Office Title: RESP-FIT: Technology-Enhanced Self-Management in COPD

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PROTOCOL TITLE:
RESP-FIT: Technology-Enhanced Self-Management in COPD

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1.0 Objectives / Specific Aims

Advances in mHealth technology and the ubiquity of smart phone access (~65% of adults in SC have a smart phone: ~75 % of youth older >12yrs) provide a viable approach for improved patient-provider interactions (8-17). Co-Investigator Ron Teufel, MD, collaborated with The Technology Applications Center for Healthful Lifestyles (TACHL) to develop the Smartphone Asthma Monitoring System (SAMS) with funding from a SCTR pilot award (UL TR000062) to transform post discharge phone call into a mobile technology platform. This monitory system will be repurposed and evaluated in an adult population with COPD, hence the renaming of **Smartphone Airway Monitoring System (SAMS 3.0).** Numerous studies have demonstrated that exposures to environmental "cues" are associated with respiratory exacerbations, including locations (e.g., exposure to high allergen content –roaches in unkempt houses, etc.), situations (e.g. exercise, stress exposure), negative affective states and environmental context (e.g., time of day, after school outdoor activity). TACHL, in collaboration with various research teams funded by Verizon, Macey & Kellogg Foundations, Duke Endowment, and NIH, has successfully developed several smartphone-enabled biofunction monitoring, medical regimen adherence, and ecological momentary assessment (EMA) systems to assess an individual's emotional state, physical symptoms, functional status, and exposure to relevant environmental triggers (e.g., stress, physical exertion). The relay of self-reported information, biofunction data, and regimen adherence data in conjunction with GPS location tracking of use and associated pollen and pollution counts makes it possible to give a valuable report to a clinician to interact in real time with the patient. These interactions can be automated based on the guidelines (e.g., American Thoracic Society guidelines for COPD) and provider preference and/or live with the use of our evolving telemedicine infrastructure.

Further development of this mHealth solution (SAMS), in combination with a training regimen for the first time, will make this innovative approach to chronic respiratory disease more cost effective and sustainable over time (less personnel required). Preliminary work has been completed at MUSC to develop the SAM system and incorporate objective real-time measurement of medication use with self-report and Bluetooth enabled smart inhalers, EMA probe questions, and COPD follow up questions. **Testing the feasibility and acceptability of adding a low-risk respiratory strength training regimen, including review of video captured training session, to the current version of SAMS is one goal of the current proposal.** Ultimately our goal is to improve disease control and reduce the frequency of acute care visits for COPD in our state.

Specific Aim 1: To evaluate the feasibility and optimize the acceptability, feasibility, adherence, and performance of technology-enhanced self-management and training regimen through quantitative data (e.g. medication adherence, peak flow, and activity monitoring) in males and females with COPD.

Specific Aim 2: To assess preliminary signs of efficacy of RESP-FIT with respect to PImax, PEmax, dyspnea, fatigue and self-efficacy. If successful, this intervention will provide participants with the tools to self-manage dyspnea in their homes, thus impacting fatigue and physical activity.

Specific Aim 3: To integrate the current version of SAMS (e.g. Ecological Momentary Assessment, recent discharge follow-up questions, training progress via Bluetooth devices or manual entry, video capture of training technique including feedback and smartphone delivered telehealth visits) with adults with COPD.

Exploratory Aim 4. To determine if reducing dyspnea, increasing self-efficacy, and decreasing fatigue (i.e., goals of aim 2) results in increased physical activity and improved sleep as measured by activity trackers.

Primary hypotheses to be tested: Our overarching hypothesis is that a training regimen consisting of RMST along with technology-enhanced symptom-tracking will decrease dyspnea, dyspnea-related activity avoidance, and fatigue. Additionally, this application proposes to further develop SAMS which currently integrates EMA probe questions covering COPD symptoms and preventive care use with the

new functions, use in an adult population with COPD, video captured training technique and logging of RMST training sessions. Up to thirty adults with COPD (age over 40) will complete the study and use the SAMS app for 6 weeks in the natural environment (**Figure 1**). We will evaluate the acceptability, feasibility, adherence, perception of privacy, and performance of RESP-FIT + SAMS through quantitative methods to further optimize the app and related study procedures for the next phase of testing (i.e., large scale efficacy RCT).

Figure 1. Respiratory Fitness (RESP-FIT) and Smart Phone Airway Monitoring System (SAMS) application architecture schematic depicted with encrypted data transfer showing interactions with patients and researchers

2.0 Background

SIGNIFICANCE – Importance of the Problem: Dyspnea and fatigue are prominent comorbidities of chronic obstructive pulmonary disease (COPD), the third leading cause of death in the United States (CDC, 2016). Both dyspnea and fatigue are associated with exercise intolerance, activity avoidance, and functional impairment, which combine to reduce quality of life in those with COPD (Al-shair et al., 2016). We propose to evaluate an intervention that targets fatigue and dyspnea through a novel respiratory muscle strength training (RMST) and physical fitness self-management program, (RESP-FIT), specifically designed to strengthen inspiratory and expiratory muscles, promote physical activity engagement, and improve quality of life in persons with COPD.

The aversive potential of respiratory restriction in COPD is devastating, leaving many patients in continual fear of suffocation. They learn to fear restrictive respiratory sensations such as dyspnea, and thus actively avoid engaging in daily activities, including exercise or physical activity (PA) that exacerbate these sensations. This negative cycle of dyspnea-activity aversion frequently results in activity avoidance, physical deconditioning, fatigue, and an overall reduced quality of life (Miller, 2014; Thomas, Decramer, O'Donnell, 2013; von Leupoldt & Janssens, 2016). Self-management interventions containing supervised exercise are effective in COPD (Jordan et al., 2015), but there remains an urgent need for evidence-based interventions to address the physical deconditioning cycle and subsequently improve self-management of dyspnea and fatigue.

Respiratory muscle strength training (RMST). RMST is an empirically-validated therapy for improving ventilation and airway defense in a range of non-patient (adolescents, healthy adults, healthy elderly) and patient populations. Among those who have been studied are patients with various degenerative conditions, including neurological and respiratory diseases associated with weakened or damaged respiratory musculature (Luciaga et al., 2014). Respiratory muscle strength trainers (Figure 1) are small, portable, and easy to use. Through application of a pressure threshold, that must be surpassed in

order to inhale or exhale through the device, respiratory muscles are forced into a state of "overload" wherein contractile forces are increased and, over time, respiratory muscle strength and coordination increases. These increases are able to be measured by sampling maximal inspiratory and expiratory pressures (PImax, PEmax) via a hand-held manometer. Our previous pilot work demonstrates increased PImax in patients with COPD following IMST, with improved dyspnea and load compensation (the ability to overcome respiratory resistance) (Martin and Davenport, 2011; unpublished work in review). However, effects of RMST improved dyspnea on fatigue in COPD are unknown.

3.0 Intervention to be studied

RESP-FIT. The RESP-FIT program is a 6-week respiratory muscle strength training intervention adapted from previous RMST training regimens (Sapienza, Troche, Pitts & Davenport, 2011; Martin & Davenport, 2011; Hegland et al., 2016), consisting of 1) five training days/week using a combined IMST/EMST training device to which we will add Bluetooth enabled frequency and pressure intensity feedback monitoring to determine adherence and precise timing for device threshold intensification (i.e., increasing resistance training) 2) individualized, progress-based text message training reminders and prompts related to timing and intensification calibration, and 3) use of a Fitbit for remote monitoring of physical activity and hours slept at night. The training device is calibrated at 70% of each individual's baseline PImax and PEmax. Similar to other muscle strength training programs, exercises are done at regular intervals during the week (5 breaths, 5 times a day, 5 days a week; the participant will receive graphical illustration of RESP-FIT training frequency and intensity achieved, and based on their training regimen, will be prompted and/or reinforced via SMS text messaging. Note, this feedback system allows personalized, calibrated, and efficiently timed adjustments of resistance training intensity as respiratory muscle strength improves, rather than simply increasing levels weekly. As the use of an accelerometer or remote tracking device alone may affect physical activity, a control group will receive only the Fitbit. **This study proposes to assess the initial efficacy of RMST by obtaining estimates of variability in fatigue secondary to dyspnea, using a technologically-enhanced RESP-FIT intervention.**

RESP-FIT Training: Participants will be trained on a combined expiratory-inspiratory (EMST/IMST) muscle strength training device. The EMST/IMST device is a blue-tooth enabled, adjustable pressure respiratory muscle trainer (with a 22 mm OD adapter) capable of providing a pressure threshold resistance to both exhalation and inhalation on a continuous scale between 1.5 to 20 cm H2O pressure. For each participant, the valve will be set at 75% maximum pressure threshold. In the event that the participant cannot tolerate this pressure threshold, the valve setting will be lowered by 2 cm H2O (to a minimum pressure threshold of 6 cm H2O pressure) until tolerance is achieved. Participants unable to tolerate a maximum pressure threshold of 6 cm H2O will be discontinued from the EMST/IMST device and, after rest, begin use of a low-no resistance device (described below). Participants will be instructed to inhale through the nose and exhale slowly and as deeply as possible through the EMST/IMST trainer 6 times. Participants unable to exhale only through the device will be instructed to pinch their nose closed during exhalation. The number of breaths and pressure setting will be set based on prior clinical experience with the EMST/IMST device, found to provide the greatest effect on dyspnea in patients with COPD. The relationship between exhaled tidal volume, exhaled peak airflow and pressure in the EMST/IMST device was measured previously on a custom manufactured lung simulator for 50 breaths. At an average exhaled tidal volume of 643 ± 17 ml with a peak expiratory flow of 61.6 ± 12.1 l/min, the pressure inside the RMST device was 13.8 ± .6 cm H2O when the device was set at 10 cm H2O.
A Respironics Pflex® (model # HS553) inspiratory muscle trainer will serve as the low-no resistance device for this investigation. The Pflex® is designed as a resistive trainer for exhalation and inhalation and features an adjustable orifice through which air is inhaled or exhaled. The diameter of this orifice can be progressively decreased, from a setting of "1" (least resistance to exhalation/inhalation) to "6" (most resistance to exhalation/inhalation). However, for the purposes of this investigation, the Pflex® will be physically altered so as to prevent the device from supplying resistance to exhalation or inhalation. Specifically, each Pflex® will be set at largest opening, position 1. Additionally, a 3mm hole will be drilled into the device body to further reduce the resistance to airflow. Participants will be instructed to inhale through the nose and exhale slowly and as deeply as possible through the low-no resistance device 6 times. Participants unable to exhale only through the devices will be instructed to pinch their nose closed

during exhalation. As with the RMST device, the relationship between exhaled tidal volume, exhaled peak airflow, and pressure in the low-no resistance device was previously measured with a lung simulator for 50 breaths. At an average tidal volume of 650 ± 10 ml, with a peak expiratory flow of 59.5 ± 12.9 l/min, the pressure developed inside the modified low-no resistance Pflex® device was 2.2 ± 1.7cm H2O.

Environment and Preliminary Studies of Direct Relevance to the Proposed Work:
Our interdisciplinary team represents experts in nursing, respiratory physiology, pulmonology, symptom management, biostatistics, and information technology. Since coming to MUSC in 8/2016, Dr. Miller has established collaborative relationships with researchers and clinicians while working with TACHL.

Experience in mHealth Development: Dr. Ron Teufel has significant experience in smart phone app development, software, server and peripheral hardware interface development. Dr. Miller has significant experience in measurement of objective and subjective breathing responses.

Experience in clinical COPD research: Dr. Strange has conducted numerous clinical COPD studies. Dr. Beiko has conducted studies analyzing biomarkers in COPD. Dr. Miller has conducted several laboratory studies in pediatric and adult populations, including adults with COPD and anxiety.

4.0 Study Endpoints

Study end points include: Successful study completion, participant consent withdrawal, and PI termination due to failure to adhere to the protocol, loss of contact with the patient, and/or unexpected adverse events.

5.0 Inclusion and Exclusion Criteria/ Study Population

Potentially eligible participants will be identified through a combination of a medical chart review, use of breathing symptom survey, and a Pulmonary Functioning Test (PFT) - if there is not one on record within the past 6 months.

Inclusion Criteria

- 40 years of age or older; and
- Able to read and write English; and
- Diagnosed with COPD (PFT values: FEV1/FVC <0.7 and FEV1% predicted < 80% - within the past 6 months); or Dyspnea score of greater than “2” on the Modified Medical Research Council (MMRC) questionnaire.

Exclusion Criteria

- Pregnant female or less than 1 year post-partum; or
- Diagnosed cognitive deficit or observed lack of understanding during the informed consent process; or
- Mobility impairment; or
- Lack of 3g WiFi access in place of residence; or
- Unwillingness to wear physical activity tracker daily, follow protocol, and/ or attend study visits.

Inclusion of a diverse population
COPD is not a population specific disease. Participants from all racial and ethnic backgrounds will be encourage to volunteer as participants. However, pregnant females and females less than 1 year post-partum (via self-report) will be excluded, as pregnancy affects fatigue and the perception of dyspnea due to increased abdominal pressure on the diaphragm and potential displacement of abdominal organs.

Exclusion of children

COPD is disease primarily exclusive to late adulthood. Children are therefore excluded from this study.

6.0 Number of Subjects
N= 30 adult participants.

7.0 Setting
This is not a multi-site trial. All aspects of this study will take place on-campus at MUSC or at the participant's place of residence. Informed consent will be conducted in the privacy of a patient room. The initial baseline and final study visits will occur at SCTR Nexus Research Center. All other study visits will be conducted either electronically over the tablet or by phone with the participant at their place of residence.

8.0 Recruitment Methods
Study recruitment flyers advertising the study will be posted within MUSC among general population patient clinic waiting room and elevator areas. Study recruitment will also take place in the clinics of MUSC and via referral during an admission for COPD exacerbation, or within the first 2 weeks after discharge. Any MUSC clinician who provide cares to the target population can initially approach potentially eligible patients about the study, and if interested provide them with the contact details for the Study Team. With the patient's verbal permission, the provider may also provide the patient's contact information to the Study Team. Upon initial contact with the patient, patients will be verbally prescreened per the inclusion/exclusion criteria by our study team and given more information about the study. For those prescreened eligible and interested patients, and an informed consent meeting will be set-up at MUSC Nexus Research Center at the patient's convenience.

Additionally, for the purposes of this study and in direct alignment with the mission of the CON P20 Symptom Self-Management Center, we will employ the use of MUSC Bioinformatics Center (BMIC) core services to identify and recruit patients across the MUSC Enterprise that meet the study inclusion/exclusion criteria and that have granted authorized research contact permission in MyChart through the electronic 'opt in' EPIC designation. Once these potentially eligible patients are identified, we will then contact them by telephone using a script to determine if they are interested in study participation.

9.0 Consent Process
Research activities will not be conducted without the patient's written informed consent. Informed consent will be conducted by the PI and/or their designee as noted on the study delegation log, and will occur in the comfort and safety of a private clinic room prior to any screening procedures being conducted and/or data collection. Potential participants will be given the informed consent document to read and review in advance, and/or may have it read to them by the researchers, if they prefer. After reviewing the consent document, the patient will be given the opportunity to ask any questions about the study that they may have, and will be requested to demonstrate what is expected from them should they agree to enroll in the study through a questioning of their understanding of study procedures and risks. Prior to consenting, all questions will be resolved to the patient's satisfaction. If a participant does not appear to understand the information contained within the Consent document or of what is expected of them as a study subject, then the study coordinator will review the consent document again with the participant. If after this second review, the subject does not demonstrate an understanding, they will not be enrolled in the study. Only participants, with no observed cognitive impairment, will be consented and enrolled into the study.

The consent form will meet the requirements of the Code of Federal Regulations and the MUSC Institutional Review Board; and, include the following elements:

- The purpose, nature, and objectives, potential risks and benefits of the intended study.
- The length of study and the likely follow-up required.
- The name and a contact of the investigator(s) responsible for the protocol.
- The right of the participant to accept or refuse study interactions and to withdraw from

participation at any time.

All consented subjects will be given a copy of their executed and countersigned Consent form. The researchers will maintain a means of contact with all enrolled study participants in the eventuality that reconsenting of currently enrolled participants is needed and/or the disclosure of new study information is warranted to previously enrolled participants.

10.0 Study Design / Methods

This is a randomized longitudinal controlled observational study using a mixture of qualititative and quantitave methods. The study will recruit 30 participants and utilize a control group experimental design with dependent pretest and posttest to derive data regarding (1) feasibility and (2) within-participant effect size of the RESP-FIT intervention in terms of satisfaction, use and adherence, technical issues and acceptability, and self-reported symptom severity (dyspnea and fatigue). In addition, information satisfying Exploratory Aim 4 (frequency of physical activity) will be obtained. Patient data (Table 1 below) will be collected at baseline, 6 weeks (post-treatment) and 14 weeks (2 month follow up). This study will enable further development of SAMS using our patient centered iterative design guided by feedback from a convenience sample. When completed, 30 adults (15 in each group) will have used SAMS for 6 weeks. **(see Fig. 2 Study Design)**.

Objective Measures:

Data Collection	Measures	Data sources and time points
Demographics	Age, health history, race/ethnicity, rural/urban residence, insurance	Participant interview and medical records
Clinical Characteristics	FEV1/FVC Self-reported hospitalizations/exacerbations	Participant interview and medical records; PFT baseline and at second study visit
Maximal Inspiratory & Maximal Expiratory Pressure Generated	MIP and MEP recorded using a calibrated MicroRPM respiratory pressure meter, units in cm H_2O ; a surrogate parameter for respiratory muscle weakness/strength	Collection and calibration at baseline, and at second study visit.
Physical Activity: Steps	# of steps taken daily (via Fitbit Alta)	Daily
Physical Activity: Patterns of Active Minutes	# of minutes active throughout the day (via Fitbit Alta)	Daily
Sleep	Hours of Sleep (via Fitbit Alta)	Daily

Participative Measures:

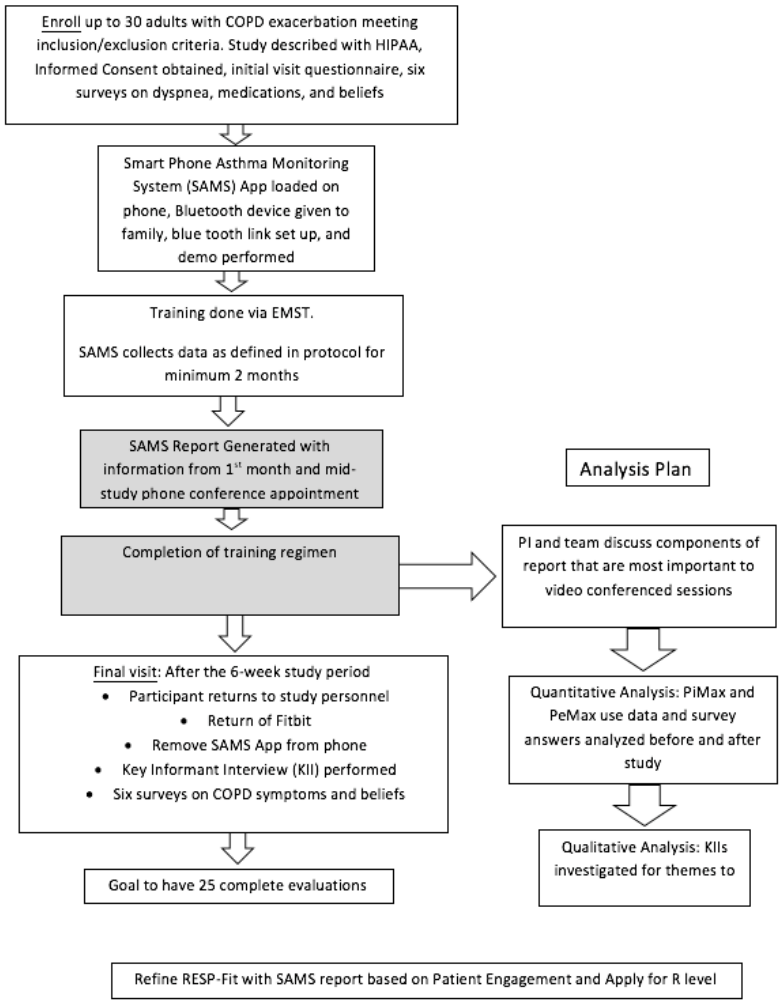
Data Collection	Measures	Data sources and time points
St. George's Respiratory Questionnaire	Impact of COPD on: 1. Overall health (symptom severity, symptom frequency) 2. QOL (impact component, activities that are limited by breathlessness, social functioning, psychologic burden) 3. Perceived Well-being	Participant interview/questionnaire; baseline and after intervention
PROMIS v1.0 Fatigue	Monitoring of sample representativeness; types of recruitment activities; rates of recruitment; % eligible, consented, provided with informational session	Participant interview/questionnaire; baseline and at each session
PROMIS v1.0 Dyspnea: Functional Limitations	Functional Limitations	Participant interview/questionnaire; Baseline
PROMIS v1.0 Dyspnea: Task Avoidance	If tasks are avoided How often tasks are avoided	Participant self-report; Baseline and at each study visit

PROMIS Self-Efficacy	Self-efficacy	Participant self-report; Baseline and at each study visit
PROMIS v1.0 Sleep Impairment	Sleepiness during the day; impairment	Participant self-report; Baseline and at each study visit
PROMIS v1.0 Sleep Disturbance, short form	Falling asleep	Participant self-report; Baseline and at each study visit

Other Measures:

Maintenance: Projection of future adoption	# COPD patients who would continue intervention; patient perception of the intervention	Patient interview at end of study
Feasibility:	Acceptability, utility of intervention	Patient interview at end of study

Figure 2: Feasibility Study of RESP-FIT with SAMS Report: Pilot Intervention with Quantitative/Qualitative Assessment



Participants: Subjects will be 30 adults, aged 40 and older, with mild to moderate COPD, defined as a spirometric diagnosis of (FEV1/FVC <0.7 and FEV1 % predicted < 50%), with the ability to understand written and spoken English, and who report dyspnea greater than "2" on the Modified Medical Research Council (MMRC). Participants must be willing to continually wear a FitBit activity monitor, and have access to a smartphone or Wi-Fi/Data-enabled iPad and with willingness to download the FitBit and

SAMS apps. Participants without access to a smartphone or Wi-Fi/Data-enabled iPad may be loaned an iPad for the duration of their training and given comprehensive training on the use of the device. Pregnant females and females less than 1 year post-partum (via self-report) will be excluded, as pregnancy affects fatigue and the perception of dyspnea due to increased abdominal pressure on the diaphragm and potential displacement of abdominal organs. Exclusion criteria also include lack of cognitive ability to complete questionnaires, mobility impairments, memory impairments and dementia. We will not exclude participants with comorbid depression or history of substance abuse, as we will be including depression in our analysis as well as to have a representative sample.

Procedures: Recruitment for 6-week trial: Study recruitment will take place in the clinics of MUSC as well as by telephone with patients across the MUSC Enterprise that meet the study inclusion/exclusion criteria and have granted authorized research contact permission in MyChart through the electronic 'opt in' EPIC designation. Participants may also be recruited by via referral during an admission for COPD exacerbation, or within the first 2 weeks after discharge. If additional participants are needed, advertisements will be placed at the clinics of MUSC and our team will accept referrals from any MUSC provider regardless of recent hospitalization. Referrals will be screened for eligibility by our study team. An advertisement is included in the IRB submission (see supplemental file "Advertisement").

Technical Training: After receiving complete verbal overviews and signing informed consent (and assent), participants will have SAMS installed on their phone; receive a demo of SAMS. Patients with COPD are commonly instructed on how to perform a peak flow, but our team will ensure they understand this process and if a peak flow device is needed, we will supply this device (e.g., digital or manual peak flow meter depending on availability). Participants will be given our study coordinators and PI's telephone number should technical or procedural questions arise during the study. TACHL staff will take service tech calls, as done on other TACHL studies. Participants will be instructed to carry their phone during waking hours for the 6-week trial and to use the video capture training technique at least 1 time per week during the study period.

Randomization and Training Regimen: Following collection of pre-training baseline measures, participants will be randomly assigned 50/50 to either a Standard of Care (SOC) Control Group (n=15), or a SOC + EMST/IMST Group (n=15). Participant randomization will be stratified by gender and dyspnea grade as measured on the MMRC. Those participants assigned to the SOC control group will receive a Fitbit monitoring device, but no intervention beyond that which is typically provided to patients seen within the MUSC Clinic. Participants randomly assigned to receive SOC+EMST/IMST will receive six weeks of clinician-guided, scripted RMST. This training will be facilitated by the PI using a custom-designed and constructed EMST/IMST trainer. Non-invasive measurement of maximum expiratory and inspiratory pressures (PEmax and PImax; described previously) will be obtained in order to set pressure threshold of the EMST/RMST device. The first week of EMST/IMST training will be conducted with the device set at 75% of the average initial PEmax collected at pre-training baseline. After a nose clip is placed the participants will be taught a four-step procedure: 1) take a breath in, 2) wrap lips tightly around the EMST/IMST trainer mouthpiece, and 3) exhale quickly and forcefully until you hear the popping or whistling sound of the device valve opening, and 4) continue blowing forcefully for two seconds. Once the participant is able to do a five-breath trial, another five-breath trial will be completed with the participant allowed as much independence as appropriate. The participant will receive a text message each day reminding them to complete his or her training and "remain active today." Participants in the SOC group will receive a text message reminding them to "remain active today." The daily training session will be as follows: 1) five sets of five-breath exhalations (25 breaths total) completed each training day, 2) each exhalation within a set will be separated by approximately one minute, and 3) each five-breath training set will be separated by five minutes. A Bluetooth-enabled "use" button on the EMST/IMST device will log the times the participant has used their training device. Each participant will be provided with a diary to record five sets of five-breath training trials on five days each week. Our experience indicates that EMST/IMST takes approximately 20 minutes each day. PEmax will be reassessed weekly, by the research clinician across the six-week treatment period and readjusted to 75% of the participant's current PEmax. If no changes in PEmax are observed week to week, treatment

will be continued without increase in the pressure threshold training level. All participants will be managed according to standard treatment protocols used within the MUSC Pulmonary Clinic. Detailed records will be kept pertaining to mortality and morbidity as well as use of inpatient and outpatient hospital facilities, medication use, frequency and duration of disease exacerbations, as well as general response to treatment. All dependent variables will be obtained, for all participants at baseline, mid-intervention (3 weeks post baseline), at intervention end (6 weeks) and 14 weeks (2 months) post baseline.

Monitoring period: As per our standard monitoring period with SAMS, participants will receive a daily EMA reminder text. Answering the EMA questions on a smartphone requires 30-45 seconds of time. Probes will occur to not interfere with typical sleep schedule or during school hours. EMA sessions will capture COPD symptoms and emotion/mood over the course of the day. If patients have not filled out an EMA in 3 days, a reminder text will be sent. EMA probe question responses will transfer to RedCap, as TACHL has done with other studies. Data will not be stored on the phone. The participants will be requested to perform video capture of training technique 1 time per week. A reminder will be sent during convenient waking hours if this has not been performed.

Activity Tracking: A Fitbit activity tracker will be provided to each participant and comprehensive instruction offered on its use. This activity tracking device is worn on the wrist and only removed for bathing or other activities involving water, as the devices are water-resistant but not waterproof.

Quantitative and Qualitative Assessments: Participants will complete quantitative and qualitative assessments of acceptability, feasibility, and performance of the SAM system including: Assessments/Measures. 1) Enrollment Screening and Assessments. During the screening: demographic data, current prescription for COPD controller medication, general medical history including COPD severity and co-morbid conditions, access to mobile technology, contact information to schedule final visit, and most recent ambulatory visit will be collected. For patients that meet inclusion/exclusion criteria during the enrollment encounter, validated surveys on self-efficacy (e.g. PROMIS Self-Efficacy), and COPD symptoms (e.g., St. George's Respiratory Questionnaire) will be also administered. In accordance with our P20 center, PROMIS measures (Pain, Fatigue, Dyspnea, Task Avoidance) will be administered. 2) EMA Questions (see attachment for details). As per previous SAMS study, questions will assess: COPD symptoms (cough, wheeze, mucus), emotional status/mood (happy, angry, anxious, stressed, relaxed, and bored; 0=not at all, 4=extremely), and scheduled COPD preventive care and health seeking behavior questions. 3) Acceptability Ratings (initial visits and at 2 mo): The Mobile App Rating Scale will assess the following aspects of SAMS: a) engagement (including fun, interest, customization, interactivity, and target audience) b) functionality (performance, ease of use, navigation, design) c) aesthetics (layout, visual appeal, color, and style) d) information (accuracy, goals, quality, quantity, clarity and credibility). 4) Quantitative outcomes: During the final visit validated surveys on adherence (e.g., Self-report Adherence), self-efficacy (e.g. PROMIS Self-Efficacy), and COPD symptoms (e.g., St. George's Respiratory Questionnaire) will be administered and compared to the enrollment survey responses.

One time per week of the study, the patients will be requested to perform video capture of training technique that will be reviewed by our PIs to determine beneficial elements of this video. If applicable, we will also compare return visits to the emergency department and hospital between previous enrollees in the last version of SAMS in a pediatric population. This "on the shelf data" of previous enrollees will be compared to the new enrollees with telehealth visits. 5) Qualitative Key Informant Interviews Qualitative data will be obtained via open-ended interview questions on the acceptability topics above. Interviews will be recorded for transcription and qualitative analyses will be applied using qualitative software program to determine themes in participant responses, which will prompt modifications to the SAMS program. Interviews may be performed over the phone if convenient for the family.

Participant Compensation: Participants will receive $25 for screening, and $25 at the initial enrollment visit for completion of the initial enrollment assessment and surveys (total of $50 if enrolled). Additionally,

at the post study evaluation, they will receive up to $75 for logging into app, wearing their Fitbit, and bringing back the study devices (e.g., Fitbit), completing EMA and surveys, and the brief key informant interview. Final visit compensation will be based on adherence to the study protocol including symptom data entry, EMA reports, telehealth visit, and final visit surveys/KIIs. Each day will be valued at $2.50 and reimbursement will depend upon adherence to the study protocol including ensuring EMA symptom and training data is available for 5 days manually (for a total of $12.50/week) for a total of $75over the six-week period. Tracking of reimbursement amount during the study will be delivered via the App in a compensation log. $50 will be reimbursed for completing Visit 2 at Week 6, and another $50 for completing the two-month follow-up visit. Total up to $225= $75 (EMA and training data $12.50/week x 6 weeks) + $50 at Visit 1 + $50 at Visit 2 + $50 at Visit 3.

11.0 Specimen Collection and Banking

Not applicable

12.0 Data Management

Statistical Analysis: Primary analyses for this pilot feasibility study center on patient satisfaction, treatment fidelity and adherence, with a secondary focus on changes observed on fatigue and dyspnea scales (obtained from the SGRQ), PImax and PEmax change, physical activity (steps per day and active hours per day), physical activity engagement (PROMIS activity engagement scale), and sex based differences. Treatment satisfaction will be measured qualitatively through analysis of recorded post-intervention interviews. Training frequency will be automatically assessed by the Bluetooth enabled tracker, which will also be developed to measure pressure changes to evaluate treatment gains for PImax and PEmax. Pre- and post-intervention data will be analyzed for correlation between symptom severity and respiratory muscle strength (PImax and PEmax) along with mean steps per day. Post-Intervention data collection will include PEmax, PImax, PROMIS and SGRQ scales (see above) to compare to baseline measures. The sample will be characterized using descriptive statistics for all variables, as appropriate. T-tests or non-parametric Wilcoxon rank sum tests will be used to compare continuous demographic and baseline clinical variables and chi-square or Fisher's Exact Test will be used for categorical (e.g., survey responses). An overall indicator of acceptability/usability will also be a) adherence via a % of total EMA assessments completed. Comparisons between device use and reported affective states, stress levels, COPD symptoms over previous 1-2 days will also be examined. We will also gather information from the post-trial interviews via qualitative analyses on aspects of the SAM program that would benefit from refinement. Qualitative data will be presented as themes of domains relevant for refinement of SAM. Exploratory Quantitative Analyses: Nonparametric analyses will compare emergency department visits and hospitalizations with SAMS EMA question responses. Comparisons will be run on EMA ratings and training use.

Sample Size: The purpose of this pilot study is not to confirm or refute hypotheses about treatment effectiveness (with corresponding emphasis on establishment of sufficient power for hypothesis testing); rather, we seek to demonstrate feasibility of the intervention and to obtain estimates of variability for the secondary outcome measures. Therefore, sample size was determined for pragmatic reasons rather than power (Leon, Davis & Kraemer, 2011). For this pilot study, we will recruit approximately 30 patients with COPD and, basing our estimated attrition on previous investigations, we anticipate that approximately 25 of these patients will complete all study-related visits. For this project's secondary aims (continuous outcome measures of self-efficacy, fatigue, and dyspnea), we use an in intent-to-treat analyses and 95% confidence interval (CI) estimates of the within group change scores (pre- to post-treatment) with precisions ranging from ±0.20 to ±0.78. These correspond to estimated standard deviations of change scores of these variables, ranging from 0.5 to 2.0.

Data Management. Data report forms (DRF) for all data collection will be developed by the PI and study team. The Research Electronic Data Capture (REDCap) system provided through MUSC CTSA will be used to enter questionnaire and measurement data. REDCap is a secure, web-based application designed exclusively to support data capture for research studies. Only authorized study personnel will have access to the data tracking system. Data management including data quality assessment

(completeness and accuracy) will be done by the PI. Screening and post study questionnaires will be completed using a tablet based presentation or directly with the participant in paper format if so desired. Questionnaires will be entered into a HIPAA compliant and secure data management and storage. Key Informant Interviews will be recorded and transcribed. Transcription will only include the study ID number without PHI. EMA data, video capture, and training data submissions will be stored in a standard file format in RedCap and immediately erased from any portable storage device. Research staff will conduct daily checks of data transfer. A linkage file for the study ID number and PHI will be maintained in a password-protected server behind the MUSC firewall in order to link the questionnaire data, video, interview data, and EMA data. At the end of study, all patient video recordings will be deleted and erased from the research record.

Participants' data will not be stored on the cell phone but will be encrypted and sent to password protected server storage before being deleted from the phone. No PHI data are stored on the Bluetooth device therefore if lost no risk exists. Data will be collected and maintained on TACHL's secure research drive maintained by the Medical University of South Carolina. Databases are on password protected secure servers located behind the MUSC firewall. Access to these files will be limited to authorized members of the research team. Other authorized persons, such as regulatory authorities, may also have access to these records.

Data sharing with the NINR/NIH: As a condition of this National Institutes of Nursing Research (NINR) award, de-identified patient data will be shared by the researchers with the NINR and stored electronically on an NIH password protected secure server (https://cdrns.nih.gov/). The purpose of sharing this information is to build a NINR repository of data using Common Data Elements (CDE) for future research purposes among the general scientific community and for public health benefit. Patients will be allocated a random identifier through the NIH supported GUID Tool. The GUID Tool (https://cdrns.nih.gov/node/39) is a customized software application that generates a Global Unique Identifier for each study participant. The GUID is a subject ID that allows researchers to share data specific to a study participant without exposing personally identifiable information (PII). The GUID is made up of random alpha-numeric characters and is NOT generated from PII/PHI. As such, it has been approved by the NIH Office of General Counsel. GUID Generation complies with HIPPA regulations for the protection of PII/PHI. Patients are made aware of this data sharing agreement with the NINR/NIH in the study's Informed Consent document. Further protections are afforded to participants through an NIH Certificate of Confidentiality conferred upon the study.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

There is a well-developed and NIH/NINR prepared DSMP that involves the use of a Safety Monitoring Committee (SMC) that shall meet semi-annually post initial study enrollment. The Committee is comprised of key individuals that include: an independent safety monitor (ISM), a biostatistician (BS), and the Program Manager (PM). Post initial study enrollment, the SMC will convene semi-annually and all reports will be forwarded to the IRB and Sponsor in accordance with institutional policies and sponsor requirements.

SECTION A. Safety Monitoring Committee (SMC)

The study's SMC will be comprised of the following individuals, who will perform data safety management and monitoring of the study:
Erin Silverman, PhD, CCC-SLP, CCRC **I**ndependent Safety Monitor (ISM)
Martina Mueller, PhD Biostatistician (BS)
Mohan Madisetti, MSc. Program Manager (PM)

Individual Roles and Responsibilities

Principal Investigator, (PI). Although not part of the SMC, as PI, Dr. Miller will overall be responsible for the immediate protection of all human participant study participants enrolled in the study.

Independent Safety Monitor, (ISM). **Dr. Silverman** is a certified research coordinator and adjunct faculty member at the University of Florida, Division of Pulmonary, Critical Care & Sleep Medicine. She is a clinician with a doctorate in Communicative Sciences, with specialty areas of airway physiology and respiratory muscle strength training. Dr. Silverman will act as the study's Independent Safety Monitor (ISM). Dr. Silverman has no real or apparent conflict of interest that would affect his/her performance in this role on the study. Dr. Silverman will correspond semi-annually with the SMC to review de-identified cumulative AE study data to assess any impact on the safety of participants or on the ethics of the study. As the ISM, he/she will be responsible for reviewing all cumulative reported SAE related to study treatment and data safety monitoring reports generated by the BS to provide study recommendations to the PI, MUSC's IRB and NINR. Dr. Silverman will be immediately notified of the occurrence of any SAE by the PI or PM and will be provided with the necessary study information to provide an informed recommendation in real-time regarding the protocol and human participant safety.

Martina Mueller PhD, Biostatiscian (BS). Dr. Mueller is a Professor in the College of Nursing with a joint appointment in the Department of Biostatistics, Bioinformatics and Epidemiology (DBBE) at MUSC. Dr. Mueller has served and is currently serving as a member of several NIH/NINR R01/R21 DSM Boards, and Committees. Dr. Mueller will be responsible for conducting semi-annual interim analyses, generating semi-annual AE safety reports from the electronic study research database and disseminating de-identified information to the ISM and other members of the SMC. The interim data analyses will only include safety related results; analyses in regards to study outcome will not be performed. The interim AE reports will provide typology, frequency data and outcomes of all reported and documented AE in the electronic study database. With no patient contact, Dr. Mueller has no apparent conflict of interests to serve in this capacity.

Mohan Madisetti MSc, Program Manager (PM). Mr. Madisetti is the P20 Progam Manager at the College of Nursing and a member of MUSC Institute of Human Values with Fellowship certification in Research Ethics. Mr. Madisetti has served and is currently serving as a member of several NIH/NINR R01/R21 DSM Boards and Committees, and FDA Industry Sponsored Clinical Trials. With no patient contact, Mr. Madisetti has no apparent conflict of interests to serve in this capacity. Mr. Madisetti will be responsible for the classification of all reported adverse events (AE) and for ensuring that all serious adverse events (SAE) are forwarded to the PI and ISM in real time and in compliance with MUSC IRB policies and procedures. In addition, and in conjunction with the PI, Mr. Madisetti will be responsible for amending the protocol in accordance with the ISM recommendations, submitting reportable SAEs and protocol deviations to MUSC IRB, and, submitting annual Progress Reports to the NIH/NINR through MUSC's OSRP. He will also be responsible for maintaining the regulatory binder, ensuring data management validation and verification of the electronic study research database, conducting monthly internal quality control audits on all participant records, notifying the PI of any deficiencies, and the forwarding of reportable SAE to the NIH/NINR Program Official through MUSC's OSRP within 72hrs of IRB review and acknowledgement

SECTION B. Procedures for Safety, Risk and Confidentiality

1. Monitoring Study Safety

From the initial screening of participant by inclusion and exclusion criteria to the informed consent process to the provision of participant study instruction to staff training in Good Clinical Practices (GCP) and regulations pertaining to the Conduct of Human Participant Research to study contact with participants to internal monthly quality control audits and protocol fidelity monitoring to the real-time review of AE by the ISM to the oversight of MUSC's IRB, procedures for monitoring study safety are consistently afforded throughout study. Specific study safety procedures include:

- Participants will be screened for inclusion and exclusion per the protocol; the PI shall verify 100% of participants' eligibility prior to study enrollment through review of inclusion and exclusion criteria with potential participants.
- Participants will be fully informed as to all know risks and the possibility of risk from study participation in the informed consent process. **These risks are minimal.**

- Participants will be instructed to notify the researchers of any/all suspected or experienced adverse events whether they believe them to be related or not to the intervention.
- All reported participant AEs will be tracked through to resolution.
- All investigators and researchers will maintain active CITI Human Subject Research and Good Clinical Practice training.
- The PM will conduct a monthly internal quality control audit of all participant records to ensure compliance with MUSC IRB regulations; the PI and Program Coordinator (PC) will work together to correct any errors.
- The PI and/or designee will observe and evaluate ten (10%) percent of eligibility screening visits, informed consents and study instructions performed by IRB approved study personnel and provide feedback and/or retraining of study personnel if fidelity to both applicable federal regulations and the protocol is not observed.
- The BS willl generate semi-annual AE reports for the PI and SMC to review.
- The ISM will have access to real-time study data and will be able to provide immediate recommendations to the PI.
- Investigator performance and compliance will be provided for through MUSC IRB and ORI study oversight.

2. Minimizing Research-Associated Risk

Diligent study safety monitoring will be conducted by all member of the research team and the SMC throughout the conduct of this study in compliance with the following required elements of MUSC IRB's continuing review process:

- Tracking and follow-up of participant accrual (inc. withdrawn consents) will minimize risk by identifying, disclosing, and mitigating any potentially unknown risk(s) of harm to study participants.
- Timely and appropriate reporting of informed consent process deficiencies, protocol deviations, privacy breaches, conflicts of interest, and/or changes in personnel.
- Ongoing soliciting, monitoring and appropriate reporting of adverse event activities.
- Timely and appropriate IRB submission of safety-related documents such as audit reports, sponsor progress reports, ISM reports, and other materials or communications that might impact the safe conduct of this study.
- Active cooperation with the IRB, ACO, sponsor, and other applicable entities in the event of a random or for-cause internal or external audit.

Institution-Wide Assurances

This protocol will be conducted fully in keeping with the signed MUSC IRB Principal Investigator Statement of Assurance and Department Chair's Statement of Assurance, when submitted to the IRB as a required component of the MUSC IRB Human Research Review Application.

3. Protecting Confidentiality of Participant Data

Certificate of Confidentiality. This study will be conducted in accordance with recently enacted policy regarding the automatic granting of Certificates of Confidentiality to NIH/NINR federally funded research. Participants will be made aware of their rights and the limitations of the release of Protected Health Information during the Informed Consent process.

Participant Screening and Enrollment. All data from participants screened for the study will be entered into an electronic study database. Designated research staff will collect, gather, and enter required data (written informed consent, HIPAA Authorization, and demographics) onto study data forms. Screened patients who do not meet study eligibility will have specific screening data entered into the study database. The collected data will be helpful in examining the patient population and feasibility of enrollment criteria and will include reason for exclusion. All dates will be shifted and other Personal Health Information (PHI) will be removed from the study database upon study completion. All data obtained from this study will be used for research purposes only and will comply with Federal HIPAA regulations.

Master Screening and Enrollment Logs will used by the PM to prepare reports on accrual and attrition for the PI and SMC.

Case Report Forms (CRF). All proposed study specific case report forms (source documents) for data collection will be designed by the PI, and, when possible, transferred into electronic Case Report Forms (eCRFs) for use in the study's REDCap database. These study specific eCRFs source documents (study logs for correspondence, compensation and other forms such as pre-eligibility screens) will be coded by the participant's unique study ID# for all data collected including study instruments will be maintained in the participant research record. Completed instruments that require signature on a paper CRF will be scanned and uploaded into the study database to all for remote electronic safety monitoring as well as maintained on file in accordance with MUSC policies and applicable Federal Regulations for the Conduct of Human Participant Research.

Binders. The PC will prepare and maintain a participant-specific CRF binder for each participant containing all non-eCRFs records. A regulatory file will be maintainedby the PM to include the IRB-approved Protocol, original Informed Consent documents, HIPAA forms and other required study-related regulatory documents. All paper research records and CRFs will be maintained in a locked file cabinet, stored in a room for research files that is accessible only via a password protected entry system that features security cameras, within the College of Nursing. Access to the research records, study database and PHI's will be restricted to study personnel as approved by the PI and MUSC IRB. As with all studies conducted at MUSC, this study is also eligible for a random audit by MUSC Office of Compliance.

Data Processing. This study will use Research Electronic Data Capture (REDCap) for data capture and management. REDCap is a software toolset and workflow methodology for the electronic collection and management of research and clinical trials data. REDCap provides secure, web-based, flexible applications, including real-time validation rules with automated data type and range checks at the time of data entry. Exports are made available for several statistical packages including SPSS, SAS, SATA, R and Microsoft Excel. The study-specific REDCap electronic database will be designed and developed by the PI, CI, or PC. The provision of REDCap is made available through the South Carolina Clinical & Translational Research (SCTR) Institute at MUSC with NIH Grant awards UL1RR029882 and UL1TR000062.

Data Security. Ensuring data security, compliance with 45 CFR 46 and maintaining the integrity of PHI is a top priority. MUSC has Standard Operating Procedures (SOP) to ensure a high level of data security while coordinating electronic and paper data management activities for clinical research trials. The REDCap study database will be hosted in the Biomedical Informatics secure data center at MUSC, a secure environment for data systems and servers on campus, and includes firewall, redundancy, failover capability, backups and extensive security checks. The secure data center has strict access control; only authorized core personnel may access the facility un-escorted. Only authorized users are allowed to connect to the network, and the security of the network is actively monitored. Power and environmental controls have several layers of backups, from interruptible power supplies to alternate and redundant feeds to the local utility company. The REDCap system administrator contributes to the maintenance of institutional disaster recovery and business continuity plans. Load balancers and a highly fault tolerant SAN infrastructure contribute to high availability.

The REDCap system itself has several additional layers of protection including password protection. Access to the data and its security is managed institutionally by sponsored login IDs through a Shibboleth login with an MUSC issued NetID and features a user account management filter that controls who can access the data and to what degree. All personnel must pass an employment background check before being issued an ID. Password complexity, history and expiration standards are implemented at the institutional level. Access to individual REDCap projects and their data is managed by the owner of the project. All transactions are securely delivered to the application using Secure Sockets Layer (SSL – SHA-1 with RSA Encryption; 2048-bits). It is then transmitted internally (behind the firewall) to the database server. All transactions are logged at the server layer (httpd logging), application

layers (REDCap logs activity to a database table), and the database layer, using both query and binary logging. This feature provides audit trails for all changes, queries, data exports and reports. MUSC Information security policies are available at: https://mainweb-v.musc.edu/security/policy/

Data Entry. Only MUSC IRB approved study personnel that are authorized to have access to the REDCap study database will be granted password access. Study personnel using computers that are connected to the Internet will directly enter data into the remotely housed database. As such, no electronic study data will be stored on hard drives and/or any portable electronic devices. Additionally, all personnel with access to the database will have current University of Miami CITI training in the Conduct of Human Subject Protections, and HIPAA and Information Security trainings that are completed annually. Each participant will be assigned a unique study identifier, all PHIs will be masked, and data exports will be limited to the PI or the PC for generating reports and the conduct of statistical data analysis.

Data Monitoring. Ongoing quality control procedures will be implemented for data collection, storage and processing. The PM will conduct routine monitoring of the study database and generate a monthly report for review at study team meetings. Standing agenda items for these meetings will include participant recruitment and retention, AE's, protocol deviations, data integrity and overall study conduct. The PI and PC will work to resolve and validate discrepant data. Discrepancies that warrant clarification will be sent to appropriate parties for review and resolution. All data entry and changes made in the study database by authorized study personnel will be automatically logged by REDCap, and provide a transparent visible audit trail for reviewers.

SECTION C.
Procedures for Identifying, Reviewing and Reporting Adverse Events

1. Identifying. Potential minimum risks identified for participants are outlined in the Protection of Human Participants and will also be outlined in the IRB-approved informed consent document. Additional unknown risks may occur and, if so, will be identified through diligent monitoring by the PI or PC throughout the conduct of this study. During the informed consent process, participants will be advised of the potential risks of participation as identified in the IRB-approved informed consent document and reminded throughout the study that the researchers should be promptly informed about any concerns regarding potential side effects, adverse events, or clinical deterioration. Participants will also be instructed to notify the PI, PC, and/or designee of any suspected adverse events immediately if possible. The PI or PC will maintain an electronic record of all reported adverse events and notify the ISM of all reportable events as they occur. The ISM will have real-time access to the study database to review and monitor all reported SAE that were reported as related to the intervention. Additionally, the BS will generate and provide de-identified cumulative administrative human participant semi-annual safety reports for the ISM and SMC to review.

2. Reviewing. Adverse events will be initially be assessed and graded by PM and then reviewed by the members of the SMC according to the following MUSC's IRB Adverse Event Reporting Policy http://academicdepartments.musc.edu/research/ori/irb/HRPP/HRPP Guide Section 4.7
   - **Expected/Anticipated**—Identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
   - **Unexpected/Unanticipated**—Not identified in nature, severity, or frequency in the current protocol, informed consent, investigator brochure, or with other current risk information.
   - **More Prevalent**—Occurs more frequently than anticipated or at a higher prevalence than expected.
   - **Serious**—Results in death, is life threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity, cancer, overdose, or causes a congenital anomaly/birth defect.

The relationship of adverse events to study participation will be determined by the SMC according to the MUSC IRB Adverse Event Reporting Policy:

- **Unrelated**—There is not a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.
- **Possibly Related**—The adverse event may have been caused by the drug, device, or intervention, however there is insufficient information to determine the likelihood of this possibility.
- **Related**—There is a reasonable possibility that the adverse event may have been caused by the drug, device or intervention.

3. **AE and UPIRSOS Reporting.** All reportable AE and unanticipated problems (UPIRSOS) experienced by participants will be reported to the NIH/NINR and MUSC IRB in compliance with their Adverse Event Reporting Policy requirements, using the IRB's password protected on-line secure server adverse event reporting system. Within 24 hours after a reportable AE, SAE or unanticipated problem has been reported by the participant, it will be graded by the PM, forwarded to the study's ISM for review, and then will be submitted by the PI to MUSC IRB. The Institutional Official(s) will review the event and discuss the report with the IRB Chair and the Director of the Office of Research Integrity. After IRB review and acknowledgement, the PI will further review, and the PI or PM will forward a copy of the reportable AE, SAE or unanticipated problem and IRB acknowledgement letter to the NIH/NINR Program Officer through MUSC's OSRP. The activities will be reported to the NIH/NINR within 72hrs. In addition, all cumulative reportable AE, SAE and unanticipated problems included in the ISM reports will be submitted to the NIH/NINR in the PI's Annual Progress Reports.
4. **Examples of Potential Reportable Adverse Events:** In accordance with MUSC IRB Adverse Event Reporting Policy, an AE is reportable is it meets all of the following criteria: 1) is unexpected 2) is related and/or possibly related, and 3) is serious and/or suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Additionally, per MUSC's policy all participant deaths, protocol deviations, complaints about the research, and breaches of confidentiality are reportable events. An example of an AE would be new onset chest pain and discomfort (symptom) that could potentially be associated with an acute exacerbation of COPD. The participant's parent reported he/she recently ran out of his/her medication. The steps to be taken include withdrawing the subject from the study and inviting him or her to restart the study after symptoms subside. An example of an SAE would be the death of a participant from acute chest syndrome or stroke, which although would be viewed as unexpected and unrelated to the intervention is nonetheless a reportable serious event. No further steps would be taken except to review, grade and report the event. An example of an unanticipated problem would be the participant trips and falls while retrieving their phone to read a text message reminder. The steps in this case would be to report the event as per the IRB and NINR policy, and to discuss appropriate actions regarding whether the participant should remain in the study with the ISM and SMC. These events and problems will be reported in accordance with the IRB and NIH/NINR policy as noted in Section C.3.

SECTION D. Multi-site Monitoring and Compliance

This is not a multi-site study.

SECTION E. Assessment of External Factors

The PI will conduct a semi-annual assessment of external factors through a review of literature related to new developments in the areas of COPD self-management, symptom management (including pain and fatigue), symptom reporting and other approaches that may have an impact on the safety of participants or on the ethics of the study. To determine whether any changes are necessitated to the study protocol, the ISM and the other members of the SMC will review any identified literature or product safety data that may pose as a potential impact to the risk benefit ratio study and/or safety of study participants.

SECTION F. Interim Analysis

This study aims to test the feasibility of a multi-component, technology-based intervention to promote self-management and symptom management among patients with COPD. To our knowledge, there are

no similar interventions specifically designed for this patient population and purpose. As such, the PI and BS will generate semi-annual qualitative interim analysis reports on a) adverse events; and b) data obtained during phone call and returned end-of-study surveys to understand issues related to the uptake, usability, and adoption of this platform among this population. We will evaluate the screening and enrollment procedures, barriers to participation and retention, including, safety, adherence, acceptability, technology problems encountered if any, and user feedback from the participants and providers. This information gained from this structured process will be used to both guide the refinement of the current protocol and to inform the design of a larger efficacy trial. Interim analysis of outcome variables (dyspnea, pain, and fatigue) was not considered to avoid inexact inferences and increased chance of error due to few data points, as well as potential for bias if interim results were known to the investigators. Therefore, there are no planned stopping rules for this study.

14.0 Withdrawal of Subjects

Participants may voluntarily elect to withdraw their consent at at time for any or no given reason while enrolled in the study. The PI may withdraw participants from the study at any time if they decide it is in the participant's best interest, if they do not follow the investigator's instructions, and/or if they fail to maintain to contact with the researchers or attend study visits. Withdrawals of participants may also occur if there is a protocol violation or early study closure. All data gathered fom withdrawn participants will be used in the analysis plan under an Intention-to-Treat (ITT) model.

15.0 Risks to Subjects

The risks associated with this breathing intervention are not considered greater than those that patients would otherwise be exposed to when receiving normal standard of care (SOC) and performing breathing exercises at home. However, as with all studies, there are inherent risks involved with the conduct of human subject research that gathers Protected Health Information (PHI). Participants will be made aware of these risks during the Informed Consent process. Identified study risks include: Loss of privacy, emotional distress, physical discomfort, and randomization.

Loss of privacy: PHI from participants will be gathered and stored electronically on secure and encrypted servers and there are risks associated for the loss of privacy and confidentiality. As well as having a comprehensive DSMP that details data safety, handling, monitoring, storage and security procedures, we will further minimize the potential for loss of confidentiality through the physical separation of participant names from their research record.

Emotional distress: Some of the questions the researchers ask participants may be upsetting, or make them feel uncomfortable answering them. Patients will be instructed that if they do not wish to answer a question, they can skip it and go to the next question.

Physical distress (a): The lung exercise breathing device used is called Respironics Pflex (model#HS553). Risks involved while performing breathing exercises may include dizziness, feeling short of breath, or coughing during deep inhalation. Patients will be informed that if the experience any distress to immediately stop performing the exercises and if they are having any unusual feelings go to the nearest emergency department.

Physical distress (b): Pulmonary functioning tests (PFT) are non-invasive tests. The risks of this procedure may include: dizziness during the tests, feeling short of breath, and coughing brought on by deep inhalation. Certified MUSC Pulmonologists will monitor participants for any signs of distress and follow institutional procedures for handling adverse events.

Randomization: Participants are being assigned to a study group and treatment program by chance. Group A's breathing exercise program may prove to be less or more effective or have more or less or unknown side effects than Group B or other available treatments.

16.0 Potential Benefits to Subjects or Others

Because this proposal focuses on delivery of preventive COPD care it does represent an immediate benefit to an individual due to the potential for improved preventive care delivery to improve symptoms and morbidity. Furthermore, it is hoped that this proposal will contribute to generalizable scientific knowledge and may change the management of COPD in the future. A product developed with patient/provider engagement could be adopted en-masse and improve COPD patient outcomes on a larger scale. Accordingly, the researchers view the anticipated risk benefit of study participation is favorable.

18.0 Drugs or Devices

This study does not involve the use or storage of any drug product. All investigational supplies and materials are readily commercially available and are not industry regulated. All study supplies (breathing inhalers and tablets) will be inventoried and stored in a locked cabinet, behind a locked door by the researchers. Study supplies will be dispensed individually to each participants after enrollment and group assignment.