral therapy to treat anxiety related to advanced cancer;[41] and training of oncology nurses in psychological skills to manage stressful patient and family encounters,[42] among others.

Recognizing the limited availability of such unique collaborative teams across cancer centers, we seek to test novel models of care that can be widely accessible and feasible to implement. We therefore have partnered with the Dana-Farber Cancer Institute (DFCI) and their leading nurse researcher in symptom management (Dr. Cooley) to test our proposed dyspnea intervention. We will train oncology nurses at both sites to deliver behavioral techniques shown to be effective for breathing retraining and reducing distress. Nurses are well-qualified for administering this type of intervention as they are integrated in

the oncology care setting, can assess both the medical and psychosocial factors associated with dyspnea, and provide expert symptom management.

Theoretical Basis of Proposed Brief Behavioral Intervention for Dyspnea

The experience of dyspnea involves interactions among physical, psychological, and social factors.[43] We therefore propose to test the efficacy of a brief behavioral intervention to reinforce adaptive coping responses to dyspnea. Leading investigators of cognitive-behavioral therapy (CBT) have posited that a combination of biological factors and stressful life events can result in maladaptive distress through an interactive cycle of physiological, cognitive, and behavioral symptoms. The primary features of this cycle include increased autonomic arousal, negative biases in perception, and avoidance of threatening stimuli.[44] Moorey et al.[45] further elaborated the CBT model to understand the ways in which individuals adjust to having cancer. They argue that cancer and its symptoms (e.g., dyspnea) represent a legitimate sense of danger to one's physical and social well-being, triggering vulnerability in one's beliefs about being able to cope with this threat. Noting the bi-directional relationships among physiology, cognition and behavior, the theorists suggest in their Cognitive Model of Adjustment to Cancer that schemas related to the self (i.e., view of the self) and to survival (i.e., view of the disease, degree of control over cancer and its symptoms) play central roles in the maintenance of distress. Given the legitimate threat to survival and changes in self-schema due to the symptoms of advanced lung cancer, the dyspnea intervention has been tailored to incorporate strategies for managing the complex interplay between the medical and psychological concerns. Targeting each domain, the intervention includes 1) psychoeducation to enhance cognitive understanding of dyspnea, 2) relaxation practice to reduce physiological stress, and 3) behavioral coping skills for managing acute dyspnea.



Summary of Significance

The proposed study is significant in that it targets the markedly prevalent and burdensome symptom of dyspnea with a brief nurse-administered behavioral intervention that has potential for cost-effective scalability and broad dissemination across cancer care settings. Furthermore, the intervention techniques are evidence-based and derived from sound theory, providing significant clinical benefit with minimal burden of care to patients.

Preliminary Studies

Rate of Dyspnea is High in Patients with Non-Small Cell Lung Cancer and Associated with Distress.[28]

Our team explored the frequency of dyspnea and the risk of panic disorder and depression symptoms among patients with newly diagnosed non-small cell lung cancer (NSCLC). Consecutive patients presenting for initial consultation at the Massachusetts General Hospital Thoracic Oncology Clinic completed a survey of current symptoms, including dyspnea, panic disorder, and depression symptoms. Among 624 patients (mean age=63.7; SD=12.1; 52.6% female), 48.1% reported at least moderate dyspnea. Dyspnea was independently associated with higher risk of panic disorder symptoms (odds ratio=2.19, 95% CI=1.11-4.31, P=0.02). Younger age and major depression symptoms were also associated with higher risk (P<0.01). In conclusion, almost half of the patients with newly diagnosed

non-small cell lung cancer reported dyspnea, and patients with dyspnea were more than twice as likely to endorse panic disorder symptoms relative to patients without dyspnea.

A Tailored Cognitive-Behavioral Intervention Alleviates Anxiety in Patients with Terminal Cancer.[48]

For this NCI-funded randomized trial (R03CA128478, PI: Greer), we used mixed methods to examine the feasibility and preliminary efficacy of cognitive-behavioral therapy (CBT) to reduce anxiety in patients with terminal cancers. Based on qualitative feedback from patients, we adapted the CBT intervention by developing treatment modules for relaxation, coping with cancer worries, and activity-pacing. Adults with incurable malignancies and elevated anxiety (Hamilton Anxiety Rating Scale; HAM-A>14) were then randomized to individual CBT or a wait-list control group. Primary outcomes included: 1) the number of completed CBT visits, and 2) change in HAM-A scores from baseline to 8-week follow up per a treatment-blind evaluator. Forty patients with terminal cancers were randomized (CBT n=20, Wait-list Control n=20), and 80% of CBT patients completed at least 5 of the 6 sessions. Of the total 109 completed CBT sessions, 45 (41.3%) occurred either on the same day as other hospital appointments (n=25, 22.9%) or during chemotherapy infusions (n=20, 18.3%). Linear regression analyses, adjusted for baseline scores, showed that those assigned to CBT had greater improvements in HAM-A scores compared to the control group (Adjusted Mean Difference=-5.42; 95% CI=-10.84, -.001; p=.05), with a large effect size for the intervention (Cohen's d=.80). Providing CBT tailored to the concerns of patients with terminal cancer was not only feasible but also led to significant improvements in anxiety.

Nursing Interventions Are Feasible for Symptom Management in Patients Receiving Chemotherapy.[49]

Drs. Temel and Greer recently completed a RCT of a proactive nursing intervention to improve symptom management after chemotherapy administration in patients with early stage lung, breast and colon cancer. We enrolled and randomized 120 of 137 eligible patients (88%). Those in the intervention group (n=60) received twice weekly phone calls from an oncology nurse after the patients' first two chemotherapy infusions. Only two patients withdrew from the study and did not complete post-study assessments. Although the study showed no differences between groups in the primary outcomes, it nonetheless demonstrates the feasibility of enrollment, retention, and collection of patient-reported measures within the context of nursing intervention trials.

A Brief Nurse-Administered Intervention Reduces Dyspnea in Patients with Advanced Lung Cancer.[23]

We examined the feasibility, acceptability, and utility of delivering a brief behavioral intervention for dyspnea in patients with lung cancer at the point of care. For this single-group pilot trial, eligible patients included those with advanced lung cancer (stage III or IV non-small cell [NSCLC] or extensive stage small cell [SCLC]) from the ambulatory care clinic who reported at least moderate breathlessness. The manualized intervention consisted of two sessions in which nurse practitioners taught participants breathing and relaxation techniques within the infusion clinic and encouraged home practice. Participants completed measures of dyspnea (Modified Medical Research Council Dyspnea Scale [MMRCDS]), QOL (Functional Assessment of

Illustrative Patient Quotations

- *"It was convenient because it was during the appointments, and it wasn't too long. I thought it was an excellent use of time, and it was integrated very nicely with what was going on."*
- *"The [breathing exercises] helped me when if I started to lose my breath, to really slow myself down, instead of taking shallow breath to my lungs, I learned to hold all the air in and then let it back out and fill my lungs faster than taking short little breaths, and I found that was the most helpful part of the program."*
- *"The nurse was engaging and very good at responding to and expanding on any kind of question I had."*

Cancer Therapy-Lung Trial Outcome Index [FACT-L TOI]), and anxiety and depression symptoms (Hospital Anxiety and Depression Scale [HADS]) at baseline and six weeks post enrollment. Of the 32 patients enrolled in the study (56.3% Female; Mean Age=63.34, SD=7.96 years), 84.4% (N=27) completed all study procedures. Comparing the baseline to post-assessments, we found significant improvements in MMRCDS (p<.001), FACT-L TOI (p=.01), and HADS-Depression Subscale (p<.001) scores, with corresponding moderate to large effect sizes. In this sample of patients with advanced lung cancer, we observed a high completion rate for the two- session intervention. Patients also reported improvements in dyspnea, QOL, and distress. Based on participant exit interviews (see illustrative quotes), 95.5% of patients rated the intervention favorably for its convenient location of delivery, low burden, effective coping skills, and positive social support.

Measuring Performance Status with Actigraphs Correlates with Dyspnea in Patients with NSCLC.[47]

Dr. William Pirl recently completed a pilot study to evaluate the feasibility of using actigraphy to measure performance status in 42 patients with metastatic NSCLC. Participants wore wrist actigraphs for three days prior to completing questionnaires assessing symptoms, including dyspnea, and their activity level. Eastern Cooperative Oncology Group performance status (ECOG PS) has a clinically meaningful difference in scores based on whether a patient is inactive for at least half the time they are awake. Actigraphy objectively captures the percentage of time a person is immobile but awake. Actigraph reports of participants' percent time spent immobile but awake ranged from 4-50% (Mean=18%, SD=11%). Percent of time awake and spent immobile was correlated with physician report of ECOG PS (r=0.44, p=.004). Patient-reported dyspnea on the FACT-L was associated with three assessments of physical functioning: physician report of ECOG PS (r=-0.52, p<.001); patient-reported walking speed (r=-0.51, p=.001); and percent of time awake and spent immobile (r=-0.36, p=.02). Based on our findings, we will use actigraphy as an objective measure of physical activity in the current study.

Summary of Preliminary Studies: For the past decade, our team has successfully collaborated on numerous supportive care studies for patients with lung and other cancers. The above studies highlight our accomplishments in demonstrating the need to treat dyspnea; developing and testing behavioral interventions in cancer; implementing nurse-administered symptom management trials; and using novel technologies for assessment.

Innovation of Proposed Study

The proposed study is **innovative with respect to the 1) novel model of delivering the intervention at the point of care within outpatient oncology setting, and 2) multimethod assessment of patient outcomes**. Given that patients with advanced lung cancers can be quite ill, the burden of additional appointments for behavioral treatment of symptoms represents a significant barrier to accessing services. Thus, we propose to address this concern by administering a point-of-care intervention that involves cross-disciplinary training and delivery within the flow of oncology care. The PI team is uniquely qualified to oversee such a program. Drs. Greer, Temel, and Cooley possess expertise in behavioral medicine/cognitive-behavioral therapy, thoracic oncology/palliative care, and nursing practice/cancer symptom management, respectively. This team will train and supervise the oncology nurses in delivering the evidence-based dyspnea management intervention. We elected to develop a minimally intensive behavioral intervention that can be easily implemented, involves home-based practice, and avoids barriers to scheduling multiple outpatient visits, especially for those suffering from considerable symptom burden. Specifically, we are proposing a streamlined dyspnea management intervention, to be completed over two 30-45minute sessions in tandem with outpatient clinic appointments or virtually via telephone or secure video visit. Although recent studies have shown

benefit from more complex, multi-component, intensive interventions for dyspnea,[37,46] such approaches require considerable clinician resources and time, which are neither scalable nor feasible for patients with advanced cancer undergoing burdensome treatments. Moreover, we observed in our prior study that patients greatly appreciated being able to meet with the nurse interventionists and learn the behavioral skills in the infusion clinic rather than having to make extra visits to the hospital.[23] Thus, providing the brief intervention at the point of care in the outpatient oncology setting or virtually represents a new model of cancer care that is feasible for implementation outside a grant-funded environment. Such an approach could be easily deployed to larger populations.

Finally, in addition to measuring self-report outcomes of dyspnea, quality of life, anxiety and depression, we will assess the effect of the brief intervention on functional status using actigraphy. We have piloted the use of actigraphy in the study population (see Preliminary Studies), observing strong correlations between self-reported dyspnea and objective activity levels in patients with metastatic lung cancer. To our knowledge, no prior studies have incorporated this multimethod approach to evaluating dyspnea intervention outcomes, which could serve as a new, state-of-the-art methodology for measuring performance status in patients with cancer.

2.0 OBJECTIVES

2.1 Primary Aim

To demonstrate the efficacy of the brief behavioral intervention for improving self-reported dyspnea (primary outcome) in patients with advanced lung cancer

Hypothesis: Participants with advanced lung cancer who are randomly assigned to receive the brief behavioral intervention will report statistically and clinically significant improvements in dyspnea compared to those assigned to usual care.

2.2 Secondary Aim

To demonstrate the efficacy of the brief behavioral intervention for improving patient quality of life, mood symptoms, and activity level (secondary outcomes) in patients with advanced lung cancer

Hypothesis: Participants with advanced lung cancer who are randomly assigned to receive the brief behavioral intervention will experience statistically and clinically significant improvements in quality of life, mood symptoms, and activity level compared to those assigned to usual care.

2.3 Exploratory Aim

To explore mediators and moderators of the effect of the brief behavioral intervention on patient-reported outcomes

Hypothesis: Intervention effects on patient-reported dyspnea will be mediated by improved mastery in managing breathlessness and potentially moderated by patient demographic and clinical factors (e.g., gender, age, performance status, and disease comorbidity).

3.0 RESEARCH SUBJECT SELECTION

3.1 Patient Eligibility Criteria

3.1.1 Inclusion Criteria

The patient eligibility criteria will mirror those in our successful pilot study.[23] To be eligible for the RCT, patients must have:

1) A diagnosis of either NSCLC, SCLC, or mesothelioma, not being treated with curative intent

2) Self-reported shortness of breath (a score of 2 or greater on the Modified Medical Research Council Dyspnea Scale)
3) Eastern Cooperative Oncology Group (ECOG) Performance Status from 0 (asymptomatic) to 2 (symptomatic and in bed <50% of day)
4) The ability to respond to questions in English
5) Primary cancer care at the Massachusetts General Hospital (MGH) Cancer Center, Dana-Farber Cancer Institute (DFCI), Mass General Cancer Center at Newton-Wellesley Hospital, and Mass General/North Shore Cancer Center-Danvers
6) Age >18 years

3.1.2 Exclusion Criteria

Patients will be excluded if they have:
1) Cognitive or psychiatric conditions prohibiting study consent or participation.
2) A treating clinician who reports that the patient is inappropriate for the study

4.0 RESEARCH SUBJECT ENTRY

4.1 Patient Screening

In our pilot study, we asked clinicians to identify patients with dyspnea by reviewing their clinic schedules at the weekly thoracic oncology staff meeting. While we enrolled study participants rapidly in the pilot study, this recruitment method required the clinician to have knowledge of patients' dyspnea. However, oncology clinicians often fail to recognize or underestimate dyspnea.[50] Thus, relying on clinician awareness of patients' symptoms is unlikely to identify all eligible patients for study participation. Therefore, in the current proposal, we will identify patients for study participation based upon their self-report of dyspnea using a validated standard screening measure (i.e., MMRCDS). We will institute the same patient screening procedures in the participating thoracic oncology clinics at Massachusetts General Hospital, Dana-Farber Cancer Institute, Mass General Cancer Center at Newton-Wellesley Hospital, and Mass General/North Shore Cancer Center-Danvers as we share the same scheduling and health record systems. As a point-of-care intervention, we will screen all patients with lung cancer receiving care in the outpatient clinics and approach them in person or via telephone. By reviewing the electronic scheduling system and health record module documenting cancer stage, we will identify all patients with advanced lung cancer who are scheduled for visits in the subsequent week.

A partial HIPAA Authorization will be obtained for the collection of protected health information (PHI) prior to consent. The waiver will allow the study staff to identify potential eligible patients to recruit and contact. It will also prevent ineligible patients from being contacted and burdened with an in-person or telephone screen for a study for which he or she would be ineligible. Additionally, the waiver would allow patients to be screened with the MMRCDS prior to consent, reducing any emotional distress associated with consenting to a study for which they are potentially ineligible. Having access to PHI will both optimize patient recruitment opportunities, while decreasing burden on ineligible patients. The use and disclosure of this information does not involve more than a minimal risk to privacy.

The study staff will review and collect information on the cancer diagnosis, stage, date of outpatient oncology clinic appointments, Eastern Cooperative Oncology Group (ECOG) Performance Status, age, language, phone number and patients' self-reported MMRCDS score before administering consent. Information collected from screened patients will be stored in a password-protected computer file that is stored on a secure, HIPAA-compliant Partners network drive. Only

information relevant for contacting and screening the participants will be stored on this database. This secure procedure will prevent any improper use and disclosure of PHI.

For patients who screen eligible on the MMRCDS (shortness of breath ≥ 2 on MMRCDS), their data will be scanned and securely stored in a secure, HIPAA-compliant Partners network drive. For patients who do not screen eligible on the MMRCDS, their data on this measure will be destroyed immediately. For more information on the protection of patient data, see section 5.5.3.

Before approaching the patients meeting the above criteria, the study staff will inform the oncology health care team (i.e., oncologist, advanced practice nurse, palliative care specialist as appropriate) of their patient's potential eligibility for study participation via email or in person. The study staff will also notify the cancer care team of their plan to approach the patient regarding study participation at the next scheduled visit or via telephone should the team not respond with any reservations. Clinicians who express that they do not wish to receive these emails will be approached in clinic for permission to discuss study participation with patients. All other clinicians will be sent an email containing the patient's name and medical record number and the request for study staff to approach the patient. A member of the cancer care team will be informed at least two business days prior to approaching the patient for the first time. If a clinician prefers that we do not approach her or his patient for study participation, we will collect the reason for this request. Finally, we will state in the email or in person that study participation does not preclude the clinicians from medically treating the dyspnea per their clinical judgment.

Once the oncology health care team has been informed and has not refused study staff to approach their patient, a study staff member will approach the patient in the infusion unit outpatient clinic, or via telephone to inquire about their experience with dyspnea. If the patient reports having dyspnea, the trained study staff member will explain the study. If the patient indicates interest in the study, they will be asked to complete a brief single-item screen to determine if they meet eligibility criteria (i.e., shortness of breath ≥ 2 on MMRCDS) for participation. To decrease participant burden, this brief screening measure will be given prior to consent. For patients who are approached via telephone, the MMRCDS will be administered verbally, via mail, or electronically. If the patient screens ineligible, the patient will not be consented and their MMRCDS will be appropriately discarded by the study staff using HIPAA-compliant procedures immediately. Patients who report shortness of breath score of ≥2 on the MMRCDS breathlessness measure will be eligible to continue to the next stage of the study.

For patients who screen eligible on the MMRCDS, the trained study staff member will perform consent procedures and administer the baseline assessments. Following the completion of the baseline assessments, the patient will be randomized to receive the intervention or standard care.

Otherwise, given that patients with advanced lung cancer develop new symptoms over time, patients with a score of <2 on the MMRCDS who agree to be approached again will continue to be screened with the brief measure every three months.

4.2 Patient Recruitment and Enrollment

After the oncology care team has been informed and has not refused study staff to approach their patients, a trained study staff member will contact potential participants in-person or via telephone to explain the study and offer a brief screen to confirm whether the patient is eligible to participate. If an oncology clinician reports that the patient is being treated with curative intent or otherwise does not meet eligibility criteria, study staff will document the reason. If eligible, the informed consent process may be completed through either modality as detailed in this section. 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. All willing participants that provide consent will then be registered by study staff (see below).

4.2.1 In-Person Informed Consent Process

Participants will be asked to complete the MMRCDS scale evaluating shortness of breath to confirm that their breathlessness is sufficient to participate (as discussed in section 4.1). All patients who screen positive on the MMRCDS shortness of breath measure (i.e., a score of $\geq$ 2 on the MMRCDS) will be considered eligible for the study.

After confirming eligibility based on the MMRCDS, the study staff will then perform consent procedures by presenting the patient with a detailed, HIPAA-compliant consent form to be signed by each participant following the explanations by the study staff.

4.2.2 Verbal Informed Consent Process

We are requesting an alteration of HIPAA to allow for 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. The verbal consent procedures can accommodate external factors such as safety concerns for patients or study staff, hospital guidelines, a lack of clinic space or patient time constraints.
Patients are coming into the hospital less regularly to receive in-person care, which limits our ability to approach them onsite for consent procedures. Remote electronic consenting is not feasible for many patients in our population as it requires technology and technical skill that some patients lack, potentially leading to a selection bias among enrolled participants. Consenting by mail is also not feasible given the patient population has advanced lung cancer with a poor prognosis and mailing the consent form to and from the participant would likely create delays in enrollment of several weeks negatively impacting enrollment, retention and completion of study procedures. Verbal consent reduces patient burden and attrition and allows for greater flexibility while assuring patient safety in response to changing healthcare practices due to the COVID-19 pandemic.

A study staff member will contact the patient via telephone to offer study participation and determine eligibility using the recruitment and screening script. Patients who screen positive on the MMRCDS shortness of breath measure (i.e., a score of $\geq$2 on the MMRCDS) will undergo verbal consent procedures using the suggested verbal phone script provided within the HIPAA-compliant verbal consent form. All patients who provide verbal consent will receive an unsigned copy of the written informed consent. If the patient does not answer the phone, the clinician or study staff member may leave a voicemail (see appendix 8.11 for suggested language for the voicemail).

4.2.3 Baseline Completion

Patients will be asked to complete the baseline questionnaires in person, via mail, telephone, or electronically. Once patients complete baseline questionnaires, the study staff will provide them with a wrist actigraph and activity log. Patients will be instructed on the

proper use of the actigraph and told to wear it and complete the activity log for the following 3 days. When this 3-day period ends, a study staff member will call the participant and notify them of their study group assignment. Patients will either return the actigraph at their next clinic visit or will mail it back to study staff via FedEx paid for by the study.

Using data from our electronic billing systems, we estimate that approximately 480 patients with advanced lung cancer receive treatment at the MGH Cancer Center and DFCI per year. Although studies show that approximately 50% of patients with metastatic cancer endorse some degree of shortness of breath, we conservatively anticipate 30%-40% of patients will report shortness of breath ≥2 using the MMRCDS (resulting in approximately 140-190 eligible patients per year). Based on the high accrual rates observed in our previous supportive care studies, and low patient burden for the proposed trial, we estimate 60% accrual to this study. Thus, we will be able to achieve successfully our recruitment goal of 220 patients during the 4-year enrollment period.

4.3 Randomization and Registration

MGH Biostatistical Core will be responsible for generating one randomization scheme. Randomization will be stratified by cancer type (NSCLC versus SCLC versus mesothelioma) and study site (Massachusetts General Hospital Cancer Centers versus Dana-Farber Cancer Institute).

The registration and randomization procedures are as follows:

- Obtain written informed consent or verbal consent from the participant prior to the performance of any protocol specific procedures or assessments.
- Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criteria as described in the protocol and reflected on the eligibility checklist.
- The DFCI study staff will confirm eligibility criteria and fax or email the following documents to the study staff at MGH: deidentified signed consent form/s and a completed eligibility checklist.
- A member of the MGH study staff (independent from study staff who recruit, enroll and administer assessments to participants) will perform randomization procedures using a randomization schema stratified by cancer type and study site.
- The MGH study staff will fax or email the information about randomization to the study staff at DFCI. The MGH study staff may also call the study staff at DFCI to verbally confirm registration and randomization.
- Both MGH and DFCI will register eligible participants from all sites in the Clinical Trials Management System (CTMS) Oncore, as required by DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101). This must occur prior to the initiation of protocol-specific procedures or assessments.

5.0 STUDY DESIGN & METHODS

5.1 Study Design.

We will conduct a randomized controlled trial (RCT) of a brief two-session behavioral intervention for dyspnea management in patients with advanced lung cancer.

5.2 Selection of Instruments.

We selected instruments based on our theoretical framework of the intervention, which seeks to reduce dyspnea sensations (physiological), improve understanding and perceptions of mastery in coping with the symptom (cognitive), as well as enhance activity/performance status (behavioral).

Outcome Measures:
Modified Medical Research Council Dyspnea Scale (MMRCDS): The MMRCDS is a one-item scale with a 5-point grading system to evaluate patients' degree of dyspnea.[59,60]

Cancer Dyspnea Scale (CDS): The CDS is a twelve-item scale that assesses the multidimensional nature of dyspnea in cancer patients. [72]

Functional Assessment of Cancer Therapy-Lung (FACT-L): The FACT-L quality of life tools assess physical, social/family, emotional, and functional well-being (27 items) and lung cancer specific symptoms (8 items) over the past 7 days.[61]

Hospital Anxiety and Depression Scale (HADS): The HADS assesses symptoms of anxiety (7 items) and depression (7 items) over the previous week.[62]

Godin-Shephard Leisure Time Physical Activity Questionnaire (GSLTPAQ): The GSLTPAQ is a brief assessment of the frequency and the extent of typical exercise during free time over the course of one week (4 items).[63]

Potential Mediator and Moderators of Intervention Effect
Chronic Respiratory Disease Questionnaire (CRQ): The CRQ is a validated 20-item measure that assesses physical and psychological aspects of chronic respiratory disease including "mastery," or perceptions of control over the disease, and its effects on quality of life and functioning.[64,65]

Eastern Cooperative Oncology Group Performance Status (ECOG PS): Study participants will be asked to choose the functional rating which best describes their performance status in the past week.[66]

Demographic Questionnaire: Participants will self-report their age, sex, race/ethnicity, marital status, religion, education level, and tobacco use (both prior and current use) at baseline. On 8/20/2017, we amended this questionnaire to include two questions about tobacco use. For all patients who completed baseline prior to this date, we will administer the two tobacco use questions at the next assessment point (week 8, week 16, or week 24).

Objective Performance Status Measure
Wrist Actigraphs: An actigraph is a portable, wristwatch-sized accelerometer device that detects and logs wrist movement over time in the form of activity counts. We will use Spectrum Plus (Philips Respironics USA), which is a watch-sized device that can be worn comfortably during activities of daily living, including sleeping, bathing, and exercise. Spectrum Plus detects and logs wrist movement to measure physical activity and has a light sensor to determine day and night time hours. Spectrum Plus has a rechargeable battery and is fully waterproof. Data from Spectrum Plus are retrieved using specialized software. Study participants will also receive a 3-day activity log to complete while wearing the actigraph to supplement the recording of their activity level and confirm their sleep/wake schedule. Patients will record the times they woke up, got out of bed, napped, went to bed, and turned out the lights each day while wearing the actigraph. All study participants

will be given an Spectrum Plus and activity log at the time of completing the baseline assessment. Participants will be asked to wear the actigraph and complete the activity log for two 3-day periods during the study, at baseline and week 8. The study staff will explain that the actigraph should be worn on their non-dominant wrist continuously for each 3-day period, including while bathing and exercising. The study staff will contact participants via telephone to remind them when to begin using the actigraph and activity log. In our previous study assessing the feasibility of using the actigraph in patients with metastatic lung cancer, all study participants wore the actigraph for the full 3-day period and completed the activity log.[47]

5.3 Description of Intervention

5.3.1 Clinician Training and Supervision

In our prior pilot study, we created a clinician manual that includes step-by-step instructions for teaching the behavioral strategies for managing dyspnea. This manual was developed and partially adapted from an evidence-based cognitive-behavioral treatment for anxiety in patients with advanced cancer.[48,51] Given that a primary aim of the proposed study is to improve access to care for patients, we will train oncology nurses (at each study site) in the administration of the brief intervention for delivery in the outpatient and infusion clinics or virtually via telephone or secure video visit. We will use HIPAA-compliant, hospital-approved Zoom videoconferencing. The study nurses will first review the manual and then participate in a comprehensive didactic training session with the PI team (i.e., Drs. Greer, Temel, and Cooley) to reinforce learning of the intervention components as well as to clarify the process for administering the intervention within the outpatient setting or virtually via telephone or secure video visit. The training sessions will include practicing and role playing the delivery of the intervention with Dr. Greer, who is a licensed clinical health psychologist with expertise in developing and testing cognitive-behavioral interventions for patients with cancer. Once the randomized trial begins, the study nurses will be asked to complete an intervention guide/checklist detailing the exercises for use in session and to document administration of the intervention components with each participant. Drs. Greer, Temel, and Cooley will also hold regular, ongoing teleconference calls with the nurse interventionists to provide supervision, address any participant concerns that arise, and reinforce protocol adherence. At least 80% of the intervention sessions will be audio-recorded to allow for circumstances with unexpected technological difficulties. We will randomly select 10% for Dr. Greer (or trained study staff member) to review to ensure fidelity

5.3.2 Delivering the Dyspnea Management Intervention

Patients assigned to the brief behavioral intervention for dyspnea will participate in two sessions. Sessions one and two will be administered in-person, via telephone, or via institution approved secure videoconferencing technology.

Session One: The first session of the brief behavioral intervention consists of having the patients learn evidence-based approaches for dyspnea management including: 1) psychoeducation, 2) relaxation training for reducing physiological stress, and 3) behavioral techniques for managing acute breathlessness.[20] For the psychoeducation component, the study nurses will provide participants with a brief overview of the cognitive-behavioral model and describe how breathlessness activates the physiologic stress response. Specifically, the nurse will explore with the patient the types of thoughts that breathlessness triggers (e.g., “I can’t get enough air; my cancer must be getting worse”) and associated physiologic (e.g., chest tightness, heart racing) and behavioral responses (e.g., avoiding

strenuous activity or physically demanding tasks) that perpetuate stress, deconditioning and worsening dyspnea. The nurses will discuss in detail the nature of the stress response to help the patients understand the physiologic changes in their body as a result of breathlessness and to empower them to use coping strategies to calm the body. Next, patients will learn to manage acute breathlessness with several evidence-based techniques including pursed-lips breathing,[52] use of a battery-operated handheld fan (blowing air toward the face),[53] and postural techniques to minimize work of breathing.[54,55] Commonly used for chronic obstructive lung disease,[56] pursed-lips breathing provides natural resistance to lengthen the exhalation phase, strengthen respiratory muscles, and release "trapped" air from the lungs. Finally, as a daily practice to reduce overall physiological stress, participants will receive training in relaxation exercises, including diaphragmatic breathing and guided breathing meditation.[57,58] Individuals who are unable to take full, deep breaths due to severe lung disease may modify diaphragmatic breathing by focusing on slowing the breath and extending the expiratory phase rather than taking deep inhalations. The study nurses will instruct patients to practice these relaxation exercises every day at times when not experiencing acute dyspnea. Participants will receive instructional pamphlets, handheld fans, and audio-recordings of the guided breathing exercise for daily practice. Participants will receive study intervention materials in-person, via mail or email. Participants with smart phones will be able to download the recorded exercises to their phones, while those without this technology will receive MP3 players with recordings of the exercises.

Session Two: The second session of the dyspnea intervention will focus on patients' adherence to the study protocol, review of home-based practice of techniques for acute dyspnea and breathing exercises, identification and problem-solving of any obstacles to practicing the intervention techniques, and reinforcement of information and behavioral skills covered in session one. Sessions one and two will take place approximately 2-3 weeks apart and will last no more than 30-45 minutes, as we observed in our prior trial. Participants may complete this session in person or virtually via telephone or secure video visit.

5.3.3 Usual Care

Patients in both study groups may receive any usual care for their dyspnea as deemed appropriate by their clinicians. Cancer care clinicians commonly prescribe opioids, benzodiazepines and nasal canola oxygen for patients with dyspnea, though these interventions tend to have minimal benefit. In addition, some patients may undergo procedures for pulmonary complications that can impact their respiratory status, including draining pleural effusions and stent placement or radiation therapy for bronchial obstructions. MGH and DFCI Pulmonology clinicians will provide consultative guidance for the investigative team on such cases in the study, regardless of group assignment. While the study staff will track medical therapies and procedures through the electronic health record for patients in both study groups, participation in this study will not impact use of these modalities. We do not anticipate the study groups to differ significantly in their use of medical therapies, though these factors will serve as control variables in the final analyses as necessary.

After completion of the final study follow-up, patients randomized to receive usual care will be offered the study intervention materials to be delivered either in person, via mail or email. They will also be offered the opportunity to meet with a study clinician in person, by phone, or via secure video to review the materials and ask questions. At the time of

enrollment, patients will be made aware that these resources will be available upon completion of the final study assessment.

5.4 Data Collection Procedures

5.4.1 Timing of Data Collection

The following table depicts the assessments, measures and time points for the proposed data collection.

	Screening	Baseline	Weeks 8, 16, 24	Post Study
Chart review for eligibility and baseline clinical characteristics	X			
Modified Medical Research Council Dyspnea Scale (MMRCDS)	X	X	X	
Cancer Dyspnoea Scale (CDS)		X	X	
Demographic Questionnaire		X		
Functional Assessment of Cancer Therapy-Lung (FACT-L)		X	X	
Hospital Anxiety and Depression Scale (HADS)		X	X	
Godin-Shephard Leisure Time Physical Activity Questionnaire (GSLTPAQ)		X	X	
Chronic Respiratory Disease Questionnaire (CRQ)		X	X	
Self-report ECOG Performance Status		X	X	
Actigraph and activity log (for 3 days)		X	X (week 8 only)	
Chart review for treatment, medical orders, service utilization				X

5.4.2 Data from the Electronic Health Record

Clinical information regarding tumor type (NSCLC, SCLC, mesothelioma), date of diagnosis of advanced disease, previous cancer therapies, current treatment regimen, and performance status will be collected at baseline. The post study review of the electronic health record (EHR) will include information on disease progression, any changes in cancer treatment, and number of emergency department (ED) visits and hospitalizations during the study period.

Medical comorbidity will be assessed at the time of baseline data collection with the Charlson Comorbidity Index (CCI).[67] We will review health records for the presence of (1) pulmonary, cardiac, hepatic, and renal disease, (2) current and other malignancies, and (3) other morbidities (diabetes, cerebrovascular disease, and rheumatologic conditions) and assign the appropriate CCI score.

Medical orders: We will collect data on medications to alleviate dyspnea (e.g., opioid analgesics), supplemental oxygen, and procedures for managing pleural effusions or bronchial obstruction.

Dr. Temel (Co-I), a thoracic oncologist, will oversee the collection of clinical information from the EHR as well as the review of medical scans to determine whether participants'

disease progressed during the study period.

5.4.3 Data Storage

Study source documents, including but not limited to signed informed consent forms, completed eligibility checklists, and participant questionnaires, will remain confidential and be scanned and stored on secure Partners computers and in REDCap. Since these records necessarily contain patient identifiers, only study staff will have access to them.

Study staff will scan completed source documents, which may include identifiers such as participant names, upon their completion. Location, time, and date of the scanning of the document will be recorded. After the source document is scanned and the corresponding electronic document is confirmed to be legible, it will be collected and destroyed immediately. Study staff will destroy the original copy of the source document by following MGH procedures of destroying documents with Personal Health Information (PHI).

If a patient requests to view his or her data collected by the actiwatches (activity, mobility and sleep statistics), study staff can provide patients with this data. 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 completed. Data abstracted from the electronic health record in Section 5.4.2 will be maintained in REDCap. REDCap (Research Electronic Data Capture) is a free, secure, HIPAA-compliant web-based application hosted by the Partners HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Vanderbilt University, with collaboration from a consortium of academic and non-profit institutional partners, has developed this software toolset and workflow methodology for electronic collection and management of research and clinical study data. Data collection projects rely on a study-specific data dictionary defined by members of the study staff with planning assistance from Harvard Catalyst | The Harvard Clinical and Translational Science Center EDC Support Staff. The iterative development and testing process results in a well-planned data collection strategy for individual studies. REDCap provides flexible features that can be used for a variety of research projects and provides an intuitive interface to enter data with real time validation (automated data type and range checks). The system offers easy data manipulation with audit trails, reports for monitoring and querying participant records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

5.5 Description of Study Processes

The following tables provide an overview of the study timeline and the timing of recruitment, enrollment, and participant contact.

Time Point	Study Procedure
Months 0-3	Study Staff Training: • Hire and train oncology nurses in content and delivery of the brief behavioral intervention for dyspnea • Hire and train 2 research assistants in study procedures, recruitment, enrollment, data collection, etc.

Months 4-54	Randomized Controlled Trial: • Enroll and randomly assign 220 patients (110 per study group) to receive either the brief behavioral intervention for dyspnea or usual care across study sites (i.e., MGH Cancer Center, DFCI, Mass General Cancer Center at Newton-Wellesley Hospital, and Mass General/North Shore Cancer Center-Danvers) • Complete 8,16, 24-week post assessments and data extraction from the electronic health record
Months 55-60	Analysis and Submission of Follow-up Grant Proposal: • Complete data analyses and submit primary manuscripts • Prepare and submit grant proposal for large-scale multisite dissemination and implementation study

Point of Contact	Timing	Study Procedures
Initial screen and consent	Upon clinician approval	▪ Screen in outpatient clinic, infusion suite or via telephone ▪ Patients will self-report shortness of breath (using the MMRCDS) ▪ If MMRCDS score ≥2, study staff will obtain informed consent and email oncology clinician to notify that the patient screened positive for dyspnea ▪ If MMRCDS score <2, study staff will screen patient again in 3 months
Enrollment - Baseline self-report assessment Randomization notification	Upon confirmation of prescreen eligibility	▪ Participant completes self-report battery of questionnaires ▪ Provide patient with wrist actigraph and activity log with instructions to wear for the 3 days following the baseline assessment. ▪ After 3 days, study staff calls and informs patient of randomization and schedules session one for intervention participants. ▪ Participant returns actigraph watch and activity log in-person or mails it back to study staff.

Session One (if randomized to dyspnea intervention group)	Within 6 weeks of enrollment and baseline data collection	▪ Nurse interventionist delivers Session One either in clinic or virtually by phone or secure video ▪ Study staff will contact participant to schedule Session Two
Session Two (if randomized to dyspnea intervention group)	After session 1, within 8 weeks of enrollment	▪ Nurse interventionist delivers Session Two either in clinic or virtually by phone or secure video
Follow-up – Week 8 Assessment	8 weeks after baseline data collection	▪ Participant completes follow-up questionnaires either in person while in clinic or remotely via mail, REDCap email, or telephone. ▪ Study staff instructs participant to wear actigraph and log activity for the 3 days following the completion of their week 8 self-report assessments. Study staff collects actigraph and activity log from participant via mail. ▪ For the procedures listed above, the study staff member delivering the assessment will remind the patient not to inform them of whether they received the intervention for breathlessness.
Follow-up – Week 16 and 24 Assessments	16 and 24 weeks after baseline data collection	▪ Participant completes follow-up questionnaires either in person while in clinic or remotely via mail, REDCap email, or telephone. ▪ For the procedures listed above, the study staff member delivering the assessment will remind the patient not to inform them of whether they received the intervention for breathlessness.

5.5.1 Instrument Administration

A study staff member blind to group assignment will administer study assessments at baseline and multiple follow-up time points (at weeks 8, 16, and 24) with a +/- 2 week window to accommodate patient schedules. The assessment battery takes approximately 30 minutes to complete. The baseline and follow up assessments (at 8, 16, and 24 weeks) will occur either in clinic, by mail, telephone or online via REDCap. We selected the six-month time frame for follow-up assessment to evaluate the long-term impact of the intervention on patient outcomes while recognizing the limited life expectancy of patients with advanced lung cancer. The self-report measures have strong psychometric properties and been well validated in previous studies.

If a participant expresses that he or she is not willing or able to complete the self-report packet in full, the study staff will offer an abbreviated version containing the primary outcome assessments (MMRCDS, CDS, HADS, and FACT-L). This short form will only be offered if a patient initially refuses to complete the entire questionnaire packet. Each participant will receive the actigraph at enrollment and will be instructed to wear the watch for the 3 days following their baseline assessment. In preparation for Week 8 follow-up, participants will receive the wrist actigraph either in person in clinic or by mail.

Patients will be instructed to wear the actigraph device for the 3 days following the completion of their 8-week self-report assessment. After this 3-day period, study staff will arrange a FedEx pick-up to retrieve the actigraph device.

If a patient passes away while in possession of an actigraph, we will call the person identified as a contact in the Participant Locator Form to offer our condolences. We will also explain that we will send a prepaid envelope to them addressed to our study staff, and instruct them to place the actigraph in the envelope, seal it, and send the envelope back to us in the mail (USPS). If we cannot reach the patient's contact by phone, we will send the prepaid envelope along with a note offering our condolences and instructions on how to return the actigraph.

We will call the patient's contact person up to three times, allowing for at least three business days between each phone call if we cannot reach the contact person. At the time of enrollment, we inform the patient that the contact person is someone who we will call if the patient is unreachable. The participant typically lists his/her designated primary caregiver or spouse, who usually lives with the patient. On the rare occasion that this person does not live with the patient, we will work with the contact person to problem-solve how to reach out to someone who lived with the patient or has access to the residence in order to retrieve the actigraph and mail it back to the study staff in the prepaid envelope. If it is not possible, then we will consider the data to be lost. We do not anticipate this to be a frequent occurrence.

5.5.2 Intervention Administration

Patients assigned to the brief behavioral intervention for dyspnea will participate in two sessions. The first session will occur at the patients' next scheduled clinic visit (either in the infusion suite or the outpatient clinic) via telephone, or via secure video following baseline data collection. The first session must occur within six weeks of the baseline data collection. Chemotherapy regimens for patients with advanced lung cancer are typically administered every two to three weeks. Thus, the six-week window will allow all enrolled patients to have a scheduled appointment, with additional time should their treatment be delayed for any reason (e.g., holidays or low blood counts). In the unlikely event that the patient is unable to come to the hospital for the first intervention session before the six-week window closes, the patient will be mailed the necessary study materials and receive the first session over the telephone or via secure video to remain in window. In the rare cases that the patient is still unable to complete the first session before the six-week window closes, the patient will be re-administered their baseline assessments either at their next appointment or by mail, telephone, or online via REDCap. Study procedures will reset from the new baseline assessment.

The second session will occur at the patient's subsequent clinic visit, over the telephone, or via secure video, within eight weeks of the baseline data collection.

Participants in both arms of the study will receive usual care for their dyspnea under the care of their clinicians.

5.5.3 Special Concerns

Breach of confidentiality is a concern in all studies with human subjects. Patient participants will be completing self-report assessments; thus safeguards will be put in place to ensure that participant information is kept private and confidential. All electronic data will be stored in password-protected computer files and online databases (i.e. REDCap), accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept in a separate password-protected computer file. Data will not be shared with individuals other than study staff.

5.5.4 Compensation

Study participants will not receive compensation for participating in this study or for completing questionnaires.

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

a. Serious Adverse Events. Given that this study is a randomized trial comparing a brief behavioral intervention compared to a usual care control group, we do not anticipate any study-related events meeting the FDA definition of a SAE (i.e., any fatal event, immediately life-threatening event, permanently or substantially disabling event, event requiring or prolonging inpatient hospitalization, or any congenital anomaly). The proposed study population is comprised of individuals diagnosed with advanced lung cancer who frequently experience disease worsening, high rate of symptoms, and hospitalizations from the underlying disease and/or side effects of treatment. Therefore, as advanced lung cancer is a chronic-type terminal illness, regular fluctuations in cancer-related symptoms, disease worsening, hospitalizations, emergency department visits, and deaths are to be expected throughout the study, and we will not consider or report such events as SAEs in this trial.
b. Non-Serious Adverse Events. 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, the majority of non-serious adverse events in our prior supportive care studies have been due to patient discomfort with the study questionnaires.

5.6.2 Anticipated Reactions

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

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

Participants may also find some of the breathing exercises from the dyspnea intervention uncomfortable during sessions and during home practice.

5.6.3 Reaction Management

Following the explanations by the study staff, participants will either sign a detailed consent form or provide verbal consent. The consent process will include all of the 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. The PI will review all informed consents within one week of their completion. All study staff will complete the required human subjects training before they are allowed to work on any human subject aspects of the study.

The need for further intervention and referral regarding anxiety and depression symptoms will be determined by clinical cutoffs on the subscales of the Hospital Anxiety & Depression Scale (HADS) and by clinical assessment of the trained study nurse should any participant note heightened emotional distress and/or suicidality. Both the anxiety and depression subscales scores of the HADS range from 0 to 21, with a score of 11 or greater indicating definitive anxiety or depression. A score of less than 7 is considered normal, and a score of 8-10 on each subscale suggests probable anxiety and depression. Study patients whose scores increase from the normal or probably range to the more severe range for depression (i.e., $\geq$ 11) will be called by qualified study staff (e.g., Dr. Greer, a licensed clinical psychologist, or similarly trained designee) to determine if the patient requires further intervention for his or her mood symptoms. Study staff will also assess for any suicidal ideation and ensure that the patient is not at any risk for self-harm. If the patient needs further outpatient services for depression, including pharmacotherapy, or is at risk for self-harm requiring hospitalization, study staff will make the necessary referrals for treatment. For example, for patients who are distressed but in no danger to self or others, study staff will refer either to the MGH Oncology Social Work Service or to the MGH Ambulatory Psychiatric Services (617-724-5600), including the Cognitive-Behavioral Therapy Program. If suicidality or risk of harm to others is otherwise discovered at any study visit, the participant will be referred to appropriate services. Specifically, in the case that hospitalization is required, study staff will contact and escort the patient to the MGH Acute Psychiatry Service (617-726-2995), with the aid of the MGH Police & Security if necessary (617-726-2121). Study staff assessments of patient distress and/or risk will be documented in the electronic medical record so that the clinical team is notified of any potential need for increased support.

If participants find the dyspnea intervention uncomfortable and/or upsetting during intervention sessions or during home practice, the participants or the study interventionists delivering the intervention may page the PI (Dr. Greer) at any time. Dr. Greer is a licensed clinical psychologist with extensive experience delivering cognitive behavioral treatments for individuals with advanced lung cancer (see previous clinical studies).

The PI, co-investigator team, and the nurse study interventionists will meet at least monthly to review study progress, ensure proper implementation of the intervention, and review any adverse reactions that occur. The PI and the study staff for this study will also meet weekly to review consents and collected data to ensure proper adherence to study protocol.

6.0 STATISTICAL ANALYSIS

6.1 Study Endpoints

6.1.1 Primary and Secondary Endpoints

The primary outcome is comparison of the MMRCDS and CDS severity scores at 8-week post-assessment between study arms, controlling for baseline values.

The secondary outcomes will be comparison of quality of life, anxiety, depression, and activity level between study groups. To assess quality of life, we will compare the post-assessment (8-week) FACT-L scores between study arms, controlling for baseline values. To evaluate anxiety and depression symptoms, we will similarly compare the continuous scores as well as rates of depression and anxiety symptoms reported per HADS score at 8 weeks between study arms, controlling for baseline values. To assess activity level, we will compare the percentage of time spent immobile but awake on actigraphy and self-report weekly leisure-time physical activity score at 8 weeks between study groups, controlling for baseline values.

6.2 Sample Size and Power Calculation

Although we observed a large effect size for the brief behavioral intervention on patient-reported dyspnea in our previous trial (Cohen's d=1.0), we chose to be conservative in estimating the sample size to power the proposed RCT given the inclusion of usual care control group, proposed tests of mediation and moderation, and rate of attrition observed in our pilot trial (i.e., 16%). Therefore, if a total of 200 study participants complete this two-treatment parallel-design study, the probability is 80% that the study will detect a treatment difference in the primary and secondary outcomes at a two-sided 0.05 significance level (if the true difference between treatments is 0.40 times the standard deviation (i.e., the lower bound of a medium effect size).

6.3 Analysis Plan

6.3.1 Aim 1

Aim 1: To demonstrate the efficacy of the brief behavioral intervention for improving dyspnea (primary outcome) in patients with advanced lung cancer.

Hypothesis 1: Participants with advanced lung cancer who are randomly assigned to receive the brief behavioral intervention will report statistically and clinically significant improvements in dyspnea (per self-report MMRCDS and CDS) compared to those assigned to usual care.

Analysis: Analyses will begin with descriptive and graphical summaries of the endpoints. As the MMRCDS is an ordinal measure, the statistical significance of between-group differences in the primary outcome will be assessed first with the Wilcoxon-Rank Sum test and then with generalized estimating equations (GEE), with appropriate covariates. The CDS is a continuous interval measure, and we will assess between-group differences in these scores using general linear models (GLM). All statistical tests will be two-sided with an alpha level of .05. For these primary outcomes, we will examine between-group differences (i.e., intervention versus control) in MMRCDS and CDS scores at the 8-week post-assessment, controlling for baseline values. In the event that the effect of the intervention differs by cancer type, use of opiate medication or other patient characteristic, we will examine these variables as interaction terms in the GEE and GLM analyses. We will also evaluate generalized linear mixed models of the longitudinal data, allowing us to

account for dependency among MMRCDS and CDS scores over time and to control for demographic and clinical factors, such as disease progression, (as necessary for any imbalances in baseline variables) when examining between-group differences in the MMRCDS and CDS scores across the multiple study time points (i.e., baseline, 8, 16, 24 weeks). Finally, we will compute the effect sizes and Reliability Change Index[68] to assess practical and clinical significance of the differences in the primary and secondary outcomes. The GLM model will generate an effect size estimate, which can also be calculated by hand ($d=Mean_{\text{change score CBT group}} - Mean_{\text{change score control group}}/SD_{\text{pooled}}$). Cohen[69] utilizes cutoffs of 0.2 for a small effect, 0.5 a medium effect, and 0.8 for a large effect.

6.3.2 Aim 2

Aim 2: To demonstrate the efficacy of the brief behavioral intervention for improving quality of life, anxiety, depression, and activity level (secondary outcomes) in patients with advanced lung cancer.

Hypothesis 2: Participants with advanced lung cancer who are randomly assigned to receive the brief behavioral intervention will experience statistically and clinically significant improvements in quality of life (FACT-L), anxiety and depression (HADS), as well as activity level (per self-report Godin-Shephard Leisure-Time Physical Activity Questionnaire and the percentage of time spent immobile but awake on actigraphy) compared to those assigned to usual care.

Analyses: The statistical significance of between-group differences for the continuous secondary outcomes will be assessed with general linear models (GLM) and linear mixed models, with appropriate covariates and an alpha level of .05. We will examine the between-group differences (i.e., intervention versus control) at 8-week post-assessment for each specific secondary outcome (all are continuous variables), controlling for baseline values. In the event that the effect of the intervention differs by cancer type, use of opiate medication or other patient characteristic, we will examine these variables as interaction terms in the GLM analysis. We will explore independent improvements in these secondary outcomes by adding changes in MMRCDS or CDS severity scores as a covariate. Finally, we will also again estimate practical and clinical significance of these outcomes (using Cohen's d and Reliability Change Index) and conduct linear mixed models to examine the trajectory of between-group differences in these variables across all study time points.

6.3.3 Aim 3

Aim 3: To explore mediators and moderators of the effect of the brief behavioral intervention on patient-reported outcomes.

Hypothesis 3: Intervention effects on patient-reported dyspnea will be mediated by improved mastery in managing breathlessness and potentially moderated by patient demographic and clinical factors (e.g., gender, age, opioid use, performance status, and disease comorbidity).

Analyses: We will conduct bootstrapped tests of mediation to determine whether group differences in self-reported dyspnea (outcomes: MMRCDS and CDS) are mediated by improved mastery in managing the symptom (mediator: CRQ). Finally, we will create interaction terms for the GEE analyses and linear mixed models to examine whether differences in reported dyspnea are moderated by patient factors (e.g., gender, age, opioid use, etc.).

6.3.4 Exploratory Analyses of Service Utilization

Although we likely will not have sufficient power to examine statistically the intervention effects on service utilization, we will at a minimum calculate descriptive statistics on

rates of ED visits and hospitalizations by study group. Otherwise, if possible, we will conduct Fisher's exact tests and logistic regression to explore differences in rates of ED visits and hospitalizations between groups, controlling for any confounders as needed.

6.4 Handling of Missing Data

The analyses will initially focus on the study completers to estimate the effect of the brief behavioral intervention in patients with advanced lung cancer who completed the protocol as intended without imposing assumptions about missing data. We will also use the intention-to-treat principle with all randomized subjects, conducting sensitivity analyses to explore how various assumptions about missing data and differences between completers and non-completers affect the estimated outcomes. If data appear to be missing at random, we will employ multiple imputation methods. However, if we find that patients do not complete the study because of disease worsening, suggesting missing data are not random, we will employ maximum likelihood estimation from incomplete data, under the direction of our biostatistician, Ms. Muzikansky.

6.5 Potential Problems, Alternative Strategies and Benchmarks for Success

The potential problems and alternative strategies that we considered in developing this study proposal pertain to the selection of interventionists, length of treatment, and nature of the control group. Specifically, we recognize that patients with advanced lung cancer may benefit from meeting with clinical psychologists and/or social workers with trained expertise in behavioral medicine. Although increasing contact with such clinicians may enhance the robustness of the intervention, we are responding to the present challenges that exist in meeting the psychosocial and symptom management needs of patients with cancer. Access to supportive care for oncology patients is limited not only by the inadequate number of mental health and palliative care providers, but also by insufficient training of existing clinicians with respect to empirically-supported techniques, such as cognitive-behavioral approaches.[43] In our national survey of community oncologists, a majority reported that they lack access to mental health providers for referrals.[70,71] We therefore decided to administer the point-of-care dyspnea intervention, delivered by trained oncology nurses, as we observed that this approach was feasible and preferable to patients with advanced lung cancer. Similarly, prior studies of comprehensive dyspnea management interventions include numerous visits with multiple medical providers across several months.[37,46] Given the disease burden of the patient populations in the proposed study, we chose to keep the intervention brief, delivered in tandem with existing outpatient appointments. Despite this short-time frame of the targeted behavioral intervention, we nonetheless observed a large effect size for self-reported dyspnea over time in our pilot study.[23] Interventions that can be integrated within the flow of care that are minimally resource intensive yet effective have greater potential for broad adoption and implementation across diverse cancer care settings. Finally, we elected to conduct a RCT with a usual care control group rather than employ alternate experimental methods, such as a wait-list crossover or staggered treatment design, because of the shortened life expectancy of the study population. We also considered, but ultimately did not include, an attention-matched control group given the lack of an alternative, evidence-based psychosocial comparator as well as potential ethical considerations of asking patients with advanced disease to meet with a clinician for some sort of "sham" treatment. Moreover, no data suggest that attention alone would influence dyspnea. Otherwise, we will not limit access to usual care but rather examine the effects of the behavioral intervention above and beyond usual care.

Benchmarks for success in the proposed study will not simply include a replication of our successful pilot study showing significant effects of the brief behavioral intervention on dyspnea management. We also aim to increase the generalizability and reach of the intervention by training oncology nurses and including a second study site. Also, we will consider clinically meaningful

improvements in quality of life (i.e., ≥5 point change on FACT-L) and a Reliability Change Index≥1.96 for the outcomes as other markers for success. If we do not achieve these benchmarks, we will utilize qualitative methods to gather feedback from the relevant stakeholders (i.e., patients, nurse interventionists, etc.) to ascertain ways to modify the intervention content and/or delivery in order to maximize its effectiveness and adoption in multiple cancer care settings.

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