Title: Capnography-Assisted Learned Monitored (CALM) Breathing Therapy for COPD

Investigator: Annamaria Norweg, PhD

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RESEARCH STRATEGY

A. SIGNIFICANCE.

A.1 Significance and Biological Relevance of the Proposed Clinical Trial.

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability in the US and worldwide.[1-3,4,5,6] COPD is characterized by airway obstruction, hyperinflation, abnormal levels of carbon dioxide (CO_2) and oxygen (O_2), dysfunctional breathing patterns, and low physical activity (PA). Dyspnea (labored, uncomfortable breathing), the primary symptom of COPD, has devastating and debilitating effects on patients' physical and emotional well-being.[7,8,9,10] An estimated 15 million Americans (6.3% of the adult population) have COPD.[11] Its prevalence is increasing due to aging of the world's population, continued exposure to risk factors, and improved diagnosis.[4,12] There is a higher prevalence of anxiety disorders in COPD (up to ~50%) including panic disorder (PD; up to 10 times higher), than in the general population.[13-15]

A.1.1 Dyspnea and Dysfunctional Breathing in COPD. Dyspnea consists of several qualitatively distinct sensations, such as air hunger (a sense of insufficient air), increased "urge to breathe", "chest tightness", and feeling "starved for air".[16] It relates to two main constructs: breathing effort and air hunger.[17] Dyspnea is the principal reason that patients with COPD seek medical and rehabilitation services. Dyspnea is driven by chemosensors that sense abnormalities of CO_2 gases in the blood controlling inspiratory drive and mechanosensors in the ribcage (outside of the lungs) that sense the work of breathing.[18,19] Dyspnea has sensory-perceptual (intensity and quality), affective distress, and impact or burden domains.[18,20,21,22] Dyspnea and associated anxiety contribute to a vicious circle of abnormally rapid breathing (tachypnea), air trapping, and lung hyperinflation, leading to further dyspnea and PA limitations and impaired quality of life (QOL).[23]

Dysfunctional breathing is "an alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms".[24,p.1-2] People with COPD tend to breathe rapidly and shallowly through the mouth, relying on excessive upper chest and accessory respiratory muscle use, and hold their breath frequently.[25] This inefficient, thoracic-dominant breathing pattern (movement of upper thorax without lateral costal expansion[26]) contributes to dyspnea, CO_2 retention, and reduced exercise tolerance.[27,28] Both hypocapnia (low CO_2) and hypercapnia (high CO_2) occur in COPD depending on the stage of disease (**Fig. 2**).[29,30] Given that respiratory muscles are under both brainstem and skeletal muscle control, patients can learn self-regulated breathing to manage their symptoms.[27,31-33]

A.1.1.1 Low CO_2 Levels (Hypocapnia) and Dyspnea in COPD. More than O_2, abnormal CO_2 output is a marker of an inefficient breathing pattern.[34,35,36,37,38] All patients with COPD demonstrate breathing inefficiency, marked by an elevated ratio of ventilation to CO_2 output (V_E/VCO_2). In mild to moderate COPD, fast breaths eliminate too much CO_2, causing hypocapnia.[39,40] Hypocapnia produces bronchoconstriction (airway smooth muscle contraction), bronchospasm, and vasoconstriction (decreasing pulmonary oxygen delivery), which reduce alveolar ventilation-perfusion matching (**Fig. 2**).[41] Hyperventilation-induced hypocapnia creates an acid-base disturbance (alkalosis) inducing panic attacks.[42] [43] Emotions (stress, crying, and laughter), via autonomic vagal excitation, induce hypocapnia.[44]

A.1.1.2 High CO_2 Levels (Hypercapnia) and Dyspnea in COPD. In severe COPD, the pattern of breathing (abnormally rapid and shallow breaths) contributes to CO_2 retention (hypercapnia) (**Fig. 2**).[45,46] Hypercapnia then triggers anxiety and panic, especially in adults with anxiety disorders.[47,48] In a vicious cycle, rapid breathing due to exercise intolerance and emotional stress causes hypercapnia. Hypercapnia then increases ventilation, resulting in a cycle of increasing anxiety, panic, shortness of breath, and risk of ventilatory pump failure (neuromechanical dissociation), and related hospitalizations and mortality in COPD.[49,50-52,53,54,49,55] Chronic hypercapnia is associated with poorer prognosis in COPD.[30]

A.1.2 Anxiety, Abnormal CO_2, and Impaired Interoception in COPD. Anxiety in the sense of worry or nervousness is defined as "apprehensive anticipation of future danger" with both internal and external focus.[56,p.7] Panic is distinct from this more general anxiety or nervousness, because it relates to the feeling that a terrifying event is imminent or in progress[56] and can trigger an intense physical (e.g., dyspnea) and emotional response (e.g., extreme fear). Anxiety disorders include generalized anxiety disorder (GAD), PD, social anxiety disorder, and specific phobias. People with anxiety disorders also have elevated anxiety sensitivity (AS).[57] AS, a cross–anxiety disorder construct, is "the tendency of certain individuals to view interoceptive sensations as dangerous or threatening".[58,p.384] These distorted beliefs impair coping behavior and cause profound physiological dysregulation of respiration and autonomic nervous system.[59] High AS worsens anxiety and panic, particularly as patients become overly focused on and fearful of internal (interoceptive) sensations.

Common anxiety symptoms seen in people with COPD across anxiety disorders with high AS include respiratory dysregulation (i.e., hyperventilation, higher breathing variability, and sighing), ruminative flooding of thoughts, physiological hyperarousal, hypervigilance and attentional bias to threat, and profound avoidance of experiences associated with anxiety symptoms (e.g., avoiding dyspnea-causing activities).[40,47,60,17,61-63] Anxiety increases inspiratory neural drive[38] and is associated with overactivity of stress-related systems or excessive *allostasis* (adaptive processes of activating physiological systems to maintain homeostasis).[64,65]

CO_2 hypersensitivity is considered a biological (neurochemical) marker of anxiety disorder.[61] Biomarkers are "traits that are specific to certain disorders or syndromes".[66, p.322] CO_2 challenges (inhaling air with greater proportion of CO_2) have anxiogenic and panicogenic effects.[61] Greater anxiety and panic attacks are induced via CO_2 challenges (e.g., 5% CO_2 inhalation) in patients with anxiety disorders (especially those with PD) compared with healthy controls.[61] Panic attacks induced in the lab are associated with low CO_2 at end of exhalation or end-tidal ($ETCO_2$) and high breathing variability.[47] Anxiety causes long-term changes in partial pressure of CO_2 (pCO_2) related to accelerated and irregular breathing pattern.[67] Characteristic open-mouth breathing contributes to upper-chest, hypocapnic breathing, especially in anxious patients.[39] Patients with COPD and anxiety might have a lower set-point (neural coding) for CO_2 due to chemo-hypersensitization and greater sympathetic nervous system activation, subsequently increasing hyperventilation.[36,38,68,69]

Panic has been described as a "false suffocation alarm" in which patients show CO_2 hypersensitivity and abnormal pH buffering (an exaggerated compensatory alkalotic buffering) after hyperventilation and alkalosis.[70] Many of these panic-like features are present across anxiety disorders in patients who have high AS. Anxiety moderates the cerebral blood flow effect of CO_2 during hypocapnia and hypercapnia, explaining the greater symptoms of CO_2 changes with anxiety disorders (**Fig 2**). Anxiety results in extreme awareness of interoceptive sensations, causing lower accuracy of signals.[71,72,62] Lower accuracy is experienced as distorted or amplified dyspnea disproportionate to lung function.[73]

A.1.3 CALM Breathing.

A.1.3.1 CALM Breathing Core Exercises and Components. CALM Breathing is a 4-week complementary, mind–body breathing therapy with biofeedback. It links CO_2 changes to dyspnea and anxiety symptoms and targets breathing efficiency and self-efficacy in COPD. It addresses dysregulated, inefficient breathing patterns (habits) and faulty beliefs or interpretations of dyspnea symptoms as key modifiable determinants of abnormal CO_2 levels and poor symptom management.[25,26] CALM Breathing focuses on helping participants to regain quicker breathing control and recovery when challenged to reduce dyspnea distress.[74]

CALM Breathing consists of eight 1-hour sessions, twice per week, and 10 core exercises, which are all guided by capnography biofeedback (**Table 1**). Each core exercise is followed by a debriefing to explore participants' responses and discuss related beliefs and any misconceptions. An example of a misconception is that dyspnea indicates that one needs more air.[75] Participants learn to identify dyspnea contextual cues and triggers (conditioned stimuli) and reinforcements to unlearn dysregulated breathing pattern habits.[76,77,78] During debriefings, the interventionists monitor any relaxation-induced anxiety (RIA) to help prevent it leading to panic. RIA is "paradoxical increase in physiological, behavioral, and cognitive aspects of anxiety with efforts to relax".[79,p.2] Participants are asked if they became more tense or experienced any disturbing or worrisome thoughts, memories, or images.[80] RIA can be overcome during slow breathing therapy.[79]

Fundamental to CALM Breathing is the application of motivational interviewing (MI) principles to establish a collaborative relationship and cultivate change talk.[81] MI is a "client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence".[82,p.326] In each session, collaborative goals are set for home-based exercises for three target behaviors: 1) slow breathing pattern, 2) completion of home breathing exercises, and 3) lifestyle physical activity perseverance.[83]

A.1.3.2 CALM Breathing: Capnography Biofeedback. Biofeedback is a coaching, behavioral method that offers continuous, live feedback of physiology.[84,85] Capnography works synergistically with breathing therapy. Capnography measures and records pCO_2 in exhaled breath ($ETCO_2$), which is a measure of pulmonary gas exchange.[35,86] A capnograph offers both numeric values of CO_2 and qualitative information on airflow patterns (e.g., breath holds or apneas,[87] sighs, effort, aborted exhales, and breath-to-breath regularity).[88,87] Exhaled CO_2 also provides a reliable measurement of RR.[89] Objective biofeedback data of $ETCO_2$, RR, and airflow patterns in CALM Breathing provide clear, immediate biofeedback to guide breathing therapy.

The primary study capnograph will be the FDA-approved Handheld Capnograph and Oximeter (PC-900B, CMI Health, GA) in-session, with integrated arterial oxygen saturation (SpO_2) sensor (**Fig. 1A**). The accuracy

of the Capnograph is ±2 mmHg for values of 0–40 mmHg and ±5% for values >41–70 mmHg, which meets International Organization of Standardization (ISO) standards for CO_2 reading.[90] The Capnograph will be used with nasal cannula. We will also use the CapnoTrainer[91] to display CO_2 waveforms in-session (**Fig. 1B**).[89]

Table 1. CALM Breathing Core Exercises.

	Exercise	Description
1.	Slow, nasal respiration	Exercises are quiet, nasal inhalation and exhalation (≤10–12 breaths per min at rest)[92,93] focused on lengthening exhalation. Practice is predominately relaxed (eupneic) breathing at rest in supine as well as in sitting and standing recovery postures (e.g., supine or semi-reclined positions, forward-leaning in standing or sitting with hands supported).[77,94,95] In later sessions, slow breathing is practiced with tailored, simulated breathing challenges (e.g., speaking freely, walking and talking, or timed mental arithmetic) for transfer of learning.[96]
2.	Pursed-lips breathing (PLB)	PLB is "nasal inspiration followed by exhalation through partially (almost) closed [relaxed] lips,"[97,p.344] focused on lengthening exhalation, with tailored ≤ 5-min physical challenges, chosen by participants (e.g., stepping in place, walking, or stair-climbing).[77]
3.	Positioning of the tongue	Participants practice placing and maintaining their tongue on the roof of their mouth (behind top teeth on hard palate) to correct open mouth breathing and facilitate nasal breathing with closed lips. Open-mouth breathing impairs respiratory mechanics and exercise tolerance, contributes to forward head posture, and is a risk factor for obstructive sleep apnea.[98,99]
4.	Control pause (CP)	CP is a breathing maneuver post-exhalation of ~2–5 seconds; participants notice and count the length of the natural pause between breaths. Increasing pause time is important to slow the breath. Exercise facilitates regaining trust in the body's physiology. The three phases of the breath are emphasized: 1) inspiration, 2) post-inspiration, and 3) expiration (pause).[100,101]
5.	Volume-regulation	Exercises focus on regulating size and/or depth of breaths (or breath volume) for more efficient breathing (less wasted ventilation).[27]
6.	Breathing interoceptive awareness	*Width breathing*: Participants notice and allow their lower ribs to laterally expand and elevate sideways and contract (bucket-handle motion).[102] *Length breathing*: Participants feel their belly rising and falling, and ribcage elevating and lowering (pump-handle motion). Patients learn to *de-recruit* abdominal expiratory muscles for energy efficiency.[14] Sighing is discouraged because it triggers arousal.[103] Exercises facilitate *allowing* rather than habitual manipulating of the breath.
7.	Breath counting	To promote slow breathing and improved interoceptive accuracy ("objective accuracy to detect bodily sensations"),[104,p.130] participants count breaths in sets of 5–10 breath counts (e.g., "in, out, pause, 1; in, out, pause, 2" and so on) initially cued by the therapist and then practiced independently.
8.	Humming	Humming is a type of resistance breathing pattern used to promote rhythmical, prolonged exhalation cued with participants' preferred music.[105]
9.	Breathing differentiation training	Biofeedback facilitates differentiating rhythmical versus arrhythmic breathing (e.g., breath-holds, aborted breaths, avoiding transition times) to facilitate interoceptive accuracy.[48] Participants learn to estimate their $ETCO_2$ levels and accurately count their number of breaths based on interoceptive cues. They learn to differentiate somatic cues and $ETCO_2$ changes resulting from breathing (e.g., shallow versus deeper breaths).
10.	Coordinated breathing	The exhalation phase of the breath is coordinated with ribcage stretches.[106] Breathing exercises with movement improve body awareness, grounding (reconnection with the body),[107] and sense of embodied self;[108] relieve muscle tension; and improve chest wall mechanics. Ribcage stretches include active shoulder rolls, head rolls, arm reaches overhead, forward bends and spinal rolls, pelvic tilts, side bends, spinal twists, and thoracic extensions.

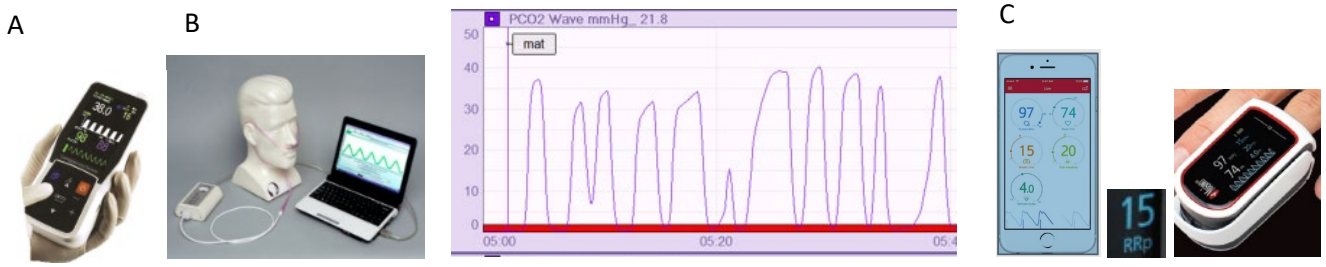

Figure 1. A) Capnograph PC-900B; B) CapnoTrainer, including capnogram. C) MightySat™ pulse oximeter with RR biofeedback.

A.1.3.3 CALM Breathing Home-Based Exercises and Adherence Strategies. Participants will be encouraged to practice home breathing exercises (especially audio-guided *slow nasal respiration* and *coordinated breathing* with RR biofeedback) for 10–20 min per day. Participants will receive a printed-out

"Home Breathing Exercises" hand-out during their first session. In addition, PLB with physical exertion will be promoted. Adherence strategies include collaboratively setting goals (action plans), logging home breathing exercises for self-monitoring, and therapist monitoring of recorded RR data.[109,110,83,111] At home, participants will use the MightySat™ fingertip pulse oximeter device for RR biofeedback to monitor their slow breathing exercises (**Fig. 1C**). Participants will receive a printed out "Pulse Oximeter" education hand-out during their first session. The FDA-approved RR biofeedback device uses photoplethysmography and algorithms to detect variations in blood flow and volume in skin; accuracy is verified for 4–70 bpm.[112-114] MightySat device uses Bluetooth to interface with a health app and stores 72 hours of data. Participants will be trained to use the MightySat™ in the first CALM Breathing session; its correct use will continue to be reinforced in-session (to ensure safety and quality of home practice).

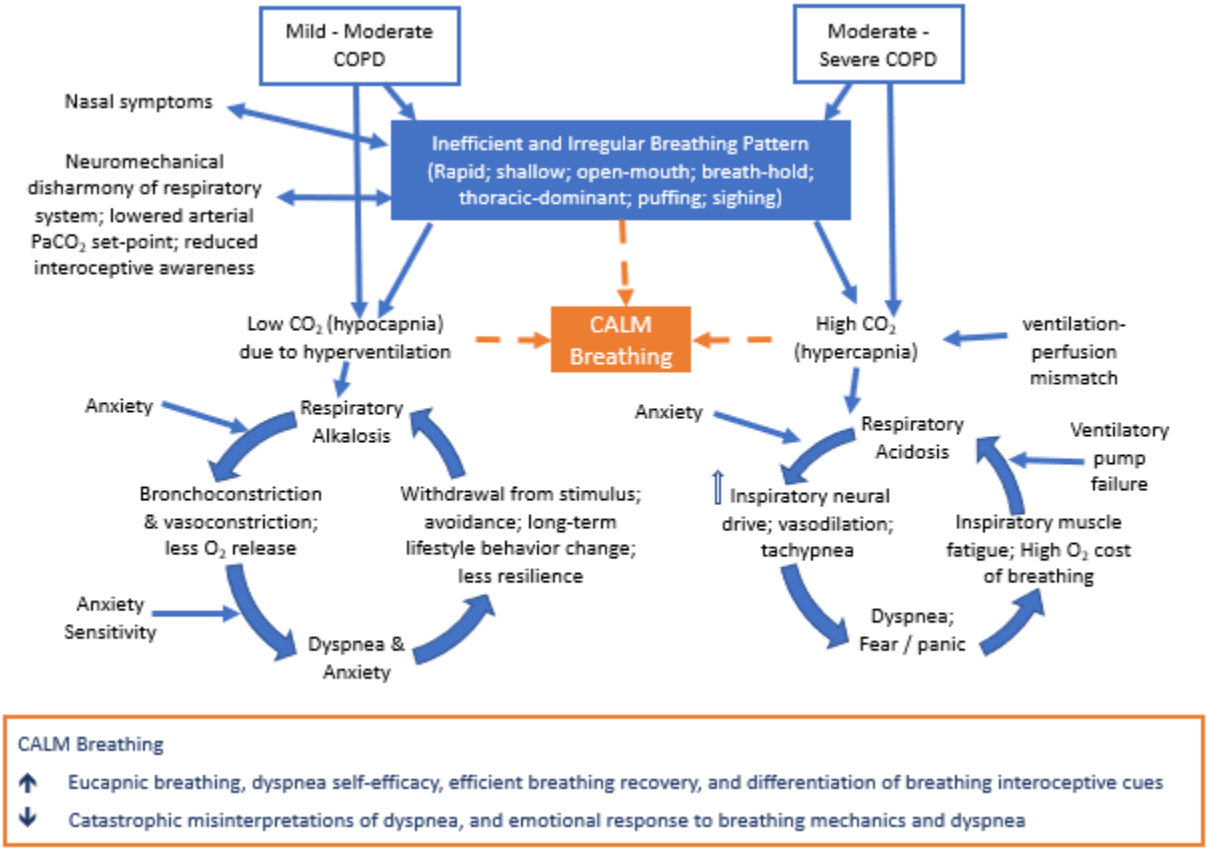

Figure 2. CALM Breathing Conceptual Model.

A.1.3.4 CALM Breathing: Conceptual Framework. *Generative Model of Perception.*[48] This is a top-down neuropsychobehavioral model based on recent understanding of normal brain functions involved in the perception of bodily sensations. The brain represents the world by both exteroceptive sensations (e.g., sight) as well as interoceptive sensations from inside the body. Interoception is "the sense of the internal physiological condition of the body"[115,p.971] monitored by the nervous system for survival and evolutionary adaptation to the environment.[17,65] It is the mind's way of listening to the body. Interoception consists of monitoring of blood chemistry (CO_2), afferent sensory stimuli from visceral organs, and interoceptive perceptions and inferences.[115] Breathing is one of several interoceptive channels.[65] The brain is continuously generating, testing, and reforming predictions ("best guesses") based on sensory data and prior expectations.[116] The brain learns to minimize differences between predictions and sensory signals (prediction errors or surprise) and optimize homeostatic-allostatic control via autonomic reflexes as a regulator for survival.[48] When sensory inputs are noisy and unclear (have low inferred precision), which is common with anxiety, interpreting internal states is influenced by priors (reducing influence of sensory inputs).[117] Priors are cognitions and emotions that actively contribute to perception. Stress symptoms stem from low allostatic self-efficacy (a metacognitive belief of low capacity to self-regulate bodily states, such as dyspnea).[108]

Interoceptive Exposure and Learning Theory.[56,118] Through interoceptive exposure to breathing sensations, CALM Breathing is theorized to reduce CO_2 hypersensitivity and physiological arousal to respiratory stimuli.[60,72,119,120,73] Exposure to breathing stimuli without negative consequences is designed to extinguish

classically conditioned emotional responses to breathing stimuli.[56,60] The rewards of more regulated breathing are reinforced. Interoceptive exposure promotes subjective sense of physiological well-being and trust of the body.[60,121]

A.1.4 Knowledge Gaps. COPD clinical studies have not adequately focused on breathing therapy that includes anxiety and physiological measures as important endpoints.[122, 123, 33] While breathing strategies are strongly supported for dyspnea relief and exercise tolerance by expert opinion, existing evidence is from small-scale studies.[77] PR is a comprehensive intervention that includes aerobic and strengthening exercise training, breathing exercises, and education.[77] While PR is effective in improving dyspnea, QOL, and exercise capacity in COPD,[124] the contributions of breathing therapy exercises, a component of PR, are less known. Anxiety is associated with worse PR outcomes: greater dyspnea and perceived functional impairment post-PR, and worse QOL and 6-minute walk distance (6MWD).[125,126] Therefore, there are knowledge gaps for how to improve PR outcomes, including uptake, especially for anxious patients.[127]

A.1.5 Barriers and Treatment Limitations in Symptom Management for COPD. Currently there are limited dyspnea and anxiety treatment options, and management is suboptimal.[128,129,70,130] The standard of care for COPD is pharmacotherapy and supplemental O_2,[12] but bronchodilators and corticosteroids provide only minor relief of dyspnea and airflow obstruction.[19,38] Supplemental O_2 relieves dyspnea by slowing breathing pattern and reducing hyperinflation.[131] However, short-term supplemental O_2 use has low patient acceptability.[132]

Because a comprehensive PR program can improve symptoms, exercise tolerance, and QOL, guidelines strongly recommend it, but it is grossly inaccessible to most patients with chronic lung diseases and underutilized worldwide.[127,133,134] Overall real-world uptake of PR by patients with COPD is 1–2% due to significant barriers.[135] A recent systematic review identified key barriers to PR uptake in COPD as fear of dyspnea, fear of exercise and exhaustion, and belief it would not be beneficial, among other reasons.[136] Recent studies further suggest that PR post-acute exacerbation of COPD (AECOPD) might not be acceptable for patients, with an uptake of only 9%.[137,138,139] Based on our research, real-world PR drop-out rates in COPD are >40%. In one study (N = 128), the main reason for not attending an initial PR assessment or dropping out post-AECOPD was feeling unwell or too breathless.[137] PR teaches pursed-lips breathing only during physical exercise challenges, when a person's respiratory system and emotional state are typically significantly stressed, and mechanical and chemical demands are greatly amplified, possibly limiting the opportunity to learn self-regulated breathing. By not addressing anxiety, PR offers more limited learning opportunities for desensitization, and exposure to dyspnea in PR may actually trigger increased anxiety in some anxious patients. Therefore, PR doesn't address breathing irregularity and anxiety simultaneously, which is essential to optimizing treatment in COPD.[140] In contrast, CALM Breathing is designed to extinguish emotional responses to breathing mechanics and CO_2 symptoms.

Inspiratory muscle training using devices that add a resistive load to strengthen inspiratory muscles does not improve COPD clinical outcomes.[77,141] In addition, noninvasive positive pressure ventilation (NPPV) might be a useful adjunct to PR for COPD to unload respiratory muscles to relieve dyspnea.[77] However, NPPV is a labor-intensive, costly intervention, requiring expertise to use it, and has low adherence and high drop-out rates (up to 44%) because of discomfort.[142 77] NPPV might not be practical in a non-hospital setting.[142]

The efficacy of traditional cognitive-behavioral therapy (CBT) treatments for anxiety and dyspnea in COPD is uncertain. CBT compared with a control condition in a meta-analysis had only a small effect on improving anxiety in older adults, indicating a need for new approaches.[143] Adults with hypocapnia were twice as likely to drop out of CBT.[144] A meta-analysis found low quality evidence of the efficacy of psychological therapies for COPD and anxiety.[145] Breathing retraining is not offered to patients with COPD outside of rehabilitation.

Breath practices are also central to yoga, tai chi, and other Eastern traditions. While a few studies are underway or have been completed,[149-153] scientific evidence of their efficacy as adjunctive treatments in PR is still very limited.[154,155] Further, limited data is available outside Asian populations.[146] Evidence to date suggests these therapies may not be fully accepted by Western populations with COPD; for example, in a mindfulness study of men with moderate to severe COPD, 52% of participants withdrew.[156] Further, yoga in its many forms may also need to be adapted to better target the breathing challenges of COPD for optimal benefit. More than increasing interoceptive awareness, with scientific premise, CALM Breathing systematically targets dysfunctional breathing patterns to promote slow, eucapnic breathing and interoceptive breathing accuracy and self-efficacy specifically for dyspnea symptom relief.[99]

A critical barrier to progress in the field of anxiety management for COPD is stigma associated with the classification of anxiety as a mental illness.[13] Many patients with COPD delay seeking treatment for anxiety or go without needed care. CALM Breathing might be a more acceptable, less stigmatizing mind–body intervention compared with traditional mental health interventions,[147] and may improve anxiety and dyspnea.

There is little and conflicting evidence for the use of antidepressant and anxiolytic medications for relieving dyspnea and improving QOL.[130] Psychopharmacological treatments for anxiety have reduced long-term efficacy and can cause severe side effects, dependence, adverse reactions, cognitive impairment, and falls, as well as addiction and relapse in older adults.[70,130,148-151] Medication does not build long-term coping and information-processing skills or behavior change.[107] International practice guidelines recommend an integrative approach of combining medication with psychological or mind–body interventions.[12,152]

A.1.6 Significance and Impact of the Study in Clinical Practice. This trial addresses two significant comorbidities, anxiety and COPD. The gained knowledge could change the treatment paradigm for COPD patients.[127,153] CALM Breathing has potential important downstream effects on reducing fearful activity avoidance. $ETCO_2$ biofeedback simplifies learning to promote breathing and PA behavior change.[154] CALM Breathing focuses on reducing dyspnea and safety-seeking behaviors that contribute to deconditioning, a sedentary lifestyle, and persistence of a cycle of high anxiety levels. Compared to traditional PR, the monitored home-based breathing exercise program boosts therapy dose, and establishes routines for long-term behavior change.[153,110,155] This study addresses a critical knowledge gap of how to improve PR use. CALM Breathing offers a needed bridge or stepping-stone to prepare patients for PR to potentially improve PR utilization.[12,136,156,157,138,156] As such, CALM Breathing meets the definition of a *transitional care intervention* ("a time-limited intervention designated to promote safety and timely transfer of patients across care settings"[158]).

Expert consensus supports establishing *breathlessness rehabilitation* for COPD.[153] In a recent breathlessness workshop for COPD and chronic heart failure with 74 stakeholders, only 36% agreed with the statement "exercise training was the most important component of rehabilitation for breathlessness".[153,p. 235] Instead, they believed that psychological and educational components of rehabilitation were also important for dyspnea remediation.[153] As advocated by these stakeholders, by preceding exercise training, CALM Breathing may work in synergy with PR to improve physical and mental health outcomes.

B. INNOVATION AND GENERALIZABILITY OF POTENTIAL FINDINGS.

CALM Breathing, a complementary approach and adjunct to PR, is innovative because:

i. Novel therapeutic targets of $ETCO_2$ and RR levels are used to improve both breathing pattern efficiency and anxiety in COPD; immediate goal-directed feedback of capnography nudges skill acquisition.[78,140,94,88,89] CALM Breathing uses a novel application of capnography to integrate CO_2 biofeedback with breathing therapy while attending to anxiety sensitivity.[159,160]
ii. Timing of CALM Breathing (before PR) offers a phased approach to PR uptake to address important barriers to PR acceptance, readiness, and utilization.
iii. CALM Breathing includes novel home-based device-assisted RR biofeedback and data recording to monitor breathing exercise quality, motivate behavior change, and enable adherence checks.[153,110,155]
iv. Our approach includes novel physiological and anxiety outcome measures, including change in ventilation patterns (RR and $ETCO_2$), lacking in other COPD breathing therapy studies.
v. Innovative coaching (MI) is implemented, which emphasizes collaboration and shared decision making.
vi. CALM Breathing translates neuroscientific understanding of sensory perception to treat dyspnea.[48,161]

CALM Breathing is scalable because it does not rely on smartphone delivery. This could be important for older patients, as the use of smartphones in adults 65+ years old is only ~53%.[162]

C. SUPPORTING DATA, CLINICAL EVIDENCE, AND RATIONALE FOR THE PROPOSED CLINICAL TRIAL.

C.1 Benefits of Slow Breathing.

Slow breathing activates the parasympathetic nervous system, via the right and left vagus nerves, to soothe and calm the mind. Slower RR prevents a feedback cycle of panic in a dyspnea crisis to prevent ventilatory pump failure.[49,163] Slow PLB reduces anatomical dead space (V_D) and increases the amount of CO_2 removed (breathing efficiency) as its primary mechanisms in COPD.[164] PLB reduces hypercapnia by improving the elimination of CO_2 and alveolar-capillary diffusion.[14,165-167] PLB decreased $ETCO_2$ and RR in patients with

severe COPD.[168] PLB has been endorsed in evidence-based practice guidelines to relieve dyspnea in advanced COPD.[128,130] PLB reduced RR and increased tidal volume in a systematic review.[169]

Device-guided slow breathing training when combined with PR program (using a pneumotachometer interfaced with a computer display of respiratory and goal feedback) reduced dynamic hyperinflation in moderate to severe COPD compared with both PR alone and breathing training alone.[32] Adherence was 75–76.5% for research-based PR. Both ventilation feedback groups slowed their breathing by increasing expiratory time, supporting the benefits of goal-directed biofeedback in breathing therapy.

C.2 Device-Guided Capnometry-Assisted Respiratory Training (CART) Approach.

Participants with PD (N = 69) receiving a 4-week capnometry-guided respiratory intervention had improved panic severity, increased $ETCO_2$, and improved anxiety control.[170] Also, CART increased $ETCO_2$, decreased distress, and improved asthma symptoms at follow-up in adults with asthma compared with a comparison group of slow breathing and awareness training (SLOW) with RR feedback alone (N = 120).[31]

C.3 Role of Recovery Postures and Chest Wall Stretches with Breathing Exercises in COPD.

For hypercapnia, the energy demands of breathing are reduced by supine and forward-leaning postures with arms supported.[26,130] Supine posture augments prolonged expiratory time and abdominal ribcage tidal volume compared to sitting ($p < 0.01$).[171] In a study (N = 23), 13 adults with COPD showed paradoxical indrawing movement of the lower ribcage with inspiration in sitting, which was corrected by a supine posture.[172] Recovery postures allow cephalad positioning of the diaphragm and ribcage, reduce a kyphotic posture, improve chest wall compliance for improved efficiency of the ventilatory pump,[173] and regulate autonomic nervous system arousal.[94,95] Chest wall muscle stretches and augmentative postures inhibit activation of accessory muscles of respiration and facilitate synchronous motion of the chest and abdomen.[106]

C.4 Relationship between $ETCO_2$ and $PaCO_2$.

$ETCO_2$ is a good estimate of arterial pCO_2 for patients with stable COPD in non-acute respiratory distress and spontaneously breathing (non-intubated) ($r = 0.89$).[174] $ETCO_2$ evaluates relative changes of $PaCO_2$ with acceptable accuracy to guide breathing therapy.[175] Accuracy of $ETCO_2$ is enhanced in CALM Breathing with the promotion of slow, longer exhalation, which reduces dead space,[164] to better reflect alveolar pCO_2.[87,175]

D. APPROACH.

D.1 Supporting, Preliminary Data from Research Team.

This study builds on our previous pilot trial called Capnography-Assisted Training in COPD to slow the BreatH (CATCH) (N=31).[176] CART was combined with a 10-week PR program. Randomization to CART+PR or PR alone was 2:1. Thirty-one participants with mild to very severe COPD enrolled in the study; 58.1% were female; 32.2% had mild to severe GAD-7 anxiety symptoms; and 30.8% were taking anxiety or depression medication. Adherence to CART sessions was 73.5% overall (n=22) and 100% for participants who completed PR (n=13). CART participants completed 61% of home breathing exercises based on logs. Mean number of PR sessions completed was 14.14 (7.37) for CART+PR and 11.44 (9.81) for PR alone (n=31). Fourteen people with mild to very severe COPD were also interviewed post-treatment using a topic guide.[177] We identified five main themes: *PR Adherence*, *Learning to Breathe*, *Impact on Health*, *CART Dose*, R*ecommending CART to Others* (**Table 2**). A majority (67%) of participants requested more than six CART sessions for maximum benefit. Results provided preliminary evidence of the feasibility and acceptability of CALM Breathing exercises, session structure and therapy space needed, and coaching approach (MI). Participants' feedback was used to refine CALM Breathing (e.g., frequency, timing, session structure, and home-based breathing exercises). For example, we simplified the home breathing exercises and biofeedback device, revised symptom tracking, and added written goals and confidence ruler to the exercise log.[159,111] We also revised the interview questions.

Table 2. Example Themes and Quotes of Acceptability of CART– CATCH Study.

Theme	Subthemes	
Adherence		*It helped me to get along with and keep up and not give up.* (ID: 1016, Female, 75 yrs)
Learning to Breathe	CO_2 Biofeedback	*The one thing I really enjoyed was the capnometer and seeing the breaths. Seeing a physical measure of what a breath is…. As soon as I saw what a good breath was, and what bad breathing was, on the moving graph then it kind of reinforced the way I should be breathing.* (ID:1008, Male, 78 years)

	Mind–Body Connection	*The fact that I have been able to see on the screen the difference in being able to relax, focus on my breathing, the intake of air and exhalation, and seeing it on the screen and the differences. I saw a big difference and not only do I see it, but I feel it….I've been aware of how my feelings impact my breathing and …how I can regulate and change it and I think that has been extraordinarily helpful.* (ID: 1025, Female, 82 years)
Impact on Health	Relief of Dyspnea	*I felt like it helped a lot because I've become aware of my breathing and I think I was breathing much more shallowly before. I would always hold my breath on exertion, so it basically, solved a lot…. I didn't realize that I was breathing the way I was…. I don't think I was breathing as regularly or as in control as I am now*. (ID: 1024, Female, 75)
	Reduced Anxiety	*It helped not only with the breathing itself, but even with the calming of the nerves…. Especially people that are nervous about it, just controlling your breathing, you automatically calm down.* (ID: 1011, Female, 61 years). *It's like all stops because you are concentrating on [breathing], and it's peaceful there. So, I really liked that part. It stays with you. Because you know, if you can be calm and you can be peaceful, you can be breathing all right. And you won't be feeling those frightening feelings.* (ID: 1030, Female, 65 years).

In our observational study (N = 445) of adults with COPD, 36% of participants had mild to severe GAD-7 anxiety symptoms. We found self-reported physician diagnosis of anxiety even higher with a prevalence of 42%.[140] In our study on anxiety and COPD (N = 182, mean age 52 ± 16 years),[57] 50% had any of six anxiety disorders with a DSM-IV-based screening. A higher Anxiety Sensitivity Index (ASI) score was independently associated with higher dyspnea severity, more activity avoidance due to dyspnea with obstructive lung disease, and poorer ratings of subjective health.[57] Mean ASI score was 18.4 for those with dyspnea.

D.2 Recruitment and Clinical Trial Experience.

Our study team has successfully collaborated on previous COPD and breathing therapy research.[176,177] Dr. Norweg has successfully recruited over 600 patients with COPD in her research work. Our team also has an extensive track record of publishing our clinical trials.[176,178-180]

D.3 Experimental Approach.

Aim 1: To evaluate the feasibility of CALM Breathing before PR.

Aim 2: To measure the acceptability of CALM Breathing before PR.

D.3.1 Study Design. To achieve Aims 1 and 2, we will use a single-blind prospective RCT. In Phase I, participants will be randomized 1:1 to one of two groups: CALM Breathing (N = 20) and Wait-List control (N = 20). In Phase II, both groups will be offered a 10-week PR program (care as usual). Access to timely initiation of PR will be facilitated. We will use a hybrid design to evaluate feasibility and acceptability.[181]

D.3.1.1 Rationale for Study Design. *Why Use a Waitlist Design?* We chose a waitlist control group as a usual care comparison group because PR intake evaluations are typically scheduled 6 weeks in advance of implementation. Therefore, 4-week CALM Breathing could fit seamlessly into PR programs and not delay standard of care. A qualitative study found that waiting for PR increased patients' feelings of uncertainty and lack of control regarding their care.[182] Our experience shows that once referred to PR, patients are motivated to start some form of therapy right away. CALM Breathing can leverage patients' motivation and reduce feelings of uncertainty. A target sample size of 40 subjects is justified based on the primary outcomes of feasibility and acceptability, and transition of participants to a 10-week PR program.

D.3.1.2 Rationale for Study Need. This study is part of our phased approach to refine, optimize, and test the feasibility of CALM Breathing. Preliminary participant feedback from our CATCH study was applied to adapt and design CALM Breathing (including its dose, schedule, delivery, and home program). This pilot builds on initial lessons learned and identifies intervention areas still needing greater development to assure the success of a future large trial, targeting a subpopulation at risk, that is, those with COPD and anxiety.

The purpose of this pilot study is to establish success benchmarks of CALM Breathing and to test feasibility of:

1) recruiting a target group of adults with COPD and concurrent anxiety, including building a partnership with Columbia University Irving Medical Center's (CUIMC's) pulmonary department; ensuring adequacy of recruitment and study referral procedures;
2) using ASI-16, DMQ-CAT, and VAS dyspnea anxiety assessments for eligibility screening;
3) randomizing participants to CALM Breathing and Wait-List;

4) assessment procedures; confirming our estimates of time needed to administer assessments; evaluating participant ratings of assessment burden; and testing that target timelines and blinding are achievable;[183]
5) facilitating timely PR intake assessment initiation (to limit wait);
6) implementing manualized CALM Breathing, including adequacy of dose (timing, frequency, and session duration), fidelity procedures, and transportation funds; attention will be given to additional considerations and tailoring needs of patients with significant anxiety sensitivity and/or anxiety disorders;
7) implementing home-based breathing exercise component (e.g., new RR device fidelity checks and new distribution of therapist-guided audio exercises using an MP3 player to improve adherence rate);[181,184,185]
8) retaining participants at 3-month follow-up post-PR, including ensuring adequacy of retention strategies.

D.3.2 Participant Eligibility and Recruitment. Participants will be recruited from CUIMC's / New-York Presbyterian Hospital's outpatient PR program patient referral list. Participants will also be recruited from a cooperating clinical site, CUIMC's / New-York Presbyterian Hospital's Pulmonology Medicine Department, CUIMC'S/ New-York Presbyterian Hospital's Primary Care Medicine Department and New-York Presbyterian Lawrence Hospital Pulmonology Medicine Department. We will also plan to make use of CUIMC's RecruitMe platform. To facilitate participant recruitment and partnership building, we will partner with the Dr. Angela DiMango, MD and Dr. Charles Murphy, MD from CUIMC's/New-York Presbyterian Hospital's Pulmonology Medicine Department and Dr. David Buchholz from CUIMC's/New-York Presbyterian Hospital's Primary Care Medicine Department. CUIMC has a high volume of racially diverse patients with COPD. Feasibility of conducting this study is facilitated by a single Institutional Review Board (IRB) and a single-clinic recruitment site.

D.3.2.1 ***Inclusion Criteria***: Eligible participants will be adult males or females with COPD in stable condition; have elevated anxiety symptoms;[57,186] have dyspnea symptoms; and require ≤8 hours per day of supplemental oxygen. All participants will receive standard care of pharmacotherapy with bronchodilators.[77,12] Participants taking anti-anxiety medication (e.g., selective serotonin reuptake inhibitors, SSRIs, and serotonin norepinephrine reuptake inhibitors, SNRIs) must be stably medicated for at least 4 weeks prior to study entry,[152] with no plans to change psychotropic medication dose.

D.3.2.2 ***Exclusion Criteria***: Participants may not have suicidal ideation or suicidal behaviors within the past year (score of >1 on psychologist interview-administered Clinician Suicide Assessment Checklist, which is a Modified Columbia-Suicide Severity Rating Scale-CSSRS).[187] Participants cannot have morbid obesity (body mass index (BMI) > 40) or neuromuscular disease or be pregnant. Participants not eligible for CUIMC's PR program and those who have received PR training in past 12 months will be excluded. Concurrent receipt of short-term or new physical therapy, speech therapy, mindfulness, or meditation-based therapies (e.g., Mindfulness Based Stress Reduction) will not be permitted. Cognitive impairment will be screened by the Mini Mental State Exam, with score of ≤23 used as an exclusion criterion, to control for cognitive impairment and learning challenges.[188] [See Study Record for full eligibility criteria.]

D.3.2.3 Rationale for Eligibility Criteria. Assessments for elevated anxiety symptoms are based on our previous research.[22,57,189] No diagnosis of an anxiety disorder is required since participants with elevated anxiety symptoms could benefit from CALM Breathing. An inclusion criteria of anxiety symptoms (rather than anxiety disorder) increases the generalizability and potential impact of CALM Breathing, targeting anxiety and somatic symptoms such as occur with breathing in COPD. We will use accepted standards of spirometry testing to classify COPD patients (using grades 1 to 4) according to severity of airflow limitation.[12] Neuromuscular disease can affect $PaCO_2$.[30] Obesity is associated with hypercapnia. Our threshold of hypercapnia of $ETCO_2 > 50$ mmHg is widely used.[190] Pregnancy can reduce ventilatory control, resulting in hyperventilation, hypocapnia, and alkalosis.[191] We have attended to prescription medication as a confounder. We will adjust for stable antidepressant use (SSRIs and SNRIs) in statistical analyses. Excluding patients taking antidepressants would reduce generalizability.[192]

D.3.3 Study Groups and Interventions.

D.3.3.1 Capnography-Assisted Learned, Monitored Breathing (CALM) Intervention. The 4-week CALM Breathing therapy will consist of eight 1-hour individual treatment sessions over 4 weeks pre-PR (**Tables 1, 3–4** and section A.1.3). The dose (of 8 sessions plus daily exercises) was primarily guided by participant feedback from our previous CART trial, as well as other breathing therapy trials.[31,193,194]

D.3.3.2 Fidelity Procedures. To improve the internal validity of study findings, comprehensive fidelity methods will be implemented.[195] These methods will include standardizing interventionist training and supervision protocols; manualizing CALM Breathing; and monitoring and measuring intervention implementation and

receipt. Intervention fidelity is "the extent to which an intervention's core components have been implemented as planned".[196,p.377] Two interventionists will be trained and certified by Dr. Norweg to implement CALM Breathing. A 12-hour, standardized training program will be developed consisting of biofeedback demonstrations, case studies, and a mock visit (7 hours); manual assessment techniques (1 hour); and dyspnea, anxiety, behavior change, and MI principles (4 hours).[197,83] Clinicians will implement CALM Breathing. For certification, Dr. Norweg will review recordings and written notes of the first three sessions of CALM Breathing and provide detailed feedback.[198] A random selection of 20% of audio-recorded CALM Breathing intervention sessions and written notes (drawn from different therapy phases)[198] will be audited by Dr. Norweg and discussed during regular supervision meetings to improve interventionists' competence and prevent intervention drift. A fidelity checklist will be used with core CALM Breathing components included. The checklist will use a 0–2 scoring scale and include three domains: session structure, session content, and session tailoring (adapted from another fidelity checklist[199]). For coaching, the Motivational Interviewing Treatment Integrity Scale (MITI-4) will be used, which is well validated and includes four global ratings–Cultivating Change Talk, Softening Sustain Talk, Partnership, and Empathy, with a 1–5 scale.[200-202] CALM Breathing attendance will be tracked closely by the RA. We implemented fidelity monitoring with regular supervision meetings and MITI-4 in our prior CART study.

D.3.3.3 Wait-List Control Group (Study Phase I). After referral to CUIMC's PR program, participants randomized to the Wait-List control group will be put on a PR wait list (usual care).

Table 3. CALM Breathing Sessions.

Session	Session Plan	Min
1	• Introduce CALM Breathing; combine initial interview with capnography assessment; manually evaluate respiratory muscle function and assess for lower ribcage paradox (in supine and sitting). • Introduce mind–body connection; educate about role of CO_2; discuss link between the breath and emotions. Educate about anxiety, and the cycle of breathing and panic, and related physiology. Discuss overall goals, homework, and target goals; train in RR device and exercise log use.	40 20
2–8	• Review homework exercise log and recorded RR data; problem-solve barriers. • Implement tailored CALM Breathing exercises (at rest and with low-moderate intensity) and MI. • Collaboratively set target behavior goals and discuss home-based breathing exercises. Borg dyspnea score: max. 4.[77]	10 40 10

D.3.3.4 PR Intervention (Standard Care Phase II). CUIMC's PR program will be delivered as part of care as usual (**Table 4**). A wait of approximately 6 weeks for PR is typical at New-York Presbyterian / CUIMC

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Table 4. Comparison of Interventions.

	Traditional outpatient PR (rolling admission)	**CALM Breathing**
Components	Group exercise training (ET) combined with PLB training.[77,203]	Individual interoception-based breathing therapy with capnography[17,72,77] (non-exercise training[204]).
Home Program	Unmonitored walking exercise 1–2 days/week; no biofeedback monitoring.	Monitored home-based breathing exercises; RR biofeedback; goal setting; exercise logging.
Coaching	Traditional monitoring and verbal cueing.	Motivational interviewing.
Personnel	PT	PT, EP, occupational therapist, or nurse.
Frequency	1-hour sessions, twice per week for 10 weeks.	1-hour sessions, twice per week for 4 weeks.
Exercises	• ET of muscles of ambulation with exercise equipment, such as treadmill or NuStep (30-min), plus 15-min strengthening exercises; O_2 supplementation. No breathing biofeedback. • PLB instruction only during exercise training.	• 10 core breathing exercises with $ETCO_2$ biofeedback in recovery postures at rest and with body movement (gentle stretches and, in later sessions, brief low-moderate intensity PA). • Breathing biofeedback ($ETCO_2$, RR, airflow pattern).
Education	• Verbal and written information.	• Education on anxiety; COPD Patient Guide.[205]

Note: EP = exercise physiologist. O_2 = oxygen. PLB = pursed lips breathing. PT = physical therapist. RR =respiratory rate.

D.3.4 Study Assessments and Rationale. Study outcome assessments will be implemented at baseline, 4 weeks (±2 weeks), and at a 3-month follow-up (±2 weeks). Baseline characteristics will include demographics, social history, smoking status, hospitalizations in the last 12 months, medications and supplemental oxygen use, BMI, mMRC,[12] living situation, depression[206], cognitive deficits,[207] and literacy.[208] All participants will be administered the Mini-International Neuropsychiatric Interview (MINI)[209] by a psychologist to diagnose

psychiatric disorders (anxiety, depression, bipolar disorder, and psychosis). This psychological assessment (not part of standard care) is important to ensure patient eligibility, reduce study risk, and assist with psychological management of participants. All clinical outcome measures are well validated and sensitive to change in COPD or older adults. Medication dosage, intervention doses, and adverse events will be monitored.

D.3.4.1 Outcome Measures.

Feasibility (Aim 1): 1) number of participants recruited within 12 months and reasons for excluding patients; 2) drop-out rate and number of participants lost to follow-up; 3) CALM Breathing treatment session attendance rate and homework adherence; 4) fidelity of CALM Breathing implementation; and (5) facilitation of efficient transition to PR (Phase II). [See Study Record and Statistical Design Plan for more information.][210]

Acceptability (Aim 2): The acceptability of CALM Breathing will be evaluated based on mixed methods data collected from CALM Breathing attendance, drop-out rate, and satisfaction ratings, and from semi-structured interviews.[181,211] Overall satisfaction of CALM Breathing and homework breathing exercises will be evaluated using stand-alone single items from FACIT treatment satisfaction instrument.[211] To assess themes related to satisfaction and addressable challenges, we will conduct 20–30–min semi-structured, in-depth interviews using open-ended questions, either in person or by phone, post-CALM Breathing at 4-weeks and at 3-month follow-up.[177,212,213] Open-ended questions provide an opportunity for greater understanding of acceptability, satisfaction, and addressable contextual challenges of an intervention, that cannot be elicited from closed-ended items alone.[214] Participants will be asked a series of open-ended questions developed from our previous qualitative research.[177] To promote honest answers, as much as possible, interviewer will be blinded to patient social status. Those who dropout will also be interviewed and asked about their experiences with the intervention and reasons for dropping out. The interviewer (research assistant, RA) will receive intensive training from Dr. Raveis and Dr. Norweg prior to conducting open-ended interviews. Dr. Raveis will review the transcripts of initial interviews, critique them, and provide feedback before additional interviews are conducted. Throughout the data collection, Dr. Raveis will monitor the data quality by randomly reviewing selected subset of interview transcripts, to assess that the interviewer is continuing to maintain neutrality, facilitating spontaneous flow of material with non-directive and unstructured questions, and using appropriate transitions to move the discussion from one topic to another, while eliciting range, depth and personal context in the interview. Interviews will be audio-recorded and transcribed by the RA. Coders will be separate from the interviewer; and will receive intensive training and supervision from Dr. Raveis. Coders will use coded transcripts. Coded transcripts will be analyzed with Dedoose software.[215] [See SDP for more details on qualitative analyses.]

Secondary Outcome Measures. *Clinical*: Dyspnea (Chronic Respiratory Disease Questionnaire, CRQ, dyspnea, DMQ-CAT, and modified Borg scale),[22,216,217] anxiety (GAD-7 and Perceived Stress Scale),[218,219] 6MWD,[217] PA,[220] $ETCO_2$ and RR, QOL[221,222], and lung function[223], and quality of life (PROMIS SF V20 Social Roles, V10 Fatigue, V10 Sleep Disturbance, V20 Physical Function). PR Utilization/Engagement: We will measure PR uptake, treatment initiation, attrition rate, and patient activation (using the unidimensional 13-item Patient Activation Measure[224,225]), and acceptability of the Massimo Pulse Oximeter (using the "System Usability Scale)".

Mediating (Process) Outcomes: Interoceptive awareness (MAIA scale),[161,226] AS (ASI-16),[227,186] dyspnea self-efficacy,[22] nasal symptoms (SNOT-20),[228] objective sleep (Actigraphy, Sleep Diary and Nonin Wrist Ox2) and depression (PHQ-9). [206,229] [See Study Record and SDP.]

D.3.5 Statistical Considerations: Feasibility and Acceptability Success Benchmarks (Aims 1 and 2).

Benchmarks were guided by our prior CART study and other studies.[200,230]

D.3.5.1 Primary Outcome: Feasibility. We will calculate % and means to determine whether the following success criteria are met; **Table 5**.[32]

Table 5. Feasibility Success Criteria.	
1.	40 participants are recruited within 12 months (±3 months).
2.	≥75% participant retention at 4-week (±2 week) evaluation and 3-month follow-up.
3.	CALM Breathing session attendance is ≥70%.
4.	CALM Breathing homework exercise adherence is ≥70% for (5 days/week) using RR device data or exercise log.
5.	A mean of 1 is achieved on CALM Breathing fidelity checklist items and mean of 4 on MITI-4 scale.

6.	PR intake assessment is scheduled for week 6–10 for ≥75% of all participants.

D.3.5.2 Primary Outcome: Acceptability. Acceptability *a priori* success benchmarks are: (1) ≥70% CALM Breathing attendance; (2) CALM Breathing drop-out rate is ≤10–15%; and (3) mean of ≥2 "good" satisfaction rating for CALM Breathing treatment overall (item 8 of FACIT; 0–4 scale).[211] [See SDP and Study Record].

D.3.5.3 Secondary Outcomes. Hypothesis testing will not be conducted for secondary outcomes.

D.3.6 Challenges and Alternative Strategies.

We have carefully examined the number of potential participants and are confident we have the pool of participants needed. Strategies to ensure participant recruitment efficiency and retention have been carefully considered.[231,232-234] We considered reducing the number of secondary outcomes in our assessment battery but decided it was important to include multiple outcomes for improved rigor.[235] To maintain assessor blinding, the RA (not blinded) will evaluate treatment session and homework adherence outcomes that could reveal intervention group allocation.[192] We will use an iterative process to maximize the likelihood of meeting success benchmarks.[236] We considered offering CO_2 biofeedback for home exercises to increase the dose. However, to keep the home program feasible and easy to carry out, we decided to have participants focus on only one biomarker (RR). If the study findings do not support future clinical trials of CALM Breathing, sub-group analyses will be conducted to illuminate the results (e.g., analyzing feasibility by gender or anxiety level). Revisions might then be made to the study eligibility criteria and/or CALM Breathing intervention.

D.4 Study Milestones.

Table 6. R34 MILESTONES (Months 0-24)	Year 1				Year 2				
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Aim 1: Evaluate Feasibility of CALM Breathing									
Start-up: Develop recruitment materials (flyer) and intervention manual; Obtain IRB approval; Develop data management and tracking systems; Develop manual of procedures (MOP); Hire and train study staff; Establish data safety monitoring board.	X	X							
Ensure timely execution of agreements	X	X	X	X	X	X	X	X	
Screen and recruit 40 study participants				4	12	12	12		40
Complete enrollment/baseline data collection				4	12	12	12		40
Complete 4-week post-intervention data collection				4	12	12	12		40
Complete 3-month follow-up data collection					4	12	12	12	40
Collect primary and secondary endpoints and adverse events				X	X	X	X	X	
Complete treatment fidelity audits				X	X	X	X		
Complete data safety/monitoring reports		X		X		X		X	
Complete quality control	X	X	X	X	X	X	X	X	
Obtain annual IRB renewal					X			X	
Conduct statistical analyses				X	X	X	X	X	
Submit manuscripts to peer-reviewed journals for dissemination				X	X	X	X	X	
Disseminate findings at conferences					X	X	X	X	
Aim 2: *Evaluate Acceptability of CALM Breathing*									
Analyze CALM Breathing acceptability				X	X	X	X	X	
Disseminate findings at conferences and through publications					X	X	X	X	
Submit study results to ClinicalTrials.gov								X	

D.5 Study Organization and Research Team.

At Columbia University Irving Medical Center, CALM Breathing will be led by **Dr. Anna Norweg**. Dr. Norweg is an expert in breathing techniques, capnography biofeedback, MI, and behavioral change in COPD. The research team is highly qualified and experienced. At Columbia University, collaborators represent leaders and experts in the fields of rehabilitation (**Dr. Stein**), exercise physiology, COPD, and pulmonary clinical trials (**Dr. DiMango, Dr. Murphy, and Dr. Buchholz)** and neuropsychology (**Dr. Pavol**).

NYU is a subcontract site (IRB study #: i20-00751_CR1). To complete our study team, we will collaborate with **Dr. Naomi Simon** (who will continue to serve as multiple-PI), **Dr. Oh** (a specialist in biostatistics), and **Dr. Raveis** (a specialist in qualitative analyses). 3-month re-evaluations of 4 already randomized participants occurred at NYU. No new participant recruitment or retention procedures will occur at NYU. The procedures that will occur at NYU include: (1) Dr. Simon will guide and oversee the implementation of the study remotely from NYU via email and Zoom meetings; (2) Dr. Raveis will assist with training the RA in qualitative study procedures and supervise the coding of transcribed interview data remotely via email and Zoom meetings –

transcripts will not include any identifiers; and (3) Dr. Oh will conduct quantitative data analyses for the study using a coded dataset and work closely with the PIs via Zoom and email.

D.6 Future, Large-Scale Clinical Trial.

With achievement of clearly established success benchmarks and milestones, we will demonstrate readiness to proceed to implement a large, adequately powered Phase III efficacy trial.[237] The primary hypotheses for the future clinical trial will be that CRQ-dyspnea and 6MWD mean differences will be greater (≥ minimal important differences, MID) in CALM Breathing compared with waitlist control group at 4 weeks. Two primary outcomes of symptom impact are indicated, which have been rated by stakeholders as important.[238] Our Phase III study will have a 12-month follow-up period. We will also explore mechanisms of CALM Breathing.

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