Leveraging Technology to Address Access and Adherence to Conventional Hospital-Based Pulmonary Rehabilitation in Veterans with COPD

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Research Protocol Narrative
(Guidelines for Preparation adapted from VHA Handbook 1202.1)

Title: Leveraging Technology to Address Access and Adherence to Conventional Hospital-Based Pulmonary Rehabilitation in Veterans with COPD

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(1) Rationale

(a) Statement of the Problem.

Conventional, hospital-based pulmonary rehabilitation (PR) programs are effective and the standard of care in patients with chronic obstructive pulmonary disease (COPD). PR faces two significant problems: (1) most patients with COPD who would benefit from PR cannot access it, and 2) there is no effective strategy to maintain exercise adherence and benefits after completing PR. This application addresses both issues. We propose a randomized controlled trial (RCT) to test the efficacy of an Internet-mediated, pedometer-based intervention to increase physical activity (PA) in persons with COPD who cannot access PR, compared to usual care. We also propose a non-randomized study to explore the ability of the technology-based intervention to maintain PA, exercise adherence, and clinical benefits, after persons with COPD complete conventional PR.

COPD affects more than 16 million individuals in the United States and is the nation's third leading cause of death. Patients served by the Veterans Health Administration have a high prevalence of COPD at 11-19%. Despite maximal medical therapy, patients with COPD characteristically experience breathlessness, which leads to a downward spiral of physical inactivity, deconditioning, and functional disability. PA, assessed by questionnaire or directly measured with accelerometry, is significantly reduced even at the early stages of disease. Low PA is associated with poor outcomes in COPD--increased risk of acute exacerbations (AEs), hospitalizations, and death, independent of lung function. Thus, PA may be a modifiable factor that impacts risk of COPD-related morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend regular PA for all patients as standard of care.

Conventional, supervised PR programs clearly reduce breathlessness, and improve health-related quality of life (HRQL) and exercise capacity. However, they face significant challenges of access and adherence. The majority of patients with COPD who would benefit from PR cannot access it. Programs are typically based at large medical centers or outpatient medical offices, require specialized resources, and ask patients to travel 2-3 times a week—major barriers for the many Veterans who are geographically dispersed. In addition, there is no effective strategy to maintain PA and exercise adherence, and extend the benefits of PR, after patients complete a PR program. PR programs, typically 9-12 weeks in duration, focus on short-term aerobic fitness, rather than long-term engagement in PA. In the absence of a maintenance strategy, benefits diminish toward pre-intervention levels as early as 3-6 months after program completion. Disappointingly, for those who complete a PR program, less than half are regular walkers one year later.

We developed Every Step Counts (ESC), a technology-mediated intervention based on the Behavioral Theory of Self-Regulation, to target sedentary behavior, promote PA, and alleviate deconditioning. ESC couples a dynamic website with pedometer use to directly monitor step counts. The website provides individualized step-count goals, iterative feedback, education on disease self-management, motivation, and an online community of social support. In two randomized studies in Veterans with COPD (Moy RRD CDA-2 and Richardson HSRD Merit), we demonstrated ESC's safety, feasibility, and efficacy to increase PA. Accessible via the Internet with availability from home at any time, ESC could be an ideal low-cost platform to address the limitations of conventional PR. ESC may be an efficacious strategy to promote PA in the many patients who cannot attend PR, and may maintain exercise adherence and benefits after patients complete a PR program.

(b) Hypotheses or Key Question.

We propose to study the efficacy of the ESC intervention to increase PA in persons with COPD who cannot access conventional PR. We propose a RCT to randomize 120 participants referred to PR but who cannot attend. They will be randomized 1:1 to ESC or usual care for 3 months. In the ESC group, participants will be

instructed to reach the step-count goals with moderate intensity exercise. The usual care group will receive general written instructions to engage in moderate intensity exercise. We will also conduct a non-randomized study in 96 persons with COPD who have completed conventional PR to explore the ability of ESC to maintain engagement in PA and exercise, and extend the benefits of PR, for up to12 months. We will also add a critical pre-implementation component to this study that will gather data from the perspective of patients and organizational stakeholders (e.g., providers, administrative staff) who are involved in the care for COPD patients at VA Boston, and cost data of whether implementing ESC is economically feasible.

This study has the potential to provide an immediate solution to a pressing clinical need and change our standard of care. Our technology-based intervention may be an efficacious strategy to promote PA, ameliorating deconditioning and functional disability, in the millions of Veterans with COPD who cannot access a conventional hospital-based PR program. These patients would otherwise receive nothing.

(c) Specific Objectives.

Our technology-based PA platform is potentially an ideal solution to address the access and adherence barriers of conventional PR. It may be particularly efficacious in the subgroup of highly debilitated patients with COPD who would benefit from PR but cannot access it and currently receive nothing. Our intervention can reach rural Veterans. ESC is safe and engaging in persons with COPD. Increasing PA can improve exercise capacity. Building on our previous work, our proposal focuses on a high need population who would benefit from even small increases in PA. We propose a rigorous approach that will provide evidence for web-based health programs which are a vital step forward in the care of Veterans. We demonstrate our ability to recruit and retain participants and our experience with outcome assessments and repeated measure analyses. The proposed project 1) focuses on a highly significant health problem, 2) has a sound theoretical foundation, 3) uses an innovative approach with proven efficacy, 4) has fundamental data supporting the likely success of the project, and 5) has an experienced multidisciplinary team. This proposal has high potential to significantly impact the care of a vulnerable elderly population with chronic disease.

Primary Aim 1: Determine the efficacy of a web-based intervention, ESC, to increase PA (measured directly with a pedometer and a questionnaire that assesses intensity), compared to usual care, in persons with COPD who are referred to conventional PR but who cannot access it.

Secondary Aim 2: Estimate the effect of the ESC intervention on (a) exercise adherence, (b) exercise self-efficacy, (c) HRQL, (d) dyspnea, (e) anxiety and depression, (f) exercise capacity, and (g) risk of acute exacerbations and COPD-related hospitalizations, compared to usual care.

Exploratory Aim 3: Assess the ability of ESC to maintain PA and exercise adherence, and extend the benefits of PR, in participants with COPD who have completed conventional PR.

Exploratory Aim 4: Conduct a cost-effectiveness analysis of ESC by estimating direct costs and effectiveness of ESC including downstream expenditures from related healthcare utilization.

Exploratory Aim 5: Assess VA employee stakeholders' perceptions of ESC, and identify potential barriers and facilitators to future implementation of ESC.

(2) Background and Significance

(a) Background.

COPD is a Major Chronic Disease among Veterans that Impairs Functional Status.

Chronic obstructive pulmonary disease (COPD), a major cause of global morbidity, is projected to become the third leading cause of death in the world by 2020 (1,2). Patients served by the Veterans Health Administration (VHA) have a high prevalence of COPD at 11-19% (3); in VISN1 in FY 2017, 9% of outpatient Veterans had the ICD-10 diagnosis of COPD. Annually, nearly 500,000 Veterans receive care for COPD, with acute exacerbations (AEs) the 4th leading discharge diagnosis from VA hospitals (4,5). Despite maximal medical therapy, patients with COPD characteristically experience breathlessness, which leads to a downward spiral of sedentary behavior, physical inactivity, muscle deconditioning, and functional disability (6-9). Even at the early stages of disease, persons with COPD spend significantly greater amounts of time being sedentary, and thus reduced time in physical activity (PA), compared to healthy subjects (10-12). COPD is also associated with

aging-related comorbidities such as cardiovascular disease, diabetes mellitus, and osteoporosis—all of which may further contribute to functional limitations (13,14).

Persons with COPD with Higher Levels of Physical Activity have Better Outcomes.

Engagement in PA, assessed by questionnaire or directly measured with accelerometry, is a modifiable health behavior that affects COPD-specific outcomes, independent of lung function (15-22). Persons with COPD with a higher daily step count have a significantly lower risk of dying, independent of forced expiratory volume in one second (FEV_1) (16-18). We have shown that persons who walked the least at study entry have risks that are 2 and 6 times higher for AEs and COPD-related hospitalizations, respectively, compared to those who walked the most over a median follow-up of 16 months (19). Patient self-report of any moderate to vigorous PA (MVPA) predicted a lower risk of 30-day hospital readmission after an index COPD hospitalization, compared to those who reported no MVPA (20). These studies of daily step count, of any amount and intensity, support that every step walked can positively impact the disease course (16-22). Based on these compelling observational studies, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend regular PA for all persons with stable COPD as standard of care (6).

Conventional Pulmonary Rehabilitation has Significant Barriers to Access and Adherence.

The current standard of care to promote PA can be broadly separated into (1) exercise counseling and (2) referral to conventional, supervised pulmonary rehabilitation (PR) (23-24). Brief, episodic general advice to increase PA from a healthcare provider has limited success (23). Conventional, supervised PR programs clearly reduce breathlessness, and improve health-related quality of life (HRQL) and exercise capacity (24). By reducing overall muscle deconditioning, PR programs optimize symptoms, PA, and exercise capacity despite irreversible lung disease in COPD (24). Although PR is an integral part of the clinical management of patients with COPD, PR programs face two significant problems: (1) most patients who would benefit from PR cannot access it, and (2) there is no effective strategy to maintain engagement in PA and benefits after patients complete a PR program (25,26). Programs are available to only a small fraction of patients with COPD. The American Association of Cardiovascular and Pulmonary Rehabilitation website lists 561 certified PR programs in the US for the estimated 16 million Americans diagnosed with COPD (24). Less than 13% of the potential candidates who would benefit from PR are referred by their healthcare providers (27). An analysis of over 33,000 Medicare beneficiaries with COPD from January 1, 2003 to December 31, 2012 showed that only 1,239 persons (3.7%) used PR in 2012, with a dismal increase in utilization of 1.1% over the 10 years (28). There is geographic disparity in availability since most programs are located at tertiary care centers and require patients to travel to the program 2-3 times a week (29-31). In the National Emphysema Treatment Trial, participants who lived > 36 miles from the treatment facility were less likely to complete PR (32,33). In the VA with regional medical centers, distance is a significant barrier. For those who do complete conventional PR, there is no standardized intervention to maintain PA and the benefits of PR (24,26,34-36). PR programs, typically 9-12 weeks in duration, focus on short-term aerobic fitness and exercise capacity; they do not consistently result in sustained increases in PA assessed by community-based walking (37). Only 41% of persons described themselves as regular walkers in the year after completion of PR (38). In the absence of a maintenance strategy, gains in exercise capacity and HRQL diminish toward pre-intervention levels as early as 3-6 months after program completion (24,39).

Promoting Physical Activity is an Important First Step on the Path to Increasing Aerobic Fitness.

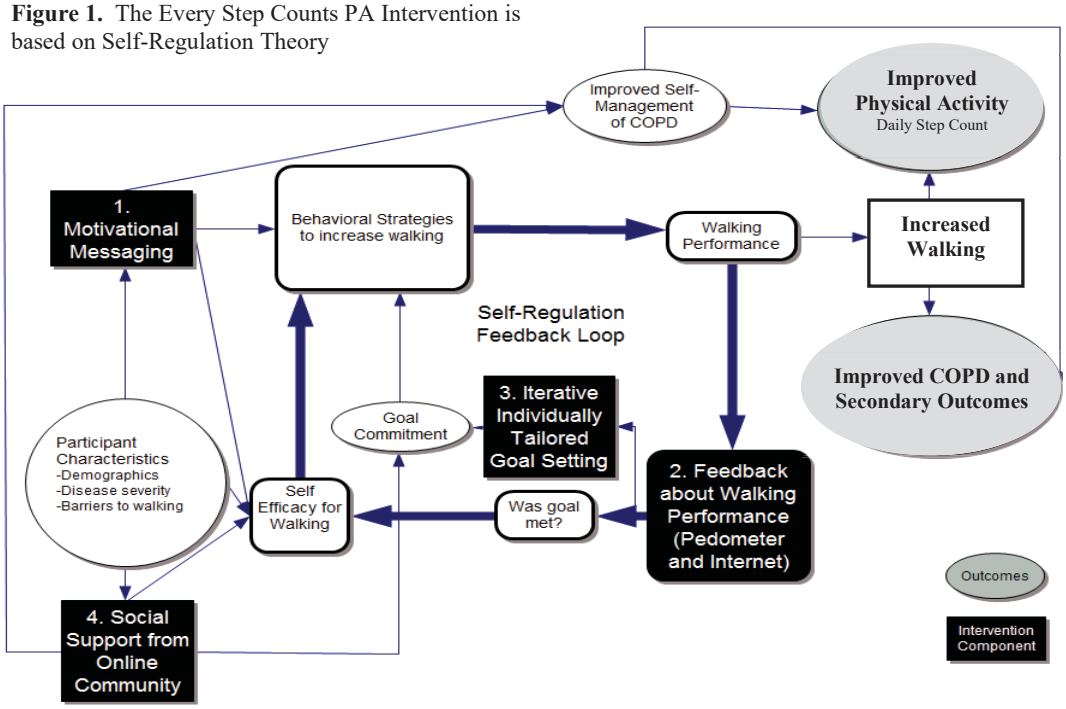
Increasing PA and improving exercise capacity are two related, but distinct, goals in COPD management (15,40). Exercise capacity is the amount of exercise patients are physically capable of doing, while PA reflects the amount of activity patients actually perform in their everyday lives (41). Unlike non-COPD populations, the symptom of breathlessness drives the negative cycle leading to functional limitation in the COPD population. Dyspnea leads to sedentary behavior and physical inactivity; muscle disuse leads to deconditioning and lower limb muscle dysfunction; any further PA results in more dyspnea even in the absence of any deterioration in lung function (6-9). Traditionally, hospital-based supervised PR programs have focused on short-term improvements in exercise capacity, as measured by in-clinic tests like the 6-minute walk test (6MWT) (24). However, promoting lifestyle and community-based PA has emerged as an equally important goal in the care of patients with COPD

(15,40). Higher levels of PA, directly measured with pedometers and accelerometers, are associated with better outcomes in COPD--decreased risk of AEs, hospitalizations, and death--independent of lung function (16,19). Getting patients to walk more to ameliorate existing or prevent further deconditioning prepares the patient to engage in higher intensity exercise training for future gains in exercise capacity. Increasing PA, of any amount and intensity, is the first, but distinct step in a pathway to increasing aerobic fitness and exercise capacity in this population. Interestingly, conventional PR, which improves exercise capacity, does not always increase PA in the home setting (37-39,42,43). Since PR is inaccessible to the majority of persons with COPD and it does not consistently increase PA, there is a need to bring an intervention to the patient to promote engagement in PA and exercise.

Every Step Counts Couples a Website with a Pedometer to Promote Physical Activity.

We developed Every Step Counts (ESC) to increase lifestyle PA (decrease sedentary time), alleviate existing and prevent further deconditioning, and lessen the burden of disease in COPD (44-47). ESC is a dynamic, web-based program, easily accessed from home via a Universal Resource Locator (URL), that interfaces with a pedometer. Dr. Richardson (Co-Investigator) originally developed the intervention to promote walking in sedentary persons with cardiovascular disease risk factors (44,45). The intervention is based on Self-Regulation Theory which emphasizes an iterative process of behavior change (48-50) (Figure 1). Persons working towards a behavioral goal learn from successes and failures, and use this knowledge to develop effective behavioral strategies to achieve their goal. Accurate self-monitoring, feedback, goal setting, and social support are critical components of the cycle of self-regulation (48-50). ESC supports the cycle of self-regulation with four unique components to promote walking: 1) objective walking assessment and iterative feedback, 2) individualized step-count goals, 3) motivational messages and educational content, and 4) online community (Figure 1).

Figure 1. The Every Step Counts PA Intervention is based on Self-Regulation Theory



1) Objective Walking Assessment and Feedback: The Omron HJ-720ITC (Omron) pedometer has been used in our research program because it accurately measures step counts in the majority of persons with COPD and interfaces with our web-based platform (51). Participants can upload date and time-stamped step-count data to the website using their personal computer. They can view detailed graphs that provide their most up-to-date walking history by the hour, day, or week (Figure 2). The pedometer provides real-time feedback with on-instrument display of step counts.

2) Individualized Step-Count Goals: Uniquely, ESC uses an automated algorithm to compute gradually incrementing, individualized step-count goals (46,47). Updated weekly goals are personalized using step-count data uploaded by the participant, accurately reflecting current levels of walking. Goals are not necessarily increasing over time. If a participant is sick and records low step counts for one week, the subsequent week's goal will be lower than that for the week when the participant was sick. Goals are clearly displayed on the webpage (Figure 2).

3) Motivational Messages and Educational Content: Unlike commercially available devices and applications, our website contains motivational and educational content developed by pulmonologists and behavioral psychologists that addresses the specific needs of persons with COPD. They face general and disease-specific barriers to starting and maintaining a walking program (52,53). Engagement in PA depends on many factors such as dyspnea, anxiety, depression, exercise self-efficacy, social support, the physical environment, and season. The online motivational messages provide cognitive and behavioral techniques for addressing these factors and overcoming barriers. Online educational content about disease management and the benefits of PA provides strategies to adopt and maintain PA routines. These features are intended to promote exercise self-efficacy and confidence, and encourage engagement in PA. Content of the online education mirrors topics commonly taught in the education component of conventional PR; namely, dyspnea management, medication use, oxygen use, nutrition, anxiety and depression, strategies for long-term behavior change, smoking cessation, COPD self-management, and management of AEs. The educational tips fire every other day and the motivational messages fire monthly, resulting in a dynamic and engaging website.

4) Online Community: The web-based intervention fosters social support with an online forum where users can 'talk' to each other to share strategies to overcome barriers to exercise. The forum content is constantly changing. We have conducted regular fun events such as a "Walk across America" challenge. We added everyone's step counts each week to reach US destinations, and then rewarded everyone with a flag pin when they reached the opposite coast. Richardson et al. showed that subjects with access to an online community remained engaged for a longer time and were less likely to drop out than those without access to an online community (45). Furthermore, participants who posted more frequently on the online community increased their daily step counts more that those who posted less frequently (45).

Unlike currently available devices and applications that monitor PA and provide static goals generalized for healthy individuals, our automated goal-setting algorithm provides dynamic and individually tailored step-count goals. Our intervention has COPD-specific content that is unique. There is a monthly "In the Spotlight" where a pulmonologist posts up-to-date content on COPD care and research (Figure 2). Our theory-based intervention is simple, automated, and the most rigorously studied to date (54-57). There is no other website currently available that has the 4 unique components offered by ESC (feedback, individualized goals, education and motivation, and online community). The efficacy of our ESC intervention to increase PA has been documented in 2 randomized controlled trials (RCTs) (Richardson HSRD Merit and Moy RRD CDA-2) (54-57; see Preliminary Studies). A separate study (Moy VA RRD Merit "The Effect of Physical Activity Promotion on Short and Long-term Outcomes in COPD") is currently enrolling participants to understand the causal relationships between changes in daily step count and changes in COPD outcomes such as exercise capacity, dyspnea, HRQL, and risk for AEs and COPD-related hospitalizations. This ongoing study is distinct from our proposed work, and enrollment will end before the proposed work begins.

Figure 2. Example of webpage with 4 core components

Research Team

Our research team has multidisciplinary experience in performing clinical research in COPD, assessing PA and clinical measures of COPD status, using web-based interventions, and performing advanced statistical analyses. As a Staff Pulmonologist, Director of the Pulmonary Rehabilitation Center at VA Boston, and Associate Professor of Medicine Harvard Medical School, Marilyn Moy, MD has witnessed first-hand the functional disability experienced by Veterans with COPD. Dr. Moy has extensive experience assessing short- and long-term outcomes in persons with COPD. She has expertise in monitoring PA, activity data collection, and analysis of PA data. Dr. Moy has published one of the first papers characterizing daily step count in a US cohort with COPD. Caroline Richardson, MD, Professor of Family Medicine at the University of Michigan has collaborated with Dr. Moy on her projects examining web-based interventions to promote walking in persons with COPD. Dr. Richardson developed the web-based exercise intervention and has expertise in the objective assessment of PA, the epidemiology of PA and cardiovascular disease, and the development and testing of interventions to promote PA in adults with chronic disease. Eric Garshick, MD is Associate Chief of the Pulmonary Section at VA Boston and a senior researcher with expertise in study design and statistical analyses of cross-sectional and longitudinal data. In addition, DeAnna Mori, Ph.D., Director of Behavioral Medicine at VA Boston, has expertise in using telehealth interventions to enhance behavioral compliance and promote PA in patients with diabetes mellitus. She will provide content and methodological expertise. David Gagnon, Ph.D. has expertise in analyzing clinical trials data and modeling longitudinal data. Drs. Moy, Richardson, Garshick, Mori and Gagnon have coauthored several manuscripts. Stephanie Robinson, Ph.D., received funding from the National Heart Lung and Blood Institute's Massachusetts Consortium for Cardiopulmonary Implementation Science Scholars program to add a critical pre-implementation component to this work. Dr. Robinson is an investigator at the Center for Healthcare Organization and Implementation Research (CHOIR) and has co-authored work with Dr. Moy. Collectively, they have the expertise in COPD assessments, pedometers and web-based PA interventions, behavioral medicine, and advance statistical methods to successfully complete the proposed work.

(b) Significance.

ESC is one of the first technology-based interventions that have been demonstrated to increase PA in COPD. Unlike other PA interventions described to date (58-61), ESC's personalized goal-setting algorithm, COPD-specific content, and complete automation are unique and innovative. Given its low cost, and convenience of being available any time at home via a URL, ESC appears ideal to address the limitations of access and adherence in conventional PR. This proposal has high public health significance, providing an immediate solution to a pressing clinical need. Our web-based intervention may be an efficacious strategy to promote and sustain PA, ameliorating deconditioning and functional disability, in the millions of Veterans with COPD who cannot access a conventional hospital-based PR program and who would otherwise receive nothing. The results of our study can bring an exercise program directly to patients and improve the rehabilitative care of persons with COPD.

(c) Relevance to Veterans Health.

The VHA has a strong commitment to providing care to persons with COPD and supporting research directed at COPD-related disability. The 2012-2016 Strategic Plan of the VHA Office of Research and Development identified chronic disease as an area of focus and specifically includes research in COPD rehabilitation (Strategic Objective 2.11). The proposed research addresses Rehabilitation R&D Service's priority area to improve Veterans' health-related quality of life by reducing disease burden and maximizing functional recovery. The results of this study have strong implications for translation into clinical practice, providing an accessible PA intervention to Veterans with COPD living with significant disability. Leveraging technology to enhance access and adherence is aligned with the VA's FY 2018 − 2024 Strategic Plan which clearly envisions increased trends in usage of technology by Veterans. "VA is rapidly expanding the use of telehealth, mobile app, online applications, and videoconferencing capabilities to deliver benefits and care to Veterans no matter where they live. Most importantly, improvements to mobile devices and apps will enable VA providers to connect to Veterans across the country to provide timely and convenient care." The study's overall impact on VHA can be enormous.

(3) Work Accomplished

Funded by Rehabilitation R&D CDA-1 (2006-2009), CDA-2 (2009-2014), and Merit O1150-R (2014-2018) to Dr. Moy, we have published the peer-reviewed papers listed below:

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(4) Work Proposed

(a) Provide a timetable describing the sequence of the proposed research.

	Yr 1				Yr 2				Yr 3				Yr 4				Yr 5			
Activity	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Train Staff																				
Obtain IRB Approval																				
Enroll and Randomize to ESC or Usual Care																				
3-Month Follow-up in RCT																				
Enroll in Observational Cohort Study																				
3-12 Months of Follow-Up Observational Cohort Study																				
Data Cleaning, Analyses, Manuscript Preparation																				

(b) It is useful to specifically relate each experiment to particular hypotheses and/or key questions. Describe the research design, methods, and procedures to be used to accomplish the specific aims of the application.

Overview of Study Designs.

During the Covid-19 pandemic, we will virtually conduct all enrollment, baseline and follow-up study visits including the qualitative interview using a combination of telephone calls and the use of the non-public facing, secure, and fully VA-authorized platform Cisco Webex for video interactions with study participants. PHI and PII will not be recorded or stored using Webex. Participants will be allowed to receive VA emails (encrypted via Azure RMS) using their personal emails and to use their personal emails to dial in to Webex.

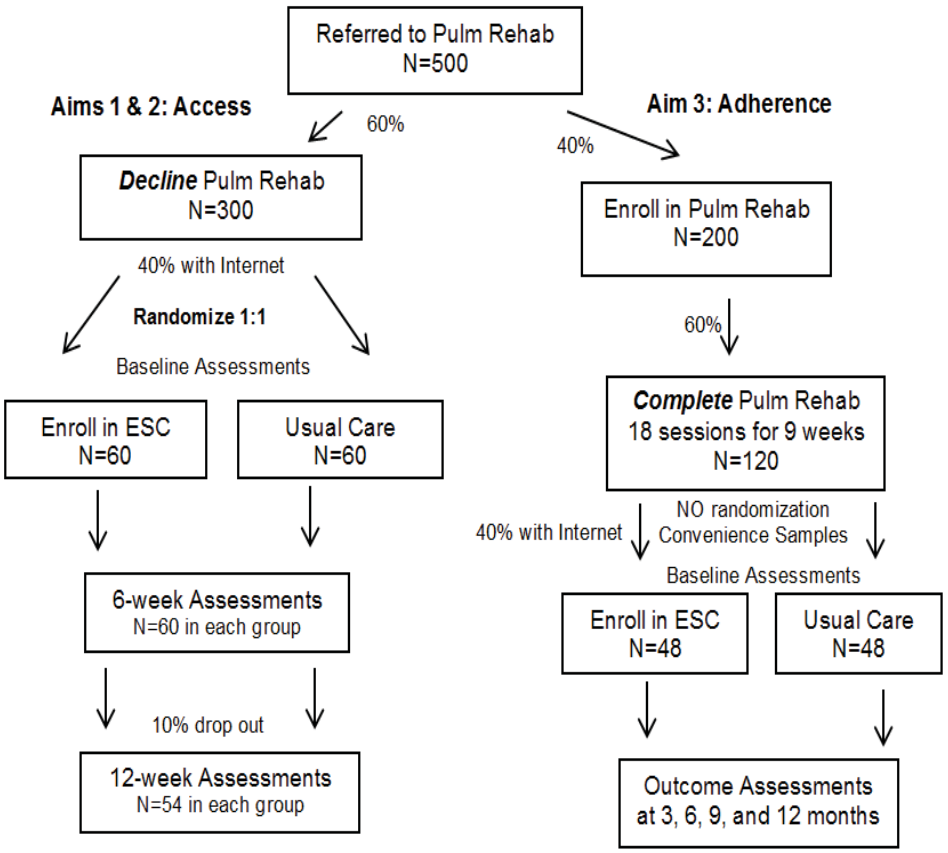
As of June 2021, we will give participants the option to take part in some or all of the study visit in person. The in-person visit will include obtaining informed consent (baseline visit only), performing the 6-minute walk test, performing a blood draw, and/or administering questionnaires at the baseline and follow up study visits.

We propose 2 separate studies to address the issues of access and adherence in conventional PR in COPD. This 2-pronged approach will most efficiently accomplish our Specific Aims. As our primary aim, we propose a RCT to study the efficacy of ESC to increase PA in persons with COPD who decline PR, compared to usual care. As an exploratory aim, we propose a non-randomized study to examine the ability of ESC to maintain PA and exercise adherence, and extend the benefits of PR, after completion of conventional PR. These

study designs allow all persons willing to enroll in conventional PR to receive it, since PR is standard of care. We do not propose a direct comparison of ESC with conventional PR.

In 2017, VA Boston's PR program received 167 consults to evaluate patients for PR. Of these, 101 (60%) declined to come in for an evaluation when called by the clinical staff. The remaining 40%, the majority of whom have COPD, enrolled in the PR program. Approximately 60% of enrolled patients completed all 18 sessions of the program, and 67% completed at least 14 sessions. These numbers, typical of other institutions nationally, provide conservative estimates for our study design and highlight (1) the high percentage of patients whom providers believe would benefit from PR but who do not access the program, and (2) the feasibility of achieving our recruitment goals for the proposal.

The two studies will enroll a total of 300 participants (i.e., enroll is the number who sign the ICF) concurrently over 48 months (Figure). For Aim 5, we will also recruit 15 VA Boston Healthcare System employees who are involved in the care of patients with COPD and/or pulmonary rehabilitation. Approximately 500 patients with COPD will be referred to PR. We anticipate that 60% will decline PR and be asked to participate in our RCT. We estimate that 40% of those who decline PR will have Internet access and agree to participate. We anticipate that 120 subjects will be randomized 1:1 to either ESC or usual care. In this proposal, ESC will include exercise instructions to reach the step-count goals with moderate intensity walking using a regimen that was previously studied in healthy adults and subsequently shown to be safe in persons with COPD (66,67). Daily step count at 12 weeks (3 months) is the primary outcome. Secondary outcomes include exercise adherence, exercise self-efficacy, HRQL, dyspnea, anxiety, and depression. We choose these secondary outcomes as they are addressed in the educational and motivational content guided by Self-Regulation Theory. The ESC website provides cognitive and behavioral skills to adopt and maintain PA routines. Thus, we examine whether ESC impacts these secondary outcomes, since improvements could lead to increased engagement in PA. We will also assess exercise capacity and healthcare utilization to explore whether they are associated with changes in PA. Longitudinal follow-up will occur at 6 and 12 weeks. At the 12-week assessment, we will ask a consecutive sample of patients if they wish to participate in an optional 30-45 minute qualitative feedback interview that will ask them about their experience using ESC. We will aim to sample 15 patients from each study (CAPRI-1 and CAPRI-2). An iterative, inductive and deductive process will be used. As new, insightful information emerges, we will adjust the interview guide to ask questions about concepts that emerged during the process. Interviews will be audio recorded and professionally transcribed. Initially, we will interview 30 patients. Interviews will continue until few new concepts are emerging and/or saturation is reached if the anticipated interviews are insufficient. In qualitative research, sample size is determined by saturation, or when few new themes emerge with additional interviews. The number of interviews is in concordance with other robust qualitative studies. A phone call and assessments will occur at 3 months. We conservatively estimate a 10% loss to follow-up at 3 months. In our previous studies, loss to follow-up has been low: 4.4% at 3 months, 4.2%



at 4 months, and 10.5% at 12 months (55-57). We choose a follow-up duration of 3 months to mirror the typical 9 to 12-week duration of conventional PR. For our exploratory aim, we estimate that 40% of referred patients will enroll in conventional PR (Figure). We conservatively estimate that 60% of those in the PR group will complete all 18 sessions and 40% will have Internet access and agree to enroll in the study. We will enroll a convenience sample of 48 subjects in the ESC group and 48 subjects in the usual care group for a minimum of 3 months and a maximum of 12 months, depending on date of study entry. Outcome assessments will occur at the end of PR and then every 3 months. A follow-up duration of up to 12 months will allow long-term assessment of PA engagement, exercise adherence, and maintenance of benefits after PR completion. To perform the cost-effectiveness analysis, we will estimate intervention costs, including labor costs which will include activity logs kept by the research assistants.

For both studies, the Fitbit Inspire HR will be the pedometer used as part of the ESC intervention and for outcome assessment of daily step counts. We will ask participants to voluntarily choose to put their step counts on the Fitbit website. The Fitbit Inspire HR captures purposeful walking and tracks daily step counts for goal calculations (51). Although there are many pedometers and PA trackers commercially available, we choose the Fitbit Inspire HR because it is technically able to interface with our website and has good accuracy in the COPD population (69).

(c) Describe the experimental design and/or approach and how the data will be collected, analyzed and interpreted. Describe new methodologies to be used and why they are preferred over existing methods. Include the following.

STUDY #1

Specific Aims 1 and 2: Randomized Controlled Trial in Persons who Decline Conventional PR

Study Population

All patients with a diagnosis of COPD who are referred to the VA Boston PR program and decline PR with the clinical staff will be asked to participate in this RCT by the research staff. We emphasize that standard clinical care is the highest priority. Patients referred to PR will receive PR if they want it. Study participation will be offered by research staff after it is absolutely clear to the clinical staff that the patient will not enroll in PR. Patients are not allowed to self-select into the PR or research study groups. Recruitment will occur over 48 months to randomize 120 subjects in the RCT (Figure 6). We anticipate enrolling 3-4 eligible subjects each month through the first quarter of Year 5. We will also recruit by sending a recruitment letter to patients who have visited the Outpatient Pulmonary Clinics since 2005. We will also recruit from patients with COPD who have been seen in the Pulmonary Function Laboratory, the Women's Health Clinic, and the Primary Care Clinics. For interested persons, we will phone screen for those who meet national recommendations for referral to PR but who have not participated in PR. PR is recommended for patients with COPD who experience shortness of breath that interferes with daily activities despite use of medication. Participants who have previously received care at the VA Boston Healthcare System but have moved away from the VA Boston during recruitment, enrollment, or follow-up will still qualify to participate in this study if they are interested.

Informed Consent

If informed consent is conducted remotely, documentation of written informed consent will be obtained as follows. We will provide participants with the Informed Consent and HIPAA Authorization forms using either (1) Docusign in real time or (2) overnight UPS in which case study staff will overnight express ship the paper versions of the consent forms and obtain consent by VVC and not start activities until the participant overnight express ships the signed forms back to us.

Study staff will document in the CPRS research note that the signing of the Informed Consent and HIPAA Authorization was witnessed. We will document the consent process on a "note to file." We will begin study activities after obtaining the written informed consent.

If the baseline visit is conducted in person, study staff will conduct informed consent with the subject. Signing of the informed consent and all research testing will occur at VA Boston. Study staff will make a copy of the informed consent to give to the participant at the in-person baseline visit.

As of October 2021, for virtual study visits, we will be obtaining virtual consent with the VA application Docusign. We were approved for Docusign on 9/2/2021 by ORD and have attended the training sessions. If Docusign is unable to work during virtual study visits, study staff will overnight express ship the paper versions of the consent forms and obtain consent by VVC and not start activities until the participant overnight express ships the forms back to us.

Baseline Visit

When interested subjects are scheduled for the baseline visit, study staff will email, fax, or hand deliver a medical clearance form to their healthcare provider for approval which must be received prior to randomization and assignment to a study arm. At the baseline study visit, after informed consent has been obtained, we will review the participant's medical history and obtain information about demographics, cigarette use, and prior participation in pulmonary rehabilitation. Comorbidities of coronary artery disease, congestive heart failure, diabetes, and other diagnoses that affect the lower limbs (osteoarthritis or degenerative joint disease, hip or knee replacements, rheumatoid arthritis, chronic low back pain, lumbar spine disease, peripheral vascular disease, or peripheral neuropathy) will be noted. We will record medication use and current use of supplemental oxygen. Weight and height will be measured and/or obtained from the medical records. This is for the most recent measurements of height and height for the calculation of body mass index (BMI). We will assess history of AEs, antibiotic/corticosteroid use, ER visits, and hospitalizations in the 12 months prior to study entry. Season of enrollment will be recorded since participants will most likely experience changes in season during the 3-month study period (57,64). Baseline data will characterize subjects, ensure balance between groups, and identify potential confounders. Assessment of primary and secondary outcomes will be completed in both groups (described in Table 1). Participants will complete the questionnaires on their own, while study staff stay on the video call with them to answer any questions they may have. To assess intensity of PA reported at baseline, we will administer the 9-item Rapid Assessment of Physical Activity (RAPA) which categorizes activity level as sedentary, underactive, and active (67,75). If a subject does not have time during the study visit to complete the study-related questionnaires, he/she can finish the questionnaires at a time after the visit. If study is conducted virtually, questionnaires will be returned to study staff in a pre-paid mailer.

If study is conducted in person, three tubes of blood (2 tablespoons) will be drawn by venipuncture, promptly hand-delivered to Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) at VA Boston, and processed and stored for biomarker analyses.

We will verify the accuracy of the Fitbit in each subject by comparing measured to manually counted steps during a standardized in-clinic walk of 800 feet (244 meters). Subjects can use assistive devices such as a cane if they typically use one for walking. Persons evaluated in person and using an assistive device in whom the Fitbit has >90% accuracy in capturing step counts during the in-clinic walk will be eligible.

Subjects will be asked to wear the Fitbit for 10 days to assess baseline level of walking. Research staff will assist participants in setting up Fitbit pedometers. Subjects will choose a username and password that will allow them to log in to the study website if assigned to the intervention. Subjects will provide the phone number which they will use to receive the randomization assignment. The Fitbit will have a sticker covering the digital display to prevent feedback. Subjects will be instructed to perform their usual physical activities and exercise. In addition to obtaining baseline step-count data, this run-in period will allow us to gauge subject compliance with wearing the devices.

All subjects will be asked to wear the devices for 10 days to assess baseline level of walking. They will be given detailed instructions on use of the pedometer, which will include instructions on how to use the Fitbit, so they can upload their step count data at home. This Fitbit account setup will be for uploading the data to the study team and we will work with participants to choose account username and passwords that will not include any identifying information. Subjects will only be able to access their step counts through the study website if randomized to the intervention. Participants with $\geq$ 7 wear days on the Fitbit will be eligible for randomization. A wear day is defined as one with $\geq$200 steps per day on the Fitbit. All participants will be given a prepaid mailer.

Those randomized to the control group will return the Fitbit to study staff. Those randomized to the intervention group will keep the Fitbit. Medical clearance will have been obtained from a healthcare provider prior to randomization.

It is expected that some subjects may be unable to complete all the proposed assessments during the study visits. Furthermore, subjects may refuse to complete any portion of the study assessments. If willing, subjects may complete any missed assessments on a later date and return the questionnaires to study staff by USPS.

The following inclusion and exclusion criteria describe the characteristics of the study population, which will include men and women aged 40 and older.

Inclusion Criteria are:

a) Male and female subjects, greater than or equal to 40 years of age
b) Clinical diagnosis of COPD defined as: 1 of the following as testing-based evidence of COPD (any documented $FEV_1/FVC < 0.70$, chest CT evidence of emphysema) AND at least 2 of the following as clinical evidence of COPD (≥ 10 pack-year cigarette smoking history, taking an antimuscarinic inhaler such as ipratropium or tiotropium, diagnosis of COPD written in a provider's note or on problem list)
c) Have declined participation in a conventional pulmonary rehabilitation program
d) Medical clearance from healthcare provider to participate in an exercise program
e) Have Internet connection and Bluetooth capability, and access to video platform Cisco Webex[#]
f) Answer yes to "Does your shortness of breath interfere with your functioning?"
g) Answer no to "Are you interested in joining PR now? If they answer yes, they will be ineligible and the PI will place a consult to PR for further evaluation
h) Competent to provide informed consent
i) Willingness to make return visits and be available by telephone for duration of study

Exclusion Criteria are:

a) COPD exacerbation in the previous 1 month
b) Prescribed supplemental oxygen for activity[+]
c) Inability to ambulate with or without assistance
d) Use of assistive device for walking such as cane or walker[*]
e) Inability to complete questionnaires
f) Inability to collect at least 7 of 10 days of baseline step counts
g) Participation in a pulmonary rehabilitation program at time of screening or within the previous 3 months
h) Participation in another exercise-related research study at time of screening
i) Plans to participate in an exercise-related research study in the next 3 months
j) Average baseline step counts of greater than or equal to 10,000 steps per week

[#]For those who wish to participate virtually.

[+]If participant has an in-person visit, oxygen will be assessed during the 6MWT to determine if subject's oxygen is stable during activity. If a participant has an in-person visit and oxygen is documented during the 6MWT and stays above 85%, he/she will be eligible to participate.

[*]If a participant uses an assistive walking device but we have previously shown that the Fitbit pedometer is accurate in him/her (before the study was transitioned to virtual) he/she will be allowed to participate in the study. If a participant has an in-person visit and Fitbit accuracy is documented during use of the assistive device he/she will be eligible to participate.

Randomization.

Eligible subjects will be randomized 1:1 to (1) verbal and written instructions to exercise (usual care) or (2) pedometer and Internet-mediated walking program (ESC). Since the sample size is relatively small, we will use blocked randomization, with unpredictable block sizes, and a computer-generated sequence of random

numbers, with the allocation scheme concealed and unpredictable. Study staff will call the participant to inform him/her of the assignment. To ensure blinding, study staff communicating randomization assignments to subjects will be different from study staff conducting follow-up assessments.

Verbal and Written Instructions to Exercise (Usual Care).

Using a standardized script at the randomization phone call, study staff will deliver verbal instructions to slowly and steadily increase one's walking and exercise each week. Participants will be asked to perform exercise of moderate intensity for at least 30 minutes on most days of the week, defined as a dyspnea level of 4-5 on the Borg scale and taking 1-2 minutes to recover (66,67). Use of the Borg rating scale for dyspnea will be reviewed with each participant. Exercise is defined as planned PA, outside of activities performed as part of one's daily routine. Exercise can be walking in the community or using exercise equipment at a local gym. Adapted written materials from Huong Nguyen, PhD, which are currently used at the University of Washington and VA Boston, reinforce the verbal instructions. Participants will receive this 45-page spiral-bound book with information about aerobic and strength training exercises, the Borg scale for rating dyspnea, an action plan for identifying symptoms of a COPD AE, and how to resume exercise after a COPD AE. It also contains information about oxygen use during exercise and available resources for smoking cessation. At each study visit, participants will be encouraged to regularly review this written resource to optimize full saturation over time. To measure exercise adherence, subjects will be asked to complete a simple 2-question paper log every day, on which they will track whether they exercised that day. Participants who choose to come into the VA and are usually prescribed oxygen with activity will be instructed to wear oxygen when walking and exercising for the study The next in-person study contacts will be at 6 and 12 weeks, and a phone call at 6 months. The testing window is +/- 4 weeks from the participant's target 6-month phone visit date.

Pedometer and Internet-Mediated Walking Program (ESC).

After randomization to ESC, participants will be instructed to remove the sticker from the Fitbit pedometer and will be mailed detailed instructions about the website. They will be asked to wear the lightweight, unobtrusive Fitbit pedometer every day during the 12-week intervention period. Subjects will be instructed to upload their date and time-stamped step-count data to the study website as often as they wish, but at least weekly. The first goal will be calculated from the baseline step counts. Each Sunday thereafter, the study computer will run the goal calculation algorithm and provide each participant with his/her daily step-count goal for the week. The week's step-count goal will be prominently displayed on each subject's personal study web page in the text and the graphs (Figure 2). Participants will be instructed to exercise and reach their individualized step-count goals with walking of moderate intensity for at least 30 minutes on most days of the week, defined as a dyspnea level of 4-5 on the Borg scale and taking 1-2 minutes to recover (66,67). We will review use of the Borg rating scale for dyspnea. Patients will be reminded that every step counts and some PA is better than none. Subjects will have access to a personalized web page where they can view graphical displays of step counts and walking progress. They will be encouraged to read the motivational and educational messages, and participate in the online community (Figure 2). To measure exercise adherence, subjects will be asked to complete a simple 3-question paper log every day, on which they will track whether they exercised that day. The next in-person study contacts will be at 6 and 12 weeks, and a phone call at 6 months. The testing window is +/- 4 weeks from the participant's target 6-month phone visit date.

Research staff at the University of Michigan will maintain the website on their computer servers. Dr. Richardson and her staff will finalize content and develop specifications of the website for dedicated use with the proposed protocol, beta-test the specifications, monitor step-count data during the intervention phase, maintain the Web-based applications for the intervention, and provide data from the website for analyses.

The specific items involved with developing, testing, and maintaining the website include:

a) Procuring, managing and securing database and Web servers, system-level software and site/user licensing required to run the system.

b) Ongoing management and maintenance of the system and system security throughout the study.
c) Performing website modifications for automated weekly step-count feedback, and educational and motivational messages.
d) Modifying website to include educational content about engaging in moderate intensity exercise.
e) Beta testing website prior to launch and routine regular maintenance.
f) Providing back-up of step-count data. This task also includes automated backup software and scheduling, as well as obtaining and securely storing physical backup media.

g) Capturing, maintaining, and securing delivery of step-count data for analysis.
h) Capturing and reporting data on frequency of website use. Each time a participant logs in, or uses a link, an automated digital log entry occurs.

There is no other website currently available that has all the unique components offered by WEB (feedback, individualized goals, and educational content and motivational messages).

Of note, we have had significant experience working with this website/platform and have not had any adverse events. It is currently used for Dr. Moy's study IRB #2791 that has been approved by the VA Boston IRB. VA Boston IRB protocol #2328 was also approved to use the same website/platform, and is currently in Data Analysis Only. The same rigorous standards to protect security, privacy, and confidentiality of participants and their data will be used in the current study.

Follow-up Research Visits

If conducted virtually, prior to each follow-up visit, study staff will mail the participant the questionnaires and a prepaid return envelope with outcome Assessments (Table 2). Baseline and follow-up testing at 6 and 12 weeks will be conducted by study staff who are blinded to group assignment. At each follow-up visit, study staff will remind participants not to disclose intervention received. Unblinded staff will oversee all tasks related to the exercise logs and the monitoring devices, such as mailing out and handling returned logs/devices and replacing batteries. Follow-up research visits will be conducted when subjects are in stable clinical status, where at least 2 weeks have elapsed since the time of their last dose of prednisone or antibiotic for treatment of a COPD exacerbation. All changes in medication or clinical status will be noted, any potential adverse events recorded.

If conducted in person, at each follow-up visit, study staff will remind participants not to disclose intervention received. Unblinded staff will oversee all tasks related to the exercise logs and the monitoring devices, such as mailing out and handling returned logs/devices and replacing batteries. Follow-up clinic visits will be conducted when subjects are in stable clinical status, where at least 2 weeks have elapsed since the time of their last dose of prednisone or antibiotic for treatment of a COPD exacerbation. All changes in medication or clinical status will be noted, any potential adverse events recorded.

Primary Outcome. Physical Activity: We will assess daily step count to reflect level of PA in both groups. We choose daily step count because it is meaningful to patients and easy to understand, unlike vector magnitude units, and does not depend on algorithms for calculation like energy expenditure (76,77). At baseline, subjects will be instructed to wear the Fitbit for 10 days during all waking hours. The Fitbit Inspire HR is worn on the wrist. The Fitbit data will be used to calculate the first step-count goal if the participant is assigned to the website intervention. At baseline, participants will be instructed to perform their usual PA and exercise. They will be instructed to remove the devices at night and put them in a place where they will remember to wear them first thing in the morning, such as with their alarm clock, watch, eyeglasses, or breathing medicines.

They will be given detailed instructions on use of the pedometer, which will include instructions on how to use the Fitbit, so they can upload their step count data at home. This Fitbit account setup will be for uploading the data to the study team and the account username and password will not include any identifying information. Subjects will only be able to access their step counts through the study website if randomized to the intervention. Participants with $\geq$ 7 wear days on the Fitbit will be eligible for randomization. A wear day is defined as one with $\geq$200 steps per day on the Fitbit.

After baseline monitoring, those assigned to the web-based intervention will be instructed to remove the sticker from their Fitbit and asked to wear it every day. Those assigned to the usual care group will return the Fitbit to study staff.

During the follow-up research visits at 6 and 12 weeks, we choose 14 days of monitoring to achieve the highest reliability and to capture variations seen on weekend days (10,51,64). The usual care group will receive a Fitbit by USPS at weeks 6 and 12 to wear for 14 days and return by postage-paid mailer. In both groups, at the follow-up assessments, the Fitbit will have a sticker covering its face so no feedback is given to the user.
At baseline and follow-up, we will administer the RAPA questionnaire to assess intensity of PA (67,75). Analyses of PA at baseline and follow-up will include daily step count, and the RAPA assessments.

Table 1. RCT Study Measures	Baseline	6 weeks C06	12 weeks C12	6 months P06
Demographics	x			
Comorbidities and Medications	X	x	x	
Daily Step Count	x	x	x	x
6-Minute Walk Test	x	x	x	
800-ft Walk Test	x			
4-meter Gait Speed Test	x		x	
Rapid Assessment of Physical Activity (intensity)	x	x	x	x
Physical Activity Recall Questionnaire	x	x	x	
Barriers to Exercise	x	x	x	
Exercise Adherence (Exercise Logs)	x	x	x	
Exercise Self-Regulatory Efficacy	X	x	x	x
St. George Respiratory Questionnaire	x	x	x	x
Bristol COPD Knowledge Questionnaire	X	x	x	
MMRC Dyspnea scale	X	x	x	
Beck's Depression Inventory-II	x	x	x	
Epworth Sleepiness Scale	x	x	x	
MOS Social Support Survey	x	x	x	
Brief Pain Inventory (short form) and Numerical Rating Scale for Pain	x	x	x	
Healthcare Utilization	X	x	x	x
EQ-5D Health Utilities	X	x	x	
Veterans Rand 36 Item Health Survey (VR-36)	X	x	x	x
CHAMPS Physical Activity Questionnaire	X	x	x	x
Enrollment in Conventional Pulm Rehab			x	x
Qualitative Feedback			x	
Usability Questionnaire			X	
Blood Draw for CRP and IL-6	X		X	
RA Activity Log	X	X	X	

Secondary Outcomes (detailed in Table 1):
a. Exercise Capacity
Performing the 6MWT will be voluntary part of the protocol if the participant is willing to have an in-person study visit. The 6MWT will be performed according to American Thoracic Society (ATS) guidelines (86). Staff performing the 6MWT will be trained in Basic Life Support. Emergency treatments, including nebulizer therapy, an automated external defibrillator, and a code cart, will be available. With standardized prompts, participants will be asked to cover as much distance as possible in 6 minutes. Subjects can use assistive devices such as a cane. Oxygen saturation and Borg dyspnea rating will be assessed before and after the 6MWT is performed. We will take this opportunity to teach participants how to use the Borg scale to engage in exercise of moderate intensity at home. Subjects will use supplemental oxygen if already prescribed oxygen during activity. If oxygen saturation < 85% is observed, subjects will be temporarily excluded (baseline) or suspended from study

participation (follow-up) until evaluated by their primary provider. If the subject is unsteady on his/her feet during the initial short walk to assess device accuracy and is a fall risk, the 6MWT will not be performed. We choose 6MWT distance as the measure of exercise capacity, as opposed to maximum oxygen consumption or workload on a cardiopulmonary exercise tolerance test (CPETT), because it is easy to perform and a minimum clinically important change of 30-54 meters has been established (87,88). Given the burden to the participant, risk of adverse events in this sick group of patients, and the limited information gained since many patients with COPD do not reach anaerobic threshold, we decided against administering CPETTs.

b. Exercise Adherence: We will measure exercise adherence by patient self-report. Subjects in both groups will be asked to complete daily logs. The paper log is intentionally simple to minimize burden and potential influence to be part of the intervention. Subjects will circle a yes/no response to 2-3 questions about whether exercise was performed that day. Subjects will bring completed logs to their follow-up visits or will be given a prepaid return envelope to mail logs to study staff. Exercise adherence, calculated weekly or monthly, will be defined as > 70% of days with self-reported exercise. 70% is chosen since all participants are instructed to exercise most days (5 of the 7 days) each week.

c. Exercise Self-Regulatory Efficacy: The belief in one's ability to self-regulate and exercise regularly when faced with challenges is a key variable that influences engagement in exercise. The Exercise Self-Regulatory Efficacy Scale for persons with COPD measures exercise self-regulation, and incorporates items from Resnick's self-efficacy scale for older adults and McCauley's self-efficacy questionnaire for sedentary adults (78). The 16-item questionnaire is reliable and valid in COPD (78).

d. HRQL: Respiratory-specific HRQL will be assessed with the St. George's Respiratory Questionnaire (SGRQ) (79). We will examine the composite Total Score (SGRQ-TS) as well as the subscales of Activity, Symptoms, and Impact. Lower SGRQ scores indicate better health status. The minimal clinically important difference (MCID) for the SGQR-TS is $\pm$ 4 units (80). The SGRQ has been used extensively in COPD.
d. Dyspnea: The MCID has been determined to be $\pm$ 5 units (82). Dyspnea will also be assessed using the Modified Medical Research Council scale (responses 0-4 with 4 being the most dyspneic) (83).

e. Depression: Depression will be screened for with the Beck's Depression Inventory-II (85). The Beck's questionnaire will be administered and scored by study staff while the participant is in person or available by remote video connection. We will do the following in real time while the participant is in person on Webex with study staff. Dr. Moy, the PI, or her MD designee, will be notified immediately and will join in person or over the Webex video session in real time to assess the participant if he/she reports suicidal thoughts (response of 2 "I would like to kill myself" or 3 "I would kill myself if I had the chance") on question 9 of the Beck's. Evaluation will be made for need for referral to the ER for further evaluation and treatment. Dr. Moy will notify the participant's usual provider. A score of 14 or higher suggests a clinical diagnosis of depression. If responses meet the cut-off scores indicating possible depression or anxiety, with the patients' permission, Dr. Moy, the PI, will inform their medical and mental health providers of the results (within 24 hours) for further evaluation and/or treatment. The clinical diagnosis of depression or anxiety, and suicidal ideation, will need to come from the participants' mental health or primary care providers. We are not diagnosing them in the research study.

We will have information regarding the participant's physical address, we will look up and document in advance the emergency information immediately available (local police and fire), and obtain the name and contact information of someone else who may be with the person (if applicable). We will have access to the phone numbers of the VA Suicide Prevention Coordinators.

f. Healthcare Utilization: Acute Exacerbation and Hospitalization History: Assessment of AEs and COPD-related hospitalizations is based on both self-report and medical chart review. During the study, all subjects will be instructed to call study staff with any changes in clinical status or medications. Most patients remember the occurrence of AEs because they are well-defined periods of worsening symptoms that require treatment with an antibiotic and/or prednisone (83). At all contacts, study staff will assess changes in symptoms, changes in

medications, prednisone and antibiotic use, visits to the emergency room, and hospitalizations. At each study visit, participants will be asked to provide the dates and locations of all hospitalizations since the previous visit. Patient report will prompt study staff to request hospital discharge summaries, medication records, chest X-ray reports, CT scan reports, and any additional information. Patient reports will be verified with review of hospitalization and pharmacy records both in and outside VA facilities, whenever possible. Dr. Garshick's major role on the project is to adjudicate the clinical events during the study. He will have no involvement in the day-to-day conduct of the study and will be blinded to subjects' treatment assignment and baseline test results. He will review subject responses and all medical records to determine if an AE or COPD-related hospitalization has occurred. An AE will be clearly defined as "a complex of respiratory symptoms (increased or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days, requiring treatment with antibiotics or systemic steroids" (84). Occurrence of AEs within 14 days of each other will be considered a single AE (85,86). This definition will also be used at the baseline visit for assessment of occurrence of AEs in the year prior to study entry.

g. Markers of Systemic Inflammation: Blood will be collected by venipuncture in three 10 mL purple top EDTA tubes. Samples will be hand-delivered to MAVERIC for processing and storage. Samples will be centrifuged and the plasma isolated. Plasma will be stored in 1 mL aliquots and frozen at -80 ^{0}C. For the analysis of CRP and IL-6, aliquots will be sent to the Clinical & Epidemiologic Research Laboratory, Department of Laboratory Medicine at Children's Hospital in Boston, a state-of-the-art laboratory that specializes in micro-analysis and is dedicated to testing for research studies. This laboratory has performed our previous CRP and IL-6 analyses, and these assays are standardized and highly reproducible.
C-Reactive Protein (CRP): The concentration of CRP will be determined using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN), using reagents and calibrators from Denka Seiken (Niigata, Japan). In this high sensitivity assay, an antigen-antibody reaction occurs between CRP in the sample and an anti-CRP antibody that has been sensitized to latex particles, and agglutination results. This antigen-antibody complex causes an increase in light scattering, which is detected spectrophotometrically, with the magnitude of the change being proportional to the concentration of CRP in the sample. This assay has a sensitivity of 0.03 mg/L. The day-to-day variability of the assay at concentrations of 0.91, 3.07 and 13.38 mg/L are 2.8, 1.6 and 1.1%, respectively.
Interleukin-6 (IL-6): IL-6 is measured by an ultra-sensitive ELISA assay from R & D Systems (Minneapolis, MN). The assay employs the quantitative sandwich enzyme immune assay technique. A monoclonal antibody specific for IL-6 has been pre-coated onto a microtiter plate. After the samples, standards, controls and conjugates are added to the wells, IL-6 is sandwiched between the immobilized antibody and the enzyme-linked antibody specific to IL-6. Upon the addition of substrate, a color is generated that is proportional to the amount of IL-6 present in the sample. The minimum required volume for this assay is 200 µL. The assay has a sensitivity of 0.094 pg/mL, and the day-to-day variabilities of the assay at concentrations of 0.66, 1.97 and 8.16 pg/mL are 12.2%, 7.6%, and 9.9%, respectively.

We will also administer the following:
4-meter gait speed as a measure of overall frailty.
PA Recall Questionnaire,
Barriers to Exercise,
Bristol COPD Knowledge Questionnaire,
Epworth Sleepiness Scale,
MOS Social Support Survey,
Brief Pain Inventory (short form) and the one-item Numerical Rating Scale for pain,
EQ-5D Health Utilities
CHAMPS Physical Activity Questionnaire
Veterans SF-36
Usability Questionnaire

Enrollment in PR: We will offer conventional PR to all participants who complete the research study. We will compare the numbers between groups who enroll in PR within the first 3 months of completing the RCT.

A semi-structured qualitative survey will assess participants' perceptions of exercise behavior or use of ESC over time. This interview will be audio-recorded and transcribed using a VA-approved transcription service (i.e., Centralized Transcription Services Program; CTSP). Interviews will be audio-taped using a VA approved digital recorder and audio-recordings will be stored on a VA secure server with limited access. Consistent with principles of qualitative analysis, we will use content analysis, including the constant comparative method, to identify and tabulate key themes emergent from the data regarding use of ESC in patients with COPD. Our approach will be both deductive and inductive. A small core of team will develop, review, and modify as necessary our codes and analyze the text for themes and patterns. Qualitative data management software, such as Nvivo 12, will be used to support this work. Upon completion of coding, additional members of our research team will examine the findings and discuss further themes.

A technology usability questionnaire will assess participants' perceptions of the website and pedometer used in the study.

At any time, if a subject experiences a medical problem that prevents walking and exercise, s/he will be suspended from the study. S/he will resume the study when s/he has returned to baseline clinical status.

It is expected that some subjects may be unable to complete all the proposed assessments during the study visits. Furthermore, subjects may refuse to complete any portion of the study assessments.

6-Month Phone Call
Participants will be contacted by telephone at month 6. They will provide an interim history of home exercise and answer questions about symptoms, medications, AEs, and hospitalizations that occurred since the previous contact. Subjects will receive a mailing with questionnaires (SGRQ, Exercise Self-Efficacy, and RAPA) to complete at home. They will also be mailed a Fitbit to wear for 14 days and return by prepaid mailer.

Monitoring for Adverse Events (AdEs)

We have convened an independent, external Data and Safety Monitoring Board (DSMB) to review recruitment and follow-up rates, and monitor adverse events, SAEs, and unanticipated problems. The DSMB is composed of Vincent Fan, MD, a pulmonologist and expert in telemedicine methods in COPD at the VA Puget Sound Health Care System and University of Washington; Elizabeth Klings, MD, a pulmonologist and expert in PR and COPD clinical trials at Boston University School of Medicine; and Gloria Yeh, MD, MPH an expert in PA interventions in persons with COPD and clinical trials at the Beth Israel Deaconess Medical Center, Boston. They will meet every 6 months, and as needed, by telephone conference. All related adverse events, SAEs, and unanticipated problems will be reported immediately to the VA Boston IRB. They will meet every 6 months, and as needed, by telephone conference. They will monitor the number of adverse events (AdEs) and serious adverse events (SAEs) and unanticipated problems between the 2 arms of the study.

Although the proposed study presents minimal risk, there is the potential for AdEs related to increased walking and exercise. Based upon our pilot study with ESC, the most common SAE will be hospitalizations for a COPD exacerbation, which are unrelated to the exercise intervention. The most common AdEs will be musculoskeletal injuries. In order to minimize risk, subjects will be enrolled in the study only if they have medical clearance from their healthcare provider. In addition, subjects will be screened for clinically active cardiovascular disease (such as angina or decompensated congestive heart failure) and exercise-induced hypoxemia as part of baseline testing. Subjects in both arms will be instructed to notify their healthcare provider if they experience any change in their clinical condition, and to notify study staff of any change in medications, urgent care visits, emergency room visits, or hospitalizations. During the study, subjects will be regularly monitored for adverse effects of exercise during research visits and telephone contacts. In addition, participants can report adverse events (AdEs) by telephone at any time. The PI will contact participants by telephone if any reported AdE suggests clinical deterioration warranting immediate medical attention. All SAEs and unanticipated problems

will be reported to the IRB in real time. If an event is possibly, probably or definitely related to the intervention, it will be classified as intervention related.

Assessment of Treatment Fidelity

To promote treatment fidelity in both groups, study staff will review instructions to slowly and steadily increase walking and exercise with participants every 3 months (98). To measure treatment fidelity in both groups, subjects will complete daily exercise logs (98). The exercise log is intentionally simple to minimize its potential influence to be part of the intervention. Subjects circle a yes/no response to 2-3 questions about whether exercise was performed that day. Subjects will return the logs by mail to study staff every month, and review them in person every 3 months. Compliance with treatment in both arms will be defined as having >70% of days (~5 out of 7 days/week) with exercise. We propose an intention-to-treat analysis since the reasons for noncompliance may be related to COPD severity. Thus, all subjects will be analyzed and not excluded based on compliance. As a sensitivity analysis, however, we will examine 6MWT distance and secondary outcomes on a per-protocol basis, where noncompliant subjects ($\geq$30% of days with no exercise performed on logs) from each treatment arm will be excluded from the analysis (Table 2).

The most important factor affecting compliance is the complexity of the intervention. Our experience indicates that the proposed intervention poses minimal participant burden. The intervention is designed to foster compliance, using a dynamic website and immediate feedback. Subjects upload step counts and visit the website at their convenience. We believe that maintaining a dynamic website with relevant and changing content will keep participants engaged in the intervention. Feedback from the graphs is most commonly used by participants and will encourage engagement. We will provide a user-friendly written guide to all the features of the website. We will measure treatment fidelity specific to the intervention group by tracking numbers of (1) no-wear days of the pedometer, (2) subjects who require telephone call reminders to upload, and (3) logins to the website.

Minimizing Attrition and Handling Missing Data

We will do everything we can to minimize attrition and missing data. Our run-in period prior to randomization (when at least 10 days of baseline step counts are required to be collected from an eligible participant) will screen out those who may be potential dropouts. We will structure the research visits and follow-up telephone contacts such that each participant interacts with the same research assistant on each occasion. Monetary compensation has been shown to be the best strategy to achieve protocol adherence and minimize missing outcomes data (78). We will reimburse subjects $50 at each research visit for their travel-related costs, time and effort. Each participant will keep the Fitbit after he/she completes the study. Medical problems and temporary suspension from the PA program will be the most common reason for missing outcomes data. We have designed the testing windows to minimize missing data. At 6 and 12 weeks, testing will be allowed within a window of ± 2 weeks.

Statistical Analyses. Primary Analysis (Aim 1). Prior to analyzing the outcomes, we will summarize and compare baseline demographic and clinical variables by group. Any unbalanced characteristics will be assessed as potential confounders in multivariate analyses. Analyses will be performed with the SAS statistical software package (9.4, SAS Institute; Cary, NC). Analysis of the RCT will use the intention-to-treat approach, and subjects will be considered to be in his/her assigned group no matter how much he/she participated in it. Analyses will use the step-count data at baseline, 6 and 12 weeks. We a priori define a no-wear day as one with < 200 steps and < 8 hours of wear time, and follow-up monitoring periods with $\geq$ 8 (out of 14) no-wear days will be considered missing (52,64,68). These definitions will be applied identically to both arms, ensuring that the average step counts used in the analyses represent typical walking over the monitoring periods. To determine the efficacy of the web-based intervention to increase daily step count at 12 weeks, compared to usual care, we will use generalized linear mixed effects models with repeated measures (95). This approach will use values of daily step count at baseline (averaged over $\geq$ 7 of 10 days) and at 6 and 12 weeks (averaged over $\geq$ 7 of 14 days). We will assess the between-group effect (ESC intervention versus usual care) and the within-group effect (repeated over time) on daily step count. We will assess the interaction between group and time (group*time)

on daily step count. Models will have daily step count as the dependent variable, and group, time, and group*time as independent variables. We will use PROC MIXED in SAS to perform the analyses given its flexibility of modeling the variances and covariances, its robustness in accounting for correlated data (repeated measures data), and its flexibility in handling missing data. We will examine both compound symmetry and AR(1) correlation structures. The mixed models will robustly handle the 2 most common types of missing data that we will encounter—those missing not at random (due to AEs or hospitalizations) or missing completely at random (user forgot to wear device). Models will account for differing baseline characteristics, season of monitoring, and changes in season during the study period (55,57). Baseline characteristics for patients who do not have step-count data at 12 weeks due to death or health events will be compared to those of patients who complete the study. PA intensity classifications from the pedometer and RAPA at each time point will be analyzed in a similar fashion as the daily step counts.
Anticipated Results: We anticipate that subjects in the ESC group will have significantly higher average daily step count and PA of higher intensity than subjects in the usual care group at 12 weeks.

Power Calculation: Our main comparison is daily step count at 12 weeks between the ESC and usual care groups. We use a convenience value of a difference of 1,000 steps per day for our power calculations, which is well within the range (599-1131 steps per day) of the published clinically important difference for step counts (62). We use a number slightly higher than the 800-steps per day observed in our previous study (57) since we expect to see greater improvements in this functionally limited group referred to PR, the control group will not receive a pedometer, and we are intentionally promoting exercise of moderate intensity. Using the sample size formula for the comparison of the means of 2 independent samples and s.d. of 1,840 for the between-group difference in daily step counts (57), we calculate that at least 54 evaluable subjects in each group at 12 weeks will allow detection of a difference of at least 1,000 steps per day between groups with a power of 80% and α=0.05. We will randomize 120 subjects to have at least 108 evaluable subjects (54 in ESC and 54 in usual care) at 12 weeks, given an estimated 10% dropout rate (Figure 6).

Secondary Analyses (Aim 2). The secondary analyses will complement the primary findings and inform future research. The analysis plan is similar to that for the primary outcome. We will use generalized linear mixed effects models with repeated measures (PROC MIXED in SAS) to assess the effect of the ESC intervention versus usual care on exercise capacity, exercise adherence, exercise self-efficacy, HRQL, dyspnea, and depression and anxiety. We will analyze values of the secondary outcomes at baseline, 6 and 12 weeks. Models will examine the between-group and within-group effects on the secondary outcomes, and additionally allow us to assess the interaction between group and time (group*time). Models will have the secondary outcome as the dependent variable, and group, time, and group*time as independent variables. Models will account for differing baseline characteristics, season of monitoring, and changes in season during the study period (55,57). Given the count data and expected Poisson distribution of number of AEs and hospitalizations, negative binomial regression models (PROC GENMOD) will be used to calculate risk ratios for AE and COPD-related hospitalizations (91). The models will include number of AEs (or hospitalizations) as the dependent variable, group as the main predictor, as well as number of AEs (or hospitalizations) in the year prior to enrollment, and any unbalanced baseline characteristics.

Anticipated Results: Subjects in the ESC group will have higher exercise capacity, greater exercise adherence, greater exercise self-efficacy, better HRQL, less dyspnea, less anxiety and depression, and lower risk for healthcare utilization, compared to the usual care group.

Power Calculations: A sample size of 108 evaluable subjects at 12 weeks determined by the primary outcome of daily step count will also allow detection of significant differences in the secondary outcomes. We can detect an effect size of 0.55 s.d. units with 80% power and α=0.05. For example, using the s.d.s obtained from our cross-sectional observational study, we can expect to detect a change of at least 10 units in SGRQ-TS (64). In addition, as an estimate for anticipated differences between arms, we examined the mean SGRQ-TS in those who walked above and in those who walked below the median daily step count in our observational data (64). We observed a difference of 7 units in SGRQ-TS, which is greater than the MCID of 4 units (80). While

the preliminary observed estimate of difference is slightly lower than our calculated detectable estimate, we anticipate there will be sufficient power to detect differences in these secondary outcomes when the analyzed groups are differentiated by the ESC intervention, since our power calculations based on groups dichotomized at the median step count are conservative.

STUDY #2

Specific Aim 3: Exploratory Non-Randomized Study in Persons who Complete Conventional PR

Participants, Outcome Assessments, and Follow-Up.

Participants who complete a conventional PR program will be asked to participate in this study examining whether ESC, compared to a usual care group, can maintain PA, exercise adherence, and extend the benefits of PR. Completion of conventional PR will be defined as attending a standard pulmonary rehabilitation of at least 8 weeks duration within 24 weeks prior to study entry. Completion is further defined as attending 65% of the program's sessions with a minimum of 10 sessions. Eligibility criteria, the ESC and control interventions, and outcome assessments are similar to those for the RCT. We anticipate enrolling a convenience sample of 48 subjects who will be interested, eligible, and have Internet access to use the ESC platform. We will enroll an additional 48 subjects who will receive usual care, and whom we will contact via telephone and USPS mailings. Participants who have previously received care at the VA Boston Healthcare System but have moved away from the VA Boston during recruitment, enrollment, or follow-up will still qualify to participate in this study if they are interested.

The following inclusion and exclusion criteria describe the characteristics of the study population, which will include men and women aged 40 and older.

Inclusion Criteria are:

a) Male and female subjects, greater than or equal to 40 years of age
b) Clinical diagnosis of COPD defined as: $\geq$ 1 of the following as testing-based evidence of COPD (any documented $FEV_1/FVC < 0.70$, chest CT evidence of emphysema) AND $\geq$ 2 of the following as clinical evidence of COPD (≥ 10 pack-year cigarette smoking history, taking an antimuscarinic inhaler such as ipratropium or tiotropium, diagnosis of COPD written in a provider's note or on problem list)
c) Have completed participation in a conventional pulmonary rehabilitation program in the past 6 months
d) Competent to provide informed consent
e) Willingness to make return visits and be available by telephone for duration of study

Exclusion Criteria are:

a) COPD exacerbation in the previous 1 month
b) Inability to ambulate with or without assistance
c) Use of assistive device for walking such as cane or walker*
d) Inability to complete questionnaires
e) Inability to collect at least 7 of 10 days of baseline step counts
f) Participation in another exercise-related research study at time of screening
g) Plans to participate in an exercise-related research study while enrolled in this study
h) Average baseline step counts of greater than or equal to 10,000 steps per week

*If a participant uses an assistive walking device but we have previously shown that the Fitbit pedometer is accurate in him/her (before the study was transitioned to virtual) he/she will be allowed to participate in the study. If a participant has an in-person visit and Fitbit accuracy is documented during use of the assistive device he/she will be eligible to participate.

No matter which group a participant chooses, he will be encouraged to use the maintenance exercise program offered through the VA Boston Pulmonary Rehabilitation program.

Assessments of outcomes known to improve after PR (SGRQ-TS, dyspnea) as well as daily step count, exercise intensity, exercise adherence, exercise self-efficacy, anxiety, depression, and healthcare utilization (see Table 2) will occur at the baseline research assessment. We anticipate that the only significant difference between the two groups will be Internet access, but they will be well characterized at study entry to assess for any other differences. Participants in the ESC group will be given a Fitbit, step-count goals, and access to the ESC website. Participants in the usual care group will be given written instructions (Appendix 4) to exercise.

Since they have safely completed a conventional PR program, all subjects should find it easy to follow the instructions to walk with moderate intensity for at least 30 minutes most days of the week. In addition, medical clearance from a healthcare provider will not be obtained.

Subjects will be enrolled for a minimum of 3 months and a maximum of 12 months, depending on date of study entry. Participants will not be expected to complete all in-person study visits. All subjects enrolled through the first quarter of Year 4 will have 12 months of follow-up (Table 3). Follow-up outcome assessments will occur at 3, 6, 9 and 12 months. A semi-structured qualitative survey will assess perceptions of exercise behavior or use of the intervention over time. Reasons for self-reported declines in exercise or loss to follow-up will be ascertained.

Table 2. Study Measures	Baseline	3 month	6 month	9 month	12 month
Demographics	x				
Comorbidities and Medications	x	x	x	x	x
Daily Step Count (Fitbit)	X	x	x	x	x
6-Minute Walk Test	X	x	x	x	x
800-ft Walk Test	X				
4-meter Gait Speed	X	x	x	x	x
Rapid Assessment of Physical Activity (intensity)	x	x	x	x	x
Physical Activity Recall Questionnaire	X		x		x
Barriers to Exercise	x		x		x
Exercise Adherence (Exercise Logs)	X	x	x	x	x
Exercise Self-Regulatory Efficacy	x	x	x	x	x
St. George Respiratory Questionnaire	X	x	x	x	x
Bristol COPD Knowledge Questionnaire	x		x		x
MMRC Dyspnea scale	X	x	x	x	x
Beck's Depression Inventory-II	X		x		x
Epworth Sleepiness Scale	X		x		x
MOS Social Support Survey	X		x		x
Brief Pain Inventory (short form) and Numerical Rating Scale	X		x		x
Healthcare Utilization	X	x	x	x	x
EQ-5D Health Utilities	X	x	x	x	x

Veterans Rand 36 Item Health Survey (VR-36)	X	X	X	X	X
CHAMPS Physical Activity Questionnaire	X	X	X	X	X
Qualitative Feedback		x			x
Blood Draw for CRP and IL-6	X		x		x
Usability Questionnaire		x			

We will reimburse subjects $50 by check for each study visit for their time and effort. Each participant will keep the Fitbit after he/she completes the study. Medical problems and temporary suspension from the PA program will be the most common reason for missing outcomes data. We have designed the testing windows to minimize missing data. At 3,6, 9, and 12 months, testing will be allowed within a window of ± 1 month.

Exploratory Analysis (Aim 3). This analysis is exploratory and no power calculation is made. Within the ESC group, daily step count, intensity of exercise, exercise adherence, exercise self-efficacy, SGRQ-TS, dyspnea, anxiety, depression, and healthcare utilization at 3, 6, 9 and 12 months will be compared to baseline values using paired T tests. Changes in outcomes within the ESC group will be compared to changes in the usual care group at each time point using unpaired T tests. Analyses will account for the correlated data, any missing data at each time point, differing baseline characteristics between groups, season of monitoring, and changes in season during the study period (55,57).

Anticipated Results: The ESC group will maintain PA, HRQL, exercise adherence, exercise intensity, and other outcomes at 3, 6, 9, and 12 months compared to baseline. Decreases from baseline over time in the ESC group will be less than the changes in the usual care group.

Specific Aim 4: Exploratory Cost-Effectiveness Analysis

Participants and Outcome Assessments.

We will collect cost data from CAPRI-1 and CAPRI-2. To assess cost-effectiveness, we will examine direct costs of the intervention (cost identification), effectiveness of the trial (measured by changes in HRQL). We will track intervention costs through activity logs kept by research personnel to estimate labor costs.

Data Collection and Analysis.

We will develop a cost-utility model of the intervention over a 12-month time horizon. Intervention costs will be determined through micro-costing methodology, where all actual expenses including time and labor costs that can be attributed to the intervention will be determined. The EuroQol will be administered in CAPRI to directly assess patient preference-based health status. Cost effectiveness ratios will be calculated to produce cost in dollars per quality-adjusted life-years (Cost/QALY). Effectiveness will be determined as change in health utilities from baseline to follow-up compared to the control randomization groups.

Specific Aim 5: Exploratory Stakeholder Perception Assessment

Participants and Outcome Assessments.

To address our exploratory objective to assess stakeholder perceptions of ESC, we will recruit VABHS employees who are involved in the care of persons with COPD and pulmonary rehabilitation (15 in total). We will identify eligible employees by using Outlook and provider names available from the VABHS website. We will also work with contacts at VABHS to identify potential participants. Following a modified snowball strategy, we will also ask participants to identify others who may be eligible to participate. Eligible participants will meet the following requirements:

a) Employed at VABHS
b) Involved in the care of persons with COPD and/or the pulmonary rehabilitation program at VABHS

c) Willingness to meet either in person or virtually over Cisco Webex for the study visit and have interview audio-recorded

Once we have identified eligible individuals, employee recruitment will be conducted via email, with the potential to send up to two follow-up emails for eligible staff. Emails will include a study information sheet attachment outlining details of participation. Each email response will be archived on the VA Boston secure server, and a member of the research team will document interest or refusal to participate in a password protected Excel spreadsheet. We request a waiver of documentation of informed consent for all portions of Aim 5. We will obtain verbal informed consent from staff who want to enroll. We are requesting a waiver of HIPAA authorization for all portions of Aim 5. The IRB-approved verbal informed consent process will be completed via Cisco Webex prior to initiation of the study procedures. During the informed consent process, research staff will review a script that confirms eligibility and reviews the study information sheet that was sent to potential staff participants with the recruitment email. Potential employee participants will again be reminded that participation is voluntary and that a choice not to participate will not affect the individual's employment. Potential subjects will have as much time as they wish to ask questions and consider their participation before indicating consent. If they decline to participate, their identity will be protected. No manager will be present when the actual recruitment (i.e., recruitment being the process of reviewing the informed consent form, answering employee's questions, and completing the consent process) takes place. In addition, employees may end the interview, decline to answer individual questions, and/or decline to have their interview digitally recorded at any time during the interview. The consent process will address potential risks and discomforts. To guard against possible risks and discomfort, the questions will not focus on highly personal information; for example, the questions will focus on employees' perceptions about the intervention and technology, and their experiences providing care for their patients. Only once verbal informed consent has been obtained will the subject be considered enrolled and added to the master list of enrolled study subjects. The master list will be secured in compliance with all VA confidentiality and information security requirements.

Data Collection and Analysis.

Staff participants enrolled in Aim 5 will each participate in an individual study visit call via Cisco Webex that will last approximately 60 minutes. During the study visit call, Dr. Robinson and/or Ms. Sliwinski will present the employee with a short PowerPoint presentation describing ESC (15 minutes), conduct a semi-structured qualitative interview (30 minutes), and ask them to fill out a survey (15 minutes). The interview will elicit information about their views on current hospital-based pulmonary rehabilitation, ESC, and barriers and facilitators they foresee trying to implement it into care for patients who cannot access traditional pulmonary rehabilitation. The survey will ask about the employees' role within VA and COPD care, and their perceptions on ESC. Interviews will be audio-recorded using a VA-approved encrypted recorder and transcribed by a VA-approved transcription service. Survey data will be captured over REDCap behind the VA firewall, where staff will remotely enter survey responses as they are collected. The presentation, interview guide, and survey will be submitted to the Boston IRB with this protocol. As in the patient interviews, we will use an iterative, inductive and deductive process; as new, insightful information emerges, we will adjust the interview guide to ask questions about concepts that emerged during the process.

<u>Data Management</u>

We will conduct a training session and mock study visit before initiating enrollment to ensure uniformity in procedures and data collection. Study staff will communicate by secure VA email and participate in conference calls regularly to ensure valid, accurate, and consistent methods in data collection. All data will be coded with a unique study identification number. Outcomes data will be collected by paper and pen and stored in study folders, locked in study staff offices. Databases located on an internal computer drive within the VA firewalls will be used for data storage. Data will be entered in Access databases, cleaned, and exported to SAS for statistical analyses. University of Michigan staff will manage the step-count data associated only with each subject's study ID. All computers and data files will be password-protected and backed up at regular intervals. All data will be processed and analyzed in aggregate.

Study data will be entered into a data repository at VA Boston and used for future studies approved by an IRB.

A Data Use Agreement is not needed between this study and IRB #2999 Pulmonary Research Data Repository (PI Dr. Moy) since direct consent and HIPAA authorization will be obtained from participants

Information Security
Although Cisco Webex is secure and fully VA-authorized, it is not a VA site and is not controlled, monitored, or managed by the VA. There is a small chance that a person not connected with the study may gain access to the video study visits. There is a risk of loss of privacy if participants choose to hold their Webex video study visits in public.

Participants are enrolled at VA Boston. The study website is maintained by staff at the University of Michigan who have no direct contact with any study participants.

Study records, and audio recordings are identified only by an assigned unique study ID. One master list links the study ID with the participant's name and other identifiable information. This master list is located on a secured network behind the VA firewalls.

Study data will be collected by paper and pen. The paper documents are stored in locked file cabinets in locked offices. These data will be entered in duplicate by study staff into Access databases, which are located on a shared drive on the secured network behind the firewalls of VA Boston. These databases are located behind the VA Boston firewalls and will be accessible only via VA secured and password protected desktops in locked study staff offices. All study data in the databases will be identified only by the participant's unique study ID.

All audio recordings will be identified only by the participant's unique study ID. All interview audio-recordings will be transcribed and de-identified so research team members can review transcripts and participate in coding. Transcription will be done by a transcription service which meets VA security standards. Interviews will be audio-taped using a VA-approved digital recorder. The recorder will be stored in a secured office in the staff's home with limited access. Audio-recordings will be immediately uploaded to and stored on the VA Boston secure server with limited access.

All blood samples will be identified only by the participant's unique study ID. Samples hand-delivered to MAVERIC. Samples are processed and stored at MAVERIC. Blood samples will be stored in freezers located behind locked doors at VA Boston for an indefinite period of time. Only approved VA employees have access to the areas where blood samples are kept.

For Aim 5, we will take the following protective measures with regards to our employee participants. In our communications with VA employees, including our verbal informed consent, we will convey that participation is voluntary. In addition, we will not reveal provider participants' names or participation in our research to their managers or their colleagues. Protection of confidentiality will be ensured by not identifying audio recordings, surveys, or interview data with participants' names or other identifying information, including patient information. We will ask all participants to speak only about their experience and perceptions of ESC and to avoid any mention of any patient names or other identifying information. Only research staff will have access to identification numbers that identify our data, and these identification numbers will be stored on a VHA server. Survey data will be captured over REDCap behind the VA firewall, where staff will remotely enter survey responses as they are collected.

The study uses a website created and maintained by Dr. Caroline Richardson and her staff at the University of Michigan. They have no direct contact with any study participants. After the account is created, participants access the website using their unique username and password. Participants will upload step-count data, which they own, to the website over the Internet. These data are stored on a study server on a secure network behind the firewalls of the University of Michigan. Per policies of the University of Michigan, the website is secured, the

study server is located on a secured network, and data are backed up at regular intervals. The data stored on the study server are: username and password, and step count numbers. No protected health information (PHI) will be stored on the study server.

Of note, we have had significant experience working with this website/platform and have not had any adverse events. It is currently used for Dr. Moy's study IRB #2791 that has been approved by the VA Boston IRB. VA Boston IRB protocol #2328 was also approved to use the same website/platform, and is currently in Data Analysis Only. The same rigorous standards to protect security, privacy, and confidentiality of participants and their data will be used in the current study.

In addition, test results from this research study as well as hospitalization records, laboratory test results, and radiology reports from care provided outside of the VA may be disclosed to the members of the Data and Safety Monitoring Board who oversee this study. This information would be associated only with the participant's unique study ID.

Removal of access to research study data will be accomplished for study personnel when they are no longer part of the research team.

In accordance with VA Policy, procedures are in place for reporting incidents. All incidents will be reported immediately to the PI, the VA Boston Information Security Officers and Privacy Officers, and to the VA Boston Institutional Review Board.

(d) Discuss potential problems and limitations of the proposed methods and/or procedures and possible alternative procedures to achieve the specific aims.

Originally, we had proposed a pragmatic trial design to directly compare those who declined PR but enrolled in ESC to those enrolled in conventional PR. The lack of a RCT was a significant limitation. We had considered a RCT which randomized patients enrolled in PR to either ESC or PR, but rejected this study design because we did not believe there was equipoise. It would preclude patients who wanted PR from receiving it, denying them standard of care. Logistically, it was not feasible to enroll the needed numbers given (1) the low referrals to PR, (2) the high percentage who decline PR, and (3) the need for Internet access. In the resubmissions, we now focus on the high-need patients who cannot access PR. Offering the ESC option to these patients who would otherwise receive nothing is ethically sound. The current study design allows all persons who want PR to receive it. We no longer propose a direct comparison of ESC to PR. Aim 3 is exploratory because it is not feasible within the scope of this application to power a RCT of those who complete PR with sufficient follow-up time. Aim 3 will provide pilot data to support a future multi-site RCT to definitively address this question.

Strengths and Limitations. We address a significant clinical problem. We propose a concrete solution to reduce functional disability in Veterans with COPD who cannot access conventional PR. The proposed study aims to reduce physical inactivity and target deconditioning as the first step toward increasing aerobic fitness and exercise capacity in COPD. The number of people who use the Internet continues to increase, making a technology-based approach ideal to reach a large number of Veterans. Our multidisciplinary team has demonstrated expertise. The analytic plan carefully accounts for treatment fidelity and missing data. We will enhance recruitment of women and provide computer access at the study site to maximize generalizability of results. Our results will be highly relevant for promoting PA in other chronic diseases--congestive heart failure, diabetes mellitus, and post-traumatic stress disorder. The detailed follow-up in the non-randomized study is a strength, allowing up to 12 months of assessments in the majority of participants. The studies may face recruitment challenges. We have an accurate assessment of the number of Veterans with COPD and Internet access referred to PR who would be eligible for the studies. Our back-up plan includes recruitment from the VA Providence PR program, which is located only 40 miles from VA Boston and with whom we have previously collaborated. If needed, we will also enroll non-Veterans from surrounding hospitals with conventional PR

programs. Flyers will be posted in VA Boston and at external institutions that have pulmonary rehab programs, including Beth Israel Deaconess Medical Center, Boston Medical Center, Brigham and Women's Hospital (Faulkner and Longwood). We will adhere to all VA research policies of enrolling non-Veterans including making sure they understand VA privacy practices. Since PR is so varied across clinical sites (24,33), limiting our proposal initially to one site is a strength. Follow-up in the RCT is limited to 12 weeks to mirror the duration of conventional PR. Longer follow-up would be informative, but was not possible given the time constraints. Our secondary outcome of exercise adherence is assessed by self-report which may have some recall bias, but participants are asked to complete the simple log every day. In the groups using the Fitbit and website, tracking steps walked and number of pedometer wear days will complement the self-reported logs. We acknowledge that our devices do not record upper extremity exercise. However, lower extremity exercise is the most effective and best-validated portion of PR programs (96). In summary, we are confident that we will complete the studies as designed on time and on budget. Secondary results on the impact of ESC on maintenance of benefits after completion of PR, healthcare utilization, and as a bridge to enrollment in conventional PR will lead to future studies.

(e) If humans or animals are to be studied, power analysis needs to be used to justify the number to be studied. Justify the species of animal to be used. If cell lines or tissue specimens are used, discuss the source of the material.

Please also see Power Calculations above. If the participant provides consent, at each of the four in-person study visits, we will take three tubes of blood (approximately 2 tablespoons) by venipuncture to be stored for investigating blood markers. Blood samples will be used to examine the occurrence of various blood protein markers (i.e., biochemicals that indicate inflammation or other related changes) that may influence overall health. Blood samples will be processed and stored at VA Boston's MAVERIC. Samples will be sent to Boston Children's Hospital for analysis of C-reactive protein and Interleukin-6. To protect confidentiality, blood samples will be stored at VA Boston MAVERIC using only a study code with no personal identifiers.

(f) <u>Human Studies Section</u>

1. Risks to Subjects

1.a. Human Subjects Involvement and Characteristics:

All patients with a diagnosis of chronic obstructive pulmonary disease (COPD) who are referred to the VA Boston Pulmonary Rehabilitation (PR) program will be eligible to participate in this research study. We will also recruit by sending a recruitment letter to patients who have visited the outpatient Pulmonary Clinics since 2005. We will also recruit from patients with COPD who have been seen in the Pulmonary Function Laboratory, the Women's Health Clinic, and the Primary Care Clinics. For interested persons, we will phone screen for those who meet national recommendations for referral to PR but who have not participated in PR. PR is recommended for patients with COPD who experience shortness of breath that interferes with daily activities despite use of medication.

We propose 2 separate studies to address the issues of access and adherence in PR. This 2-pronged approach will most efficiently accomplish our Specific Aims. As our primary aim, we propose a randomized controlled trial (RCT) to study the efficacy of our web-based intervention Every Step Counts (ESC) to increase physical activity (PA) in patients with COPD who decline PR, compared to usual care. As an exploratory aim, we propose to examine the ability of ESC to maintain exercise adherence and PA after completion of conventional PR. This overall study design allows all persons willing to enroll in conventional PR to receive it, since PR is standard of care. The PA intervention will include specific instructions to reach the step-count goals with moderate intensity exercise using a regimen that has been previously studied in healthy adults and subsequently shown to be safe in persons with COPD. We anticipate enrolling 300 male and female subjects with COPD.

To address our exploratory objective to assess employee stakeholder perceptions of ESC (Aim 5), we will recruit VABHS employees who are involved in the care of persons with COPD and pulmonary rehabilitation

(15 in total). VA employees will not receive any payment for participation in the study. Eligible participants will meet the following requirements:

a) Employed at VABHS
b) Involved in the care of persons with COPD and/or the pulmonary rehabilitation program at VABHS
e) Willingness to meet in person at the Jamaica Plain VA or West Roxbury VA or virtually over Cisco Webex for the study visit and have interview audio-recorded

To ensure that staff do not feel coerced to participate, we will make it clear that participation is voluntary, not mandatory, and that there will be no adverse consequences for non-participation. At any point during an employee's participation, if the employee should want to stop participating, they, naturally, will be allowed to do so.

1.b. Sources of Materials: Data will be collected from human subjects for research purposes. No existing specimens, records, or data will be used. Demographic information, and medical history including healthcare utilization (acute exacerbations and hospitalizations) will be obtained at baseline and follow-up research visits. The primary outcome of daily step count will be assessed at baseline and follow-up. Step count data will be obtained from the Fitbit, which all patients will wear for 10 days at baseline, and for 14 days at follow-up assessments. Secondary outcomes will be assessed at baseline and follow-up using questionnaires to assess health-related quality of life, dyspnea, depression and anxiety, and exercise self-efficacy. Subjects are asked to complete a simple daily exercise log to assess exercise adherence.

Staff participants enrolled in Aim 5 will each participate in an individual study visit call via Cisco Webex that will last approximately 60 minutes. During the study visit call, we will present the employee with a short PowerPoint presentation describing ESC (15 minutes), conduct a semi-structured qualitative interview (30 minutes), and ask them to fill out a survey (15 minutes). The interview will elicit information about their views on current hospital-based pulmonary rehabilitation, ESC, and barriers and facilitators they foresee trying to implement it into care for patients who cannot access traditional pulmonary rehabilitation. The survey will ask about the their role within VA and COPD care, and their perceptions on ESC. Interviews will be audio-recorded using a VA-approved encrypted recorder and transcribed verbatim by a VA-approved transcription service. Survey data will be captured over REDCap behind the VA firewall, where staff will remotely enter survey responses as they are collected.

1.c. Potential Risks:

Based on our previous studies using the same web-based pedometer-mediated platform to promote PA in persons with COPD, the most common serious adverse event (SAE) will be hospitalizations for a COPD acute exacerbation. These events are related to the underlying disease and unrelated to PA and exercise promotion. The most common related adverse event will be minor musculoskeletal injuries.

1.c.i. Physical Activity Monitors: There is no risk to wearing the Fitbit Inspire HR pedometer on the wrist. It is commercially available. The in-clinic walk performed by subjects to assess device accuracy may leave subjects temporarily more short of breath. Subjects will be allowed to rest and use supplemental oxygen if usually prescribed.

1.c.ii. Physiological Assessments: The 6MWT may leave a subject temporarily more short of breath. Subjects will be allowed to rest and use supplemental oxygen if usually prescribed. The 6MWT may cause shortness of breath, leg fatigue, low oxygen levels in the blood, or an irregular heart rhythm. There is a potential risk of falling during the 6MWT.

1.c.iii. Questionnaires: We will ask participants to answer questionnaires assessing symptoms, health-related quality of life, and screening for anxiety and depression. The study does not assess risk for suicide. Participants

will be given as much time as they need to complete the questionnaires. There is the risk of detecting symptoms that may lead to depression or anxiety. There is possible social and psychological risk resulting from inadvertent disclosure of medical history information. All questionnaire responses collected by paper and pen will be kept confidential and locked, and identified by study code in the working databases.

1.c.iv. Walking exercise program:
The proposed study presents minimal risk since all participants will have been deemed medically stable by their usual healthcare providers for referral to PR. All participants will be instructed to perform exercise of moderate intensity for at least 30 minutes on most days of the week, defined as a dyspnea level of 4-5 on the Borg scale and taking 1-2 minutes to recover. Potential risks related to walking and exercise, and progression of exercise include:

Risks related to breathing
Participants may experience shortness of breath while exercising. In most cases it is likely due to the underlying COPD and/or low fitness. This could be a sign of concomitant cardiac ischemia.

Risks related to musculoskeletal injury or falls
Exercise programs may result in minor musculoskeletal injury, falls, or pain.

Risks related to cardiovascular disease
Some of the participants in this study will have cardiovascular disease risk factors, and thus they are at increased risk of experiencing an adverse cardiovascular event such as angina or a myocardial infarct. Some patients may have atrial fibrillation and are at increased risk of having higher heart rates during exercise.

Risks related to chronic pain
Regular exercise, such as walking, is generally recommended for people with chronic pain. However, when starting an exercise program, it may worsen an underlying pain condition. Individuals with chronic pain may experience temporary muscle soreness or stiffness.

Risks related to diabetes
Some of the participants in this study will have diabetes. An exercise program is an important part of managing diabetes. However, there are some risks such as episodes of hyper- or hypoglycemia after exercising or problems with ulcers or sores on the feet.

Risks related to blood pressure control
Starting an exercise program may lower an individual's blood pressure. Participants who take medication to lower their blood pressure may need to have their blood pressure medication adjusted as they progress in the program. Participants who have poorly controlled blood pressure may experience high blood pressure as they progress in the program.

Risks related to hydration
Participants who are on fluid restriction or diuretics may have trouble hydrating sufficiently when walking in hot weather, and may become intravascularly volume depleted.

1.c.v. Aim 5: Aim 5 constitutes a minimal risk to subjects who are VA employees. There is the potential risk that staff who may not want to participate in the study may feel coerced to do so. We will make it clear that participation is voluntary, not mandatory. Participation or non-participation in this research will have no effect on employees' jobs. At any point during the subject's participation, if the participant should want a break or should want to stop participating, naturally they will be allowed to do so. All subjects will be provided with contact phone numbers for the PI, Research Compliance Officer, and Human Relations Specialist to call if they have questions or concerns.

1.c.vi. Risks Associated with Blood Draw: The needle stick to draw blood may cause temporary pain and/or bruising at the site of the puncture. Rarely, a blood vessel from which blood was drawn may develop a blood clot. Such a clot is not serious and requires no treatment. Also, in rare cases, fainting may occur as a result of drawing blood. These risks are the same as those you have with a standard blood draw.

1.c.vii Psychological Risks: The content of questionnaires and the motivational and educational content on the website are not controversial or likely to produce psychological distress.

1.c.viii. Social and Economic Risks: There is the potential for loss of confidentiality with the use of the Internet.

Website: The website maintained by the University of Michigan is password protected and secured. Only password and username will be stored on the website server along with daily step count information voluntarily downloaded by participants from the PA monitoring devices.

VA Boston Research Database: We use many procedures to protect the research database which is behind the VA firewall but despite these measures, there is a chance that a person not connected with the study may gain access to personal health information. Identifying information, including name, date of birth, phone number, alternate phone number, emergency contact information, gender, 6MWT distance, dyspnea score, smoking and supplemental oxygen use status, password and username, will be stored in the database along with daily step count information downloaded from the PA monitoring devices.

Use of Cisco Webex: Although Cisco Webex is secure and fully VA-authorized, it is not a VA site and is not controlled, monitored, or managed by the VA. There is a small chance that a person not connected with the study may gain access to the video study visits. There is a risk of loss of privacy if participants choose to hold their Webex video study visits in public.

2. Adequacy of Protection from Risks

2.a. Recruitment and Informed Consent: All patients with a diagnosis of COPD who are referred to the VA Boston Pulmonary Rehabilitation program will be eligible to participate in this research program. We will also recruit by sending a recruitment letter to patients who have visited the outpatient Pulmonary Clinics since 2005. We will also recruit from patients with COPD who have been seen in the Pulmonary Function Laboratory, the Women's Health Clinic, and the Primary Care Clinics. For interested persons, we will phone screen for those who meet national recommendations for referral to PR but who have not participated in PR. PR is recommended for patients with COPD who experience shortness of breath that interferes with daily activities despite use of medication. Subjects will be recruited voluntarily. Recruitment will occur over 48 months to enroll 300 subjects, and ultimately have 108 complete the RCT at 12 weeks and 96 complete the exploratory non-randomized study. For the 2 studies combined, we anticipate enrolling 5-7 subjects each month through the first quarter of Year 5. All persons with COPD who meet our inclusion criteria will be eligible to participate in the proposed research. To ensure safety, we will exclude those who have had a COPD exacerbation in the previous month. We will emphasize that usual clinical care is the highest priority. ESC will not be offered by research staff until it is absolutely clear to the clinical staff that the patient will not enroll in conventional PR. Signing of the informed consent and research testing will occur either in person or remotely (see page 10). Interested participants will provide written informed consent obtained by trained and experienced study staff. VA Boston research staff will explain the nature, scope, and possible consequences of the study in a way that is understandable to participants and answer all their questions. Participants can discuss the study with their usual healthcare providers. Subjects are under no obligation to participate. Study approval will be obtained from the VA Boston IRB.

For Aim 5, we will also recruit 15 VA Boston Healthcare System employees who are involved in the care of patients with COPD and/or pulmonary rehabilitation. We will identify eligible employees by using Outlook and provider names available from the VABHS website. We will also work with contacts at VABHS to identify potential participants. Following a modified snowball strategy, we will also ask participants to identify others who may be eligible to participate. Eligible participants will meet the following requirements:

a) Employed at VABHS
b) Involved in the care of persons with COPD and/or the pulmonary rehabilitation program at VABHS

c) Willingness to meet in person at the Jamaica Plain or West Roxbury VA or virtually over Cisco Webex for the study visit and have interview audio-recorded

Once we have identified eligible individuals, employee recruitment will be conducted via email, with the potential to send up to two follow-up emails for eligible staff. Emails will include a study information sheet attachment outlining details of participation. Each email response will be archived on the VA Boston secure server, and a member of the research team will document informed consent or refusal to participate in a password protected Excel spreadsheet. We will obtain verbal informed consent from staff who want to enroll. We are requesting a waiver of HIPAA authorization for all portions of Aim 5. The IRB-approved informed consent process will be completed via in person or over Cisco Webex prior to initiation of the study procedures. During the informed consent process, research staff will review a script that confirms eligibility and reviews the study information sheet that was sent to potential staff participants with the recruitment email. Potential employee participants will again be reminded that participation is voluntary and that a choice not to participate will not affect the individual's employment. Potential subjects will have as much time as they wish to ask questions and consider their participation before indicating consent. If they decline to participate, their identity will be protected. No manager will be present when the actual recruitment (i.e., recruitment being the process of reviewing the informed consent form, answering employee's questions, and completing the consent process) takes place. In addition, employees may end the interview, decline to answer individual questions, and/or decline to have their interview digitally recorded at any time during the interview. The consent process will address potential risks and discomforts. To guard against possible risks and discomfort, the questions will not focus on highly personal information; for example, the questions will focus on employees' perceptions about the intervention and technology, and their experiences providing care for their patients. Only once informed consent has been obtained will the subject be considered enrolled and added to the master list of enrolled study subjects. The master list will be secured in compliance with all VA confidentiality and information security requirements.

2.b. Protection Against Risks:
We estimate the total time of testing to be approximately 3-4 hours per study visit. Staff performing the 6MWT will be trained in Basic Life Support. Emergency treatments including nebulizer therapy, an automated external defibrillator, and a code cart will be available. During the 6MWTs, subjects can rest if short of breath and will be allowed to use supplemental oxygen if usually prescribed. Subjects will be instructed to bring their medications to the visit and will be allowed to take their bronchodilators if needed after performing the walk tests. If oxygen saturation <85% is observed at the baseline 6MWT, subjects will be temporarily excluded and their primary provider contacted for further care. These subjects can be reassessed for eligibility at a later date when clinically stable. If hypoxemia occurs during a follow-up 6MWT, patients will be referred to their primary providers for assessment and suspended from the study until clinically stable. Hypoxemia and dyspnea predict balance impairment and falls in COPD; both are assessed right before the 6MWT is performed. Also, if the subject is unsteady on his feet during the short walk to assess device accuracy and is obviously a fall risk, the 6MWT will not be performed. Depression will be screened for with the Beck's Depression Inventory-II. The Beck's questionnaire will be administered and scored by study staff while the participant is available in person or by remote video connection or telephone. We will do the following in real time while the participant is in person or on Webex or the telephone with study staff. Dr. Moy, the PI, or her MD designee, will be notified immediately and will join the Webex video or telephone session in real time to assess the participant if he/she reports suicidal thoughts on question 9 (response of 2 "I would like to kill myself" or 3 "I would kill myself if I had the chance") of the Beck's. Evaluation will be made for need for referral to the ER for further evaluation and treatment. Dr. Moy will notify the participant's usual provider. A score of 14 or higher suggests a clinical diagnosis of depression. If responses meet the cut-off scores indicating possible depression or anxiety, with the patients' permission, Dr. Moy, the PI, will inform their medical and mental health providers of the results (within 24 hours) for further

evaluation and/or treatment. The clinical diagnosis of depression or anxiety, and suicidal ideation, will need to come from the participants' mental health or primary care providers. We are not diagnosing them in the research study.

We will have information regarding the participant's physical address, we will look up and document in advance the emergency information immediately available (local police and fire), and obtain the name and contact information of someone else who may be with the person (if applicable). We will have access to the phone numbers of the VA Suicide Prevention Coordinators.

Subjects do not have to answer any questions on questionnaires with which they are uncomfortable. Based on our prior experience with our walking intervention, the most common SAE during the research study will be hospitalization for a COPD exacerbation. The most common related adverse event will be musculoskeletal injuries. During the study, subjects will be regularly monitored for adverse effects of exercise during research visits. In addition, participants can report adverse events at any time. Subjects in both arms will be instructed to notify their primary providers first, and then study staff, if they experience any change in their clinical condition, any change in medications, or have urgent care visits, emergency room visits, or hospitalizations. Available 24/7 for emergencies, Dr. Moy, the PI, will contact participants by telephone if any reported adverse event suggests clinical deterioration warranting immediate medical attention. During the study, if a subject experiences a medical problem that prevents walking and exercise, he/she will be temporarily suspended from the study and will resume when at baseline clinical status.

Surveys/questionnaires. Surveys/questionnaires are not stored in staff homes. The completed questionnaires are mailed via USPS to a VA Boston Healthcare System address.

Assessment of medical symptoms. Acute medical symptoms reported by the participant will be reported immediately to Dr. Moy, the PI, or her MD designee, who will join the Webex video or telephone session in real time to assess the participant. We will make sure we have information regarding the participant's physical address, we will look up and document in advance the emergency information immediately available (local police and fire), and obtain the name and contact information of someone else who may be with the person (if applicable).

Participant confidentiality and data security will be maintained at all times. Each participant will be given a unique study ID that will be used for all research purposes. Inadvertent disclosure of medical history information is guarded against by maintaining all completed questionnaires, collected by paper and pen, in a locked filing system. No data collection form will be linked to a participant's name. Study reports will be aggregated so that individual participants cannot be identified. All data will be stored in Access databases, identified only by study ID number, behind the firewalls at VA Boston. These data are backed up every night. The document linking the participant name to the study ID will be kept in a locked file separate from data collection files. Only the Principal Investigator or designee will have access to this file. Transmission and storage of step-count data will meet VA security and privacy standards (FIPS, FISMA). To avoid any violation of subject confidentiality, all data will be stored in databases, identified only by study ID number, behind the firewalls at the University of Michigan. These data are backed up every night. A confidential database linking subject identifying information with study ID will be maintained at VA Boston. Staff at the University of Michigan will not have access to this link.

We have convened an independent, external Data and Safety Monitoring Board (DSMB) to review recruitment and follow-up rates, and monitor adverse events, SAEs, and unanticipated problems. The DSMB is composed of Vincent Fan, MD, a pulmonologist and expert in telemedicine methods in COPD at the VA Puget Sound Health Care System and University of Washington; Elizabeth Klings, MD, a pulmonologist and expert in PR and COPD clinical trials at Boston University School of Medicine; and Gloria Yeh, MD, MPH an expert in PA interventions in persons with COPD and clinical trials at the Beth Israel Deaconess Medical Center, Boston. They will meet every 6 months, and as needed, by telephone conference. All related adverse events, SAEs, and unanticipated problems will be reported immediately to the VA Boston IRB.

3. Potential Benefits of the Proposed Research to Subjects and Others

There is potentially great benefit to the large number of Veterans with COPD if the proposed work leads to an efficacious strategy to promote PA in the many Veterans with COPD who cannot access conventional PR. The results may also improve long-term adherence to exercise after patients complete conventional PR. We address a persistent gap in care and significant clinical need by providing a concrete solution to address the limitations of conventional PR and operationalize the clinical response to PA recommendations with a simple, feasible, and accessible intervention. This proposal has high potential to bring a PA intervention to the patient in the setting of his/her home and community. Such a walking program would be accessible and sustainable to all who needed it. Since risks of the study are minimal, and the societal benefits are potentially large, the risk-benefit ratio is strongly on the side of benefit. There are no direct benefits to the subject.

4. Importance of Knowledge to be Gained

We propose to assess the efficacy of our web-based ESC intervention to increase PA in persons with COPD who cannot access conventional PR, compared to usual care. We will also study the ability of ESC to maintain exercise adherence and PA over the long term in persons with COPD who have completed conventional PR. Higher level of PA is associated with better outcomes in COPD, and promoting PA in COPD is a well-established recommendation. Conventional PR is inaccessible to the majority of persons with COPD and does not necessarily increase PA levels in the community. Our web-based intervention may be an efficacious and accessible alternative for the millions of patients with COPD who are referred to a conventional hospital-based PR program, but who cannot access it. By increasing PA, the intervention could decrease risk of acute exacerbations, hospitalizations, and COPD-related morbidity and mortality, improving the health of millions of Veterans and decreasing costs to the VA. Leveraging advances in technology and telemedicine, we propose a concrete solution to provide a PA program to reduce functional disability in the many Veterans with COPD who cannot access conventional PR. The proposed project 1) focuses on a highly significant health problem and population, 2) has a sound theoretical foundation to the intervention, 3) uses a technology-based intervention with proven efficacy, 4) has fundamental pilot data supporting the likely success of the project, and 5) has an experienced multidisciplinary team. This proposal has high potential to provide an immediate solution to a pressing clinical need.

The VHA has a strong commitment to providing care to persons with COPD and supporting research directed at COPD-related disability. The 2012-2016 Strategic Plan of the VHA Office of Research and Development identified chronic disease as a strategic objective area of focus and specifically includes research in COPD rehabilitation (Strategic Objective 2.11). The proposed research addresses Rehabilitation R&D Service's priority area to improve Veterans' health-related quality of life by reducing disease burden and maximizing functional recovery. The results of this study have strong implications for translation into clinical practice, providing an accessible exercise intervention to Veterans with COPD living with significant disability. Leveraging technology to enhance access and adherence is aligned with the VA's mission to increase telemedicine efforts to improve delivery of care and reach our rural populations. VA's FY 2018 − 2024 Strategic Plan envisions increased use of telehealth and online applications. Strategy 2.1.1 (VA Builds High-Performing and Integrated Delivery Networks that Leverage Both Virtual and Physical Delivery of Benefits, Care, and Services) states, "VA is rapidly expanding the use of telehealth, mobile app, online applications, and videoconferencing capabilities to deliver benefits and care to Veterans no matter where they live. Most importantly, improvements to mobile devices and apps will enable VA providers to connect to Veterans across the country to provide timely and convenient care." The proposed study's overall impact on VHA can be enormous.

5. Inclusion of Women and Minorities

Both genders are eligible to participate in this study. The large male predominance in the armed services results in the fact that enrollment in any VA-based study will be disproportionately male. Only 12% of all VA users are women. Additionally, female Veterans tend to be younger than male Veterans; since COPD prevalence increases with age, the prevalence of women with COPD in VA is expected to be lower than that for men. Accordingly, we will increase the visibility of the PR program among the providers in the VA Boston

Women's Health Clinic which provided care to 3,123 unique females in 2017. All minority subjects eligible for this study will be included. Reflecting the general Veteran population, the anticipated race distribution of all subjects enrolled will be 84% White, 10% African American, 2.8% Native American, and 2.3% Asian. It is anticipated that 3% will be of Hispanic ethnicity.

6. Inclusion of Children

No children will be included in this study since we are examining adults with COPD in this project.

(**g) Animal Subjects**: This study does not use animal subjects.

(h) Resources

(a) Research Space:

Study visits will be conducted virtually or in-person at the West Roxbury or Jamaica Plain campus.

The website is maintained by staff at the University of Michigan. Step-count data, owned by the participants, are located on the University of Michigan server.

(b) Other Research Resources:

There is a separate 300 ft^2 exam room used for research activities, such as subject enrollment, questionnaire administration. The 6-minute walk test is performed using a well-marked course in a straight corridor.

The Pulmonary Rehabilitation Program is externally accredited by the American Association of Cardiovascular and Pulmonary Rehabilitation. The program is staffed by a dedicated team of pulmonologists, physician assistant, respiratory therapist and exercise physiologist. It occupies 1,375 ft^2 of dedicated space at the Jamaica Plain campus. Patients have access to 5 treadmills, 3 upright bicycles, 3 semi-recumbent bicycles, and 6 upper body ergometers. In addition, there are 3 NuStep recumbent cross-trainers and a state-of-the-art computerized Keiser system, which provides weight training using pneumatic resistance. Supplemental oxygen is available at each piece of equipment either through oxygen piped in or via portable oxygen tanks. Within the pulmonary rehabilitation space, there is 150 ft^2 of dedicated open space for patients to gather for the educational sessions, for strength training with free weights, and for completion of questionnaires. Adjacent to the exercise area, there is a 170 ft^2 clinical testing room which houses a cardiopulmonary exercise testing laboratory and equipment for pulmonary function testing. Research study visits are also conducted in this room. The 6-minute walk test is performed in a well-marked and lighted course in a straight hallway. These resources located at the Jamaica Plain Campus, 6 miles from the West Roxbury Campus, provide flexible options for research testing to accommodate travel preferences of all research participants. The two sites are highly integrated, and share a single computer and medical records system. A shuttle bus system provides frequent transportation between the 2 campuses.

Dr. Moy's office is part of an epidemiological research group that occupies 1500 ft^2 of dedicated office space at the West Roxbury campus. Dr. Moy's office and research laboratory occupy 800 ft^2 of office space and has office network of high-speed PC's linked via a network. Software capabilities include PC-SAS, STATA, and standard data management software (Microsoft ACCESS, EXCEL, Word). There is a network of 8 high-speed PC's with large capacity data storage capacity with back up and linkage among password protected PC's provided by the hospital network.

The VA Boston Healthcare System is an academic affiliate of Harvard Medical School and Boston University School of Medicine. The VA Boston Healthcare System, West Roxbury Campus, is located 8 miles from the Harvard Medical area, which includes the Francis A. Countway Library of Medicine, Harvard Medical School, and the Harvard School of Public Health. Through the Countway Library we have computerized access

to one of the largest medical libraries in the United States that contains over ½ million books and receives over 4,000 journal titles, and access to one of the most comprehensive search services in the country.

(i) Publications from Last Funding Period (as applicable). List the complete references of all publications, manuscripts that are accepted or submitted, patents, or other printed material from the PI and/or collaborators that are based on work accomplished toward the specific aims of the proposed work and/or objectives completed during the previous funding period.
N/A

2021 COVD-19 Modifications

We will follow all current VABHS COVID-19 protocols and procedures as required. In the event that local policy requires COVID-19 testing we will inform the participant of this by phone prior to a scheduled visit. At the initial visit, study staff will obtain informed consent and then conduct a Binax Rapid Antigen test on the participant. Testing will be completed in accordance with VABHS standard operating procedures for COVID-19 Ag testing using the Abbott Binax NOW COVID-19 Ag Card test kit. The Binax testing will be conducted by study staff who have completed all required Binax testing training at VABHS. Binax test results will be entered in the participant's electronic medical record by study staff. If a participant does not have a medical record one will be created so that results can be documented as required by VA. Only participants who test negative on the Binax test will proceed to the remainder of the study visit. Participants who test positive will be offered PCR testing at the VA per the Binax Testing Research SOP or be given the option to contact their primary care provider or obtain PCR testing elsewhere. If a participant tests positive, some study visits may occur outside the study visit window. We will comply with VABHS COVID-19 protocols for as long as they are in place and will adjust procedures as necessary to maintain compliance.

(j) Literature Citations (as applicable). Include a complete citation for all references (all authors, year, title, journal, volume number, and inclusive pages). Start each citation on a new line. List citations by number in the order they first appear in the application. For renewals, the list may include, but does not replace, the citations in "Publications from Last Funding Period."

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