NYU School of Medicine
NYU LANGONE MEDICAL CENTER

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CAPNOMETRY-ASSISTED TRAINING FOR COPD TO SLOW THE BREATH (CATCH) TRIAL

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), any other applicable US government research regulations, and institutional research policies and procedures. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

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List of Abbreviations

6MWT	Six Minute Walk Test
AE	Adverse Event/Adverse Experience
Borg RPE	Borg Rate of Perceived Exertion
CART	Capnometry-Assisted Respiratory Therapy
CATCH	Capnometry-Assisted Training for COPD to slow the BreatH
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CPET	Cardiopulmonary Exercise Testing
CRF	Case Report Form
CRQ	Chronic Respiratory Disease Questionnaire
DHHS	Department of Health and Human Services
EHR	Electronic Health Record
ETCO2	End-tidal Carbon Dioxide
FFR	Federal Financial Report
FWA	Federal-wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IRB	Institutional Review Board
MBT	Mindful-Based Therapy
MOP	Manual of Procedures
MVPA	Moderate or Vigorous Physical Activity (MVPA)
N	Number (typically refers to participants)
NIDILRR	National Institute on Disability, Independent Living, and Rehabilitation Research
OHRP	Office for Human Research Protections
OHSR	Office of Human Subjects Research
PD	Panic Disorder
PHI	Protected Health Information
PI	Principal Investigator
PLB	Pursed-lips Breathing
PR	Pulmonary Rehabilitation

QA	Quality Assurance
QC	Quality Control
RR	Respiratory Rate
SAE	Serious Adverse Event/Serious Adverse Experience
SEBQ	Self-Evaluation of Breathing Questionnaire (SEBQ)
SF	Short Form
SGRQ	St. George's Respiratory Questionnaire
SOP	Standard Operating Procedure
US	United States

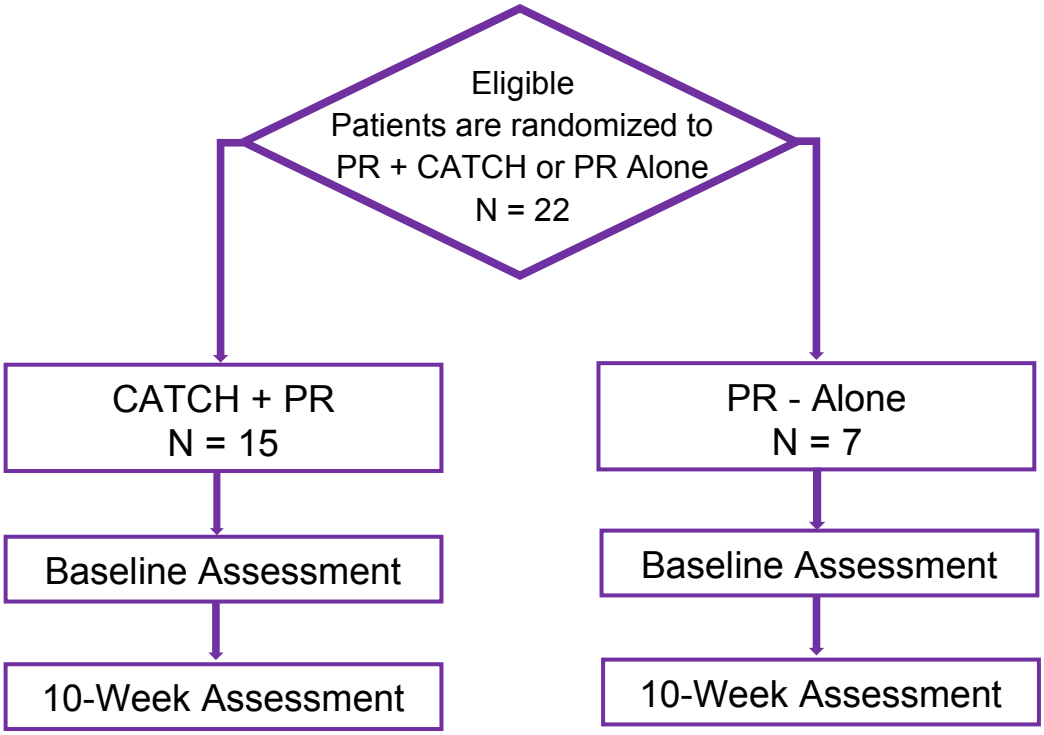
Protocol Summary

Title	**CAPNOMETRY-ASSISTED TRAINING FOR COPD TO SLOW THE BREATH (CATCH) TRIAL**
Phase	Phase 2.
Methodology	Randomized controlled trial study.
Study Duration	10 weeks.
Duration of behavioral intervention	10 weeks.
Population	Adults with chronic obstructive pulmonary disease (COPD) over 40 years of age; medically cleared to participate in Rusk Rehabilitation's pulmonary rehabilitation program; English speaking.
Study Sites	Rusk Rehabilitation (ACC-16).
Number of participants	40 participants are expected to be enrolled to produce 26 evaluable participants at 1 site.
Description of Study Intervention/Procedure	CATCH is a behavioral intervention that aims to promote optimal, selfregulated, mindful breathing. A portable capnometer is used in-session to provide continuous visual feedback of RR, $ETCO_2$, and breathing pattern. The tailored CATCH intervention will emphasize a slow, quiet, regular, nasal breathing pattern, as well as pursed lips breathing (PLB). CATCH is once weekly for 6 weeks, for a total of 6 sessions; each session is approximately 60 minutes long. The principal investigator will implement the CATCH intervention. Patients will use the Address Stress app on a smartphone or computer tablet as part of their home breathing exercises.
Reference Therapy	Pulmonary Rehabilitation Alone.
Key Procedures	Patient reported outcomes; 6MWT, CPET.

Drug/Device Template Version: 13 JUN 2016

Schematic of Study Design

Figure 1. CATCH Study Design.



1 Introduction, Background Information and Scientific Rationale

1.1 Background Information and Relevant Literature

About 14% of Americans have Chronic obstructive pulmonary disease (COPD) and it is the third leading cause of death in both the U.S.A. and the world.[1,2] The prevalence and burden of COPD on patients, their families, and society is high and will only continue to grow with the aging of the population.[3-6] COPD is characterized by progressively declining ventilatory function,[7,8] increased dyspnea, chronic inflammation, and increased sympathetic nerve activity[9]. Dyspnea (labored, uncomfortable breathing[10]) is the most prevalent, emotionally distressing, and disabling symptom of COPD; it limits physical activity, exercise tolerance, and quality of life and is associated with increased mortality.[11-13] It consists of several qualitatively distinct sensations, such as “air hunger“, increased “urge to breathe“, “chest tightness“, and feeling “starved for air“.[14] It is the main reason why patients with COPD seek medical and rehabilitation services. The insula, a sensorimotor area of the limbic system in the brain, activated during inspiration, plays an integral role in dyspnea perception by acting as an alarm center.[14-16] The high prevalence of comorbid anxiety disorders (up to approximately 40%) and panic disorder (up to 10 times higher than in the general population) in COPD[17,18,19] increases the severity of dyspnea and related disability,[20-22] and increases the risk for acute COPD exacerbations (ACOPDE) and associated hospilizations[23].

In COPD, dyspnea is associated with a vicious cycle of physical activity (PA) decline and deconditioning, leading to increased ventilatory requirements of PA, further impairement of physical function and quality of life (QOL), and social isolation; [24,25] creating a disability spiral[26]. Dyspnea and associated anxiety also contribute to a vicious circle of abnormally rapid breathing (tachypnea), air trapping, and lung hyperinflation both at rest and with physical exertion (dynamic hyperinflation), leading to further dyspnea and PA limitations and impaired QOL (see Appendix A for the COPD model underlying this study).[24] Anxiety and increased sympathetic nervous system arousal can impair the function of the diaphragm, the most important muscle of breathing; causing it to shorten, lower, and flatten (inspiratory position) and become hypertonic; limiting its functions such as venous and lymphatic return and optimal posture.[27,28]

A rapid, upper thoracic breathing pattern allows insufficient time to empty the lungs;[24,29,30] it increases the work of breathing and dyspnea, and contributes to retention of CO_2.[8] Rapid breathing and hyperinflation can worsen airway secretions and bronchoconstriction[8] and cause the loss of elastic recoil.[24] Rapid breathing due to exercise intolerance and emotional stress can lead to neuromechanical uncoupling (failure of the ventilatory pump and CO_2 retention)[29,31] and associated panic, fear, and emergency medical care.[29]

Altered breathing behavior also leads to neuroplasticity and a profound network disorganization between the sensorimotor cortex and brainstem in COPD.[15] Sensory neural coding of breathing patterns (muscle mechanics, CO2, pressure, volume, and airflow) are gated into the cerebral cortex for conscious cognitive and emotional processing based on individual threshold levels.[32]

Benefits of Breathing Training

Slow breathing training is an important rehabilitation and self-management intervention to systematically alleviate dyspnea, prevent or manage dyspnea crisis[33], manage anxiety and panic in COPD,[34-36] and improve sympathovagal imbalance[9]. Breathing techniques designed to mitigate the ventilatory consequences of COPD include pursed lips breathing (PLB), pranayama yoga breathing, diaphragmatic breathing (DB), Buteyko breathing technique,[37-39] mindful breathing[40-42], and device-guided breathing with biofeedback. Given that respiratory muscles are under both brainstem and skeletal muscle control, patients can learn to control their respiratory rate (RR) to help manage their symptoms.[8,9,39,43] In a systematic review of sixteen breathing studies of breathing exercises of four to 15 weeks for COPD, the breathing exercises were found to improve exercise capacity compared to no intervention.[44]

However, the effects of breathing training on dyspnea and functional status for COPD have been equivocal, possibly hampered by the wide variation of breathing exercises and protocols studied.[45,46] Therefore, more evidence of the effectiveness of breathing training is needed to guide clinical practice.[10,11,47] The quality of most studies of breathing exercises were reduced by the lack of assessor blinding.[44]

Study Importance and Innovation

The rationale supporting the importance and innovation of this trial study is that: (1) it uses a novel therapeutic approach; both a novel capnometer computer system and a newly developed smartphone breathing app (new to both pulmonary rehabilitation and COPD) to promote improved learning and adherence to home breathing exercises; (2) it includes anxiety and physiological outcomes omitted from

most previous COPD clinical trials of breathing training to help explain the mechanisms of treatment effects; (3) it includes allocation concealment and assessor blinding of exercise stress testing to address limitations of previous studies; and (4) it includes an expanded theoretical base of breathing training effects to potentially improve dyspnea management outcomes. This breathing study is important because it measures physiological, performance-based, and patient-reported outcomes (including anxiety) to more comprehensively study the benefits of breathing training in COPD.

The proposed study translates new theory from basic science and brain imaging studies to promote improved dyspnea management for COPD. The novel breathing training protocol is designed to both modulate perception of dyspnea at the CNS level as well as improve neuromechanical coupling (matching between respiratory effort and the mechanical response of the respiratory system). Breathing training is theorized to improve neural connections, that is, decrease activity of the amydala in the limbic system and improve prefrontal cortical regulation, as well as decrease arousal of the sympathetic nervous system.[15,32,41,48,49]

Inadequate attention has been given to the potential benefits of breathing exercises in improving pulmonary rehabilitation outcomes, including managing dyspnea and anxiety, enhancing exercise training, and improving quality of life. Previous pulmonary rehabilitation studies have not adequately focused on anxiety as an important outcome of breathing training in COPD. These trials have focused inadequate attention on respiratory training and objective measurement of respiratory physiology as important goals of exercise training in COPD.[50] This timely study is needed to advance our knowledge of the effects of breathing training with respiratory rate (RR) and end-tidal carbon dioxide ($ETCO_2$) – CO_2 at the end of an expiration - biofeedback combined with pulmonary rehabilitation, to build needed evidence and to identify whether improvements in breathing pattern translate to health benefits in COPD.[51,52,34]

Also, very little is known about the benefit and effects of mindful breathing exercises for COPD management. Mindfulness as a therapeutic approach is novel to rehabilitation and COPD management.[41,53-56] Very few clinical trial studies have been published on the effectiveness of mindful breathing exercises effectiveness and most studies were preliminary. One pilot RCT[54] showed that patients with COPD in an 8-week mindfulness group (who attended ≥ 6 sessions) had improved emotional function following mindfulness exercises compared to a wait-list control. Another pilot study showed good patient acceptability of an adapted 8-week mindfulness-based stress reduction (MBSR) program for COPD.[53] However, another RCT found low acceptability based on retention rates and no differences in dyspnea, functional status, or quality of life outcomes between a mindfulness-based breathing therapy group and a support group of veterans with moderate to severe COPD (n = 86).[57]

Capnometry-assisted respiratory training (CART) is a new, innovative approach for COPD. This is the first study to investigate the therapeutic potential of CART for adults with COPD in pulmonary rehabilitation. While CART improves asthma and panic disorder (PD) (both common comorbidities of COPD), its efficacy has not yet been investigated in adults with COPD. CART (with both RR and $ETCO_2$ biofeedback), increased $ETCO_2$, reduced respiratory impedance, decreased distress, and improved asthma symptoms at follow-up in adults with asthma compared to a comparison group of slow breathing training with RR feedback alone (n = 120).[39] In another RCT with patients with PD, a CART group showed improved PD symptoms, reduced activity avoidance and anxiety, and less disability compared with a waitlist control group (n = 37).[58]

1.2 Rationale

Hypotheses

1. Participants' change scores in the CATCH group will be significantly greater compared with those of the control group for the primary outcomes of peak HR, exercise duration, 6MWD, DMQ-CAT dyspnea, SGRQ quality of life, and exercise adherence (> % of sessions or < time to complete).
2. Ve will decrease (indicating decreased RR and improved breathing efficiency) and peak VO_2 will increase in the CATCH group (indicating improved pulmonary function) and changes will be significantly greater compared with the control group.
3. Participants' change scores in the CATCH group will be significantly greater compared with the control group for the secondary outcomes of RR, $ETCO_2$, Borg RPE, anxiety, CRQMastery, SEBQ, PROMIS-36, and Physical Activity.

Justification for hypotheses

Our hypotheses for the primary outcomes of Ve, peak VO_2, and exercise time are consistent with findings and trends from a previous COPD trial of device-guided respiratory training combined with PR.[43] By allowing more time to effectively empty the lungs during prolonged exhalation, a slow breathing pattern can improve breathing efficiency, reduce lung hyperinflation, improve diaphragmatic mobility and chest wall mechanics, resulting in less dyspnea, improved exercise capacity and tolerance, eucapnia (optimal carbon dioxide pressure), and the prevention of neuromechanical uncoupling.[8,59,24,29] In a meta-analysis of four studies of mostly severe COPD, slow breathing exercises (PLB, DB, and 3-months of yoga) improved 6MWD by 35 - 50 meters, which was beyond the minimal important difference[47].[44]

Device-guided slow breathing training when combined with PR using a pneumotachometer interfaced with a computer display of respiratory and goal feedback reduced dynamic hyperinflation and improved breathing pattern (increased expiratory time) in COPD compared with both PR-alone and breathing-training-alone groups.[43] Device-guided breathing instruction in COPD also improved self-efficacy (breathing confidence) compared with a traditional method of teaching pursed lips breathing (PLB).[60]

PLB training (quiet breathing in through the nose and out through pursed lips with expiration twice as long as inspiration) decreased respiratory rate in adults with COPD,[61,62] alleviated long-term dyspnea compared with control groups[46], and improved oxygen saturation[62]. By improving expiration, PLB reduced dynamic hyperinflation during daily activities and submaximal exercise in some patients with COPD.[62,63] Similarly, Visser[64], found that PLB decreased hyperinflation and oxygen saturation, and decreased $ETCO_2$, and RR in patients with severe COPD. PLB has been endorsed in evidence-based practice guidelines to relieve dyspnea in advanced COPD.[11,65] A systematic review of PLB for stable COPD found that PLB (1) reduced RR and increased tidal volume both at rest and during sub-maximal exercise, and (2) improved oxygen saturation.[66]

Slow-breathing exercises, such as PLB, are often provided as part of a multicomponent rehabilitation intervention or adjunctive modality to potentially boost the effectiveness of exercise training or behavioral therapy, however more research is needed.[40,67,68] A randomized study found that health coaching (consisting of daily slow breathing exercises, physical exercises, and an emergency plan combined with motivational interviewing) reduced short-term rehospitalizations and improved health-related quality of life in adults with COPD compared with usual care.[69]

Slow, controlled breathing exercises (with prolonged expiration) reduce anxiety and sympathetic nerve activity. For example, slow breathing (6 breaths per minute; 3s inspiration and 7s exhalation) reduced sympathetic nerve activity compared with 15 breaths per minute and spontaneous breathing and improved baroreflex sensitivity in patients with COPD.[9] Similarly, Buteyko-device-guided breathing training using capnometry reduced panic symptoms, panic-related cognitions, and perceived control, and increased PCO_2 to normocapnic levels in adults with panic disorder and agoraphobia.[70]

1.3 Potential Risks & Benefits

1.3.1 Known Potential Risks

The immediate and long-term risks of participation in the study are minimal. Respondents may become emotionally upset by some of the questions since the questions are based on a person's shortness of breath and related anxiety with activity performance. There is also a small risk that the breathing evaluation and capnometry feedback may initially trigger some shortness of breath, discomfort, or nervousness. In our previous research with the DMQ-CAT, no respondent has ever expressed emotional concern or upset about the questions that have been asked. Our research team has been trained in the methods to protect confidentiality and the importance of this protection. The study intervention and outcome evaluations are non-invasive.

The value of the information to be gained outweigh the minimal risks to subjects. Participants in the CATCH intervention group may benefit from biofeedback by learning to optimize their breathing and regulate their emotions to manage their symptoms. Mindfulness breathing exercises may help subjects to better manage their dyspnea and anxiety and improve their functional status and quality of life.

1.3.2 Known Potential Benefits

Evidence for Breathing Training.

Slow breathing training is a self-management, behavioral intervention to systematically alleviate dyspnea, prevent or manage dyspnea crisis[33], manage anxiety and panic in COPD,[34-36] and improve sympathovagal imbalance[9]. Given that respiratory muscles are under both brainstem and skeletal muscle control, patients can learn to control their RR to help manage their symptoms.[8,9,39,43] In a systematic review of sixteen breathing studies of breathing exercises of four to 15 weeks for COPD, the breathing exercises were found to improve exercise capacity compared to no intervention.[44]

PLB training (quiet breathing in through the nose and out through pursed lips with expiration twice as long as inspiration) decreased respiratory rate in adults with COPD,[61,62] alleviated long-term dyspnea compared with control groups[46], and improved oxygen saturation.[62] PLB has been endorsed in evidencebased practice guidelines to relieve dyspnea in advanced COPD.[11,65]

Slow, controlled breathing exercises (with prolonged expiration) reduced anxiety and sympathetic nerve activity. In particular, slow breathing (6 breaths per minute; 3s inspiration and 7s exhalation) reduced sympathetic nerve activity compared with 15 breaths per minute and spontaneous breathing, and improved baroreflex sensitivity in patients with COPD.[9] Similarly, Buteyko-device-guided breathing training using capnometry reduced panic symptoms and panic-related cognitions, improved perceived control, and increased PCO_2 to normocapnic levels in adults with panic disorder and agoraphobia.[70]

Device-guided breathing instruction in COPD improved self-efficacy (breathing confidence) compared with a traditional method of teaching PLB.[60] Capnometry-assisted respiratory therapy (CART), with both RR and $ETCO_2$ biofeedback, increased $ETCO_2$, reduced respiratory impedance, decreased distress, and improved asthma symptoms at follow-up in adults with asthma compared to a comparison group of slow breathing training with RR feedback alone (n = 120).[39] In another RCT with patients with panic disorder, a CART group showed reduced activity avoidance and anxiety, and decreased disability compared with a wait-list control group (n = 37).[58]

Evidence for Mindful-Based Therapy.

In a neuroimaging study, mindful attention to breath was shown to down-regulate amygdala activation (associated with fear processing) and improve amygdala-prefrontal integration in the brain as the mechanisms for emotion regulation.[41] A recent meta-analysis of 10 studies found a large mean effect size (Hedge's g = 0.89; 95% CI 71 to 1.08) for MBT post-intervention on anxiety compared to a waitlist control; the largest effect size was found for improving anxiety compared to other physical or medical conditions; MBT did not differ from pharmacological treatments.[71] Another meta-analysis of 47 trials found MBT had a moderate effect on improving anxiety (ES = 0.38, CI 0.12 to 0.64) compared to attention-control conditions.[72] Interestingly, for patients diagnosed with anxiety (aged 18 – 65), a third meta-analysis found MBT to have large effect sizes (Hedge's g = 0.97 and 0.95) for improving anxiety and mood symptoms respectively; with effects maintained at follow-up.[73] Nonetheless, the clinical trial studies of mindfulness have small samples sizes, poor control, and limited end points.[56]

Eight, 60-minute MBT weekly sessions were found to have good acceptability and retention rates (84%) in an RCT (n = 47) for adults with COPD.[54] A significant improvement was found in the mindfulness group for emotional function (for those who attended ≥ 6 classes) compared with a wait-list control. Further, a 12-week yoga intervention for older adults with COPD (n = 29) was found to be safe, enjoyable, and feasible and to improve dyspnea-related distress, functional performance, and walk distance compared to a usual care control group.[74] In summary, little is known about the benefit and effects of mindful breathing exercises for COPD management since mindfulness as a therapeutic approach is novel to rehabilitation and self-management.[41,53-56]

2 Objectives and Purpose

2.1 Primary Objectives

Objective 1: Test the feasibility of implementing an RCT of capnometry-assisted training in COPD to slow the breath (CATCH) intervention combined with pulmonary rehabilitation (PR) based on retention of participants with COPD and estimates of short-term treatment effects (at 10 weeks).

Objective 2: Evaluate the acceptability of the CATCH intervention as perceived by participants based on qualitative interviews, CATCH attendance, and adherence to home breathing exercises.

2a. Modify the CATCH intervention based on feedback from participants.

2.2 Secondary Objectives

1a. Compare a CATCH intervention group (CATCH + PR, n = 15) with a control group (PR alone, n = 7) on the *outcomes* of exercise capacity [peak heart rate (HR), exercise duration, ventilation (Ve), and peak oxygen consumption (VO_2)]; DMQ-CAT dyspnea; 6-minute walk test distance (6MWD); COPDspecific quality of life (St. George's Respiratory Questionnaire); and exercise adherence.

1b. Compare score differences of a 6-week CATCH intervention combined with PR (CATCH + PR, n = 15) with those of a control group (PR alone, n = 7) on the *outcomes* of $ETCO_2$, RR, Borg Rate of Perceived Exertion (RPE), anxiety, CRQ Mastery, SEBQ, physical activity (PA), and PROMIS-36 quality of life (physical function, anxiety, depression, satisfaction with participation in social roles, sleep disturbance, and fatigue); N = 22.

3 Study Design and Endpoints

3.1 Description of Study Design

We will use a prospective, RCT study design to compare primary and secondary outcomes of the CATCH group (n = 15) with a control group (n = 7). This study uses a RCT design to control for confounders, to minimize imbalances in characteristics between the groups at baseline, and to demonstrate feasibility of carrying out a RCT research protocol in preparation for a larger study.[75,76]

Random allocations to treatment group will be concealed to avoid bias.[75] The clinician who will administer the exercise stress tests pre- and post-treatment will be blinded to the treatment group assignment. We will also use a qualitative (descriptive, exploratory) study design to evaluate patient acceptability of CATCH and analyze themes of 15 semi-structured interviews.

3.2 Study Endpoints

3.2.1 Primary Study Endpoints

The primary endpoints are feasibility (retention of participants with COPD) and acceptability (qualitative data, CATCH attendance rate, and % adherence to home breathing exercises) of the CATCH intervention.

3.2.2 Secondary Study Endpoints

The secondary endpoints are estimates of short-term treatment effects (at 10 weeks), which include: exercise capacity; DMQ-CAT dyspnea; 6MWD; SGRQ quality of life; exercise adherence; $ETCO_2$; RR; Borg Rate of Perceived Exertion (RPE); anxiety; CRQ Mastery; SEBQ dysfunctional breathing symptoms, moderate or vigorous physical activity (MVPA); and PROMIS-36 quality of life (physical function, anxiety, depression, satisfaction with participation in social roles, sleep disturbance, and fatigue).

4 Study Enrollment and Withdrawal

4.1 Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

(1) is over 40 years of age; (2) has COPD documented in their electronic medical record, as defined by FEV_1/FVC of < 0.70 on pulmonary function testing (spirometry), or as shown on a chest CT; (3) can maintain oxygen saturation (SaO2) ≥ 90% on room air at rest; (4) is medically cleared to participate in NYULMC's outpatient pulmonary rehabilitation program; and (5) is English speaking. Pregnant patients will not be enrolled in the study.

4.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

(1) requires 24-hour supplemental oxygen; (2) has cognitive impairment as measured by ≤23/30 on the Mini Mental State Examination (MMSE)[77]; (3) is actively being treated for lung cancer (E.g. with chemotherapy or upcoming surgery); (4) has morbid obesity (BMI > 40); (5) is currently smoking; and (6) has unstable cardiac disease defined by a history of a myocardial infarction in the past 3 months.

4.3 Vulnerable Subjects

Vulnerable subjects will not be recruited in this study.

4.4 Strategies for Recruitment and Retention

Active recruitment efforts to ensure the inclusion of appropriate numbers of patients from each sex, racial, and ethnic group will include: 1) a paper recruitment flyer distributed to potential subjects by the study team within Rusk Rehabilitation; 2) recruitment after pulmonary rehabilitation consultation by Dr. Whiteson; and 3) use of an automated EHR alert system.

To increase retention of subjects, the research assistant will send visit reminders via the subject's preferred method of contact (phone, text, or email) 24 hours prior to all scheduled visits. Participants will also receive compensation for their time which will be pro-rated should they not complete the entire study. If retention rates drop below acceptable levels, the study team will engage CTSI Recruitment and Retention Unit (CTSI RRU) for consultation on engagement strategies and methods to improve retention.

4.4.1 Use of DataCore/Epic Information for Recruitment Purposes

This study will utilize EPIC to alert the study team of potentially eligible subjects. We will use an EHR report system. The pulmonary rehabilitation intake evaluation schedule in EPIC will also be used to alert the study team of potential participants.

Any recruitment information sent by email will utilize Send Safe email.

Once potential subjects have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate as follow:

- TP has been notified that the study team will contact potential subjects directly, by letter, phone, and/or email.

Once contact is made, approved recruitment language using a script will be used to communicate the reason they are being contacted and subjects will be asked if they are interested in participating in this specific study. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

4.5 Duration of Study Participation

The duration of study participation is approximately 10 - 12 weeks including: 1 – 2 weeks for screening and recruitment, and a 10-week intervention phase. There is no follow-up period.

4.6 Total Number of Participants and Sites

Recruitment will end when approximately 40 participants are enrolled at Rusk Rehabilitation for this single-site study. It is expected that approximately 40 participants will be enrolled to produce 22 evaluable participants due to drop-outs.

4.7 Participant Withdrawal or Termination

4.7.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE) or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Participant requires hospitalization for an exacerbation and is unable to resume their PR program within 2 weeks following an exacerbation.

5 Behavioral/Social Intervention

5.1 Study Behavioral or Social Intervention(s) Description

Capnometry-Assisted Training for COPD to Slow the Breath (CATCH) Intervention.

The CATCH intervention was developed to promote a slower, more regular, efficient breathing pattern and optimum breathing amplitude and mechanics, including improved respiratory muscle function (especially of the diaphragm), reduced dyspnea, improved autonomic nervous system regulation, and neural modulation (creating new neural connections).[15,28,78] A portable capnometer (CapnoTrainer, Better Physiology, Cheyenne, WY) will be used in-session to provide continuous visual feedback of RR, $ETCO_2$, rhythm, and depth of breathing, and ratio of inspirations to expirations. The CapnoTrainer is not FDA approved. We will be using the CapnoTrainer device under a non-significant risk device determination. Hard copy print outs from each capnometry session will be made and reviewed with patients to discuss progress.

The tailored CATCH intervention will emphasize a slow, quiet, regular, nasal breathing pattern, as well as PLB in faciliatory supine and forward leaning postures.[79] Patients will be educated to regulate the volume of their breathing, use a ratio of 40% inhalation to 60% exhalation (with breath pauses), and approximately 10 – 12 breaths per minute at rest, facilitated by a manual evaluation of respiratory pattern.[27,80,81] Chest and mouth breathing will be discouraged (because they contribute to dyspnea and can trigger bronchoconstriction and airway hyperreactivity), as will breath sounds (such as sighing), deep and rapid breathing (hyperpnea), paradoxical breathing (drawing in of the abdomen during inspiration and expansion during expiration), and forceful, irregular breathing.[82-84] Patients will also be directed to breathe mindfully ("paying attention on purpose, in the present moment, nonjudgmentally"[85, p.91]).[41,48,56] CATCH will be once weekly for 6 weeks, for a total of 6 sessions; each session will be approximately 60 minutes duration. The principal investigator will implement the CATCH intervention.

Some breathing exercises during CATCH sessions will be audio or video recorded or photographed to provide participants with additional instructions to use at home to help them complete guided home breathing exercises. For the at-home training, patients will also use the Address Stress app on a smartphone or computer tablet for tailored paced breathing exercises. The breathing app will provide auditory and visual cues for the paced exercises. Patients will also keep a breathing exercise log of total

daily minutes completed. Patients will also be instructed in upper body stretching exercises to perform daily as part of their home exercises.[86] The Address Stress app collects email address for downloading the app on a personal smartphone or tablet computer. The app transmits adherence data only via email to the study PI. It is not necessary for participants to own a smartphone or tablet computer to use the app since tablet computers will be loaned to participants as needed to access the app.

CATCH will be grounded in social cognitive theory[87] to promote behavior change, improve selfefficacy and outcome expectation, and support the use of interactive technologies to guide and motivate patients. CATCH also applies the hyperventilation model, in which hyperventilation leads to hypocapnia, dyspnea, and panic.[88] Other underlying theoretical models are the neurophysiological model of dyspnea,[31] the model of mindfulness[48], and the neurophysiological theory of functional connectivity in COPD.[15]

Pulmonary Rehabilitation (PR).

Patients in both treatment groups will participate in a 10-week (16 - 20 sessions) comprehensive PR program. As per standard of care, the control group will receive the 10-week PR program with traditional breathing training instruction only (without biofeedback). The PR program comprises two or three exercise training sessions per week implemented by physical therapists (each of 1-hour duration). PR sessions include individualized self-management education.

5.1.1 Procedures for Training Interventionalists and Monitoring Intervention Fidelity

The interventionist for CATCH (Dr. Norweg, PI) is a trained pulmonary rehabilitation professional (an occupational therapist). An intervention manual for CATCH will be developed by the PI to facilitate treatment fidelity. The interventionist will have received at least 20 hours of training in capnometry-assisted respiratory therapy prior to the study. The interventionist will also have taken the basic Mindfulness-Based Stress Reduction (MBSR) course and adopted a personal mindfulness practice for at least 6-months prior to the study. The interventionist's fidelity to the intervention manual will be monitored via regular consultation phone calls with two experienced practitioners in CART and mindfulness respectively.

Supervision of CATCH interventionist to ensure fidelity of motivational interviewing (MI) / brief action planning: Some discussions of CATCH sessions will be audio recorded and transcribed. De-identified typed transcripts of CATCH intervention discussions will be reviewed by an external research consultant and expert in MI to ensure fidelity of intervention and to provide interventionist with supervision.

5.1.2 Assessment of Subject Compliance with Study Intervention

Pulmonary rehabilitation session attendance documented in the EMR will be used to evaluate PR adherence. Adherence to breathing exercises for participants in the CATCH intervention will be evaluated using a paper breathing log. Adherence data will also be available from the AddresStress app.

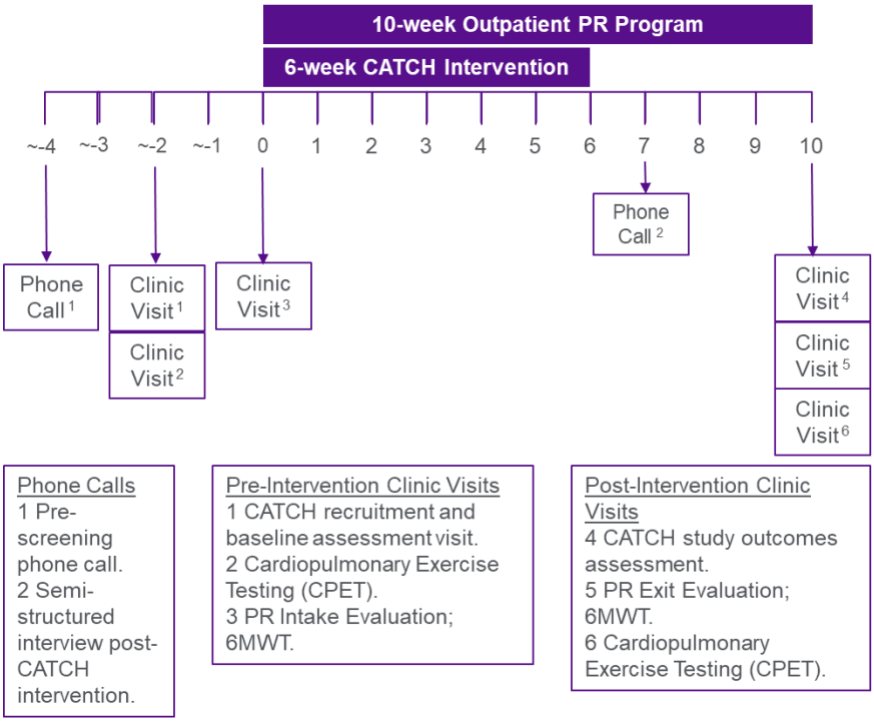
6 Study Procedures and Schedule

6.1 Study Procedures/Evaluations

6.1.1 Study Specific Procedures

See Schedule of Events – Attachment A for description of study specific procedures.

Figure 2. CATCH Scheduling of Tests.



Outcome Measures.

Exercise Capacity: Clinical treadmill stress tests will be used to measure exercise capacity pre- and post-treatment, including: peak VO_2 (ml/kg/min and % predicted based on age), Ve (l/min) at isotime (2-minutes prior to exercise termination at baseline), peak HR, and exercise duration. Exercise stress tests will be administered by a clinician as part of standard care.

Six Minute Walk Test (6MWT). The 6MWT is a standardized, performance-based test to measure exercise tolerance (functional status) using the American Thoracic Society's standardized protocol.[89] Clinicians will administer the 6MWTs as part of standard care.

Dyspnea Management Questionnaire Computer Adaptive Test (DMQ-CAT)[90]. The DMQ-CAT is a COPD-specific functional status measure that captures four dyspnea domains: intensity, anxiety, activity avoidance, and self-efficacy. Higher scores are better. It has been shown to be reliable and valid in rehabilitation and primary care patients.[91,92] The DMQ-CAT uses computer adaptive testing to tailor dyspnea items and administer up to 20 items.

St. George's Respiratory Questionnaire (SGRQ).[93,94] The SGRQ is a widely used quality of life measure for adults with chronic airflow limitation, consisting of three domains: symptoms, activity, and impacts. Lower scores indicate better quality of life. The SGRQ activity domain measures dyspnea and its functional impact. The symptoms and impacts domains measure several respiratory symptoms and psychosocial functioning respectively. Several studies have supported its reliability and validity.[93,95,96] We will use the American version for this study.[94]

Adherence to Exercise Training. Exercise adherence is the % of exercise training sessions completed and the time taken (in weeks) to complete the PR program. Adherence to daily home breathing exercises is the % completed (at least 5 minutes per day for 6 weeks; the goal is 70% adherence).

Respiratory rate (RR) (breaths/minute) and **End-Tidal Carbon Dioxide Tension** ($ETCO_2$ in mmHg). Resting RR and $ETCO_2$ will be measured during 5 minutes of quiet sitting without providing any feedback using capnometry. Nasal cannula and a sampling tube are attached to the capnometer monitor to measure post-exhaled air. Average RR and $ETCO_2$ values will be calculated.

Generalized Anxiety Disorder Scale (GAD-7).[97] The GAD-7 will be used to measure anxiety. A cut point of five or greater will be used to detect anxiety.[98]

Borg Rating of Perceived Exertion (RPE) Scale.[99] The Borg RPE scale is a 15-grade, singleitem rating scale, ranging in score between 6 and 20. Clinicians will administer the Borg RPE Scale with the 6MWT as part of routine pre-treatment and post-treatment evaluations.

Chronic Respiratory Questionnaire-Mastery (CRQ-Mastery).[100,101] The CRQ-Mastery is an obstructive lung disease-specific quality of life measure that includes four items to measure patients feeling of control over their disease. The reliability and validity of the CRQ is well established.[95,102]

Self-Evaluation of Breathing Questionnaire (SEBQ).[103] The SEBQ is a 12-item measure of dysfunctional breathing symptoms with two domains: i) lack of air (sensations of air hunger); and ii) perception of inappropriate or restricted breathing (related to work of breathing and biomechanics of breathing).

Patient-Reported Outcomes Measurement Information System (PROMIS-36).[104,105] To measure generic QOL we will implement PROMIS-36 Short Forms to measure six domains: physical function, anxiety, depression, sleep disturbance, fatigue, and satisfaction with participation in social roles. Higher scores will indicate more of the concept being measured.[104] Raw scores will be transformed into item response theory calibrations with a mean score of 50 and a SD ±10.

Physical activity (PA). PA will be total minutes per week of moderate or vigorous physical activity (MVPA).[106] To measure PA, two questions will be administered, that have evidence for construct and predictive validity.[106,107] The two questions will measure self-reported number of days per week that participants engage in moderate to strenuous exercise such as a “brisk walk” and the number of minutes on average that participants “engage in exercise at this level”.[106,p. 3]

Any adverse events and associated withdrawal from the pilot clinical trial will also be closely monitored.

6.1.2 Standard of Care Study Procedures

Cardiopulmonary exercise testing and Six-Minute Walk Tests according to practice guidelines will be performed by trained clinicians as part of standard care; see Schedule of Events – Attachment A.

7 Assessment of Safety

7.1 Data Safety Monitoring Plan

An internal committee (comprising the PI, Anna Norweg, PhD; Jonathan Whiteson, MD, co-investigator; and Francois Haas, PhD, co-investigator) will be responsible for data safety monitoring of the overall study.

Data safety monitoring reviews will be conducted every 6 months. During data safety monitoring reviews, adverse events (AE) and serious adverse events (SAE) will be reviewed and captured on CRFs. Information to be collected will include event description, time of onset, clinician’s assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event.
UPs that are SAEs will be reviewed and reported to the IRB and study sponsor within 24 hours of the investigators becoming aware of the event. Other SAE, whether related or unrelated, will be reviewed and submitted to the IRB and study sponsor within 72 hours of site awareness. Adverse events (AE) will be reviewed by the internal committee monthly. AE will be reported to the IRB and study sponsor annually.

The internal committee will review and record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

There are no predefined stopping rules for the study.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the PI shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the

form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study sponsor.

7.2 Specification of Safety Parameters

7.2.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

7.2.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

7.2.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets <u>all</u> of the following criteria:

- <u>Unexpected in nature, severity, or frequency</u> (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- <u>Related or possibly related to participation in the research</u> (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- <u>Suggests that the research places subjects or others at greater risk of harm</u> (including physical, psychological, economic, or social harm).

7.3 Classification of an Adverse Event

7.3.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

7.3.2 Relationship to Study Intervention

The clinician's assessment of an AE's relationship to study intervention is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their relationship to study intervention assessed. In a clinical trial, the study intervention must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the intervention (dechallenge) should be clinically plausible.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial intervention). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related," as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial intervention) and in

which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

7.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

7.5 Reporting Procedures – Notifying the IRB

7.5.1 Serious Adverse Event Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

7.6 Reporting Procedures – Notifying the Study Sponsor

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

8 Statistical Considerations

The sample size of 22 patients, randomized 2:1 to CATCH + PR and PR alone, provides approximately 80% power to detect a difference between groups of 1.25 standard deviations, using a two-sided, 0.05level test. We will use analysis of covariance (ANCOVA) to conduct preliminary analyses of between-group differences in mean change scores for the primary and secondary outcomes (CATCH + PR group versus PR alone control group). Age, lung function (FEV_1), and Modified Medical Research Council (mMRC) dyspnea will be used as covariates. We will use paired t-tests to evaluate within-group intervention differences (pre-intervention to post-PR intervention) at 10 weeks. We will estimate the mean change and variances for all primary and secondary outcomes. Residual scores will be checked for outliers and normality. SAS 9.2 (SAS Institute, Cary, North Carolina) will be used to conduct all quantitative analyses with significance set at $p < 0.05$. In addition, data from interviews will be analyzed using qualitative, thematic analysis to generate initial codes and broader themes.[108]

9 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

10 Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution. We will use a plan of evaluation to ensure that we meet our monthly recruitment and data collection goals; to assess the quality of our data, adherence to our research and treatment protocols, and the rigor of our research; and to prevent delays. A study REDCap database will facilitate efficient data collection and entry, minimize data errors and missing data, and ensure data are secured. We will develop a Data Collection Training Manual that contains information on all data collection procedures. The PI will closely monitor all data collection for the study.

11 Ethics/Protection of Human Subjects

11.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46.

11.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

11.3 Informed Consent Process

11.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention.

11.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

11.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain

permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

12 Data Handling and Record Keeping

12.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.2 Study Records Retention

Study documents will be retained for at least 5 years after final reporting/publication and until they are no longer needed. No records will be destroyed without the written consent of the sponsor.

13 Study Finances

13.1 Funding Source

This study is funded by NIDILRR.

13.2 Costs to the Participant

Participants will not incur any costs from participating in the study.

13.3 Participant Reimbursements or Payments

Participants will be paid $25 for each study assessment visit they complete (for a total of $50) to compensate them for their time and transportation cost for the study. Subjects will not be paid for the study treatment visits because this would be prohibitive based on the grant funds available.

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Attachment A

Schedule of Events

Activity	EHR PreScreening	Pre-Screening Call	Baseline (Week 0)	Treatment Visits (Weeks 0 – 6 ±2)	Post-Treatment Phone Interview (Week 7 ±2)	PR Discharge Evaluation (Week 10 ±2)
Study team procedures						
Informed Consent		X	X			
Screening						
Age	X		X			
Mini Mental State Examination (MMSE)			X			
Pulmonary Rehabilitation Clearance	X		X			
English Proficiency		X	X			
Pulmonary Function Testing or Chest CT results	X		X			
Medical History (active treatment for lung cancer, supplemental oxygen prescription, cognitive impairment or dementia, unstable cardiac disease / myocardial infarction < 3 months)	X		X			
Body Mass Index	X		X			
Current Smoking Status	X	X	X			
Baseline Assessment						
Modified Medical Research Council Questionnaire (mMRC)[109]			X			
Demographics / Social Economic Status			X			
Lung Function			X			

Smoking History			X			
Pulmonary Diagnoses and Comorbidities			X			
COPD Exacerbation History			X			
Primary Outcome: Feasibility						
Retention of participants: # of drop-outs and # of participants lost to follow-up						X
Primary Outcome: Acceptability (CATCH participants only)						
Semi-structured interviews					X	
% of CATCH intervention sessions attended				X		
Adherence to Breathing Home Exercises – Daily Breathing Log and Address Stress app				X		

Activity	**EHR PreScreening**	**Pre-Screening Call**	**Baseline** (Week 0)	**Treatment Visits** (Weeks 0 – 6 ±2)	**Post-Treatment Phone Interview** (Week 7 ±2)	**PR Discharge Evaluation** (Week 10 ±2)
Secondary Outcomes						
Cardiopulmonary Exercise Stress Test (CPET) – standard of care			X			X
6-Minute Walk Test & Borg RPE – standard of care			X			X
DMQ-CAT			X			X
St. George's Respiratory Questionnaire			X			X
Generalized Anxiety Disorder (GAD-7)			X			X
End-tidal Carbon Dioxide (ETCO2)			X			X

Respiratory Rate (RR)			X			X
CRQ-Mastery			X			X
Self-Evaluation of Breathing Questionnaire (SEBQ)			X			X
PROMIS-36 SF			X			X
Physical Activity (MVPA)			X			X
Adherence to Pulmonary Rehabilitation Exercise Training Sessions						X
Health Questionnaire						X