# SERENE

Supporting Evidence-based Responses to Emotional Needs in Emphysema

**Study Protocol**

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| **Study Sponsor** | *National Institute of Nursing Research (NINR)* |
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# Introduction and purpose

Patients with chronic obstructive pulmonary disease frequently experience psychological distress (i.e., depression and anxiety), which is associated with poor health outcomes and which patients, their caregivers, and clinicians have identified as the most critical palliative care need. This study will identify how an evidence-based coping skills training program, which partners patients and their caregivers to manage and overcome disease-related distress, reduces depression and anxiety among outpatients with chronic obstructive pulmonary disease. The findings will provide a better understanding of how social relationships affect patients' psychological distress and will help health systems design and implement efficient strategies for patient- and family-centered palliative care within chronic illness care, particularly those affecting health disparities populations who experience inequities in access to such services.

# Objectives

Our primary objective is to promote the well-being and outcomes of patients with chronic obstructive pulmonary disease (COPD) by understanding the mechanisms through which telephone-administered Coping Skills Training (CST) reduces depression and anxiety. This will allow us and others to refine and scale effective and efficient palliative care interventions.

We will complete three specific aims:

**Aim 1:** Identify mechanisms through which Coping Skills Training reduces patient distress.

**Aim 2:** Elucidate causes of heterogeneity in the efficacy of the Coping Skills Training program.

**Aim 3:** Identify barriers and facilitators to uptake of the Coping Skills Training program.

# Background

COPD causes patients to experience dyspnea, functional limitations, dependency, isolation, and threats of mortality.[1,2] While patients burden of symptoms is similar to or exceeds those experienced by patients with lung cancer, heart failure, and other chronic conditions, patients with COPD are less likely to receive PC throughout their illness or at the end of life.[3-8] Patients with COPD, their family caregivers, and their treating clinicians identify coping with COPD and emotional symptoms as the highest priority PC needs.[9,10] Psychological distress frequently co-occurs with COPD and has a profound impact on patient well-being and clinical outcomes, exceeding even the influence of objective pulmonary function decline.[3,11-18] Depressive symptoms, the most common form of psychological distress among patients with COPD, have been associated with worse quality of life (QOL); increased dyspnea; lower medication adherence; more frequent COPD exacerbations and hospitalizations; and a four times greater risk of being readmitted to the hospital after an acute exacerbation of COPD.[19-33] Post hoc analysis of two large, multicenter cohorts of patients with COPD confirmed that clinically significant anxiety and depression independently predicted severe respiratory exacerbations.[34] While much of the existing evidence in PC, particularly in COPD, focuses on the end of life or advanced stages of the disease,[10,35] psychological distress can occur with any level of COPD severity and the relationship to lung function is non-linear.[22,36] Therefore, identification and management of psychological distress earlier in COPD may prevent hospitalizations and declines in physical functioning.[35,37]

Treatments for psychological distress improve patients clinical and functional outcomes and reduce their disability and healthcare utilization.[21,29] Despite this, psychological distress remains under-recognized and under-treated in COPD; the majority of patients with COPD experiencing symptoms of depression or anxiety are never diagnosed or treated for psychological distress.[22,38-40] PI Joanna Harts 24-month longitudinal study among 208 patients with severe COPD (K23 HL132065) confirmed the high prevalence of depressive symptoms. Study procedures (i.e., not a component of standard clinical care) included administration of the Patient Health Questionnaire-9 (PHQ-9) to assess longitudinal depressive symptoms. Nearly 60% of participating outpatients screened positive for at least moderate depression, yet a minority of patients had ever received any behavioral health care.[41-43] The severity and prevalence of depressive symptoms was higher among patients identifying as Black or multiracial than those identifying as White. We confirmed prior evidence that psychological distress is inversely related to income.[39] These findings compound well-established inequities in COPD care.[44-49]

Health systems and clinicians recognize that psychological distress is highly prevalent among patients with COPD,[38] yet lack standardized approaches to treating distress within COPD care.[29,50] In 2019, PI Hart conducted a formative evaluation of the acceptability, needs, and perceived barriers to implementing outpatient clinical programs to reduce the psychological distress experienced by outpatients with COPD.[37] We interviewed 31 stakeholders (e.g., clinical leaders and staff, pulmonary and primary care clinicians, and patients and caregivers). Our findings confirmed that clinicians are

highly aware of the prevalence and impact of psychological distress in COPD but lack existing evidence, self-efficacy, and resources to identify and manage these symptoms. Patient and caregiver stakeholders recommended remotely delivered programs given patients functional limitations and the caregiver burdens frequently associated with in-person outpatient care.[51-54] This systematic evaluation informed our study aims, design, and intervention selections.[55,56]

Social relationships provide direct health benefits and buffer against health stressors.57 Patients and caregivers health and well-being outcomes are interdependent in COPD.[17,20,56,58-63] A classic theory in behavioral science, interdependence theory posits that in close relationships, partners rely on and influence the behavior, emotions, and outcomes of the other person.[64] Caregivers shape patients cognition and behavior through their relationships and frequent contact.[59,65,66] High-quality family relationships (i.e., a sense of cohesion, role fulfillment, problem solving, and communication) are associated with better outcomes for patients with serious illnesses.[67-71] In COPD, cross-sectional evidence demonstrates that less supportive family relationships are associated with harmful smoking behaviors, increased dyspnea, and lower QOL via higher psychological distress.[65,72] Because caregivers may directly influence patients psychological distress and subsequent health outcomes, these relationships may also be leveraged to improve patients outcomes. Despite this, dyadic interventions in COPD or PC are rare. Understanding the mechanisms through which caregivers both deliver and promote the efficacy of supportive interventions, including how family relationships may be modified to mitigate against psychological distress, is a critical gap. Filling this gap will allow us and others to develop and refine innovative models of PC that retain the least necessary components of complex interventions and overcome barriers to implementation.[73-76]

Patients exist within social environments and family structures that influence their outcomes, psychological functioning, health behaviors, and care quality.[9,20,60,61,63,65,72,77-81] Family relationship quality is critical in health and is a modifiable risk factor for psychological distress.[65] Despite this, the science of PC has not yet applied these well-established behavioral science principles, including interdependence theory, to understand the mechanisms through which PC interventions succeed.[82] The mechanisms through which psychological distress develops among patients with COPD remain unknown, contributing to the difficulty in intervention development.[83] Our proposed research will elucidate the behavioral mechanisms through which an efficacious PC intervention reduces patients psychological distress. The evidence we generate will advance the scientific understanding of this and other PC interventions, provide justification of their benefit, and present new knowledge about the role of caregivers in determining patients' well-being and clinical outcomes. The proposed research departs from the existing status quo in PC and COPD care delivery by applying behavioral science to test mechanisms through which modifying patients existing social relationships can reshape patients' health environments, providing the basis for future large-scale trials and implementation.

PC interventions are complex and multi-modal, yet patients' needs dramatically outstrip the available supply of specialty PC resources, mandating efficient models of care

delivery.[73,74,84] PC relies on specialized staff who are already in short supply, limiting the capacity to respond given the high burden of need among patients with COPD and contributing to disparities in outcomes.[7,84-86] Understanding why and how successful PC interventions work (i.e., their mechanisms of action) will allow for refinement of these interventions to target critical pathways. Our use of mixed methods facilitates this approach, providing explorative data to complement the hypothesis testing of quantitative trial data.[74,87] Our approach to identifying mechanisms of action innovates on current barriers to PC research and delivery,[35] enabling us to identify the key pathways of action, further refine the intervention based on those mechanisms, and overcome barriers to effectiveness in the highest-risk groups and those most likely to benefit.[88,89]

COPD is concentrated among individuals with lower socioeconomic status. Those with lower income, who identify as Black, and rural populations disproportionately carry the burden of COPD in the US.[46-48,90,91] Both individual and community financial wealth are associated with a lower risk of developing COPD[47,90] and, once developed, COPD outcomes are worse among patients living in poverty and patients identifying as non-White.[47,48,91-95] Reducing health care disparities among patients with and at risk for COPD is an NIH and NINR priority. Patients in these same patient groups also have limited access to PC and behavioral health resources.[96-101] Our focus on COPD and our recruitment from our selected health systems will allow us to reach large numbers of patients inadequately represented in prior research. For example, family relationship quality is strongly associated with patients COPD outcomes, yet in the study sample demonstrating this, 6% of participants identified as Black.[65] Penn Medicine is headquartered in Philadelphia, PA, where the 25% poverty rate is the highest of the ten most populous cities in the US.[102] Henry Ford Health (HFH) is headquartered in Detroit, MI, which has the highest poverty rate among all large cities (i.e., 350,000 residents) in the US at 35%.[102] Both cities have two of the highest rates of deep poverty (i.e., households earning less than half of the federal poverty limit) in the US.[102] Nearly half the residents of Philadelphia and three-quarters of the residents of Detroit identify as Black.[103] Both health systems also have networks of clinics located in rural areas. Our focus on the mechanisms of efficient PC models that can be delivered remotely in low-resource settings is critical to improving the existing inequities in PC access.

**Note:** A full reference list can be found in the uploaded “Research Strategy” document.

# Study design

We propose a randomized clinical trial to test putative treatment mechanisms through which the Coping Skills Training (CST) telehealth program administered to patients with COPD, with their family caregivers serving as coaches, improves their outcomes. Our trial will recruit 375 patient-caregiver dyads from outpatient primary care and

pulmonary clinics within the University of Pennsylvania (Penn) and Henry Ford (HFH) Health Systems. The study will be registered in clinicaltrials.gov within 21 days of enrollment of the first participant.

Eligible participants will be patients at Penn or HFH who have a documented diagnosis of COPD and confirmation of obstructive lung disease by spirometry or radiographic imaging and are experiencing distress during screening as measured by a score greater than or equal to 8 on the PHQ-8; and adult caregivers identified by eligible patients. See *Key Inclusion Criteria* and *Key Exclusion Criteria* for more details.

We selected primary care and pulmonary clinics serving high numbers of patients with COPD in each health system. These clinics also primarily serve patients from the NIH-designated health disparity populations including Black or African American and socioeconomically disadvantaged patients and patients living in underserved rural areas.

Two-thirds of patient caregivers (250 dyads) will be randomly selected to receive the Coping Skills Training (CST) telehealth program, and the remaining one-third (125 dyads) will receive Minimal Enhanced Support. Penn will administer the interventions to all consenting participants. See *Study Instruments* for more details on participant measures and administration. Active participation will occur over a 26-week period and passive participation through EHR data collection will occur over a 12-month period. See *Methods* for more details.

A subset of patients (n=20) and caregivers (n=20), as well as clinicians (n=20) (10 primary care and 10 pulmonary clinicians/clinical leaders), will be invited to participate in semi-structured interviews. Interviews will be conducted remotely by phone or videoconferencing, in line with participants' preferences.. Research staff will conduct the interview from a private room without distractions and participants will be reminded to protect their privacy by joining the interview from a private space to ensure they will not be overheard or interrupted. Patients and caregivers will participate in separate interviews guided by the attached interview guides. Interviews will be audio recorded, transcribed by a HIPAA-compliant transcription service, and identifiable information will be removed.

Calculating power to detect the indirect, or mediated, proportion of a total effect requires simulation; therefore, we will enroll 375 patient-caregiver dyads equally across the two health systems to allow for up to 20% attrition (i.e., a final sample size of 300). This sample size provides at least 80% power to detect mediators that account for a PHQ-9 score difference of at least 2.75 points and a direct effect of treatment arm on PHQ-9 scores of at least 3.25 points. Combined, these differences exceed the clinically significant difference for PHQ-9. Given that consent will be obtained from patients prior to the PHQ-9 being administered, more than 375 patients may need to be enrolled in order to meet our target of 375 dyads.

A Community Advisory Board (CAB) comprised of patients and caregivers, community leaders and advocates, and clinicians has been convened to provide additional guidance

on recruitment strategies to maximize acceptability to patients and clinicians. The CAB has collaborated in developing this proposal from its earliest stages. They guided the research aims, intervention selection, study design, and outcomes. The CAB will partner with the COPD Foundation's COPD360 Community Engagement Committee, which is formed of patients, caregivers, and caregiving experts. The CAB will review and refine study materials and procedures, assist in interpretation of results, and co-lead dissemination of findings. We will use teleconferencing to facilitate inclusion and budgeted for the necessary supplies to support members participation. PI Hart is an expert in stakeholder engaged and community-based participatory research.

Their involvement will include:

1. Up to monthly CAB meetings during the planning year to draft study plans and materials and engage in co-learning opportunities
2. Meetings and asynchronous review of the study's progress and key stages to provide input on participant retention and interpretation of results
3. Dissemination activities

# Characteristics of the study population

## Target population and accrual

**Participants enrolled by Penn researchers:** 376

**Participants enrolled by collaborating researchers (HFH):** 374

The proposed study involves non-exempt human subjects research among two populations: 1) patients with chronic obstructive pulmonary disease (COPD) who are experiencing psychological distress and 2) adult caregivers of these patients.

For our cohort study of outpatients with COPD at Penn, we identified 46 eligible patients per month using stricter eligibility criteria than proposed here. We completed enrollment of 208 patients in an 18-month period with 1.25 FTE research coordinators who conducted concurrent follow-ups. Our consent rate of eligible, approached patients was 80% and we retained over 90% of living patients through 12 months and over 85% of living patients through 24 months using best-practice methods. Our selected clinics at HFH serve over 5,800 unique patients with COPD, supporting feasibility.

Calculating power to detect the indirect, or mediated, proportion of a total effect requires simulation. In an R statistical simulation using 250 iterations, Dr. Harhay confirmed that a sample size of 300 dyads would result in at least 80% power to detect mediators that account for a PHQ-9 score difference of at least 2.75 points and a direct effect of the intervention on PHQ-9 scores of at least 3.25 points. Combined, these differences exceed the clinically significant difference for PHQ-9.

Achieving the sample size of 300 will also provide 80% power to detect treatment effect heterogeneity of roughly 4 points on the primary outcome across the patient-level variables of interest specified above, based on informed estimates of the distributions of these variables in our target sample. This calculation of power to detect statistical interactions uses an alpha of 0.10 without adjusting for multiple comparisons, as these are hypothesis-generating analyses. Enrolling 375 dyads (i.e., approximately 250 in the CST arm and 125 in the enhanced usual care arm) equally across the two health systems allows for 20% attrition (i.e., a final sample size of 300).

Additionally, we plan to interview 20 patients,20 caregivers, and 20 clinicians from both health systems for a total of 60 participants, to reach thematic saturation during concurrent qualitative data analysis.

# Key inclusion criteria

## *Patients*

1. Be at least 18 years of age
2. Have a documented diagnosis of COPD and confirmation of obstructive lung disease by spirometry (American Thoracic Society/European Respiratory Society guidelines) or radiology (imaging report indicating emphysematous changes)
3. Score greater than or equal to 8 during baseline screening using the PHQ-8
4. Identify an adult caregiver to participate with them
5. Have the ability to access a telephone or videoconferencing call up to once weekly (for approximately 30 minutes) for 12 sessions of the study intervention

## *Caregivers*

1. Be at least 18 years of age
2. Have the ability to access a telephone or videoconferencing call up to once weekly (for approximately 30 minutes) for 12 weeks

# Key exclusion criteria

## *Patients*

1. Has significant dementia or cognitive impairment
2. Documentation in the EHR that the COPD diagnosis has not yet been disclosed to the patient
3. Is under the ongoing care of a licensed behavioral health clinician
4. Requires immediate referral to specialized behavioral health management

## *Caregivers*

1. Has significant dementia or cognitive impairment

# Participant recruitment and screening

Before recruitment begins, the study team will introduce the study to clinic staff through an email and/or a presentation, as decided by clinic leadership. This introduction aims to familiarize staff with the study's objectives, potential risks and benefits, and the research team, as well as to explain the referral process for patients. Subsequent reminder emails and/or presentations will be sent periodically to ensure staff remain aware of the study while recruitment is ongoing.

## *Patients*

At Penn, patients could be recruited from both primary care and pulmonary clinics. This includes the following primary care UPHS clinics that serve patients from the NIH-designated health disparity populations including patients who identify as Black or African Americans, and socioeconomically disadvantaged populations (low income or underserved rural areas):

1. Penn Family Medicine University City
2. Penn Family Care
3. Penn Division of General Internal Medicine clinics
    a. Penn Internal Medicine University City
    b. Penn Internal Medicine - Edward S. Cooper Internal Medicine
    c. Penn Center for Primary Care
    d. General Internal Med J Edwin Wood Clinic
4. Penn Presbyterian Internal Medicine
5. Penn Lancaster General Health Family Medicine (multiple locations)
6. Penn Lancaster General Health Internal Medicine

At Penn, patients could also be recruited from three of Penn's Harron Lung Center pulmonary clinics, two of which we selected as they are both located in West Philadelphia, which is a low-income and majority-Black area of the city, and these demographics were represented in prior studies:

1. Harron Lung Center University City
2. Harron Lung Center Perelman
3. Harron Lung Center Washington Square

In addition to the outpatient primary care and pulmonary clinics, we will recruit Penn Medicine patients attending outpatient pulmonary services at Chester County Hospital by referral from clinicians. This expansion will only occur following an ancillary review by the Chester County Hospital Scientific Review Committee (Chester County Hospital Research & Evidence-Based Practice Council).

At HFH, the prioritized urban and rural clinics, including pulmonary and primary care clinics, are:

1. Henry Ford Medical Center – Detroit Northwest
2. Henry Ford Hospital Family and Internal Medicine
3. Henry Ford Hospital Outpatient Pulmonology
4. Henry Ford Allegiance Family Medicine – Albion
5. Henry Ford Allegiance Family Medicine – Mason
6. Henry Ford Allegiance Family Medicine – Brooklyn
7. Henry Ford Allegiance Family Medicine – Leslie
8. Henry Ford Macomb Health Center - Washington Township

The study employs three broad recruitment approaches to ensure adequate enrollment across both health systems, each of which will enroll patients in approximately equal numbers. To accommodate all patients, including those utilizing telehealth appointments, the study team will deploy both in-person and remote recruitment strategies. A standardized screening and outreach protocol, described below, will be employed across both health systems. The screening instruments may be administered remotely or in-person.

Before describing the approaches, it is important to note that they share common elements:

1. **EHR screening:** The retrospective and prospective approaches below will be preceded by EHR screening where the study team will confirm the patient's diagnosis of COPD. For the referral approaches, the study team will conduct EHR screening prior to contacting the patient, provided they are able to identify the patient's EHR before contacting them.
2. **Eligibility assessments:** Patients expressing interest in participating in the study will undergo eligibility assessment using the PHQ-8, Diagnostic Interview for Anxiety, Mood, and OCD and Related Neuropsychiatric Disorders (DIAMOND) (self-screener, interview), PRIME-5 Revised Screener for Early

Psychosis (PRIME-5), and Columbia-Suicide Severity Rating Scale (C-SSRS) Screening Version. The eligibility assessments can all be administered by the study team; however, patients can complete the PHQ-8, the DIAMOND self-screener, and the PRIME-5 independently by following a hyperlink or QR code to the study's self-referral REDCap database.

3. **Caregiver involvement:** Interested patients will be requested to nominate a caregiver. These nominated individuals will be contacted by the study team, with the participant's consent, for potential inclusion and will undergo a detailed informed consent process. Patients must enroll with a caregiver of their choosing. The caregiver can be a paid or unpaid adult, related or unrelated, who helps with daily activities, coordinates medical care, and/or provides emotional support. These individuals may or may not live with the patient.

The three recruitment approaches include:

1. **Retrospective approaches (remote)**
    a. **Screening prior appointments:** The study team will review past schedules of the outpatient primary care and pulmonary clinics listed above. The study team will use patients' EHRs to assess tentative eligibility (e.g., confirming a diagnosis of COPD). Patients who have visited eligible clinics in the past 12 months may be screened. The study team will engage with potentially eligible patients remotely to introduce the study and discuss potential participation before moving on to eligibility assessment. They will speak with a caregiver to introduce the study if they are present, with the patient's permission.
    b. **Contacting OASIS participants:** At Penn, individuals who have finished participation in the OASIS II study (IRB #849409) will be contacted by the study team for potential recruitment. A member of the study team will reach out to introduce the study and, for interested patients, further eligibility assessment.
2. **Prospective approaches (remote, in person)**
    a. **In-person approach:** In this approach, the study team will review upcoming schedules of target clinics using patients' EHRs to assess tentative eligibility. They will then approach tentatively eligible patients in person during their clinic visits to introduce the study and discuss potential participation before moving on to eligibility assessment. Caregivers will be approached in person if present at the clinic with the patient (not during the caregiver's own healthcare visit) or remotely with the patient's permission. If a patient does not attend their appointment (e.g., misses or cancels) or if they have a telehealth appointment, the study team will initiate contact remotely. If the patient is unable to complete the screening steps in person, the study team will schedule a convenient time to follow-up with the patient remotely.

b. **Remote approach with front desk staff:** When the study team cannot be present in clinics (e.g., due to the need to approach patients at other clinics), they may still screen upcoming appointments to identify potentially eligible patients. Front desk staff will be alerted via notes in the clinic's Epic schedule written by the study team (see *Templates for Written Correspondence* for this note and the separately uploaded *Recruitment Flyer, Study Overview for PHQ-8 Paper Version,* and *PHQ-8_Paper Version*). Front desk staff will provide the study flyer, business card, and paper version of the PHQ-8 to patients upon check-in. Interested patients can (1) complete the paper version of the PHQ-8, (2) follow the QR code or hyperlink to complete the PHQ-8, DIAMOND self-screener, and PRIME-5 independently via the study's REDCap project, or (3) contact the study team through the methods provided. Completed paper versions of the PHQ-8 forms will be placed in opaque envelopes labeled with the PI's name and office address, returned by the patient to front desk staff, stored securely in a locked cabinet in the clinic, and collected weekly by the study team. To identify and complete EHR screening for patients completing the paper forms, patients will provide their first and last names and date of birth on the paper version of the PHQ-8. Approval from the practice managers at each of the Harron Lung Center's three clinics has been obtained for this approach.

c. **Remote approach with MyPennMedicine message:** The study team may also reach out to tentatively eligible patients through messages sent via Penn Medicine's electronic patient portal, MyPennMedicine (MPM). These messages will include a REDCap link for patients to register their interest by sharing their contact information and, if willing, by completing our initial screening instruments (see "Templates for Written Correspondence" for a copy of the MPM message). The study team will send these messages in waves, limited to patients with a diagnosis of COPD and an appointment in the last twelve months at the target clinics outlined above. The MPM recruitment message will be implemented in collaboration with the PennChart Research team, and the study will be registered with iConnect, the Penn Medicine clinical research/trial portal, which can generate the short link and QR code for the study.

**3. Referrals (remote)**

a. **Patient self-referral:** Patients can self-refer through study materials, such as flyers and business cards, placed in waiting and exam rooms, or via Penn's iConnect web site. These materials will provide contact information (e.g., phone number, email address, QR code, and hyperlink) for the study team. Interested patients can either (1) follow the QR code or hyperlink to complete the PHQ-8, DIAMOND self-screener, and PRIME-5 independently via the study's REDCap project, or (2) contact the study team through the methods provided. The study team will then introduce

the study and, if the patient is interested, complete the eligibility assessments with them.

b. **Clinician-facilitated referral:** Clinicians can facilitate referrals by:
    i. Distributing study flyers and business cards to patients who might benefit from the study's coping skills training program.
    ii. Using an Epic SmartPhrase written by the study team, developed with input from the Penn Privacy Office. The study team will work with the PennChart research team to draft a SmartPhrase, which will be provided to clinicians at the target clinics. Clinicians can insert this SmartPhrase into their patients' After Visit Summary (AVS) at their discretion. Clinicians and practice managers will be trained on the study to ensure they can effectively communicate brief study details to patients during visits, making the information in the AVS less surprising. The SmartPhrase, uploaded separately (see *Templates for Written Correspondence* for a copy of the SmartPhrase), will introduce the study and provide the same contact methods for the study team as the flyers and business cards.

## *Caregivers*

Caregivers will be identified by patients. Patients will provide contact information for them. Research staff will contact caregivers by phone with the permission of the patient participant. Caregivers will be contacted after the patient completes the psychological screenings.

## *Semi-structured interviews*

A subset of participants (approximately 20 patients and 20 caregivers), as well as clinicians (10 primary care and 10 pulmonary clinicians/clinical leaders) from both health systems)will be asked to participate in semi-structured interviews. Participants will include 1) those who are offered but decline participation in the CST program and 2) those who participate in all or portions of the CST. The purpose of interviewing prospective participants who declined to enroll in the study is to identify barriers and facilitators to uptake of the CST program. The study team will use purposive sampling stratified by health system and sociodemographics including gender, race, rurality of residence, and severity of COPD to recruit participants for this component of the study based on prior research and theory. We will obtain separate consent for this additional participation, as detailed in the *Consent Process*.

# Consent process

## *Overview*

Tentatively eligible patients will be contacted by a trained member of the study team to complete an eligibility assessment, which includes the PHQ-8 for psychological distress, and the DIAMOND, PRIME-5, and C-SSRS as part of a comprehensive psychological assessment, and to obtain consent. In this multi-step process, the eligibility assessment and consent process are intertwined to minimize unnecessary collection of protected health information.

The consent process may be conducted in-person or remotely via phone calls using Webex. At the time of consent, participants will be asked to opt-in to receiving text messages, which will be sent using Mosio.

Mosio is a two-way text messaging platform that integrates with REDCap to enable the study team to send automated alerts (e.g., session and survey reminders), collect survey data (by delivering brief surveys via text message or by sending links to REDCap surveys), and engage in two-way text messaging communications (e.g., to reschedule appointments). See *Templates for Written Correspondence* for text message templates. Mosio is HIPAA- and 21 CFR Part 11-compliant, and no PHI will be transmitted via text message. Survey questions will not include PHI, and survey responses will be on a numerical scale only. Participants can opt out of text messages from our study by replying "STOP" to any text message sent through Mosio.

Where feasible, participants will provide an electronic signature in REDCap on the appropriate (patient or caregiver) e-consent form. Alternatively, verbal consent will be obtained by the study team, and a copy of the study's consent form will be sent to the participant along with other study materials by mail, email, or in person.

Both patient and caregiver must provide consent to participate. If one person does not consent, then neither can participate. If the patient consents but the caregiver does not, the patient cannot participate unless they find someone else to participate with them. If the patient does not consent, the caregiver cannot participate. If a patient or caregiver withdraws or if they are eligible but do not enroll, they will still have the option to do an interview to understand more about why the program did not work for them. Separate verbal consent will be obtained for interviews.

The three steps in the consent process are outlined below. See the separately uploaded documents *Consent Steps 1 and 2* and the patient and caregiver informed consent forms for more details. The screening instruments mentioned in the Steps that follow are described in further detail in the "Study Instruments" section below.

## *Step 1: Initial consent and eligibility assessment*

Patients may complete this first step independently or with support from the study team. If starting independently, patients/caregivers will acknowledge a series of statements about the screening process by ticking boxes in REDCap. If completing the process with support from the study team, the team will verbally obtain their acknowledgment and document it in REDCap. These statements require patients to acknowledge that they are affiliated with Penn or HFH, agree to participate with a caregiver, consent to share contact information, understand the content of the questions (e.g., emotional distress), and agree that their responses will be retained for study reporting.

Once these statements are acknowledged, patients will be prompted to share their first and last names and contact information (e.g., phone number and email address). They will then complete the PHQ-8. Patients experiencing distress, as measured by a score of at least 8 (>=8) on the PHQ-8, will be considered likely eligible and may proceed to the DIAMOND self-screener and PRIME-5, which include items focused on mania and psychosis, respectively. The DIAMOND self-screener and PRIME-5 will not determine eligibility but will dictate whether the DIAMOND interview will be conducted in Step 2 to further assess reported symptoms of mania or psychosis.

Patients who do not meet the eligibility criteria at any point in the consent process will be informed of their ineligibility and thanked for their time.

If participants start but do not complete any of the screening questions in REDCap, the study team will contact them to complete the process, assuming contact information was provided or can be found in the EHR. Patients with a qualifying PHQ-8 score are eligible to continue to the next set of screening questions (see *Study Instruments* for more details on these instruments).

This process will be replicated with the paper version of the PHQ-8 if the patient chooses this approach. The study team member will review the acknowledgments above, document the patient's responses in REDCap, and, depending on their responses to the PHQ-8, will complete the DIAMOND self-screener and PRIME-5 with the patient.

## *Step 2: Secondary eligibility assessment*

Patients with a qualifying PHQ-8 score undergo one or two additional screenings. Before proceeding, they must acknowledge the purpose of these screenings, which is further eligibility assessment, the requirement of enrolling with a caregiver, and the ineligibility of those currently attending weekly talk therapy. They must also agree to potential referrals to mental health services based on the outcome of this screening round. There is some redundancy in these statements because, for patients who completed the first step independently, it may be their first time speaking with the study team. The study team will document in REDCap that the patient has verbally agreed with these statements before proceeding to the C-SSRS.

If no handoff to behavioral health supports is required based on their C-SSRS responses (see *Risk Management Plan for Suicidal Ideation and Behavior* for more detail), the study team will conduct the DIAMOND interview if the patient has reported symptoms of mania or psychosis in Step 1. Patients with psychiatric disorders identified through the DIAMOND interview that may necessitate complex behavioral health management outside the scope of the trial, such as mania or psychosis, will be contacted by a study clinician, a clinical psychologist, within one business day. The study's clinicians will determine their eligibility to continue. For more information on handoffs to study clinicians, see *Exceptions to sharing patient information* below.

If no handoff to the study clinician is required based on their C-SSRS and DIAMOND responses, participants will continue to Step 3.

## *Step 3: Full informed consent - patients*

After confirming eligibility, the study team will explain the voluntary nature of the study, the risks and benefits of participation, alternatives to participation (including not participating), and that participants can cease participation at any time. Patients will be informed that they are responsible for accessing either a telephone or videoconferencing resource to participate and that these costs or equipment needs cannot be provided by the study team. Patients will also provide consent for the study team to collect behavioral health treatments from the EHR, as available, and to collect self-reported behavioral health treatment information. See *Informed Consent Forms* and *Recruitment and Consent Script* for more details. Once consent is obtained from the patient, the caregiver will be approached. The patient, with collaborative support from study staff, will identify the most appropriate caregiver to participate.

## *Step 3: Full informed consent - caregivers*

With the patient's permission, the study team will approach their nominated caregiver by phone (or in person if the consent process is done in person and the caregiver is present). The study team will provide caregivers with the same information described to patients. If the caregiver is willing to participate after an explanation of the study, the study team member will obtain informed consent from the caregiver. If the caregiver is not willing to participate, the study team will contact the patient to identify another potential caregiver and repeat this process.

Once consent is obtained from both patient and caregiver and the patient is confirmed eligible, the study team will elicit their preference for intervention delivery: either telephone or secure videoconferencing. This preference may be based on technologies available to the dyad and comfort with those technologies if accessible.

The study team will then randomize eligible patient-caregiver dyads via REDCap to the CST or MES arms. See *Method for Assigning Participants to Groups* for more details.

The study team at each health system will then mail the dyad their participant packet, which will contain their workbook (see the *CST Manual* and *COPD Education Manual* uploaded separately), welcome letter (see the *CST Welcome Letter* and *COPD Education Welcome Letter* uploaded separately), *Schedule of Intervention Sessions* (uploaded separately), *Mental Health Resources* (uploaded separately), *ClinCard FAQ* (uploaded separately), and physical ClinCard(s).

## *Exceptions to sharing patient information*

This consent process will emphasize that their participation, the content of discussions during the program, and their responses to study measures and tools will not impact the patients' medical care or decisions, and that this data will not be linked to their medical record or communicated to their health care teams or families. Patients will be informed that the study team is independent from the medical team that is caring for them. No information collected will be shared with the clinical team caring for the patient.

However, in cases of significant distress or urgent issues, limited information may be disclosed to ensure patient safety. Drs. Brown (Penn) and Matero (HFH) will be available on-call to discuss urgent issues or concerns with the study team, including clinical concerns that arise during screening, sessions or survey administration. This may involve providing more complex behavioral health assessments or interventions. Drs. Brown and Matero will facilitate referral to behavioral health services at Penn and HFH, respectively, for any participants that require such care after enrolling.

The study team may connect a participant to a study clinician based on the participant's responses to the C-SSRS, which is administered to all patients before enrollment. It is administered again in response to a positive response to the ninth question on the PHQ-9, which is administered at baseline and in subsequent follow-ups to patients and caregivers, or if a participant discloses suicidal ideation or behavior during an appointment. For more details on how the study team will manage suicidal ideation and behavior, please see the *Risk Management Plan For Suicidal Ideation And Behavior*, which is uploaded separately.

The study team may disclose information to the patient's clinical team if there is concern that the patient may be experiencing a COPD exacerbation. In this case, the study team will encourage the patient to contact their pulmonologist or primary care physician and advise them to contact 911 if their symptoms worsen. The study team will also send a message to alert the patient's pulmonologist and/or primary care physician. For further details, please see the *Risk Management Plan For COPD Exacerbations*, which includes a template for sending this message and is uploaded separately.

## *Semi-structured interview verbal consent process*

The study team requests a waiver of documentation of informed consent for the interview portion of the study and a "Verbal Consent Script" has been uploaded with this protocol.

A similar verbal consent process will be conducted with all interview participants. Participants will be assured that the transcripts will be securely transferred to a HIPAA-compliant medical transcription company. Their recordings will be marked with a study ID number that is not comprised of their name or birthdate. Respondents will not be asked to share any identifying information. If any personal identifiers are discussed, the transcription company will remove any identifying names or places from the transcribed text. All information on risks and benefits, permission to audio-record the interviews, and the option to skip questions and stop the interview at any time will also be provided.

# Early withdrawal of participants

Patients or caregivers requiring inpatient hospitalization for psychiatric concerns during the 12-week intervention period will not resume the Coping Skills Training (CST) program sessions (if applicable) without documented approval by the treating behavioral health clinician

Verbal abuse or harassment directed towards study staff during program sessions that is unresponsive to repeated redirection will require withdrawal from the sessions (if applicable).

# Vulnerable populations

Pregnant people (the study procedures will not affect the condition of the pregnant person or fetus).

# Populations vulnerable to undue influence or coercion

Pregnant people will not be identified or therefore excluded. The study procedures – a remotely delivered coping skills training and surveys – will have no impact on the condition of the pregnant person or the fetus.

# Methods

## Study instruments

### *Confirmatory screening and structured psychological risk assessment*

The **PHQ-8**, a measure of depression severity, will be administered to or independently completed by patients to confirm eligibility. This is not routinely administered. Patients with a PHQ-8 score of 8 or higher, indicating at least moderate depression, are eligible.

> The PHQ-8 is an 8-item, self-report questionnaire with a 4-point rating for the burden of each symptom over the prior 2 weeks, with higher scores indicating more depressive symptoms.

Then, a trained research staff member will conduct a structured psychological risk assessment if the individual is confirmed eligible by PHQ-8. This will include the **DIAMOND**, which includes a self-screener and an interview, the PRIME-5, and the **C-SSRS**. **)**. See *Consent Process* for more details on exclusionary responses.

> The DIAMOND is a semi-structured interview tool for diagnosing DSM-5 psychiatric conditions. It can be administered by trained lay individuals (i.e., by research staff) and does not require advanced behavioral health clinical training. It includes a yes/no self-report questionnaire to screen for primary symptoms, allowing for pre-interview completion to shorten the overall process. Interviewers then focus only on areas with positive responses, streamlining the diagnosis.
>
> The PRIME-5 is a brief, five-item screening tool for psychosis that uses a seven-point Likert scale to assess symptoms experienced in the past year.
>
> The C-SSRS is a widely used instrument for suicide risk assessment. Study staff trained in its use will administer the C-SSRS to identify whether someone is at risk for suicide, determine the severity and immediacy of that risk, and gauge the level of support the person needs. Patients with high or moderate risk can be connected to the study clinician to make a decision about eligibility. For more details see the *Risk Management Plan for Suicidal Ideation and Behavior*.

If confirmed eligible and not excluded, participants will be asked their preferred treatment modality (videoconference or telephone), which will be used to randomize participants. See *Method for Assigning Participants to Groups* for more information.

## *Study instruments and timepoints administered*

The study instruments used are provided in a separate document entitled "Study Instruments" (uploaded). Semi-structured interviews will be conducted with patients and caregivers. These interviews will focus on barriers and facilitators to uptake of the Coping Skills Training program. The interview guides for patients and caregivers are uploaded in the document entitled "Interview Guides (Patients and Caregivers)."

Measures will be administered using any of the below options according to participant preference:

1. Electronically, with the participant independently completing the survey using a REDCap link emailed or texted to them.
2. Over the phone or by videoconferencing, with a study team member recording the participant's verbal responses to the questions the study team member reads out loud.
3. In person, with the participant either independently completing the survey using a device provided by the team (such as an iPad) or the study team member reading the questions out loud and recording the participant's responses.
4. Shorter surveys, specifically the post-session evaluations, will be offered to participants as optional text message surveys where participants can reply to questions via text message.

See below for discussion of how specific outcomes measured at defined time points will be used for three purposes: primary outcome analysis, secondary outcome analysis, and mediator outcome analysis. Further detail can be found in the attached *Statistical Design and Power* section of the grant.

## *Program evaluation*

Participants randomized to the CST program will also complete brief session-specific program evaluations and a final program evaluation at week 12.

## *Primary outcomes*

Our primary outcome measuring patients' psychological distress will be their PHQ-9 scores 14 weeks following program initiation (i.e., 2 weeks after program completion). Setting this as the primary outcome allows us to test mechanisms leading to its improvement. The PHQ-9 is sensitive to change and was the primary psychological QOL outcome in prior CST efficacy testing.

## *Secondary outcomes*

Secondary outcomes include health-related quality of life, perceived dyspnea, patient's psychological distress, caregiver burden, all-cause mortality, time to COPD-related

hospitalization, and patients' anxiety. Secondary outcomes will be measured using the following instruments at specified time points:

### Patients

1. Patients' health-related QOL, measured by the St. Georges Respiratory Questionnaire (SGRQ), a 46-item validated scale specific to COPD, administered at baseline, 7, 14, and 26 weeks;
2. Patients' perceived dyspnea and its impact on health will be assessed using the mMRC (Modified Medical Research Council) Dyspnoea Scale and the COPD Assessment Test (CAT), administered at baseline 7, 14, and 26 weeks;
3. Patients' psychological distress measured by PHQ-9 scores at 7 and 26 weeks;
4. Patients' anxiety measured by the Generalized Anxiety Disorder-7 (GAD-7), a widely used 7-item instrument, at baseline, after 7, 14 weeks, and after 26 weeks;
5. Patient's physical activity measured by the Physical Activity Scale for the Elderly (PASE) at Baseline, 5 weeks, 12 weeks, and 24 weeks.
6. Patients' all-cause mortality up to 12 months following enrollment using EHR review to identify patient deaths. Additional data will be gathered from caregivers and confirmed through Internet obituary searches, which have proven to be highly accurate in prior work, if the death is not represented in the medical record.
7. Patients' time to next COPD-related hospitalization following enrollment in the 12-month period following enrollment using EHR review to identify COPD-related hospitalizations. Hospitalizations recording COPD as a primary or secondary diagnosis with discussion in the record that COPD was an active, primary, or contributory condition during or preceding the hospitalization will be considered a COPD-related hospitalization. Penn and HFH use Epic, which connects and reports other health systems' data in the patients' EHR, providing nearly comprehensive capture of hospitalizations. Time to COPD hospitalization will be measured in days from trial enrollment date.
8. Caregivers' perceived burden, using the Zarit Caregiver Burden Inventory, a 22-item scale capturing role and personal strain associated with caregiving and assessed at 7 weeks, 14 weeks, and 26 weeks following enrollment.

## *Mediator Outcomes*

We will then evaluate whether differences in five outcomes mediate the observed differences in PHQ-9 scores for patients based on treatment arm, drawing on existing evidence and our conceptual model of CST's theoretical mechanisms of action. We will measure these constructs at baseline, after 12 weeks (i.e., immediately after the final program session), and after 24 weeks to facilitate causal testing.

1. Family relationship quality.

   a. In COPD, unsupportive family relationships are associated with more psychological distress and poor self-management behaviors (e.g., medication adherence, exercise, and smoking cessation). Such relationships are associated with lower physical and health-related QOL via psychological distress.
   b. We will use the **Family Emotional Involvement and Criticism Scale (FEICS)**, a 7-item instrument previously used by patients with COPD to measure this construct. Patients and caregivers will independently complete 5-point Likert scales to measure perceived criticism.
2. Patient self-efficacy.
   a. Self-efficacy describes the amount of control an individual believes they have over events in their lives. Among patients with COPD, higher self-efficacy to manage dyspnea is associated with better self-management behaviors, functional status, quality of life, and lower mortality.
   b. We will measure self-efficacy for patients using the **General Self-efficacy Scale (GSE)**, a 10-item scale in which patients report perceived self-efficacy using a 4-point Likert scale. Multiple studies have used the GSE, including use by patients with COPD, and the instrument has good reliability and validity.
3. Caregiver self-efficacy.
   a. Caregivers' self-efficacy is a key component of the caregiving experience and holds potential as a target of palliative care (PC) interventions, as higher levels of caregiver self-efficacy are associated with improved caregiver and patient QOL.
   b. We will measure caregivers' self-efficacy using the **GSE**.
4. Patient loneliness.
   a. The emotional response to perceived social isolation (i.e., loneliness) is strongly associated with poor outcomes in COPD, including higher levels of psychological distress. Strengthening the functional relationship between patients and caregivers may reduce patients' loneliness.
   b. We will measure patient-reported loneliness using the 20-item **UCLA Loneliness Scale**. This instrument uses a 4-point Likert scale and is one of the most widely used measures of loneliness.
5. Caregiver psychological distress.
   a. Caregivers' and patients' psychological distress are closely associated, due to COPD creating stress, demands, and adjustments for both patients and their family caregivers.
   b. Given interdependence theory and our conceptual framework, we will measure caregivers' level of depressive symptoms using the **PHQ-9** and anxiety symptoms using **GAD-7**.

# Data extracted from the Electronic Health Records of patients

Data contained within the EHR of participating patients at Penn and HFH will be extracted. This data will be a limited dataset and contain no other direct identifiers than dates of service related to outcomes of interest. Data elements will include clinical results (e.g., pulmonary function test and 6 Minute Walk Test results), documented treatment limitations (e.g., code status changes, Do Not Intubate or Do Not Resuscitate orders, and hospice enrollment), treatments prescribed for COPD (e.g., pulmonary rehabilitation orders and medications), details of hospital encounters during enrollment (e.g., hospital and unit locations and corresponding dates/times, admission and discharge dates/times and characteristics, diagnosis codes from current and prior encounters, and procedure codes), and behavioral health referrals and medications. This data will be extracted periodically for purposes of interim and final analyses. The HFH data managers will formalize secure data protocols for transfer of EHR data with support from the PAIR Center's data managers. A Data Use Agreement will be established with HFH to cover the secure transfer of this data.

# Semi-structured interviews

A subset of participants, or eligible but not participating individuals, will provide separate informed consent to complete semi-structured interviews by telephone or videoconferencing. This informed consent will include all information on risks and benefits, permission to audio-record the interviews, and the option to skip questions and stop the interview at any time. These interviews will focus on barriers and facilitators to uptake of the Coping Skills Training program.

# Group modifications

All participants will complete measures as outlined in *Study Instruments* at baseline, 12, 14, 24, and 26 weeks.

A subset of both participants eligible for randomization who choose not to enroll in the trial and participants enrolled in the CST telehealth program will provide separate informed consent to complete semi-structured interviews by telephone. See *Consent* for more details.

# Method for assigning participants to groups

After consent, patient-caregiver dyads will be randomized to one of two intervention arms using REDCap's randomization module in a 2:1 ratio (67% to the CST arm and 33% to the minimally enhanced support arm) and with stratified randomization based on (a) preferred treatment modality (e.g., videoconference or telephone) and (b) health system. Patient-caregiver dyads will decide if they want to participate by phone or videoconference. Once they decide, they will be randomized in a 2:1 ratio for each of those modality groups to maintain balance of randomization across modalities. The content in both arms described below is delivered by research staff who are not clinicians.

# Arm 1: Intervention (Coping Skills Training program)

This program involves a 12-week program administered by telephone or videoconferencing. There are 12 weekly structured sessions that focus on building coping skills among patients with COPD, such as breathing techniques, progressive relaxation, physical activity, goal setting, and positive self-talk. Caregivers also participate in these sessions, learning the coping skills and how and when the patient may benefit from using them. Caregivers and patients together complete specific assignments between sessions that help them develop their coaching and supportive relationship while using the skills. Through the specific structure of the program, caregivers learn how to coach the patient to use the skills and support the patient in mastering them through practice and reinforcement between sessions.

Co-I Virginia O'Hayer (Jefferson) was the lead interventionalist for a prior trial of the CST program. She will provide the training to research staff prior to use and will provide ongoing oversight to ensure fidelity throughout the trial period. She will conduct training of all administering research staff prior to trial launch, including directed instruction for each of the 12 sessions and practice sessions led by the staff members. She will continue to provide ongoing training sessions to prevent drift over the duration of the study period. The CST program is fully protocolized with objectives, activities, and scripts previously created and tested for each session, which facilitates consistency.

The sessions are administered by a trained study team member and last approximately 30 minutes each. Below are the 12 session topics:

1. Introduction, Rationale, & Overview
2. Review of Life Story
3. Progressive Relaxation Training
4. Increasing your Daily Activity (Activity-Rest Cycle)
5. Mini-Practices
6. Pleasant Activity Scheduling

7. Communication Skills
8. Controlling Stress via Pleasant Imagery
9. Calming Self-Statements
10. Problem Solving
11. Coping Maintenance Plan
12. Preventing Relapse & Review of Learned Skills

Participants will also receive a mailed packet of CST materials to be used during and between the sessions. These include materials for assignments the dyad works together to complete for the following session, reinforcing their newly learned skills and the program content. Patients and caregivers will receive separate copies if they do not reside together.

If the participant prefers to carry out the intervention via videoconferencing, the study team will use Penn Medicine Zoom in alignment with Penn Medicine (UPHS and PSOM) guidance on video conference platforms and HIPAA-protected health information. In sum, personal meeting rooms will not be used, and cloud recording will be disabled. If the patient is unfamiliar with or has difficulty using Zoom, the study team may use alternative HIPAA-compliant platforms, including Penn Medicine Teams or Epic Videoconferencing.

Given our target patient population, we will also offer the full program by telephone, including secure conference line calling to facilitate participation by both the patient and caregiver. The study team will conduct phone calls using the Webex app or with dedicated study phones, Participants will indicate their preferred delivery modality (video conference or telephone) prior to randomization.

# Arm 2: Attention control (minimal enhanced support)

Participants randomized to the attention control arm will receive a 14-session telephone-delivered COPD Education Program as an attention control. Patients with COPD and their caregivers receive little to no emotional and coping support or management of psychological distress. Our minimal enhanced support augments usual care, providing an attention control for comparison.

Dyads will receive 12 10-minute weekly calls during which trained research staff will provide scripted support without the use of any specific psychoeducational techniques. Participants will receive a COPD Education workbook developed by the study team with content from The COPD Foundation. As CST participants will receive mailed materials, so will participants assigned to the control arm. This comparison arm is necessary to our aims interrogating the mechanisms through which CST works because patients with COPD often experience social isolation that may be affected by increased contact regardless of the content.

Dyads in the attention control arm will be provided the same videoconferencing and phone options as dyads in the intervention arm.

# Fidelity

To measure fidelity, 20% of the sessions will be audio-recorded. The fidelity assessments will occur at random, verbal permission will be obtained after the explanation for the reason, and recordings of sessions will be used only for that purpose. Both the intervention and attention control sessions will be recorded, to ensure there is no contamination of the control arm. Sessions will be selected through random selection stratified on site of enrollment, intervention arm, and time since study launch. The informed consent process will include recording of voice. See *Data Management* for a description of how data will be stored. The session recordings will only be used for intervention fidelity assessment.

# Administration of surveys and/or process

All participants will complete baseline measures before their first CST or MES session and follow-up surveys at 5, 7, 12, 14, 24, and 26 weeks following program initiation. Participants in the CST group will also receive post-session evaluations that focus on feasibility and acceptability. These instruments are described in the *Study Instruments* section).

Participants will elect their preferred contact methods for survey/session reminders at the time of enrollment, including phone, email, text message, and in person. Data will be managed using REDCap, which integrates with outgoing messaging via email and, through an integration with the text-messaging tool Mosio (as described in the Consent section), via text message.

# Compensation

## *Remuneration*

For the proposed study, we will enroll 375 patient-caregiver dyads, for a total of 750 participants. We will compensate enrolled participants in either arm a maximum of $100 for completion of surveys. Payment will be divided up and given according to the following schedule:

- $10 for completion of the survey before the first session of the program
- $10 for completion of the survey at 5 weeks into the program

- $10 for completion of the survey at 7 weeks into the program
- $15 for completion of the survey  at the end of the last session of the program
- $15 for completion of the survey 2 weeks after the last session of the program
- $15 for completion of the survey 12 weeks after the last session of the program
- $25 for completion of the survey 14 weeks after the last session of the program

Patients and caregivers will be reimbursed $25 per interview. Clinicians will be reimbursed $50 per interview.

Participants will be paid via Greenphire Visa ClinCards. However, to remain flexible and inclusive, we will work with the Disbursements Department in the Division of Finance to offer alternative payment methods, including Venmo and Zelle. ClinCards, as the Division of Finance's preferred payment method, will be offered as the first line option and this will be noted in the consent forms.

## *Study incentives*

We have budgeted study in-kind compensation items in support of participant retention and engagement throughout the study duration. We have budgeted the purchase and mailing of 750 customized, magnetized notepads, priced at $2.79 (including postage), to be sent to all participants 12 weeks after study enrollment. Based on our prior experience conducting prospective, longitudinal studies with COPD patients and best practices for sustaining participation among historically underrepresented research populations, this additional in-kind compensation and community building will support participants' engagement and ensure adequate collection of our primary outcome measures at 3 months and our secondary outcome measures at approximately 6 months.

# Data management

## *Overview*

A senior Data Manager at the PAIR Center will facilitate access to EHR data, ensure data confidentiality, and provide guidance on the appropriate transfer and storage of all data. They will be primarily responsible for:

- Developing and applying programs to the University of Pennsylvania Health System EHR to facilitate recruitment and enrollment activities of eligible primary and pulmonary care patients and developing and implementing data storage and transfer protocols.
- They will build the REDCap database used to collect data from both health systems and assist in training research staff to use the database efficiently.

- They will support the study PI in the organization and structure of the final analytic data sets and assist the research team in conducting final data quality checks.

All study databases will be maintained until analyses are complete and findings have been published. Access to electronic files will be restricted to personnel directly involved in the research study. The study databases will be maintained by the study PI, Project Manager, and Research Coordinator with oversight from a Data Manager. The Penn team will maintain six separate, secure study databases:

1. A Microsoft Access screening database stored on an institutionally-managed network drive to assess eligibility.
2. A REDCap database that patients can self-refer to (through the methods described above).
3. A REDCap database to document screening, approach outcomes, and consent.
4. A central REDCap database that will only contain the records for dyads where both the patient and caregiver have consented.
5. PennCRMS (Velos), a required clinical research management system designed to support and manage research, particularly subject tracking, in the Perelman School of Medicine.
6. An Atlas.ti database that will consist of de-identified transcripts and demographic data.

The Penn Medicine data manager will support the PI and PM in guiding the HFH team to create equivalent pre-consent databases. The minimum amount of PHI will be stored in each database. The central REDCap database, managed by Penn Medicine, will be used to track participants' progress through sessions, collect survey data, facilitate registration with Greenphire to issue ClinCards for payments to participants, and monitor contact with participants. This central REDCap database will hold personal and contact information such as first and last names, addresses, phone numbers, and email addresses, along with dates of birth, medical record numbers, and dates of pulmonary or primary care appointments for participants from both Penn and HFH. The central REDCap database will be partitioned using separate data access groups (DAGs). Staff from Penn will have access to both the Penn and HFH DAGs, while staff from HFH will only have access to records in the HFH DAG.

In alignment with the NIH Data Management and Sharing Policy and the data management and sharing plan submitted to NINR, we will preserve and share data from three analytic datasets with the Inter-university Consortium for Political and Social Research (ICPSR) data repository, enabling secondary analysis. These datasets include:

1. Dataset A (Quantitative) will be derived from a series of longitudinal surveys of participating patients and caregivers from the University of Pennsylvania (Penn) and Henry Ford Health Systems (HFHS). Survey data will include measures of psychological distress, health-related quality of life, perceived dyspnea, family relationship quality, self-efficacy, loneliness, and caregiver burden.

2. Dataset B (Quantitative) will be developed via abstraction of EHR data for participating patients, including clinical results, documented treatment limitations (e.g., code status changes, hospice enrollment), treatments prescribed for COPD (e.g., pulmonary rehabilitation orders, medications), details of hospital encounters for 12 months following enrollment (e.g., hospital/unit locations, dates of service, diagnosis and procedure codes), and other clinical information (e.g., BMI, all-cause mortality). All individual patient-level data will be restricted to elements collected during routine clinical care, which are available in patients' EHRs and directly accessible to certified research personnel from each institution's centralized data warehouse(s).

   Dataset C (Qualitative) will contain coded, de-identified transcripts from semi-structured interviews with approximately 20 patients, 20 caregivers, and 20 clinicians. Interviews will focus on a priori Consolidated Framework for Implementation Research (CFIR) constructs (e.g., intervention characteristics).

No information collected will be shared with the clinical team caring for the patient. The caregivers' responses to study instruments will not be shared with the patients, nor will the patients' responses to study instruments be shared with the caregivers. The structure of the interventions, however, will require patients and caregivers to reveal personal information to one another during the program sessions. Trained staff will review the principles of trust and confidentiality with participating dyads.

The text-messaging tool Mosio, which is currently supported as an integration through Penn's REDCap instance, will be used for data collection via text message (either by sending a link to complete surveys through REDCap on a browser or by sending survey questions and receiving responses via text message only). Mosio is HIPAA- and 21 CFR Part 11-compliant, but no PHI will be transmitted via text message. Survey questions will not include PHI and responses will be on a numerical scale only.

Paper copies of the PHQ-8 will be securely destroyed following their entry into the self-referral REDCap database.

During the course of the study, staff will complete C-2 Human Subject Voucher forms as ClinCards are issued to participants. These paper forms will be scanned and stored securely on a secure network drive, only accessible to the study team. The paper forms will be destroyed after being scanned. We have received confirmation from the Disbursements Department in the Division of Finance that a waiver for the collection of Social Security numbers will be granted when the study is set up in Greenphire.

## *Data security*

All identifiable study data will be stored behind firewalls on secure servers. No data will be stored on stand-alone PCs or laptops. To ensure that participant confidentiality is

preserved, individual identifiers will not be used when analyzing data. Each participant will instead be assigned a participant code for all study purposes and the study ID will be used exclusively in all analytical files. All datasets and computer files with study ID numbers will be further secured using multiple, redundant protective measures to guarantee the privacy and security of the participant data.

All data collected for this project will be stored on secure, firewalled servers in data files that will be protected by multiple password layers. These data servers are maintained in a guarded facility behind several locked doors, with very limited physical access rights. They are also cyber-protected by extensive firewalls and multiple layers of communication encryption. Electronic access rights are carefully controlled by Penn system managers. This multi-layer system of data security, identical to the system protecting Penn's medical records, greatly minimizes privacy risks. All paper records are kept in locked filing cabinets behind a locked door. Only authorized project personnel will have access to the data. All study personnel who work with these data will have undergone required human subjects training.

Audio recordings will be made of (1) selected CST and MES sessions and (2) interviews. These recordings will be captured either through the videoconferencing platform or via a digital audio recorder. When recordings are made via videoconferencing platforms, we will adhere to Penn Medicine (UPHS and PSOM) guidance on video conference platforms and HIPAA-protected health information. We will ensure that recordings are only made on computers that are encrypted and managed by PMACS / DART or UPHS. All digital audio recorders will be kept in locked filing cabinets in a locked office building at all times when they are not in use at each study site. The audio file of the interview will be transferred to and stored on the protected data servers mentioned above. The audio file will be deleted from the recorder.

The recordings of CST and MES sessions will be uploaded to PennBox to facilitate fidelity checking by the co-investigator who developed the intervention protocol. Once the fidelity checking is complete, the recording will be deleted.

The study team will upload the interview recordings directly to a HIPAA-compliant transcription company (Datagain). Study staff will be able to individually upload these files directly to the transcription company using the study ID and not a patient name. The transcription company will eliminate all names and identifiable locations so that they do not appear in the transcription document. All recordings from interviews and sessions will remain on the secure server, identified by participant ID and date (month and year), for the duration of the study and analytic period in the event primary data verification is needed or requested. They will be permanently destroyed 7 years after initial capture.

## *Data systems*

Data will be collected using the Research Electronic Data Capture (REDCap) system. Penn's Office of Clinical Research and Clinical Research Computing Unit uses REDCap as the primary electronic data capture platform, which will be adopted for this project.

REDCap is HIPAA-compliant with a user management system allowing project owners to grant and control varying levels of access to data collection instruments and data (e.g. read only, de-identified-only data views) for other users. Qualitative data from participant interviews will be transcribed and maintained in an Atlas.ti database on the secure server, along with the original audio files in the event primary data verification is requested or required.

Data transfers between HFH and Penn will be performed using a study ID, without personal participant identifiers, and through secure transfer using the REDCap data sharing platform. Mr. Brian Bayes, data manager, has extensive expertise in facilitating secure data transfer between institutions for multi-site research.

# Management of information for multi-site research where a Penn investigator is the lead investigator of a multi-site study, or Penn is the lead site or coordinating center in a multi-site study

## *Penn as lead*

The lead project manager at Penn will be the Penn IRB Point of Contact responsible for adding into HS-ERA the study sites (Lancaster General Health, Chester County Hospital, and Henry Ford Health System) that agree to rely on the Penn IRB once those IRB Authorization Agreements have been executed. The Penn IRB Point of Contact will additionally be responsible for submitting protocol-wide modifications that impact all study sites, and site-specific modifications where needed. They will communicate all changes to the site PIs and project managers at each health system during the process of submission to HS-ERA and disseminate IRB approval letters after modification approvals.

See *Data and Safety Monitoring* section for discussion of PI roles and responsibilities related to trial safety.

## *Site responsibilities and participation*

The Penn and HFH study teams will follow a standardized study protocol for screening, recruitment, enrollment, and follow up. The interventions among consented patients will be provided by trained staff with oversight by a senior member of the investigatory team to ensure efficiency and consistency. Study sites will contribute approximately

equally to the final study sample, with anticipation that each will enroll approximately 187 patient caregiver dyads.

PI Hart, together with the Co-Is and Penn and HFH Project Managers, will train and supervise all research staff in order to ensure consistent processes across the two sites. This will include a site visit to HFH in the planning year to train staff and establish procedures. Co-Is at the HFH will supervise the ongoing recruitment and procedures at their site. Investigators and key research staff from both sites will participate in regularly scheduled conference calls to review procedures and progress, ensuring consistency and success across both sites. Penn's Institutional Review Board (IRB0009947) will serve as the IRB of record. The trial will not preclude any medical care, including additional behavioral health care once enrolled, among any of the participants.

The University of Pennsylvania site has a dedicated project manager who will coordinate with HFH PIs and their project manager to ensure that all parties have the most current version of the study protocol and supplementary materials (e.g., operating procedures, data procedures, clinic training materials). During the planning year the Penn study team will meet weekly, with all Co-Is and study personnel at HFH joining calls monthly as well as email correspondence. Moving forward, regular videoconference-based virtual meetings will be established among the study staff at Penn and HFH.

A central repository will be set up to share all non-PHI study documents within a centralized platform (e.g., PennBox) accessible by site PIs, Co-Is and study staff from HFH. This central repository will ensure version control and access to the study protocol as well as documentation of any locally requested changes to the study protocol or data procedures at a given health system.

# Study procedures

## Detailed description

First, patients will be screened and designated tentatively eligible, ineligible, or excluded. See *Recruitment and Screening* for more details.

Next, tentatively eligible patients will be contacted. If they are interested, they will participate in an informed consent process. Once they provide consent, they will go through the second screening. See *Consent Process* for more details. Caregivers will also provide consent.

Consented, confirmed eligible dyads will be randomized to either the CST intervention or an attention control group. See *Section 6: Methods* for more details.

Dyads will then participate in the 12-week programs and complete follow up at designated points. See *Participant Follow-Up* and *Study Instruments* for more details. In-kind compensation items will be mailed to dyads at 12 weeks. See *Compensation* for more details. Participants will have up to 16 weeks to complete their 12 sessions.

EHR data will continue to be collected for 12 months following enrollment.

# Data collection

Data will be collected through prospective research methods, qualitative methods, and EHR abstraction. See *Study Instruments* and the attached interview guides for more details.

# Statistical analysis

Our primary analytic approach will be to conduct intention-to-treat (ITT) analyses using a negative binomial model, with patients' baseline PHQ-9 score included in the model and health system entered as fixed effect, to compare the efficacy of the intervention in achieving reduced distress among all randomized participants. Those effect sizes will be diluted, as some patients will not use the offered CST telehealth program. We will conduct all analyses with adjustment for pre-specified patient-level covariates, including modality of the program (i.e., telephone or videoconferencing) and sex (i.e., to measure differences in treatment effect based on sex), as well as fixed effects for health system to account for unobserved characteristics common to patients in a given system. We will then conduct similar analyses using per-protocol analysis (PPA) to compare the efficacy of the intervention among dyads who participate in at least 50% of program sessions. However, patient characteristics may influence the effectiveness of the intervention. The study team will evaluate causes of heterogeneity in the efficacy of the CST program in key patient groups based on prior evidence or theory. This will allow targeted treatment of the groups who benefit the most and development of strategies to avoid exacerbating existing health disparities through program implementation. We will limit our search for heterogeneity of treatment effects to variables selected based on a priori hypotheses and input from the Stakeholder Advisory Committee. The variables (a) race; (b) income; (c) gender; and (d) rurality.

For more details, see the *Statistical Design and Power* section of the original grant (uploaded).

# Risk/benefit assessment

## Risks

Potential risks include 1) breach of confidentiality of personal health information, 2) increased emotional distress due to study surveys and interviews, and 3) increased emotional distress or relational conflict related to intervention content that teaches participants to confront their emotions and apply new coping skills.

### *Maintenance of confidentiality*

Once approval is received from the Penn IRB, the study team will execute a reliance agreement with the Henry Ford Health System for their institution to rely on the Penn IRB for regulatory oversight of the study. Protection against research risks entails a series of study design elements that will a) ensure the maintenance of confidentiality of all study data and participant information, and b) certify that all research personnel are adequately trained to work with human subject data. Greater detail on the maintenance of confidentiality is discussed above in the *Participant Confidentiality* section.

### *Minimization of emotional distress*

To reduce the risk of increased distress, only study staff within the Palliative and Advanced Illness Research (PAIR) Center who have extensive training in discussing emotionally difficult topics and conducting the CST will administer the psychometric tools and the intervention. Co-I O'Hayer (Jefferson) will conduct training on the specific CST sessions prior to administration with participants. She will continue to provide oversight into intervention fidelity throughout the study period. Co-I Brown at Penn will provide direct clinical oversight through scheduled weekly meetings with the study team confirming participant eligibility and administering the interventions. These meetings will provide the opportunity for research staff to review the prior week's sessions and participant engagement with Dr. Brown, a clinical psychologist. She and Co-I Matero (HFH) will be available on-call to discuss urgent issues or concerns, including clinical concerns that arise during sessions or screening. This may involve providing more complex behavioral health assessments or interventions. Drs. Brown and Matero will facilitate referral to behavioral health services at Penn and HFH, respectively, for any participants that require such care after enrolling.

## Benefits

Participants in the study may benefit directly from either arm. The CST program is an evidence-based intervention that improves depressive symptoms, anxiety, emotional

role functioning and social functioning in prior studies. The minimal enhanced support program provides weekly contact and a mailed resource developed by a COPD patient advocacy organization, thus exceeding the current standard of care offered to patients with COPD. Patients with COPD and their caregivers prioritize attention to emotional symptoms and coping with COPD as palliative care needs and all participants in the trial will receive additional care directed towards this population-level priority. More broadly, the study will help identify new approaches to improve palliative care delivery to patients with serious illness.

# Participant privacy

Individual-level data for participants will be kept confidential and will only be stored on highly secure servers available for patient-level data. Only authorized project personnel will have access to the data and the data will be stored on servers only and not stand-alone PCs or laptops. All study personnel who work with subject identifiers and contact information will have undergone all of the required human subjects training. They will work with the data in password protected files and once enrollment and follow up are complete, all identifying information will be removed. Potential subjects will be contacted by highly trained research staff who understand the importance of subject privacy. Videoconferencing or telephone calls for the intervention arms or to administer surveys will be conducted by trained research staff who will be calling from a private location. Efforts will be made to ensure that phone calls will not be overheard by anyone who is not directly involved with the research. In the event that research staff need to leave a voicemail message for a subject, they will do so in a way that maintains subject privacy.

# Participant confidentiality

**How will confidentiality of data be maintained? Check all that apply.**

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

☒ Whenever feasible, identifiers will be removed from study-related information.

☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

☐ Other (specify):

Please see *Data Management* for more information.

# Protected Health Information

- Name
- Street address, city, county, precinct, zip code, and equivalent geocodes
- All elements of dates (except year) for dates directly related to an individual and all ages over 89
- Telephone numbers
- Electronic mail addresses
- Medical record numbers
- Internet IP addresses
- Biometric identifiers, including finger and voice prints

# Data and safety monitoring

## *Roles and responsibilities*

Program delivery and study clinician support: The CST and COPD Education programs are delivered by trained research staff who are not clinicians. Dr. Lily Brown (Penn), Dr. Nora Brier (Penn), and Dr. Lisa Matero (HFH) serve as the study clinicians, providing essential support to the research staff in managing the risk of suicidal ideation and behavior. While the research staff are responsible for delivering the program content and are referred to as either CST Educators or COPD Educators in participant-facing materials, Drs. Brown, Brier, and Matero are available to offer clinical oversight and intervention as needed.

**Principal Investigator:** Dr. Joanna Hart
Dr. Hart serves as the principal investigator and will be primarily responsible for monitoring the trial and reporting on safety to the relevant overseeing individuals and boards. Dr. Hart is an Assistant Professor of Medical Ethics in addition to her primary appointment as Assistant Professor of Medicine. She is a practicing pulmonary and critical care physician and has extensive additional experience and training in communication skills and ethics. For example, she facilitates Grieving Rounds in the Medical Intensive Care Unit and has been a long-time faculty facilitator and developer of medical school courses teaching ethics, professionalism, and communication skills. She has led multiple research projects that include patients with serious illness and their caregivers, including a cohort study of over 200 patients with severe COPD. Through this work, she has sufficient experience and expertise in overseeing the administration of psychometric instruments (e.g., Patient Health Questionnaire-9) and identifying and responding to patient distress including suicidality. She will hold weekly meetings with the investigative team, including research staff administering the study instruments and conducting the intervention, and provide quarterly reports to the IRB on trial safety.

**Co-Investigator:** Dr. Lily Brown
Dr. Brown serves as the Co-Investigator providing clinical oversight during study enrollment and intervention delivery. Dr. Brown is Assistant Professor of Psychology in Psychiatry and Director at the Center for the Treatment and Study of Anxiety During study accrual and intervention delivery, Dr. Brown will hold weekly meetings with the research staff to monitor trial safety and assist in responding to the behavioral health needs of participants that exceed the scope of the trial, including facilitating behavioral health assessments and referrals. She will report any concerns or events to Dr. Hart immediately.

**Co-Investigator:** Dr. Nora Brier
Dr. Brier will support Dr. Brown in providing clinical oversight during study enrollment and intervention delivery. Dr. Brier is Assistant Professor of Psychiatry Psychology in Psychiatry. She will perform the same duties as Dr. Brown, including reporting any concerns or events to Dr. Hart immediately.

**Co-Investigator:** Dr. Carmen Alvarez
Dr. Alvarez is Associate Professor of Nursing and has extensive experience and expertise in delivering interventions to medically underserved and marginalized communities and individuals. She will provide oversight of the trial procedures and decisions to ensure the project maximizes equity and inclusion. Dr. Alvarez with collaborate closely with Dr. Hart during the planning year to review the protocol for inclusion and at least monthly investigator meetings during trial recruitment, enrollment, and intervention delivery. She will also be available to participate in ad hoc decision making during the trial period to ensure protection of equity and principles of justice for all participants or potential participants.

**Data Manager:** Mr. Brian Bayes
Mr. Bayes has extensive experience overseeing multi-site clinical trials and ensuring data security. He is responsible for overseeing and performing data extraction and

transfer between institutions in a manner that maintains confidentiality of participants. He works within the Penn Palliative and Advanced Illness Research (PAIR) Center at Penn and has worked extensively with Dr. Hart.

**Penn IRB:** The Penn IRB (IRB00009947) will serve as the IRB for the trial.

## *Trial safety*

PI Hart will directly monitor study safety with the collaboration of Co-Is and clinical psychologists, Drs. Brown and Lisa Matero (HFH). The study will follow a 3-part data safety and monitoring plan, which will be submitted to the Penn IRB for approval:

1. Investigators at Penn and HFH will establish secure protocols for the transfer of study data using the REDCap secure data transfer function and minimizing the transfer of identifiable participant data whenever possible;
2. Data will be maintained on Penn's secure server with a minimum of personally-identifying information; and
3. PI Hart will be responsible for promptly identifying and reporting all serious adverse events, protocol deviations/violations, and unanticipated events.

Dr. Hart will provide quarterly reports to the IRB during participant accrual and intervention periods summarizing the components of trial safety included in this document. Dr. Brown will provide direct clinical oversight to ensure safety of all study participants enrolled in the intervention arms as well as provide oversight of the screening and enrollment processes at Penn. Dr. Matero will provide direct clinical oversight of the screening and enrollment processes at HFH and will facilitate HFH-based care for participants who require additional support. Drs. Brown and Matero will directly report any serious adverse or unanticipated events to Dr. Hart immediately and collaborate in reporting to the Penn IRB as needed.

# Investigator's risk/benefit assessment

Patients, family members, and clinicians identify emotional symptoms and coping with COPD as the highest palliative care priorities. Psychological distress is highly prevalent among patients with COPD and is strongly associated with poor quality of life and clinical outcomes. The opportunity to reduce this burden and provide higher quality of life for these patients far outweighs the low likelihood of risk that the study poses given our selection of interventions, study design, and proposed safeguards.

# Resources necessary for human research protection

Our study is designed with numerous overlapping layers of human subjects protections, including: 1) informed consent processes for patients and their respective caregivers; 2) exceptional data security implemented by a highly experienced research organization; 3) an experienced team of investigators who have all been trained in the responsible conduct of research and discussion of emotionally distressing topics with research participants; and 4) a clear process of protecting participants with complex mental health needs identified through study procedures.

All study investigators and staff have completed or will complete the online training program, Collaborative Institutional Training Initiative (CITI), and will maintain active certifications throughout the study. The CITI course is divided into a number of rubrics including: ethical principles, privacy and confidentiality, assessing risk, informed consent, vulnerable subjects, HIPAA privacy protections, research misconduct, conflict of interest, and regulations.

Penn and HFH research team members are further required to maintain HIPAA certification and Good Clinical Practice certification.

In aggregate, these materials provide systematic training in the fundamental issues underlying the responsible conduct of research. Dr. Hart (PI) holds faculty appointments in Medical Ethics and is an active participant in Penn's ongoing ethics seminars, including a weekly seminar on bioethics and research ethics and the Research Ethics and Policy Series co-sponsored by the Department of Medical Ethics & Health Policy, the Perelman School of Medicines Office of Clinical Research, and others.