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

Title: The Effect of Physical Activity Promotion on Short and Long-term Outcomes in COPD
Principal Investigator: Marilyn L. Moy, MD, MSc

(1) **Rationale**

(a) Statement of the Problem.

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. In Veterans, the prevalence is high; in VISN1 in FY 2012, 9% of outpatient Veterans had the ICD-9 diagnosis of COPD. In COPD, shortness of breath leads to physical inactivity and significant functional impairment and disability. The clinical course is characterized by acute exacerbations (AEs), periods of worsening that require additional pharmacological treatment. From 2002 to 2005, there were over 40,000 admissions to VA hospitals for COPD AEs. These episodes result in worsening of health-related quality of life (HRQL), a more rapid longitudinal decline in forced expiratory volume in the first second (FEV_1), and higher mortality. Furthermore, there is considerable evidence that COPD is a systemic disease. Persons with COPD have elevated biomarkers of systemic inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which are associated with increased risks of AEs, cardiovascular disease, peripheral skeletal muscle dysfunction, and all-cause mortality.

A growing body of knowledge has identified physical activity and exercise as a modifiable factor that may impact COPD-related morbidity and mortality. Epidemiological and cross-sectional studies have shown that persons with COPD who are more physically active have fewer hospitalizations and lower mortality. Specifically, walking is a simple and meaningful metric of physical activity associated with COPD outcomes. Funded by a RR&D CDA-1 (Dr. Moy), we have shown that daily step count can be accurately measured in persons with COPD and provides unique information about COPD clinical status not captured by current outcomes of pulmonary function (FEV_1), symptom of dyspnea, HRQL, or 6-minute walk test (6MWT) distance, a clinic-based test of exercise capacity. Importantly, we have shown that persons with COPD who walk the most have the lowest risk of future AEs and the lowest plasma levels of CRP and IL-6. Others have shown that a higher daily step count is associated with lower mortality in COPD, independent of lung function.

Despite the potential benefits, there have been few interventions to increase walking in persons with COPD. Counseling by healthcare providers to increase physical activity and exercise has shown limited success. Although supervised pulmonary rehabilitation programs improve exercise capacity, they are not accessible to all who could benefit from them and have low adherence rates. Novel interventions that incorporate strategies for behavioral change and that are accessible, individualized, and sustained are needed to promote physical activity and exercise in persons limited by COPD. Funded by a RR&D CDA-2 (Dr. Moy), we have developed and piloted a novel exercise intervention that combines a website with a pedometer to promote walking in persons with COPD. The program, called Every Step Counts (ESC) for Lung Health, accurately monitors walking, provides iterative feedback and individualized goal-setting in steps per day, and delivers education and motivation online. In a non-randomized study, we demonstrated its safety, feasibility, and ability to increase daily step count in persons with COPD over 3 months.

Building on the CDA-1 and CDA-2, we propose to determine the efficacy of an internet-mediated walking program compared to usual care (verbal and written instructions to exercise). We propose a 2-arm randomized, controlled study (1:1 ratio) in up to 185 persons with COPD.

Subjects will participate in the study for a total of up to 13 months. The intensive interventional phase will be 6 months during which subjects will be engaged by the website with messages, tips, an online forum community, and step count goals followed by a maintenance intervention phase of 6 months during which the subjects will receive new step count goals but no new educational materials; although subjects will be able to review content previously posted. Subjects will wear the pedometer for 14 days preceding or following the12-month in-clinic visit. For the step collection at month 12, subjects assigned to the control arm will receive a pedometer by postage mail or in person to wear for 14 days and return by prepaid mailer or in person at the 12-month in-clinic study visit. Subjects in the intervention arm will continue wearing their pedometer. Additionally, postcards will be sent during the subject's birthday month (no specific day listed) as well as a postcard during each season (spring, summer, fall, winter) with health and safety tips to enhance study engagement.

(b) Hypotheses or Key Question.

Primary Aim: To determine the efficacy of the WEB intervention to increase 6MWT distance.

Secondary Aims: To estimate the effect of the WEB intervention on (a) HRQL, as measured by the St. George's Respiratory Questionnaire (SGRQ), (b) dyspnea, (c) CRP and IL-6, (d) risk of AEs and COPD-related hospitalizations, (e) engagement in physical activity as measured by daily step count, and (f) to measure changes in body composition and bone mineral density (BMD) in a subset of participants.

(c) Specific Objectives.

We hypothesize that WEB will significantly increase exercise capacity measured by 6MWT distance at 6 months, compared to controls. We also hypothesize that WEB will improve HRQL, dyspnea, levels of inflammatory biomarkers, risk of AEs and COPD-related hospitalizations, and daily step count, body composition and bone mineral density compared to controls. Exploratory analyses will examine the mechanism of benefit of increasing physical activity in persons with COPD. We hypothesize that increases in 6MWT distance and daily step count will be significantly associated with decreases in inflammatory biomarkers and risk of AEs and COPD-related hospitalizations.

Our proposal addresses the exciting and important next steps of developing novel interventions to increase physical activity and assessing the impact of those interventions on COPD outcomes. Our intervention has the potential to (1) bring an exercise program to the vast majority of persons with COPD who cannot go to a hospital-based pulmonary rehabilitation program, (2) improve the effectiveness of current rehabilitation programs by sustaining long-term exercise, and (3) become an effective and integral part of COPD self-management programs. Ultimately, the intervention could decrease risk of hospitalizations, AEs, and COPD-related morbidity and mortality.

(2) **Background and Significance**

(a) Background.

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). In Veterans, the prevalence is high (2); in VISN1 in FY 2012, 9% of outpatient Veterans had the ICD-9 diagnosis of COPD. Despite optimization of pharmacological therapy, shortness of breath (dyspnea) is a common symptom, leading to physical inactivity, deconditioning, and significant functional impairment and disability (3). The clinical course of COPD is characterized by acute exacerbations (AEs), periods of worsening that require treatment with antibiotics and corticosteroids (4). AEs result in negative

effects on health-related quality of life (HRQL), a more rapid longitudinal decline in forced expiratory volume in one second (FEV_1), and higher mortality (5,6). AEs contribute to 31-68% of the $6.5 billion/year cost of health care for COPD patients in the US (5,7). From 2002 to 2005, there were over 40,000 admissions to VA hospitals for COPD exacerbations (8). COPD is not only a lung disease, but also a systemic disease (9). Persons with COPD have elevated circulating biomarkers of inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), which are associated with increased risks of AEs, cardiovascular disease, peripheral skeletal muscle dysfunction, and all-cause mortality (10-12).

COPD is associated with a high prevalence of cardiovascular and oncologic comorbidities (13). As in the general population, physical activity (PA) may be important in modifying risk of these comorbid conditions in persons with COPD. Furthermore, exercise capacity, measured by maximum oxygen consumption (VO_2 max) during a cardiopulmonary exercise tolerance test (CPETT) or distance walked on a 6-minute walk test (6MWT), is a significant predictor of mortality, independent of lung function in COPD (14,15). In addition to exercise capacity measured with clinic-based tests, PA measured in the field is significantly reduced in persons with COPD, compared to healthy subjects (16,17). Epidemiological and cross-sectional studies of PA, assessed by questionnaire or directly measured, have shown that PA relates to outcomes in COPD. Adjusting for % predicted FEV_1, higher levels of PA are associated with better functional status, fewer hospital admissions, and lower mortality (18-21). One study has shown that higher PA is associated with lower fibrinogen levels, an inflammatory biomarker, suggesting that increased PA may be associated with decreased systemic inflammation (22). Thus, PA may be a modifiable factor that impacts risk of comorbidities and COPD-related morbidity and mortality. Current COPD treatment guidelines state “it should be considered a high priority for future COPD therapies to ameliorate inactivity" (23-24). Engagement in PA is an integral component of COPD self-management programs (25).

Walking is a simple form of PA and exercise that most people can do. It is generally a safe, convenient, and inexpensive way to increase PA, and it can be integrated into daily activities--all factors that contribute to long-term adherence. Steps per day is an easy to understand activity unit and goals to increase walking by a certain number of steps per day are meaningful to subjects. We and others have shown a low correlation between daily step counts and measures of exercise capacity such as 6MWT distance and VO_2 max, demonstrating that daily step counts capture unique information (40,41). Total daily PA is closely related to leg activity in persons with COPD (42). Depew et al. have shown that daily step count is a surrogate for PA level (43). Higher levels of walking are associated with better outcomes in COPD. Regular walkers, defined as those who are active on most days or every single day of the week, have slower declines in overall HRQL and less progression of dyspnea during activities of daily living compared to irregular walkers with COPD (32). A 6-month home-based exercise program focused on walking improved 6MWT distance and HRQL (44). As part of Dr. Moy’s CDA-1 and CDA-2, we have shown that a higher daily step count is associated with a lower risk of future AEs and COPD-related hospitalizations (45). We have also shown that those who walk the most have the lowest plasma levels of CRP and IL-6 (see Preliminary Studies). Others have shown that a higher daily step count is associated with lower mortality in COPD, independent of pulmonary function (19). A plausible hypothesis is that daily step counts and PA affect systemic inflammation which, in turn, impacts risk of AEs, COPD-related hospitalizations, and death in persons with COPD.

Despite the potential benefits, there have been few exercise interventions to increase walking in persons with COPD. The Internet can be an effective platform for delivering an accessible walking exercise program (46,47). A 2012 Pew survey showed that 81% of adult Americans use the Internet, with those in the age range of 50-64 years as equally represented online as younger users (48). Eighteen percent of consumers, aged 65 and older, sought health information using the Internet in 2007, compared to 7 percent in 2001 (49). Previous studies of dyspnea self-management showed that 34% of persons with COPD (mean age 69 years) used

the Internet for an average of 12 hours a week (50-52). Previous work has suggested that Internet-mediated, home-based walking programs may be effective at increasing PA (53,54) and can be safe for chronically ill individuals (55,56).

Use of pedometers may increase walking and improve health outcomes. In healthy subjects, pedometers successfully promote walking for weight loss and blood pressure control (57,58). However, providing a pedometer without structure for feedback and goal setting is unlikely to achieve and sustain maximal benefits. Knowing how many steps one is taking each day is not motivating unless one also knows how much walking one should be doing. Step-count logging and goal setting are critical components of effective pedometer-based walking programs, but these tasks can be difficult. A walking program that combines a pedometer with an Internet-based program could increase the intensity and accuracy of self-monitoring, be readily accessible, reduce participant burden, and facilitate the calculation of individualized step-count goals. These features are particularly important in the Veterans Health Administration (VHA) with geographically dispersed healthcare systems and patients with complex medical problems.

Stepping Up to Health (SUH) is a Web-based walking program that interfaces with the Omron HJ-720ITC (Omron) pedometer. Dr. Caroline Richardson originally developed the exercise intervention to promote walking in sedentary persons with cardiovascular disease risk factors (59,60). The SUH intervention is based primarily on Self-Regulation Theory which emphasizes an iterative, rational process of behavior change (61,62). An individual working towards a behavioral goal learns from successes and failures, and uses this knowledge to develop effective behavioral strategies to achieve his or her goal (61) (Figure 1).

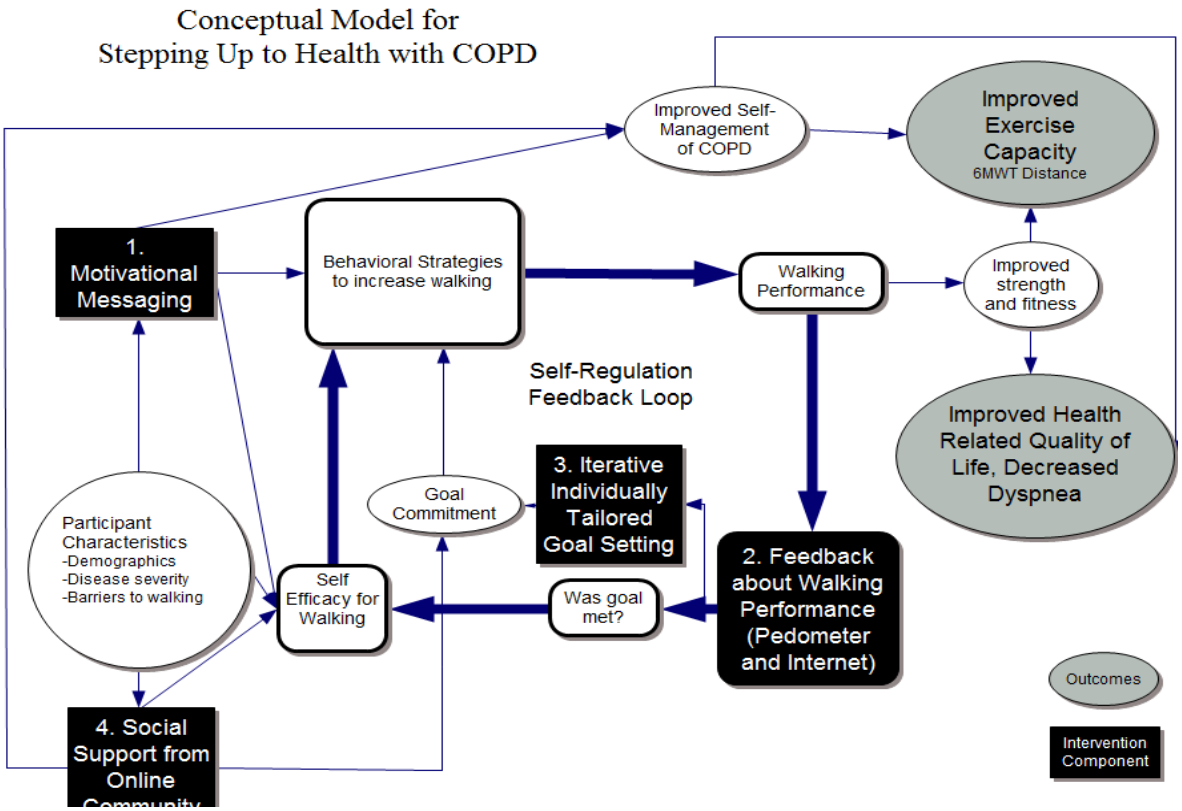


Figure 1. Conceptual Model: Self-Regulation in the Stepping Up to Health intervention

components of the cycle of self-regulation (62). SUH supports the cycle of self-regulation with four unique components to promote walking: 1) objective walking assessment and feedback, 2)

individualized step-count goals, 3) motivational messages and educational content, and 4) online community (Figure 1).

1) Objective Walking Assessment and Feedback: The Fitbit Zip pedometer used in our research program was selected because it accurately measures step counts in the majority of persons with COPD, is easy to use, and interfaces with the Internet. By connecting the pedometer to a computer with a USB device called a dongle, participants can upload step-count data to the website and view their progress using a variety of detailed graphs.

2) Individualized Step-Count Goals: Specific step-count goals are more effective than setting goals based on total distance or duration walked (62). High target goals improve performance as long as the goals are not so high that the participant believes they are impossible to achieve (63). Sudden and dramatic increases in PA may also increase the risk of injury and adverse cardiac events. WEB uses an automated algorithm to compute gradually incrementing, individualized step-count goals. Goals are based on step-count data uploaded by the participant, accurately reflecting the participant's current level of walking. Goals are not necessarily increasing over time. For example, if a participant is sick, and thus records low step counts for one week, the subsequent week's goal will be lower than the goal for the week the participant was sick.

3) Motivational Messages and Educational Tips: Persons who are sedentary or who have chronic disease face general and disease-specific barriers to starting and maintaining a walking program. Specific strategies and behavioral techniques for overcoming these barriers are addressed as part of the motivational messaging component of WEB. Education about disease management, the benefits of PA, and behavior change is also provided online, and some messages are tailored to smokers or oxygen users for more targeted and relevant information. These features promote exercise self-efficacy and confidence, and encourage compliance. Users view these materials on their website study page.

4) Online Community: An online community within the WEB website maintains social support by allowing participants to share ideas about promoting PA. Richardson et al. demonstrated that subjects with access to an online community remained engaged in the intervention for a longer time and were less likely to drop out than those without access to an online community (64). Participants who posted more frequently on the online community increased their step counts more that those who posted less frequently (64).

In a previous study, the use of SUH for 4 months resulted in an average increase in walking of approximately 2,000 steps per day (1.6 km) in individuals with type 2 diabetes mellitus, coronary artery disease, or obesity (64). In that study, a subset of persons with self-reported COPD (n=24) demonstrated an average increase of approximately 1,000 steps per day after use of SUH for 4 months (65). Another study has used the core features of SUH to promote PA in women with gestational diabetes (66), while another study is assessing the efficacy of SUH to reduce back pain in Veterans (67). Although it is well known that greater PA and exercise are beneficial, it is unclear how to increase PA in persons with chronic disease such as COPD who already experience significant functional impairment from their disease. As part of her CDA-2, Dr. Moy has modified SUH to include website content specific for persons with COPD. This adapted walking program is called Every Step Counts (ESC) for Lung Health. In a non-randomized pilot study, we have demonstrated its safety, feasibility, and ability to increase daily step counts over 3 months in persons with COPD (68).

(b) Significance.

Our proposal addresses the exciting and important next steps of developing novel interventions to promote PA and assessing their impact on COPD outcomes. WEB is unique because of its

ability to accurately monitor walking performed, individualized goal setting, educational content and motivational messages, and automation. We propose to establish the efficacy of WEB to improve short- and long-term outcomes in COPD in a randomized, controlled study. The results of the proposed study will provide the evidence needed to support the adoption of WEB into clinical practice.

WEB would significantly and positively impact the way we currently care for patients with COPD. First, WEB has the potential to bring an exercise program to the vast majority of persons with COPD who cannot go to a hospital-based PR program. Second, WEB has the potential to improve the effectiveness of current PR programs by sustaining exercise after completion of a supervised PR program. Finally, WEB could become an effective and integral part of COPD self-management programs. Once implemented, the program would be available to all persons with COPD who need it, would individualize exercise training, and could promote walking indefinitely. Ultimately, the intervention could decrease risk of AEs, hospitalizations, and COPD-related morbidity and mortality. Although significant progress has been made to understand the cross-sectional relationships between PA and COPD outcomes, the important next step of assessing how increasing PA with an intervention impacts these COPD outcomes have not previously been studied. Our proposal has the potential to provide significant insight into the mechanisms of how walking and PA favorably impact risk of COPD-related morbidity.

(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 identifies 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 current priority area of improving disabled 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. Based on estimates that 24 million people in the US have COPD (69) and our preliminary data that 33 to 64% of COPD patients are Internet users, our proposed intervention could help over 8 million persons.

A walking program that combines a pedometer with an Internet-based program could increase the intensity and accuracy of self-monitoring, be readily accessible, reduce participant burden, and facilitate the calculation of individualized step-count goals are particularly important in the Veterans Health Administration (VHA) with geographically dispersed healthcare systems and patients with complex medical problems.

(3) Work Accomplished

Funded by Rehabilitation R&D CDA-1 (2006-2009) and CDA-2 (2009-2014) to Dr. Moy, we have published the peer-reviewed papers listed below, and have presented 7 abstracts at the American Thoracic Society (ATS) meetings.

Moy ML, Janney AW, Matthess K, Ngyuen HQ, Cohen M, Garshick E, Richardson CR. An Internet-mediated walking program promotes free-living ambulation in COPD. J Rehabil Res Dev 2010:47;485-496.

Moy ML, Danilack VA, Weston NA, Garshick E. Daily step counts in a US cohort with COPD. Respir Med 2012;106:962-969.

Moy ML, Weston NA, Wilson EJ, Hess ML, Richardson CR. A pilot study of an Internet walking program and pedometer in COPD. Respir Med 2012;106:1342-1350.

Moy ML, Teylan M, Weston NA, Gagnon DR, Garshick E. Daily step count predicts acute exacerbations in a US cohort with COPD. PLoS ONE 2013 8(4): e60400.

Moy ML, Teylan M, Weston NA, Gagnon DR, Danilack VA, Garshick E. Daily step count is associated with CRP and IL-6 in a US cohort with COPD. Chest 2013 Oct 3. doi: 10.1378/chest.13-1052.
Danilack DA, Weston NA, Richardson CR, Mori DL, **Moy ML**. Perceived barriers to walking in a COPD cohort and relationship with daily step count. J of COPD 2013 (in press).
Moy ML, Teylan M, Danilack VA, Gagnon DR, Garshick E. An index of daily step count and systemic inflammation predicts clinical outcomes in COPD. Annals of ATS (accepted).
Martinez CH, **Moy ML**, Nguyen HQ, Cohen M, Kadri R, Roman P, Holleman RG, Kim HM, Giardino ND, Richardson CR. Taking Healthy Steps: Rationale, Design and Baseline Characteristics of a Randomized Trial of a Pedometer-Based Internet-Mediated Walking Program in Veterans with Chronic Obstructive Pulmonary Disease (submitted).

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 and Director of the Pulmonary Rehabilitation Center at VA Boston, 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, Associate Professor of 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. J. Allen Cooper, MD is Chief, Pulmonary Section, Birmingham VAMC and Professor of Medicine, University of Alabama Medical School. He has experience performing research studies with persons with COPD, and is aware of the importance of enrolling a diverse population of eligible subjects. Dr. Cooper was previously involved in a multi-center VA study of the medication Tiotropium in COPD funded by Boehringer Ingelheim Pharmaceuticals and Pfizer, Inc. Dr. Cooper's site recruited 145 subjects and was ranked the fourth highest recruiting site of 26 sites. Drs. Moy and Cooper currently collaborate on the multi-center NHLBI studies, "The Effect of Simvastatin Administration on the Frequency and Severity of COPD Exacerbations" and "Long Term Oxygen Treatment Trial (LOTT)." 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. Drs. Richardson, Garshick, and Mori are mentors for Dr. Moy's current RRD CDA-2. 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. 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.

(4) **Work Proposed**

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

Staff training, IRB approval and finalization of website specifications and beta testing will occur during the first 6 months of Year 1.

Recruitment and randomization would begin the second half of Year 1: Recruitment will be conducted over 30 months to achieve the goal to randomize up to 185 subjects. We anticipate enrolling 3-4 subjects per site each month through the third quarter of study year 3 (Figures 2 and 3). Between both sites, we expect to screen and enroll a total of 320 participants in order to randomize a total of 185 participants for the whole study.

Subjects will have completed their participation in the study after approximately 13 months from the first in-clinic baseline visit.

Figure 2. Gnatt Chart

	Yr 1				Yr 2				Yr 3				Yr 4			
Activity	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Train Staff																
Obtain IRB Approval																
Finalize Website Specifications and Beta Testing of Website																
Enroll and Randomize to WEB Intervention or Control																
Intensive Intervention and Outcomes Data Collection (6 months)																
Maintenance Intervention (6 months)																
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.

At VA Boston and VA Birmingham, a total of 185 subjects with COPD will be randomized with an allocation ratio of 1:1 to one of 2 arms: (1) written instructions and education to exercise (usual care) or (2) pedometer and Internet-mediated walking program. Subjects will participate

in the study for a total of up to 13 months, depending on the timing of the C12 in-clinic study visit. The intensive interventional phase will be 6 months followed by a maintenance intervention phase of 6 months and a subsequent 14-day step count collection using a pedometer at 12-months (up to 13 months). Six-minute walk test distance at 6 months will be the primary outcome to assess the efficacy of the Internet-mediated, pedometer-based walking program. Since we are studying the efficacy of a walking intervention, the 6MWT distance is the primary outcome of choice. Secondary outcomes include HRQL, dyspnea, CRP and IL-6 levels, risk of AEs and COPD-related hospitalizations, engagement in PA assessed by daily step count. Additional secondary outcomes include body composition (adiposity) and bone mineral density at baseline and 12 months (in the subset of subjects enrolled at VA Boston only). The study contact timeline and assessments are summarized in Figure 3. Subjects will have an in-clinic assessment at baseline, 3, 6, and 12 months, and a telephone call at 9 months. We anticipate drop-out at 6 months to be at most 40%, resulting in at least 55 subjects who will complete each arm of the study.

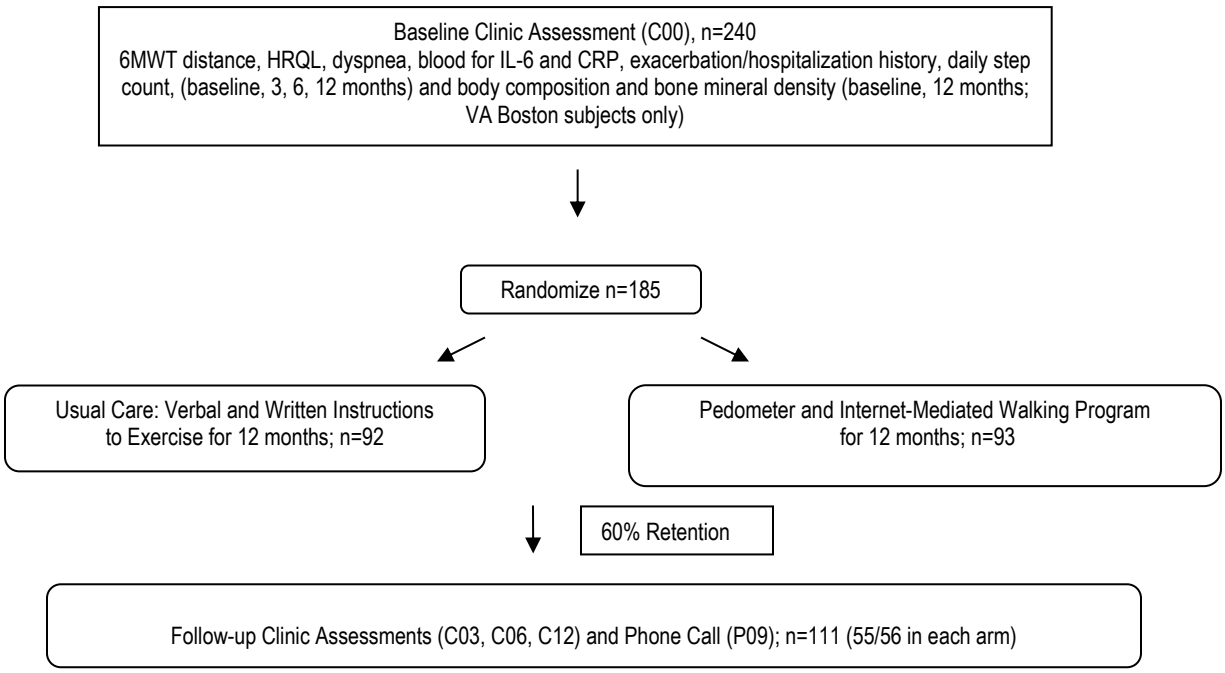


Figure 3. Protocol Summary. C=Clinic visit, P=Phone call.

Inclusion Criteria are:

a) Male and female subjects, greater than or equal to 40 years of age
b) Clinical diagnosis of COPD defined as either a ratio of FEV_1 to forced vital capacity < 0.70 or chest CT evidence of emphysema or prior documentation of FEV_1/FVC ratio of < 0.7 and clinical evidence of COPD (defined as ≥ 10 pack-year cigarette smoking history, dyspnea, or on bronchodilators)
c) Medical clearance from healthcare provider to participate in an exercise program
d) Have access to a computer with Internet connection, a USB port or Bluetooth capability, and Windows XP/Vista/7/8/10 or higher, or Mac OSX 10.5 or higher operating system, or willing to come to VA Medical Center to use study computers
e) Pedometer with >90% accuracy compared to manual counts on short clinic walk
f) Competent to provide informed consent
g) 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) Clinical signs of unstable cardiovascular disease or congestive heart failure
d) Hypoxemia during 6MWT, i.e. oxygen saturation <85% using supplemental oxygen
e) Inability to complete questionnaires
f) Inability to collect at least 5 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 12 months
j) Plans to enroll in a supervised exercise program, such as pulmonary rehabilitation, in the next 6 months
k) Average baseline step counts of greater than or equal to 10,000 steps per week

Recruitment will occur over 30 months to achieve the goal to randomize up to 185 subjects. We anticipate enrolling 3-4 subjects per site each month through the third quarter of study year (D.13 Gantt Chart). At VA Boston, we will recruit from a clinical list of over 5,500 unique patients who have visited the Outpatient Pulmonary Clinics from 2005-2013. 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. We will confirm the diagnosis of COPD by computerized medical record review. As of May, 2013, seventy eight percent or 48,425 Veterans at VA Boston and 61% or 35,697 Veterans at VA Birmingham are registered for MyHealtheVet and thus have Internet access. In addition, we will have computer stations conveniently available for use at the study sites. Subjects who do not have Internet access or who do not use Windows or Mac operating system at home, but are willing to come to the hospital to use our computers will be included. We anticipate easily meeting the recruitment goal of 185 subjects.

To increase the diversity of our population, we will over recruit African-American Veterans and female Veterans. Twenty one percent of Veterans in Alabama are African American, and 10-15% of subjects enrolled in COPD trials at VA Birmingham are African American. The large male predominance in the armed services results in the fact that enrollment in any VA-based study will be disproportionately male. Only 11 % of all VA users are women. Additionally, female Veterans tend to be younger than male Veterans, while COPD prevalence increases with age, so the prevalence of women with COPD in VA is expected to be lower than the prevalence for men. Accordingly, we will over-recruit from the VA Boston Women's Health Clinic which provided care to 3,123 unique females in FY 12, of whom 140 were diagnosed with COPD.

Our recruitment method will consist of mailings with the option to express interest by calling study staff or returning a postcard, and posting flyers and leaving brochures at the VA and also in public spaces, hospitals, and clinics with permission from individual sites (e.g. local YMCA, Brigham and Women's Hospital, Brigham and Women's Faulkner Hospital, Boston Medical Center, etc.). Subjects who do not respond to the mailing will receive a telephone call from study staff. This recruitment method has been successful for our previous COPD studies. Drs. Moy and Cooper have an existing relationship working on multi-site COPD clinical trials. Our teams have extensive experience and success recruiting and retaining subjects with COPD for clinical trials and research studies. Both VA Boston and VA Birmingham are part of the NHLBI COPD Clinical Research Network and have successfully recruited for the studies, "The Effect of Chronic Macrolide Administration on the Frequency and Severity of COPD Exacerbations" and "The Effect of Simvastatin Administration on the Frequency and Severity of COPD Exacerbations." Both sites also recruit and retain participants for the NHLBI funded "Long Term Oxygen Treatment Trial (LOTT)."

Those who express interest in participating in the study will be screened over the telephone using basic eligibility criteria. If the potential participant is a woman, then the research staff will also administer the child bearing potential telephone screening questions. If she is determined to be of child bearing potential, she will be asked to provide a urine sample for a pregnancy test. At the baseline and 12-month in-clinic study visit, she will be asked to provide a urine sample or to bring in a urine sample collected at home for a pregnancy test. If the test is positive, the DXA scan and body fat composition measurement with the Omron HBF-306CN will not be performed and the subject will have the option to end participation in the entire research study.

(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.

Baseline Visit

D.3. Baseline Visit

When interested subjects are scheduled for the baseline clinic visit, they will be mailed a medical clearance form which will have been signed by their healthcare provider. The signed clearance form must be faxed or submitted to study staff prior to randomization and assignment to a study arm. At the baseline study visit, 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. We will also assess history of AEs and related medication use in the previous 12 months since prior AE strongly predicts future AEs (83). Weight and height will be measured for the calculation of body mass index (BMI). Baseline data will characterize the cohort and allow analysis of potential confounders.

We will verify the accuracy of the pedometer in each subject by comparing measured to manually counted steps during a standardized in-clinic walk of 244 meters. Subjects can use assistive devices such as a cane if they typically use one for walking. Only persons in whom the pedometer has >90% accuracy in capturing step counts will be eligible. Eligible subjects will perform 6MWT, spirometry, HRQL assessment with the SGRQ and Veterans SF-36, and dyspnea assessment with the UCSD Shortness of Breath Questionnaire and MMRC Dyspnea Scale (Assessments described in D.6). Subjects will also complete the Barriers to Exercise Questionnaire, Physical Recall Activity Questionnaire, Bristol's COPD Knowledge Questionnaire, Exercise Self-Regulatory Self-Efficacy Questionnaire, Beck Depression Inventory, Epworth Sleepiness Scale, CHAMPS Physical Activity Questionnaire, MOS Social Support Survey, Dietary Questionnaire, and the Brief Pain Inventory (short form). If a subject does not have time during the study visit to complete the study-related questionnaires, we will contact the subject by phone to finish the questionnaires by phone at a time after the visit or send the questionnaires home with the subject to be completed and sent back in a pre-paid mailer. Three tubes of blood (2 tablespoons) will be drawn by venipuncture, overnight shipped to Massachusetts Veterans Epidemiology Research and Information Center (MAVERIC) at VA Boston, and processed and stored for biomarker analyses. Subjects recruited at VA Boston will be asked to complete a DXA scan to measure body composition and bone mineral density at the baseline screening visit. Additionally, subjects will be asked to complete a body composition reading using the Omron Fat Loss Monitor (model HBF-306CN) for comparison of body fat measurements between measurement methods. The Omron Fat Loss Monitor is a portable handheld device that the

participant grips while in a seated position for 5-10 seconds. Three readings will be taken in this fashion and will be completed in <10 minutes. The device has been approved for use in the general population except in individuals who are pregnant and who have implanted medical devices such as pacemakers and defibrillators. Although independent studies have suggested that bioimpedance monitors are safe for use in individuals with pacemakers, we will exclude any subject who has a pacemaker or defibrillator from the bioimpedance measurement. Subjects who are pregnant are excluded from both the DXA and bioimpedance measurements. If subject has undergone a DXA scan at the VA Boston Osteoporosis Clinic previously within 6 months, then the data from the Osteoporosis Clinic may be used and subject does not need to complete a scan specifically for the research study. If the DXA scan is not completed, then the body composition reading using the Omron Fat Loss Monitor (model HBF-306CN) will not be completed.

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.

Research staff will set up Fitbit Zip pedometers for all subjects who are eligible and require a 10-day baseline collection. All subjects will be sent home to wear the pedometer 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 download the Fitbit Connect software so they can upload their step count data at home and a prepaid mailer to return the Fitbit Zip if they are randomized to the control arm after baseline step count collection. This account setup will be for uploading the data to the study team and will not include any access to the Fitbit website by the subjects. Subjects will only be able to access their step counts through the study website if randomized to the intervention. The Fitbit Zip pedometer will have a sticker covering the digital display to prevent feedback. Subjects will be instructed to perform their *usual* physical activities and exercise. Subjects will provide the phone number which they will use to receive the randomization assignment.

Randomization

After collecting 10 days of baseline step counts, subjects will upload their step count data using the Fitbit Connect Software by placing their pedometer near the dongle device connected to their computer, or through Bluetooth (whichever works for their computer system). Study staff will be available to assist subjects navigate any issues with uploading. In addition to obtaining representative baseline step-count data, this run-in period will allow us to gauge subject compliance with wearing the pedometer if assigned the intervention, potentially reducing the number of drop-outs. Participants must have $\leq$ 3 no-wear days (<200 steps per day) to be eligible to be randomized. Medical clearance will have been obtained from a healthcare provider. Eligible subjects will be randomized to 1) written instructions and education to exercise (usual care) or 2) pedometer and Internet-mediated walking program. Since the sample size is relatively small, we will use blocked randomization, 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. Subjects who are randomized to intervention will choose a username and password that allow them to log in to the study website to upload their step counts. Study staff will help participants choose strong username and passwords to optimize privacy and security. Subjects who are randomized to the control arm will be asked to return the pedometer in the prepaid mailer provided and will be informed of the pedometer wear schedule and reminded that they will receive the pedometer to keep at the conclusion of study participation. To ensure blinding, study staff communicating randomization assignments to subjects will be different from study staff conducting follow-up assessments.

Written instructions and education to exercise (Usual care, Appendix 1)

Using a standardized script at the randomization phone call, study staff will deliver verbal instructions to all subjects to encourage participants to increase one's walking slowly and steadily, and to increase the amount of exercise each week. Exercise is defined as ***planned*** PA in addition to activities performed as part of one's daily routine. Daily PA is all PA performed, including exercise. Increasing daily PA and exercise are goals of the program. Exercise can be mainly walking in the community or using exercise equipment at a local gym. We intentionally do not specify duration or intensity of exercise both to mirror usual care and to avoid any confusion with walking goals instructed by the WEB intervention. Adapted written materials from Dr. Nguyen (on our DSMB), which are currently used at the University of Washington and VA Boston, reinforce the verbal instructions. All subjects will receive this 42-page booklet (Appendix 1) with information about cardiovascular endurance and strengthening exercises, an action plan for identifying symptoms of a COPD AE, and how to resume exercise after a COPD AE. The written booklet also contains information about oxygen use during exercise and available resources for smoking cessation. To enhance treatment fidelity (see D.8) and to measure compliance with the study, subjects will receive exercise logs in which they will track whether they exercised each day (Appendix 2). The next instance that participant will have contact with study staff will be at a clinic visit 3 months following the baseline visit.

Pedometer and Internet-mediated walking program

Participants randomized to the pedometer and internet-mediated walking program will continue to wear a pedometer with a holder and a security strap, and use a dongle (or Bluetooth), and will be mailed a battery tool for the pedometer, and detailed instructions about the study website (Appendix 3). These instructions have been written based on feedback from participants in a similar study to ensure understanding of website features and to maximize their use. Additionally, subjects will receive identical written instructions that the control group received encouraging subjects to increase their walking. Subjects who have been randomized to intervention will be contacted by study staff by telephone to receive website access instructions. Subjects will provide the telephone number which they will use to receive the weekly step-count goals. Subjects will choose a username and password that allow them to log in to the study website. Subjects will have access to a personalized Web page where they can view graphical displays of step counts and walking progress, motivational and educational messages, and the online community. Subjects will be asked to wear the lightweight, unobtrusive pedometer every day, except while awake or showering/bathing, during the 12-month intervention period. Subjects will be instructed to upload their 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 post each participant's step-count goal on his/her Web page. 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 4). In addition, study staff will call participants each Monday to inform them of their weekly step-count goals. In order to keep goals up-to-date, study staff will call participants to remind them to upload if they have not uploaded step counts in > 7 days.

Figure 4. Example of Web page with goal setting and feedback.

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) Designing website so that subjects who are current oxygen users or active smokers will receive tailored messages about oxygen use during exercise or smoking cessation.
e) Beta testing website prior to launch and routine regular maintenance.
f) Providing back-up of study data. This task also includes automated backup software and scheduling, as well as obtaining and securely storing physical backup media.
g) Providing study staff access to the study data systems as needed for study implementation.
h) Capturing, maintaining, and securing delivery of step-count data for analysis.
i) 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).

D.5. Follow-up Clinic Visits and Phone Calls

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 prednisone or antibiotic course for treatment of a COPD exacerbation. Participants in both arms will be seen in our research clinics at months 3, 6, and 12 (Table 5). At each follow-up visit, study staff will remind participants not to disclose treatment arm. Subjects will be reminded that they should be working to slowly and steadily increase their walking and exercise. Subjects will perform 6MWT, spirometry, and HRQL assessments. All changes in medication or clinical status will be noted, any potential adverse events recorded, and a history of any COPD exacerbations or hospitalizations in the previous 3 months ascertained. We will also assess dyspnea (UCSD Shortness of Breath Questionnaire and MMRC Scale), physical activity (CHAMPS and Moy), and depression (Beck Depression Inventory). Subjects will also complete the following questionnaires: the Barriers to Exercise, Physical Activity Recall, VR-36, MOS Social Support, Bristol's COPD Knowledge, Exercise Self-Efficacy, Epworth Sleepiness Scale, the Brief Pain Inventory (short form, administered at C03, C06 and C12), and the Dietary Questionnaire (only administered at C00 and C12). The intervention subjects will also complete the Intervention Feedback Questionnaire that asks about the subject's experience with the study website and pedometer at the 6-month and 12-month in-clinic study visits. Blood for inflammatory biomarkers will be drawn by venipuncture, packed in a shipping container with an ice pack, and transported to the MAVERIC blood lab for processing and storage. Subjects recruited at VA Boston will be asked to complete DXA scans for body composition and bone mineral density at the 12-month in-clinic visit, and additionally will be asked to complete a body composition measurement using the Omron HBF-306CN. We will exclude any subject with a pacemaker or defibrillator to minimize any potential risks. If subject has previously undergone a DXA scan at the VA Boston Osteoporosis Clinic within 6 months, then the data from the Osteoporosis Clinic may be used and subject does not need to complete a scan specifically for the research study. If a subject does not complete the study-related questionnaires during the in-clinic visit, research staff will contact the subject after study visit by phone to finish the questionnaires over the phone or send the questionnaires home with the subject to be completed and returned in a pre-paid mailer.

To objectively measure engagement in PA, the pedometer will directly measure 14 days of walking of subjects in both arms. To assess treatment fidelity, exercise logs will be collected from subjects each month. Participants will be contacted by telephone at month 9. They will provide an interim history of home exercise and answer questions about symptoms, medications, AEs, and hospitalizations that occurred during the prior 3 months. Subjects will also receive a mailing with questionnaires (Barriers to Exercise, Physical Activity Recall, SGRQ, VR-36, UCSD SOB, Bristol's COPD Knowledge, Exercise Self-Efficacy, CHAMPS Physical Activity, Beck Depression Inventory, and Exercise Logs) to complete at home. 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.

Table 5: Schedule of Clinic Visits (C), Telephone Calls (P), and Assessments (both study arms)

	Baseline C00	Month 3 C03	Month 6 C06	Month 9 P09	Month 12 C12
Medical and Exercise History	X	X	X	X	X
6-Minute Walk Test	X	X	X		X
Barriers to Exercise Questionnaire	X	X	X	X	X
Physical Activity Recall Questionnaire	X	X	X	X	X
HRQL SGRQ	X	X	X	X	X

Veterans SF-36 HRQL	X	X	X	X	X
MOS Social Support Questionnaire	X	X	X		X
MMRC	X	X	X		X
UCSD SOB	X	X	X	X	X
Spirometry	X	X	X		X
Blood Draw for Biomarkers	X	X	X		X
Beck Depression Inventory	X	X	X	X	X
CHAMPS Physical Activity Questionnaires	X	X	X	X	X
Bristol's COPD Knowledge	X	X	X	X	X
Exercise Self Efficacy	X	X	X	X	X
Epworth Sleepiness Scale	X	X	X		X
Brief Pain Inventory (Short form)	X	X	X		X
Intervention Feedback Questionnaire (Intervention arm only)			X		X
Dietary Questionnaire	X				X
Exacerbation, Adverse Event Monitoring, and Hospitalization History	X	X	X	X	X
Daily Exercise Logs	X	X	X	X	X
Daily Step Count	X	X	X	X	X
DXA Scan (VABoston site only)*	X				X
Body Composition/Bioimpedance (VABoston site only)	X**				X**

*If subject has previously undergone a DXA scan at the VA Boston Osteoporosis Clinic within 6 months, then the data from the Osteoporosis Clinic may be used and subject does not need to complete a scan specifically for the research study.
**Contingent upon DXA scan being completed. If a DXA scan is not completed during the C00 or C12 study visits, the body fat composition/bioimpedance measurement will not be completed.

D.6. Short- and Long-Term Outcome Assessments: All tests will be conducted by study staff, technicians, or physicians who are blinded to treatment assignment.

Primary Outcome: Exercise capacity: Exercise capacity will be assessed with maximal distance walked on the 6MWT, performed according to ATS guidelines (80). Both sites currently have a designated course in the hospital corridor and standardized prompts to perform the 6MWT as part of the NHLBI LOTT protocol. In general, persons will be asked to cover as much distance as possible in 6 minutes, and the distance walked will be recorded. Subjects can use assistive devices, such as a cane, if they typically (more than half the time) use one for walking. Subjects will use supplemental oxygen if already prescribed oxygen for use during physical activity. If hypoxemia, oxygen saturation <85%, is observed at the end of the 6MWT, subjects will be temporarily excluded from further study participation and their primary provider contacted for further care. These subjects can be reassessed for eligibility at a later date. Hypoxemia and dyspnea predict balance impairment and falls in COPD (89); both will be assessed by study staff immediately preceding the 6MWT. Also, the 6MWT will not be performed if the subject is unsteady on his feet during the initial short walk used to assess pedometer accuracy, and demonstrates a high risk of falling. 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. We chose 6MWT distance as the measure of exercise capacity as opposed to maximum oxygen consumption or workload on a CPETT for several reasons. First, the 6MWT is easy to perform and a minimum clinically important change (54 meters) has been established in stable COPD (90). Distance walked on 6MWT is used in the calculation of the BODE (body mass,

airflow obstruction, dyspnea, exercise capacity) index, a marker of COPD severity that predicts mortality (91). In contrast, CPETTs require specialized equipment and the clinical relevance of changes in maximal oxygen consumption or workload is unclear.

Secondary Outcomes:
a. HRQL: Respiratory-specific HRQL will be assessed with the SGRQ (82,92). We will examine the composite Total Score as well as the subscales of Activity, Symptoms, and Impact. Lower SGRQ scores indicate better health status. The SGRQ has been validated and used extensively in assessments of HRQL in COPD (82,92).
The Veterans' SF-36 questionnaire will be used to assess general health status.

b. Dyspnea (Appendix 2): Dyspnea will be quantified with the UCSD Shortness of Breath Questionnaire (93) which has been widely used in COPD research. The minimal clinically important change has been determined to be ± 5 units (94). Dyspnea will also be assessed using the MMRC scale (responses 0-4 with 4 being the most dyspneic) which is used to calculate the BODE index (81, 91).

c. Markers of Systemic Inflammation: Blood will be collected by venipuncture in three 10 mL purple top EDTA tubes. Samples from both study sites will be shipped 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 microtitre 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.

d. 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 clinic

visits and telephone 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.

e. Daily Step Count: A secondary outcome, daily step count will be used to directly measure engagement in PA in both arms. To measure baseline step count, subjects will be instructed to wear the pedometer attached to a belt or garment waistband during all waking hours except when showering/bathing for 14 days. They will be instructed to perform their usual physical activities and exercise. Subjects will be instructed to remove the pedometer at night and put it in a place where they will remember to wear it first thing in the morning, such as with their alarm clock, watch, eyeglasses, or breathing medicines. The pedometer will have a sticker covering the digital display to prevent feedback. After randomization, the pedometer is part of the WEB intervention. In addition, the pedometer will be used to directly measure PA as a secondary outcome in both arms in the following ways: In those randomized to the intervention arm and already using the pedometer, we will average daily step count over the 14 days that follow the clinic visit at months 3 and 6. For those in the usual care group, persons will be sent home from the clinic visit at months 3 and 6 with a pedometer to wear for 14 days and return by postage-paid mailer. For step count collection at month 9 subjects in the control arm will receive a pedometer by postage mail or in person to wear for 14 days and return by prepaid mailer. At the 9-month follow up visit for the subjects assigned to the control arm, the pedometer face will be covered by a sticker to prevent feedback that may affect participant walking behavior. Intervention subjects will continue to wear the Fitbit Zip through the 9-month study time point. Clinic visits will be structured so that unblinded staff will oversee pedometer-related tasks, such as distributing the pedometers and replacing batteries. Following best practices for reporting PA data, we *a priori* define a no-wear day as one with < 200 steps, and nonadherence with step-count monitoring as having 8 or more (of 14) no-wear days (45,78). These definitions will be applied identically to both arms. These restrictions will ensure that the average step counts used in the analyses represent typical walking over 14 days of the monitoring periods.

In the secondary analyses of daily step count, we will compare the number of no-wear days and the number of participants nonadherent with monitoring between arms. Nonadherence with step-count monitoring, which is different from treatment fidelity, will not affect the primary aim of the study to examine the efficacy of WEB to increase exercise capacity, as indicated by 6MWT distance.

f. Assessment of Body Composition and Bone Mineral Density (VABoston site only): We will use a 5th generation GE Healthcare iDXA dual x-ray absorptiometry (DXA) scanner with enCore configuration version 12.3 to determine BMD, to assess total body composition, and

perform regional fat and lean mass analyses. As part of the study, participants will have DXA scans performed at baseline and approximately 12 months from baseline. For BMD assessment, scanning will be performed at the hip, the distal radius, and the spine. Regions with evidence of heterotopic ossification will be excluded from analyses since this will interfere with the accurate determination of BMD. Additionally, subjects will be asked to complete a body fat reading using the Omron Fat Loss Monitor (model HBF-306CN) for comparison of body fat measurement with the DXA scan, at baseline and approximately 12 months from the baseline study visit. We will exclude any subject who is pregnant or who has a pacemaker or defibrillator to minimize any potential risks.

Other Clinical Assessments

a. Pulmonary Function: Pulmonary function testing will determine the FEV_1, with testing performed according to ATS guidelines (79). We anticipate no meaningful change in FEV_1 during the course of the study, but we will confirm this by measuring spirometry at each study visit. Both sites will use a portable spirometer (nSpire Health, Inc.). Data will be presented in absolute numbers and as percent of reference predicted values, using prediction equations from Hankinson (95).

Contraindications for PFT:
Pulmonary function testing will not be performed in subjects within 3 months following a myocardial infarction, diagnosis of an abnormal heart rhythm, abdominal or thoracic surgery, brain, ear, eye or ENT surgery, unstable angina, or oral or facial pain that could be exacerbated by a mouthpiece. PFT will not be performed if heart rate is < 40 or > 120. These conditions will be assessed with a screening questionnaire and measurement of heart rate.

Withholding of Usual Bronchodilator Therapy:
For this study, subjects are not asked to withhold their bronchodilators.

Post Bronchodilator Spirometry Testing:
Albuterol 2 puffs will be used. Subjects will be asked about time of most recent use, past allergic reaction or problems to taking albuterol, and about a history of a cardiac arrhythmia. Any positive response will require the PI or covering physician to decide whether to proceed with administration of albuterol. After administration of albuterol, the subject will be asked if they have any new symptoms. If there are questions, the PI or covering provider will assess further.

The screening form will be administered by the RA. If the participant answers no to all questions, the RA will administer albuterol. When needed as directed by the safety form, the study provider will assess the participant, either in person or by telephone. If the decision is made by the study provider to administer albuterol, then an on-site provider will be notified. On-site providers include Marilyn Moy, MD, Eric Garshick, MD, Ronald Goldstein, MD, Emily Wan, MD, Pantel Vokonas, MD, Laura Stonestreet, PA, and Pulmonary Fellow on call. There is a Pulmonary Section Impact Form in place. The study provider will complete a form documenting approval to administer albuterol or not.
We maintain a Drug Control, Storage, and Tracking log for Albuterol with columns for date and patient ID, study visit number, drug source, lot numbers, and their expiration dates.

Albuterol will be obtained from the VA pharmacy. We will use one canister of albuterol until it is depleted of medication, and we will use a single-use spacer with a one-way valve for each participant.

b. Depression: Depression will be assessed with the 24-item Beck Depression Inventory (96). Patients with a Beck total score $\geq$ 14 will, with the patient's permission, have their primary healthcare providers informed of the results, with the suggestion that they might consider referral for evaluation and/or treatment of depression. Additionally, the PI will be notified if participants report suicidal thoughts on question 9 of the Beck's, and the PI will evaluate the patient for need for referral to the ER for further evaluation and treatment.

c. Physical Activity Questionnaires (Appendix 2): We will use the community healthy activities model program for seniors (CHAMPS) Physical Activity Questionnaire (97). The CHAMPS is a 41-item instrument validated in the elderly, which assesses PA information from several domains including leisure, household, and occupational. Frequency and total time spent per week allows estimation of caloric expenditure. In addition, we will use a Physical Activity Recall checklist developed by Dr. Moy to measure free-living PA specifically in patients with COPD (20). A higher number of daily activities performed is associated with better indices of COPD status, including higher FEV_1 and lower BODE index (20).

d. COPD Knowledge: The Bristol Knowledge Questionnaire will be used to test what patients learn and understand about COPD. The 65 items require 10-20 minutes to complete and cover topics such as symptoms, exacerbations, smoking, vaccination, and medication use. It has demonstrated internal consistency, validity and reliability.

e. Exercise Self Efficacy: The belief in one's ability to self-regulate and exercise regularly when faced with challenges is a key variable that influences exercise adherence. The Exercise Self-Regulatory Efficacy Scale (Ex-SRES) for persons with COPD will be used to measure exercise self-regulation. The Ex-SRES incorporates items from Resnick's self-efficacy scale for older adults and McCauley's self-efficacy questionnaire for sedentary adults. The 16-item questionnaire has been shown to be reliable and valid in COPD.

f. Sleepiness: Epworth Sleepiness Scale

g. Social Support: MOS Social Support Survey

h. Diet: Dietary Questionnaire

i. Pain: Brief Pain Inventory

Monitoring for Adverse Events (AdEs)

We have convened an independent, external Data and Safety Monitoring Board (DSMB) to review recruitment, follow-up rates, protocol adherence, and safety results. The DSMB is composed of Elizabeth Klings, MD, an expert in pulmonary rehabilitation and COPD clinical trials and pulmonologist at Boston Medical Center, Huong Nguyen, Ph.D. an expert in telemedicine methods in COPD at Southern California Kaiser Permanente, and DorAnne Donesky, RN, PhD, NP an expert in patient-centered coaching and behavioral change methodologies and interventions in persons with COPD at Touro University of California. 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 clinic 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 respective IRBs at the time of continuing review, but would be reported to the study DSMB immediately. 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 (Appendix 2). Subjects circle a yes/no response to three 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).

Table 2. Summary of Key Study Design Features to Ensure Internal and External Validity

Eligibility Criteria	Randomization	Treatment Fidelity	Missing Data
>90% pedometer accuracy	Unpredictable Blocks	Track with daily exercise logs and enhance with every 3 month follow-ups	Most common cause of missing data (health reasons) will be same for both arms
Able to collect $\geq$ 5 of 10 days of valid baseline step count data	Allocation Concealment	Lack of treatment fidelity defined *a priori* as <70% days with exercise	Impute with least favorable value or carry forward previous values
	Blinding of RAs performing assessments	Sensitivity analysis accounting for treatment fidelity	Sensitivity analysis excluding subjects with missing data

The most important factor affecting compliance is the complexity of the intervention. Our experience indicates that the WEB program and pedometer intervention pose minimal participant burden. The WEB intervention is designed to foster compliance, using a dynamic website and immediate feedback. Subjects upload step counts and visit the website at their convenience. ESC, a similar study, has shown persistent engagement by participants at month 3, and similar retention and engagement has been shown at month 12 in a separate study. Our preliminary

data show that the use of graphs, messages, and tips by participants increases by month 3. In the current proposal, the intervention lasts 12 months, including a 6-month intensive intervention phase where the subject will have access to an interactive website with new content being posted about maintaining a walking program, as well as an online forum community, and step count goals. Following the intensive intervention phase, the 6-month maintenance phase will consist of access to the website to obtain new step count goal, as well as to upload pedometer data but no new educational content posted about a walking program. During the maintenance intervention phase (months 7-12), subjects will be able to access content posted previously about the walking program. 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 drop-outs. Time spent with the healthcare provider, the continuity of care, and the communication style of providers may improve retention. We will structure the clinic 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 disperse $50 in payment to subjects at the baseline in-clinic study visit and a $25 payment at each of the following in-clinic study visits (3-month, 6-month and 12-month) for their travel-related costs, time and effort. Additionally, subjects will be given the Fitbit Zip which was used during their participation at the end of the research study (up to 13 months). For both arms, the face-to-face clinic visits, the regularly scheduled telephone contacts between study staff and subjects, and the subject remuneration will aid in achieving our anticipated retention rate of at least 60% at 6 months. In our other COPD studies, our loss to follow-up is low, ranging from 0% to 4%, at 12 months.

Based on our previous work, medical problems and temporary suspension from the exercise program will be the most common reason for missing outcomes data in both arms. We have designed the testing windows to minimize missing data. At months 3 and 6, testing will be allowed within a window of $\pm$ 2 weeks. At months 9 and 12, testing will be allowed within a window of $\pm$ 1 month, making the total participation time up to 13 months from the baseline in-clinic study visit (C00). Despite our efforts at follow-up, some missing data are expected with multiple testing visits. We will collect the reasons for missing data such as death, COPD exacerbation, medical reasons, or non-medical reasons. We will compare the rate of losses to follow-up at 3, 6, 9, and 12 months among the two arms using the chi-square test of association. We will assess whether any baseline characteristics such as age, FEV_1 % predicted, or 6MWT distance, are associated with losses to follow-up using chi-square tests for categorical baseline data and analysis of variance for continuous baseline data. If baseline variables and treatment group are found to be associated with loss to follow-up, then the analysis models will be modified to include the differing baseline variables as covariates to provide unbiased estimates of intervention effects. For subjects who discontinue the study early due to worsening of COPD or due to death, missing outcome data will be imputed using the least favorable data observed prior to discontinuation. Missing data for subjects who miss a visit not related to worsening of COPD will be imputed using last observed data. We will also perform sensitivity analyses using the complete case method, excluding those with no observed outcome at 6 months.

Data Management

We will conduct a training session and mock study visit before initiating enrollment to ensure uniformity in procedures and data collection at both sites. The Boston and Birmingham teams will interact directly with study subjects, coordinate follow-up, and monitor AdEs. Study staff on all 3 teams will communicate daily by secure VA email and participate in conference calls every other week 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 pencil and stored in study binders, locked in study staff offices. Databases located on an internal computer drive within the VA firewalls and accessible to both VA sites 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.

Information Security

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

At both recruiting sites, study records and blood samples 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.

At VABoston and VABirmingham, study data will be collected by paper and pencil. 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 VABoston. These databases are located behind the VABoston firewalls and will be accessible only via VA secured and password protected desktops in locked study staff offices. We will request permission for access to the shared drive by Dr. Allen Cooper and his study staff at VABirmingham. This will be necessary to ensure study uniformity and that data from VABirmingam will be entered into the study databases for aggregate analyses. All study data in the databases will be identified only by the participant's unique study ID.

All blood samples will be identified only by the participant's unique study ID. Samples are overnight shipped to MAVERIC from VABoston and VABirmingham using FedEx courier. 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.

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 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: unique study ID, username and password, and step count numbers. No protected health information (PHI) will be stored on the study server. The UMich server does not track IP addresses. A Data Use Agreement between the University of Michigan and VABoston and VABirmingham will be executed before the study starts.

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 Dr. Allen Cooper and his research staff at the VA Birmingham, and 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.

Statistics (power analysis)

Prior to analyzing the outcomes, we will summarize and compare baseline demographic and clinical variables by treatment group. Any unbalanced characteristics occurring despite randomization will be assessed as potential confounders in multivariate analyses. Analyses will be performed with the SAS statistical software package (9.3, SAS Institute; Cary, NC).

Primary Aim: To determine the efficacy of the WEB intervention to increase 6MWT distance.

We focus on 6MWT distance at 6 months since we predict that the greatest difference in 6MWT distance between study arms will occur at month 6, at the end of the interventional phase. We have revised our statistical analysis plan to use 2-way factor analysis or analysis of variance (ANOVA). This approach will assess the effect of intervention versus control on 6MWT distance, using absolute measures of 6MWT distance at baseline and 6 months. Two-way ANOVA will allow us to assess the effect of treatment (intervention versus control), and additionally allow us to assess the interaction between treatment and time (treatment*time) on 6MWT distance. We will use a mixed model (PROC MIXED in SAS) to perform the 2-way ANOVA 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. Models will have 6MWT distance as the dependent variable, and treatment, time, and treatment*time as independent variables. In this approach, models will also include study site and any unbalanced baseline characteristics as covariates. Primary analyses to determine the effect of WEB on 6MWT distance will use the intention-to-treat approach to include as many randomized subjects as possible in the analyses. Subjects will be considered to be in his/her randomly assigned arm no matter how much he/she participated in it. As a sensitivity analysis, however, we will examine 6MWT distance on a per-protocol basis, where noncompliant subjects ($\geq$30% of days with no exercise performed on logs) in each treatment arm will be excluded from the analysis.

Anticipated Results: We anticipate that subjects in the intervention group will have significantly higher 6MWT distance than subjects in the control group at 6 months.

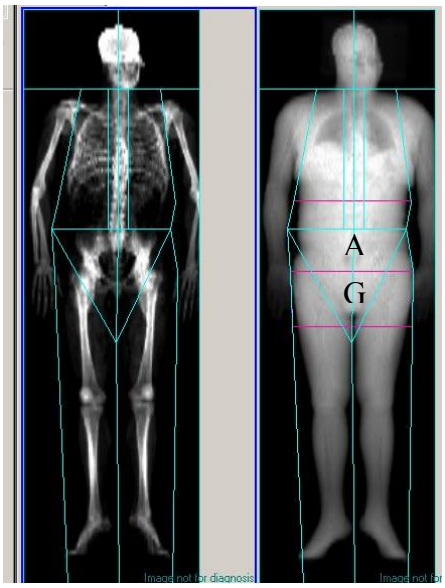
Power Calculation: This study is powered on our pre-specified primary outcome of 6MWT distance. Our main comparison is 6MWT distance at 6 months between the WEB intervention and control arms. Our power analysis is based on a widely accepted minimum clinically meaningful change in 6MWT distance of 54 meters and the published standard deviation for 6MWT distance of 80-120 meters (90). Our data in a similar Veteran population showed a standard deviation of 102 meters for 6MWT distance. We use a standard deviation of 100 meters in our power calculation. Using the sample size formula for the comparison of the means of 2 independent samples, we calculate that 55 evaluable subjects in each arm at 6 months will allow

detection of a difference of at least 54 meters between the WEB and usual care arms with a power of 80% and α=0.05. We anticipate a maximal drop-out of 40% at 6 months. In order to have 111 evaluable subjects at 6 months, we plan to enroll a total of 185 subjects.

Secondary Aims: To estimate the effect of the WEB intervention on (a) HRQL, as measured by the St. George's Respiratory Questionnaire (SGRQ), (b) dyspnea, (c) CRP and IL-6, (d) risk of AEs and COPD-related hospitalizations, (e) engagement in PA as measured by daily step count, (f) body composition and bone mineral density, and (g) pain.

Our statistical analysis plan for the secondary outcomes is similar to that for the primary outcome. We will use 2-way factor analysis or analysis of variance (ANOVA) to assess the effect of intervention versus control on SGRQ-TS, dyspnea score, CRP and IL-6, and daily step count. We will analyze absolute values of the secondary outcomes at baseline and 6 months. Two-way ANOVA will allow us to examine the effect of our intervention, and additionally allow us to assess the interaction between treatment and time (treatment*time) on the secondary outcomes. We will use a mixed model (PROC MIXED in SAS) to perform the 2-way ANOVA. Models will have SGRQ-TS, dyspnea score, CRP and IL-6, or daily step count as the dependent variable, and treatment, time, and treatment*time as independent variables. Models will also include study site and any unbalanced baseline characteristics as covariates.

Total number of AEs and COPD-related hospitalizations will be summed over the 12-month study period. Independence of individual AEs will be assured by considering subjects to have experienced a new AE only if they had been off of oral steroids and antibiotics for at least 14 days following the previous AE (86). 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 (86). The multivariate regression model will include number of AEs (or hospitalizations) as the dependent variable, treatment group as the main predictor, as well as study site, number of AEs (or hospitalizations) in the year prior to enrollment, and any unbalanced baseline characteristics.



Body Composition by DXA Scan: Body composition and regional fat analysis will be performed at the baseline study visit and the 12-month study visit using standard software available from the manufacturer. For regional fat measurements, the left and right arm cuts pass through the shoulder joints and as close to the body as possible. The leg cuts separate the hands and forearms from the legs, starting with a diagonal cut through the femoral necks. The midline separates the right and left legs. The images obtained from one of our subjects demonstrate the standard cuts that define the arms, legs, and trunk (see figure to the left). These data can be also be used to calculate a waist-hip ratio (i.e., ratio of central fat to hip fat) in a standardized fashion using the same landmarks as illustrated by the regions defined on the soft-tissue image. The DXA software can be used to define standard waist and hip regions that will allow comparability of these measurements throughout the study. The lower boundary of the central or waist region, which is also referred to as the android region (A, see figure), is the cut through the pelvis at the level of the iliac crests. The upper boundary of the android region extends upwards to 20% of the distance between the pelvis and the top of the shoulders and the lateral boundaries are the arm cuts. The upper boundary of the gynoid region of interest (G, see figure) is the region below the pelvis cut that extends downward from 1.5 times the height of the android region. Lateral boundaries of the gynoid region are the outer leg cuts.

The waist to hip fat ratio, or android to gynoid ratio, is the percent fat in the android region divided by the percent fat in the gynoid region. Percent fat mass in each region is reported as the total of the percent fat in the right and left sides. The precision of regional fat measurements is +/-1%.

Subjects will be asked to complete a body composition measurement using the Omron Fat Loss Monitor (model HBF-306CN) in order to compare body fat measurements with the DXA. Since DXA is the gold standard, the Omron Fat Loss Monitor is being examined as a cost-effective and less invasive alternative method to measure body fat composition. The monitor has been approved for use in the general population except in individuals who are pregnant or who have implanted medical devices such as pacemakers or defibrillators; we will therefore exclude any subject who is pregnant or who has a pacemaker or defibrillator to minimize any potential risks.

Anticipated Results: We anticipate that subjects in the intervention group will have better HRQL, less dyspnea, lower CRP and IL-6 levels, higher daily step count, lower adiposity, higher bone mineral density and lower risk of AEs and COPD-related hospitalizations compared to subjects in the control group at 6 months.

Power Calculations: A sample size of 111 evaluable subjects at 6 months determined by the primary outcome of 6MWT distance will also allow detection of significant differences in the secondary outcomes. Using the sample size formula for the comparison of the means of 2 independent samples, we can detect an effect size of 0.55 SD units with 80% power and α=0.05. Using the SD's obtained from our cross-sectional observational study, we can detect a change of at least 10 units in SGRQ-TS, 1.8 mg/L in CRP level, and 0.59 pg/mL in IL-6 level. In addition, as an estimate for anticipated differences between arms, we examined the mean 6MWT distance, SGRQ-TS, CRP, and IL-6 levels in those who walked above and in those who walked below the median daily step count in our observational data. We observed a difference of 1.27 pg/mL in IL-6 in those who walked above and in those who walked below the median daily step count, values greater than our detectable difference suggesting sufficient power. We found a difference of 7 units in SGRQ-TS and 0.96 mg/L in CRP. While these preliminary observed estimates of difference in SGRQ-TS and CRP are slightly smaller than our calculated detectable estimates, we anticipate there will be sufficient power to detect differences in these secondary outcomes when the analyzed groups are differentiated by the WEB intervention, since our power calculations based on groups dichotomized at the median step count are conservative. In calculating power for detecting differences in risk of AEs, we expect to observe 106 AEs in the 111 subjects completing a 12-month follow-up period based on our preliminary data. Given this rate and using the POISS_SS macro of E. Bergstralh (a Poisson power calculator), we will be able to detect a rate ratio of at least 1.70 with 80% power and 1.85 with 90% power. Again, to estimate anticipated observed differences between treatment arms, we examined the number of AEs in those who walked above and in those who walked below the median daily step count in our observational data. One hundred thirty-six AEs were observed in those who walked below the median daily step count and 76 AEs were observed in those who walked above the median daily step count, an observed rate ratio of 1.79, indicating adequate power.

Additional Analyses

Additional analyses will be conducted with repeated measures ANOVA using all time points--baseline, 3, 6, and 12 months assessments of 6MWT distance--to explore the effect of the interaction between treatment and time (treatment·time), as well as the between-subject group treatment effect (intervention versus control) and the within-subject effect (repeated over time) on 6MWT distance. We will use a mixed model (PROC MIXED in SAS) to perform the repeated measures ANOVA. We will examine both compound symmetry and AR(1) correlation structures. Models will have 6MWT distance at each time point as the dependent variable, and treatment,

time, and treatment*time as independent variables. Models will also have study site and any unbalanced baseline subject characteristics as covariates. Similarly, additional analyses will be conducted with repeated measures ANOVA using all time points--baseline, 3, 6, 9, and 12 months assessments of the secondary outcomes--to explore the effect of the interaction between treatment and time (treatment*time), as well as the between-subject group treatment effect (intervention versus control) and the within-subject effect (repeated over time) on SGRQ-TS, dyspnea score, CRP and IL-6 levels, and daily step count. We will use a mixed model (PROC MIXED in SAS) to perform the repeated measures ANOVA. Models will have the secondary outcome at each time point as the dependent variable, and treatment, time, and treatment*time as independent variables. Models will also have study site and any unbalanced baseline subject characteristics as covariates.

As outlined in our Conceptual Model, we will also explore whether increases in PA (6MWT distance and daily step counts) result in decreases in levels of systemic inflammation and risk of AEs, regardless of treatment arm. Models, adjusting for baseline 6MWT distance or step counts, will examine whether increases in PA independently predict decreases in inflammatory biomarkers and decreased risk of AEs and COPD-related hospitalizations. We will use linear regression models with change in 6MWT distance as the independent variable, and change in IL-6 and CRP as dependent variables. A multivariate regression analysis (PROC GENMOD) will be conducted with number of AEs (or COPD-related hospitalizations) as the dependent variable, and change in daily step count and baseline daily step count as independent variables. Models will account for potential confounders such as study site, season of enrollment, age, gender, comorbid medical conditions, FEV_1 % predicted, BMI, and history of prior AEs. We believe we will show that increases in 6MWT and daily step count, regardless of treatment arm, independently predict decreases in CRP and IL-6, and decreases in the risk of AEs and COPD-related hospitalizations. These exploratory models have the potential to provide significant insight into the mechanisms of the beneficial impact of walking and PA on systemic inflammation and COPD-related morbidity. The results of these exploratory analyses will provide estimates for sample size calculations for future research proposals.

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

Like most clinical trials, the study may face recruitment challenges. We believe that we have carefully examined the number of Veterans with COPD and Internet access and we have an accurate assessment of the number of potential participants eligible for the trial. We acknowledge that there is no attention control group. However, the study is designed to compare the WEB intervention to usual care. Providing attention and social support are critical components of the exercise intervention under study so it would be inappropriate to control for them. An alternative control group could be pulmonary rehabilitation (PR). However, an equivalence trial comparing a program like WEB to PR is a different question than the one we are proposing which is to study the efficacy of WEB. We believe that PR would have greater positive effects on 6MWT distance than WEB. In fact, participation in a PR program within the previous 3 months is an exclusion criterion for the proposed study. Although referral to PR is recommended for the treatment of COPD, the reality is that PR is available for only a small fraction of patients with COPD. We choose counseling, reinforced with written instructions, as the control group to most pragmatically mirror usual care.

We acknowledge that the pedometer captures ambulation, but does not record upper extremity exercise or total PA. However, total walking step count has been shown to be closely related to overall daily activity in persons with COPD, and lower extremity exercise is the most effective and best-validated portion of PR programs (24,27,42,43). Furthermore, the pedometer does not provide information about the intensity of the walking performed. However, the literature and our preliminary data suggest that all forms of walking are beneficial in COPD, whether walking as part of functional community mobility or walking as part of sustained cardiovascular exercise. There may also be selection bias of subjects who are less sick and interested in an exercise research study. In sum, the proposed study has the potential to transform current clinical management of COPD and advance our understanding of how to promote PA in persons with COPD.

(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.

k. **Human Studies Section**

(1) Risks to Subjects

1.a. Human Subjects Involvement and Characteristics:
Collaborating Sites: VA Birmingham Medical Center (Birmingham, AL)

The majority of subjects recruited for the study will be Veterans. However, we also wish to include non-Veterans to increase the generalizability of our results and to increase our recruitment pool. We anticipate enrolling up to 185 male and female subjects with chronic obstructive pulmonary disease (COPD).

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 11 % 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 over recruit from the VA Boston Women's Health Clinic which provided care to 3,123 unique females in FY 12, of whom 140 had the diagnosis of COPD. All minority subjects eligible for this study will be included. To increase the diversity of our population, we will over recruit African-American Veterans. VA Birmingham is an ideal recruitment site as 21% of Veterans in Alabama are African American, and 10-15% of subjects at VA Birmingham enrolled in COPD trials are African American. Reflecting the general Veteran population, the anticipated race distribution of all subjects enrolled will be 91% White, 6.5% African American, 1.6% Native American, and 0.9% Asian. It is anticipated that 3% will be of Hispanic ethnicity.

Inclusion of Children

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

Inclusion Criteria are:

a) Male and female subjects, greater than or equal to 40 years of age
b) Clinical diagnosis of COPD defined as either a ratio of FEV_1 to forced vital capacity < 0.70 or chest CT evidence of emphysema or prior documentation of FEV_1/FVC ratio of < 0.7 and clinical evidence of COPD (defined as ≥ 10 pack-year cigarette smoking history, dyspnea, or on bronchodilators)
c) Medical clearance from healthcare provider to participate in an exercise program
d) Have access to a computer with Internet connection, a USB port or Bluetooth capability, and Windows XP/Vista/7/8/10 or higher, or Mac OSX 10.5 or higher operating system, or willing to come to VA Medical Center to use study computers
e) Pedometer with >90% accuracy compared to manual counts on short clinic walk
f) Competent to provide informed consent
g) 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) Clinical signs of unstable cardiovascular disease or congestive heart failure
d) Hypoxemia during 6MWT, i.e. oxygen saturation <85% using supplemental oxygen
e) Inability to complete questionnaires
f) Inability to collect at least 5 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 12 months
j) Plans to enroll in a supervised exercise program, such as pulmonary rehabilitation, in the next 6 months
k) Average baseline step counts of greater than or equal to 10,000 steps per week

1.b. Sources of Materials: We expect to enroll up to 240 persons with COPD and to randomize up to 185 eligible participants. All data will be obtained specifically for research purposes. No existing specimens, records, or data will be used. Pedometer data, questionnaire data, exercise and pulmonary function data, and serum biomarker levels will be collected from human subjects and used for research purposes only.

1.c. Potential Risks. Describe the potential risks to subjects (physical, psychological, social, legal, or other) and assess their likelihood and seriousness to the subjects. Differentiate the therapeutic risk from research risk.

Therapeutic risk is the risk or potential risks associated with an intervention that is required for medical care, but occurs as part of the research. An example is an endoscopy that was required for medical follow-up of a specific illness.

This study has no therapeutic risks.

Research risk is associated with an intervention that is done only for research purposes regardless if it is an experimental intervention or a commonly used intervention, for example, an extra endoscopy. Where appropriate, describe alternative treatments and procedures, including

the risks and benefits of the alternative treatments and procedures to participants in the proposed research.

Potential Risks:
1.c.i. Pedometer: There is no risk to wearing the pedometer, which is commercially available. The walk performed by subjects to assess pedometer accuracy may leave subjects temporarily more short of breath. Subjects will be allowed to rest and will be allowed to use supplemental oxygen if usually prescribed.

1.c.ii. Questionnaires: The only possible risk of questionnaire administration involves the social and psychological risk resulting from inadvertent disclosure of medical history information. All questionnaire responses collected by paper and pencil will be kept confidential and locked, and identified by study code in the working databases.

1.c.iii. Physiological assessments: The pulmonary function test and 6MWT may leave a subject temporarily more short of breath. Subjects will be allowed to rest and will be allowed to use supplemental oxygen if usually prescribed. Subjects might feel lightheaded while breathing out forcefully to perform the pulmonary function test. Rarely a person might briefly pass out during the forced exhalation. Although it is unusual to have any discomfort, in those who have existing back pain, a forced exhalation may result in additional discomfort. The 6MWT may cause low oxygen levels in the blood or an irregular heart rhythm. There is a potential risk of falls during the 6MWT.

The breathing test (spirometry) is a standard pulmonary test that is commonly done. Discomforts include feeling lightheaded or short of breath while breathing out forcefully, cough or chest tightness/discomfort. Although it is unusual to have any discomfort, breathing out forcefully may cause additional discomfort if the subject has back pain before the test. The inhaler medication albuterol is given as part of this test. It is a short-acting medication that opens the airway. The most common side effects of albuterol include feeling shaky or experiencing a slight tremor or feeling heart beat slightly faster.

In pre-BD spirometry, if a participant has dyspnea triggered by spirometry, he will be allowed to use his own rescue albuterol inhaler. Once the patient recovers, spirometry will be repeated and these values will be used as the post-BD spirometry. No albuterol will be administered by the RA. In post BD spirometry, if a participant has dyspnea triggered by spirometry, a study provider will be notified to assess the patient and need for further use of BD or medical evaluation.

1.c.iv. Venipuncture: With the blood draw, a small amount of bleeding may happen under the skin causing a bruise that may last up to a week. 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 has occurred as a result of drawing blood. These risks are the same as those associated with a standard venipuncture performed for clinical reasons.

1.c.v. Walking exercise program: Potential physical risks related to walking and exercise include: Subjects may experience leg pain, foot pain, back pain, lightheadedness and/or dizziness with increased physical activity.

Risks related to breathing
Participants may experience shortness of breath while walking. This could be a sign of heart problems, but in most cases it is likely due to low fitness or the underlying lung problem.

Risks related to musculoskeletal injury or falls
Walking exercise programs are less likely than more vigorous exercise programs to result in minor musculoskeletal injury. However, musculoskeletal injury and falls can occur in walking programs.
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.

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

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 low blood sugar episodes 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. Likewise, participants who have poorly controlled blood pressure may experience raised 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.

1.c.vi. Psychological Risks:
The content of questionnaires and the study website are on topics not generally considered controversial or likely to produce psychological distress.

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

Website and Server: The website is password protected and secured. The server is on secured networks within the University of Michigan firewalls.

We use many procedures to protect the research database but despite these measures, there is a chance that a person not connected with the study may gain access to the website information. No protected health information (PHI) will be stored on the study server. The UMich server does not track IP addresses.

Only the following information, all of which are not identifying, will be stored on the server:

- Unique study ID
- Password and username
- Step count numbers from pedometer

1.c.viii. **Measures of body composition and bone mineral density by DXA Scan (VABoston site only):** There is a slight amount of radiation from having a bone density scan but this is less than one-tenth of the amount one would receive from having a chest x-ray and unlikely to result

in any illness from the radiation exposure. Due to the use of radiation in the DXA scan, this test will not be performed if a participant is pregnant or nursing since there may be risks that are not foreseeable. Women of childbearing potential enrolling in this study must (i) have been using a contraceptive measure (an intrauterine device (IUD), oral contraceptives, barrier methods, or abstinence) for the previous three months, (ii) must have a negative pregnancy test, and (iii) must agree to continue to use a contraception measure for the duration of the study. Women are considered to be of childbearing potential unless they have been surgically sterilized or are post-menopausal, that is, no menstrual period for more than 6 months. Nursing mothers may not participate in this study. Participants will be provided the results of their scans done at the standard sites (total hip, femoral neck radius) and told if they meet standard diagnostic criteria for osteopenia or osteoporosis. A report will be prepared that they will be asked to give to their usual healthcare provider. Any female participant who self-reports pregnancy or has a positive pregnancy test at any study visit will not perform the DXA scan and will have the option to discontinue participation in the research study.

1.c.ix. Measure of body composition using bioimpedance (VA Boston site only): To measure body fat levels using the Omron Healthcare Fat Loss Monitor (HBF-306CN), a painless, extremely low level of electrical current (50 kHz and 500 μA) is used. Subjects who are pregnant are excluded from the DXA Scan and are therefore, also excluded from the bioimpedance measurement. Although likely safe for use in those with implanted medical devices, we will exclude any subject with a pacemaker or defibrillator to minimize any potential risks. Before completing this assessment, the study staff will complete a safety screening that includes:

- Asking if s/he has a pacemaker and or defibrillator
- Requesting the subject empty the bladder beforehand

If the subject has a pacemaker or defibrillator, then the bioimpedance measurement will not be taken. The bioimpedance measurement is safe and painless, and is taken while the subject is seated. The subject will grasp 2 handles on the fat loss monitor for 5-10 seconds in the seated position while a reading is taken. Three readings will be taken in this manner to assess reproducibility.

(2) Adequacy of Protection from Risks

(a) Recruitment and Informed Consent*:* Subjects will be recruited voluntarily. At each recruiting site, we will enroll 3-4 subjects per month, over 30 months, for a total of up to 185 subjects. All persons with COPD who meet our inclusion criteria will be eligible to participate in the proposed research. Our recruitment method will consist of mailings with the options to express interest by calling study staff or returning a postcard. All subjects who do not respond to the mailing will receive a telephone call from study staff. Interested participants will be scheduled for a screening visit. Study staff will explain the nature, scope, and possible consequences of the study in a form understandable to participants and answer all their questions. Subjects are under no obligation to participate. Written informed consent will be obtained at the time of screening by study staff.

(b) Protection Against Risks.

Subjects will be eligible to participate in the study only if they have medical clearance from their healthcare provider to participate in an exercise program. We estimate the total time of testing to be approximately 3 hours per study visit, with additional time at VABoston site of up to 60 minutes at the baseline and 12-month visits that include DXA scans. We will not perform bioimpedance measurements in any subject with a pacemaker or defibrillator to minimize any potential risks. The study PI or covering physician are on site during testing and available for

questions. Staff performing the spirometry and 6MWTs 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 pulmonary function tests and 6MWTs, subjects can rest if short of breath and will be allowed to use supplemental oxygen if usually prescribed. Safety for administration of albuterol for the post-bronchodilator spirometry will be assessed with a checklist of symptoms. For the walk test, subjects will be instructed to bring their medications to the visit and will be allowed to take their usually prescribed bronchodilators if needed after performing the walk test. We exclude subjects at higher than usual risk of adverse effects from a walking exercise program. For example, subjects will be screened for active cardiovascular disease by history and for exercise-induced hypoxemia during the walk test. If hypoxemia, oxygen saturation <85%, is observed during the 6MWT, subjects will be temporarily excluded from further study participation and their primary provider contacted for further care. These subjects can be reassessed for eligibility at a later date when 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 pedometer accuracy and is obviously a fall risk, the 6MWT will not be performed.

Venipuncture will be performed by staff trained in phlebotomy. Subjects do not have to answer any questions on questionnaires with which they are uncomfortable. Inadvertent disclosure of medical history information is guarded against by maintaining completed questionnaires in a locked filing system. We will evaluate for depression with the Beck Depression Inventory. Patients with a Beck total score $\geq$ 14 will, with the patient's permission, have their primary providers informed of the results, with the suggestion that they might consider referral for evaluation and/or treatment. Additionally, the PI will be notified if participants report suicidal thoughts on question 9 of the Beck's, and the PI will evaluate the patient for need for referral to the ER for further evaluation and treatment. The clinical diagnosis of depression or anxiety will need to come from the participants' mental health or primary care providers, we are not diagnosing it in the research study.

If subject has previously undergone a DXA scan at the VA Boston Osteoporosis Clinic within 6 months, then the data from the Osteoporosis Clinic may be used and subject does not need to complete a scan specifically for the research study.

During the study, subjects will be regularly monitored for adverse effects of exercise during clinic 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. Subjects in both arms will be instructed to notify 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. During the study, if a subject experiences a medical problem that prevents walking and exercise, he will be temporarily suspended from the study and will resume when at baseline clinical status. Any AdEs that are immediately life-threatening, cause permanent or lasting harm, or require a hospitalization will receive a serious classification. All serious adverse events (SAE) and unanticipated problems will be reported to the respective IRB at continuing review but reported to the study DSMB immediately. If an event is possibly, probably or definitely related to the intervention, it will be classified as intervention-related. Based upon our prior experience, the most common SAE will be hospitalization for a COPD exacerbation. The most common AdE will be musculoskeletal injuries.

We have convened an independent, external Data and Safety Monitoring Board (DSMB). They will monitor the rates of AdEs and SAEs and unanticipated problems between the 2 arms of the study. The DSMB is composed of Elizabeth Klings, MD an expert in pulmonary rehabilitation and COPD clinical trials at Boston Medical Center, Huong Nguyen, PhD an expert in telemedicine methods in COPD at Southern California Kaiser Permanente, and DorAnne Donesky, RN, PhD, NP an expert in patient-centered coaching and behavioral change methodologies and

interventions in persons with COPD at Touro University of California. They will meet every 6 months, and as needed, by telephone conference.

(3) Potential Benefit of the Proposed Research to the Subject and Others.

There is potentially great benefit to the large number of persons with COPD if the proposed work leads to the adoption of an Internet-mediated walking program to promote physical activity in clinical practice. Such walking programs would be accessible to all who needed it and would improve short- and long-term outcomes. 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.

Although not all participants may experience benefits, some of the potential benefits of participating in the study include more effective management of COPD symptoms, increased exercise capacity, and better quality of life.

Potential benefits to others include contributing to the development of an accessible, individualized, and sustainable program that incorporates strategies for behavioral change for managing COPD symptoms to encourage physical activity in those with COPD.

The risks to the subjects are reasonable in relation to the anticipated benefits to subjects and others because each participant is required to obtain medical clearance which indicates they are healthy enough to participate in a walking program. Additionally, walking carries minimal risk, and physical activity is part of usual care for managing COPD symptoms.

(4) Importance of the Knowledge to Be Gained.

Although it is well known that greater physical activity is beneficial, it is unclear how to increase physical activity in persons with chronic disease such as COPD who already experience functional disability from their disease. Novel strategies are needed to promote physical activity and exercise in persons with COPD. The proposed pedometer-based, Internet-mediated walking program is unique because of its automation, ability to accurately monitor walking performed, individualized step-count goals, and educational content and motivational messages. We propose to rigorously assess the efficacy of the Walking and Education to Breathe (WEB) exercise intervention in a randomized controlled study and to examine its effect on short- and long-term outcomes in COPD. These are the next steps needed to rigorously examine if WEB works.

If successful in increasing 6MWT distance and improving short- and long-term outcomes, such a program would have a direct and positive impact on the way we currently care for persons with COPD. Once implemented, such a program would be available to all persons with COPD who needed it, would individualize exercise training, and could promote walking indefinitely. Based on published estimates that 24 million people in the US have COPD and our preliminary data that 33 to 64% of COPD patients are Internet users, our proposed intervention could help over *8 million* persons. The number of people who uses the Internet will continue to increase, making such an approach to promote physical activity ideal to reach a large number of patients.

Our proposal addresses the exciting and important next steps of developing novel interventions to increase physical activity and assessing the impact of those interventions on COPD outcomes. Our highly clinically relevant intervention has the potential to (1) bring an exercise program to the vast majority of persons with COPD who cannot go to a hospital-based pulmonary rehabilitation program, (2) improve the effectiveness of current pulmonary rehabilitation programs, and (3) become an integral part of COPD self-management programs. Ultimately, the intervention could decrease risk of hospitalizations, acute exacerbations, and COPD-related morbidity and mortality.

l. **Animal Subjects:** This study does not use animal subjects.

(5) **Resources**

(a) **Research Space:**

All in-person study visits will be conducted in VA space either at VA Boston or VA Birmingham. At VABoston, in-clinic study visits will be conducted at the West Roxbury, Jamaica Plain, or Brockton campus.

All blood samples will be shipped to MAVERIC where they will be processed and stored.

The website is maintained by staff at the University of Michigan. Step-count data 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, and spirometry using an Eaglet portable spirometer (nSpire Health, Inc.). Pulmonary function tests can also be performed in the dedicated research pulmonary function laboratory (150 ft^2) with a computerized Collins CPL pulmonary function system and Collins portable water seal spirometer. The 6-minute walk test is performed using a well-marked course in a straight corridor.

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.

n. **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

o. **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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Addendum to Protocol:

Brain MRI Scan Substudy

Rationale: COPD is the nation's third leading cause of death and affects up to 11% of all VA healthcare patients. Patients with COPD experience significant dyspnea despite optimization of medical therapy. In addition, over half of patients with COPD experience chronic pain--largely musculoskeletal pain. Clinically, in patients who suffer from both chronic pain and dyspnea, it is difficult to distinguish a patient's perception of one symptom, modulated or amplified by the other, using self-report and questionnaires. Yet, it is critically important to differentiate them to make accurate diagnostic and treatment decisions. Patients who experience and report pain, heightened by worsening dyspnea, may be overtreated with narcotics which can lead to respiratory suppression or opioid dependence. Similarly, a patient's report of dyspnea, amplified by worsening chronic pain, may lead to unnecessary testing for etiologies of dyspnea and undertreatment of pain. To optimize clinical management, novel objective diagnostic tools are needed to complement patient self-report and accurately distinguish symptoms in patients who have combined chronic musculoskeletal pain and dyspnea.

It is also important to understand chronic musculoskeletal pain and dyspnea because they are common barriers to engaging in PA and exercise. The clinical course of COPD is characterized by a downward spiral of dyspnea, physical inactivity, and deconditioning. Chronic musculoskeletal pain similarly leads to a negative cycle of physical inactivity and deconditioning, ultimately resulting in significant physical limitation. Although chronic musculoskeletal pain and dyspnea can be barriers, PA and exercise are powerful, but underused non-pharmacological therapies for management of these symptoms in COPD. We developed Every Step Counts (ESC), a technology-mediated intervention based on the Theory of Self-Regulation, to promote PA in COPD. ESC couples a pedometer with a dynamic website that 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, we demonstrated ESC's safety, feasibility, and efficacy to increase PA and improve health-related quality of life over 3-4 months. In preliminary studies using questionnaires, we showed that ESC can improve dyspnea. In a separate study, the same PA platform has also been shown to relieve chronic back pain in Veterans. An important next step is to understand the effects of PA interventions, like ESC, in the many COPD patients with combined chronic musculoskeletal pain and dyspnea to ultimately improve PA interventions and personalize treatment of symptoms.

Background: Unique brain activity networks and specific structural changes in the brain are traditionally associated with chronic pain stimuli. It has been shown that resting state functional connectivity, between the anterior insular cortex and brainstem periaqueductal gray, determines pain perception in healthy humans. Resting state functional connectivity magnetic resonance imaging (fcMRI) is used in brain mapping to evaluate interactions and communications between brain regions that occur in a resting state, before a sensory event or when an explicit task is not being performed. The resting pattern and strength of functional connectivity specifically within the "default mode" network (DMN) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus) have been examined in several studies of clinical disease states, as this network is reliably detected and well-characterized. The DMN is an anatomically defined brain system that is one of the most studied networks present during resting state and is one of the most easily visualized networks. It is a critical network involved in many functions with high interconnectivity with other networks and could be a sensitive network to examine in response to symptom changes. These resting communications are altered in older adults with chronic musculoskeletal pain who show greater functional connectivity between the posterior cingulate and left insula, superior temporal

gyrus, and cerebellum. Chronic musculoskeletal pain in COPD has not been studied with neuroimaging.

Currently, the central mechanisms of chronic musculoskeletal pain and dyspnea, and how they change in response to PA promotion, in COPD are largely unknown. Unique brain activity networks and specific structural changes in the brain are traditionally associated with chronic pain stimuli. It has also been shown that resting state functional connectivity determines pain perception in healthy humans. Resting state fcMRI evaluates interactions between brain regions before a sensory event or when an explicit task is not being performed. These resting regional communications are altered in older adults with chronic musculoskeletal pain. Functional connectivity among regions specifically within the "default mode" network (DMN) (posterior cingulate, inferior parietal lobes, and medial frontal gyrus) have been examined in clinical disease states, as this network is reliably detected and well-characterized. Resting state functional connectivity may be a novel biomarker, complementing patient self-report, that tracks the unique contributions of chronic pain and dyspnea to a patient's symptom complex. No studies to date have examined the relationships between subjective measures of chronic pain and dyspnea and objective measures of functional connectivity, or changes in these symptoms and functional connectivity in response to PA promotion in persons with COPD.

Objective: Assess the feasibility of conducting brain fcMRI in persons with COPD and begin to understand the central mechanisms of chronic musculoskeletal pain and dyspnea, and how they associate with physical activity. This will be done by the following:

(1) Recruit from persons who are currently or have previously participated in the WEB study to assess if they would participate in an additional in-person visit to complete an fcMRI scan assessment.
(2) Recruit up to 20 of those persons willing to receive an MRI scan at VA Boston to assess feasibility of obtaining fcMRI and gather preliminary data on the relationships between patterns of functional connectivity and shortness of breath, chronic musculoskeletal pain, and physical activity in COPD to design a future study.

Work Proposed:

Recruitment: An approved HIPAA waiver will allow contact of those who have completed the main study. We will contact these participants by letter and then by telephone if there is no response after 2 weeks. Those who are in follow-up in the main study will be approached in person, and eligible and interested participants will sign an ICF and HIPAA specific to the substudy. For all participants in the substudy, the fcMRI can be done at the same visit as scheduled for the main study or during a separate visit depending on participant preference.

Proposed MRI assessment: Among those persons willing to participate in an MRI scan assessment, we will ask up to 20 of these subjects to undergo an fcMRI scan at VA Boston. Participants will complete a dedicated VA consent form and HIPAA authorization for the MRI scan at the time of the MRI scan, as well as an MRI scan clearance form. Scans will be performed in the Neuroimaging for Veterans Research Center (NeRVe) of the VA Boston Healthcare System, and a clinical MRI technician will be present for all scans.

For the proposed substudy, additional exclusion criteria are:

- Claustrophobia
- History of seizures
- Current diagnosis of bipolar disorder, schizophrenia, or psychotic disorder
- Cognitive disorder such as dementia

- Known metal in body including shrapnel, surgical medical clips, implants, pacemakers, or metal-based tattoos
- Known or new brain lesions (including but not limited to brain cancer, metastatic cancer, subdural hematoma)

Each scan will start with 5 minutes of familiarization with the equipment and will be completed at one visit that lasts approximately 90 minutes. Physiologic monitoring will be synchronized with image acquisition. Chest expansion, oxygen saturation, and end-tidal CO_2 will be assessed. We may apply some sensors on the hand and chest, as well as install a respiration belt around the torso and a gas mask that will record breathing rate. Neuroimaging data will be acquired on a 3-Tesla Siemens (Erlangen, Germany) TIM Trio scanner, using a 32-channel brain array. Two multiecho MPRAGE (Magnetization Prepared Rapid Gradient Echo) T1-weighted anatomical scans (1 mm isotropic) will be acquired for surface reconstruction, functional connectivity seed placement, and inter-participant registration. Resting state functional connectivity data will be acquired in two runs using high temporal and spatial resolution sequences recently developed for the Human Connectome Project Lifespan study.

The scans performed in this study are for specific research purposes and are not meant to find any medical abnormalities. The results from the research scan will not be routinely shared with the participant's clinical provider, except upon the participant's request. However, if the investigators or MRI technician notice any potential incidental finding, the scan will be reviewed by a clinical radiologist who will determine whether a clinical evaluation is warranted. If there is a finding that warrants a clinical follow-up, study personnel will discuss this with the participant. If any abnormality on the MRI is noted by the research staff, the participant will be notified to follow up with his usual provider.

Eligible subjects will also complete an MMRC Dyspnea Scale assessment and the Brief Pain Inventory (short form) before having the brain MRI.

Persons will receive $25 compensation in cash for their participation in the fcMRI assessment.

In addition to the information collected from the fcMRI, we may also use other information obtained as part of the subject's participation in the main study including name, address, date of birth, and information such as SSN, pulmonary function tests, laboratory test results, X-ray images/readings, exercise tests, hospitalization records from other institutions, emergency contact information, pulmonary rehabilitation evaluations, medical history, allergies, imaging studies and reports, procedure reports, drug, alcohol, or STD treatment, genetic test results, or mental health treatment.

Risks to Subjects:

Potential Risks: Neuroimaging with MRI Scanning: Minimal risks are associated with MRI scanning. Extended periods of time in the MRI scanner can become uncomfortable. Lying down in the MRI scanner may cause back discomfort or anxiety, particularly if the subject tends to be claustrophobic. There is a risk of falling getting on and off the scanner table. There is no risk of ionizing radiation exposure with MRI.

During the MRI procedure, participants will hear many different sounds. These sounds are sharp and repetitive and can cause anxiety in some subjects. While they may be annoying, these sounds are not harmful to one's hearing.

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 substudy in a way that is understandable to participants and answer all their questions. Participants can discuss the substudy with their usual healthcare providers.
Subjects can participate in the primary RCT without obligation to participate in the brain MRI scan substudy.

Protection Against Risks: We will use all reasonable means to promote comfort including but-not limited to use of pillows and padding. Some people experience a "closed-in" feeling due to the relatively restricted space within the MRI machine. If a participant should experience such feelings, he can let the researchers know by squeezing the squeeze ball. He can do this at any time to stop the scan. We will minimize sharp sounds through the use of earplugs.

All safety precautions will be reviewed with the subject immediately prior to having the MRI. If there is any doubt as to whether the subject has metal in his body, he will be requested to have an X-ray to determine this. If the X-ray shows that there is metal in the participants, he will not be able to take part in the MRI study. If there is more than one part of the body in which metal is questionable, the participant will not be able to have an X-ray and will not be able to participate in the MRI study.

Study staff will provide pillows and close verbal communication to minimize anxiety and discomfort. The criteria for discontinuing a subject's participation in the neuroimaging protocol include the participant's request, any potential for harm, and any life-threatening or potentially disabling unintended event, including syncope, an injurious fall, new or worsened symptoms of musculoskeletal pain, shortness of breath, or chest pain, hemodynamic instability, mental status changes, dysrhythmia, angina, myocardial infarction, or anaphylaxis. These adverse events will be recorded and included in the database. Any subject who develops adverse events during the conduct of study protocols will be given immediate medical care and will be referred to his primary care physician for ongoing care.

Available 24/7 for emergencies, Dr. Moy, the PI, will contact participants if any telephone reported adverse event suggests clinical deterioration warranting immediate medical attention. 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. Neuroimaging data will be stored behind the VA firewall 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.

Analytic Approach: For neuroimaging, all analyses will be performed with complementary advanced imaging procedures for brain network mapping, including seed-based and independent component analysis procedures, to assure the robustness of the findings. We will correlate neuroimaging data with clinical data obtained at baseline in the main study, including demographics, dyspnea, chronic pain assessments, and daily step count as the measure of PA. We will perform secondary analyses to examine the potential influence of PA and clinical characteristics that may contribute to the findings. We will be somewhat exploratory in our approach in this pilot project, while also being mindful of statistical considerations. Our main image analyses will use robust and careful seed based DMN mapping procedures. Analyses will account for known contributors to the fcMRI signal including motion, respiration and cardiac signals. Neuroimaging data will be processed using a combination of FreeSurfer.20 AFNI.21 and FSL.22 based primarily on the FSFAST processing stream. Surface models will be reconstructed from anatomical images using FreeSurfer.23. Resting state fcMRI scans for each subject will be

processed using a standard stream (motion correction, time shifting, concatenation of scans, motion regressed from time series, regression of the global mean and the average time courses from the white matter and the ventricles, band pass filtering between 0.01 and 0.1 Hz). Time points, runs, and sessions with excessive motion will be excluded (0.5 mm/TR; 20 TRs/run; 30 TRs/session). Data will be sampled to and smoothed on the surface, and each brain will be warped to a surface-based template (fsaverage). Seed regions will be derived from surface-based parcellations of the cortex providing more robust anatomical representation for each participant. The vertex-wise partial correlation to the seed will allow further group-level analyses. We will focus on the DMN, but explore other networks including pain networks. We will also explore resting state functional connectivity associated with the anticipatory symptom scenarios.

Statistical analysis:
Group average correlation maps will assess cross-sectional associations between functional connectivity patterns and daily step count, dyspnea, and chronic musculoskeletal pain. We will also explore differences in functional connectivity in those with predominantly pain versus those with predominantly dyspnea.

Sample size/Power calculation: This is an exploratory proposal in a convenience sample of up to 20 Veterans with COPD. Findings from this study will inform the design and sample size of a future Merit Award application.