Active for Life: Chronic Obstructive Pulmonary Disease

NCT03201198

01-16-2021

SPECIFIC AIMS

Physical inactivity is a growing health problem in the U.S., especially for people with chronic diseases such as chronic obstructive pulmonary disease (COPD); in fact, people with COPD are among the least active.[2-9] Low levels of physical activity (PA) are associated with increased frailty[10] and negative health outcomes, including an increase in mortality and COPD exacerbations.[11-21] Although pulmonary rehabilitation is effective in increasing exercise capacity and health-related quality of life, it does not increase the day-to-day time spent in PA.[3,22,23] Establishing an active lifestyle is particularly challenging for people with COPD because of day-to-day fluctuations in symptoms that negatively affect energy levels[24] and periodic acute exacerbations of COPD that interrupt PA patterns and contribute to further declines in PA.[25-27] Increasing PA is also challenging because of well-entrenched sedentary habits.

Current PA guidelines[28,29] focus on moderate-to-vigorous physical activity (MVPA) that is too strenuous and not feasible for long term maintenance in many people with COPD. Therefore, we propose a new paradigm for promoting PA in this population: focusing on *increasing light physical activity* (LPA) rather than MVPA and *decreasing sedentary time*. Accumulating evidence suggests that substantial health benefits are associated with increases in the volume of LPA, including reduced risk of mortality[30] and metabolic syndrome,[31-33] attenuation of arterial stiffening in old age,[34] increase in mobility for people with chronic disease,[35] and delay in the onset of frailty.[36] Also, recent studies indicate that regular PA is associated with better lung health for people with COPD, including a reduced risk of hospitalization for COPD,[13,14] a slower rate of decline in lung function,[37] and fewer acute exacerbations of COPD.[12,15]

Active-for-Life (Active-Life) with COPD is a 10-week intervention designed to increase total PA with an emphasis on increasing the time spent in LPA and decreasing sedentary time. Key components of Active-Life include (a) a laboratory-based exercise program comprised of functional circuit training (FCT), walking and stretching which can easily be transitioned to the home setting with minimal equipment; (b) a behavioral component with a structured self-efficacy enhancing intervention that includes self-regulation strategies; and (c) an education component that addresses the distinct health benefits of LPA and MVPA, the negative consequences of too much sedentary time, and an action plan for dealing with acute exacerbations of COPD.

The objective is to systematically test the efficacy of our Active-Life intervention and examine theoretically-based mediators of PA outcomes for people with COPD. Our central hypothesis is that Active-Life will have positive, lasting effects on objectively measured PA and on other indicators of frailty. Active-Life integrates PA into daily life and establishes a goal for subjects: to *increase total PA, combined LPA and MVPA, by at least 60 minutes a day*. This far exceeds the effects of other published PA interventions for people with COPD[23,38] and, if successful, will advance PA science in clinically important ways. The Active-Life program was developed by Dr. Larson and her research team through a series of preliminary studies; its feasibility is well established and preliminary data are promising. Outcomes will be measured at baseline; at the end of the 10-week intervention; and at 3, 6, and 12 months after the end of the Active-Life intervention. The primary dependent variables are objectively measured PA and sedentary behavior. Secondary outcome variables are frailty indicators.

Aim 1. Determine the short term (end of 10 week intervention) and sustained effects (1 year follow-up) of the Active-Life intervention vs a program of chair exercises plus health education (Chair-HE, *active control*) on PA and sedentary behavior. The working hypothesis for this aim, based on preliminary data, is that the Active-Life group will significantly increase time spent in PA (combined LPA and MVPA) and decrease time spent in sedentary behavior compared to the active control group and that these effects will be sustained at 3, 6, and 12 months after completion of the 10 week Active-Life intervention.

Aim 2. Determine mediating effects of self-efficacy and outcomes expectation on PA and sedentary behavior outcomes of Active-Life. We hypothesize that positive changes in self-efficacy for overcoming barriers to LPA and outcomes expectations for exercise will mediate changes in the time spent in PA and sedentary behavior.

Secondary Aim. Determine short term and sustained effects of Active-Life vs active control on frailty indicators: strength, endurance, balance, walking speed and physical function. The working hypothesis is that the Active-Life group will have significantly higher scores (less frailty) on all frailty indicators after completion of Active-Life compared to the active control group and effects will be sustained at 3, 6 and 12 months.

This research addresses a key issue identified by the 2012 Institute of Medicine report: Living Well With Chronic Disease.[39] We will test an intervention to reduce the burden of chronic illness, targeting people with COPD, most of whom have multiple chronic conditions.[40] The intervention is aimed at physical inactivity, a risk factor for chronic disease. If this intervention is successful in reducing/delaying frailty it could have long reaching economic effects by decreasing health care utilization and the cost of care for people with COPD.

2. RESEARCH STRATEGY

SIGNIFICANCE

COPD is the fourth leading cause of disability [41] for adults ≥ 65 years of age in the United States. Compared to healthy older adults, people with COPD engage in 40% to 60% less PA,[42] whether tested by[5-8,15] accelerometer-based measures of activity,[5-7] pedometer measures of step counts,[4] smart monitors that identify types of activities,[8] or self-report measures of PA.[43] In fact, one recent systematic review reported that the duration and intensity of PA were 57% and 75% lower, respectively, for people with COPD than for age-matched healthy individuals.[3] Another systematic review noted that people with COPD took fewer steps/day than people with most other chronic diseases; in fact, one of the least active groups was people with COPD.[9] Given that an extremely sedentary lifestyle contributes to the disability of COPD, this has major implications for this population. Disease severity, however, had only a weak to moderate effect on PA.[2]

Furthermore, low PA is an important indicator of frailty[10,44,45] and it is consistently associated with COPD exacerbations and mortality.[12-21] Most of this evidence, which has emerged in the last few years, highlights the importance of increasing PA. However, efforts to promote national PA guidelines have not been successful with this population because MVPA is too strenuous and not sustainable for many people with COPD. We suggest that focusing on LPA is more realistic and feasible. When faced with obstacles such as an acute exacerbation, it is easier to sustain LPA; it is also easier to resume LPA during early recovery from an acute exacerbation, and less downtime reduces loss of strength and endurance. Increasing LPA is also more achievable for people without the direct supervision of a professional because, by learning how to increase their LPA, they will become more independent and capable of helping themselves. LPAs include standing, walking slowly (2 miles per hour), shopping, light house work and leisurely sports.

Significant benefits can be accrued by a lifestyle that includes a higher volume of LPA on a regular basis.[15,31,32,34,46,47] Growing evidence suggests that increasing LPA and decreasing sedentary time provides health benefits *independent of the amount of MVPA performed*.[48,49] A recent review of prospective studies also demonstrated that, *independent of total PA,* too much sedentary behavior (sitting and screen time) was associated with cardiovascular mortality.[50] Other benefits of increasing LPA include reduced risk of mortality[30] and metabolic syndrome,[31-33] attenuation of arterial stiffening in old age,[34] reduced risk of hospital admission for COPD,[13,14] and delay in the onset of frailty.[47] Even LPAs such as standing are important: greater time spent standing is associated with a decrease in all-cause mortality, including cardiovascular disease mortality.[30] The volume of LPA required to accrue health benefits is not known, but evidence suggests that replacing 30 minutes of sedentary time with LPA has the potential to improve physical health as indicated by body mass index, number of health conditions, number of medications, lower-body physical function, and general health rating.[51] However, most people with COPD do not understand the importance of increasing LPA and decreasing sedentary time.

Promoting PA in COPD. Pulmonary rehabilitation, which includes exercises and health education, increases exercise capacity and health related quality of life. However, it has not been very effective in increasing levels of PA,[3,22,23,52,53] possibly because (a) it does not adequately address the behavioral issues associated with many decades of habitual inactivity and (b) it focuses on MVPA that may be too strenuous and not feasible for long-term maintenance in people with COPD. Few pulmonary rehabilitation programs employ theory-based behavioral interventions to change PA behavior and none have focused on increasing LPA.

In our recent systematic review of interventions designed to increase PA in people with COPD, we found no powerful interventions that produced meaningful results.[38] In this review, 9 quasi-experimental and 6 randomized controlled trials were identified. Interventions included pulmonary rehabilitation (n=7), exercise (n=2), behavioral (n=2), and a combination of both behavioral and exercise interventions (n=4). Eight of the studies demonstrated statistically significant increases in objectively-measured PA, with the most successful interventions demonstrating an increase of approximately 10 minutes of walking per day. One exception, a small Italian study in which people increased walking time by 35 min/day,[54] used speed walking with weekly supervised sessions for 4 weeks, and a relatively high-cost behavioral intervention with one-to-one phone calls twice a month for 12 months. While longer interventions demonstrated a higher success rate, only 3 studies examined possible longer term effects of the interventions.[55-57] Of these 3, only one demonstrated a significant increase in PA. In a small Australian study Breyer demonstrated increases in PA at 6 months after completion of a Nordic Walking intervention (walking time, mean Δ +9.2 (SD=2.9) min./day, P=.036 and standing time, mean Δ +105 (SD=4) min./day, P<.01). Another recent meta-analysis of exercise studies (n=7) calculated a small combined effect size, equivalent to an increase in PA of approximately 5 minutes of walking a day.[23] Given the weakness of the effects seen in these studies, an intervention that has the potential to increase PA and to maintain the higher level of PA over time is a critical need.

While increasing PA is challenging for all people with chronic disease, it is particularly so for people with COPD. Behavior patterns are well entrenched and difficult to change after 3-4 decades of a very sedentary lifestyle. In addition, people with COPD experience day-to-day fluctuations in symptoms (dyspnea and fatigue)[24] and periodic acute exacerbations of COPD that interrupt PA patterns.[25-27] People report having good and bad days with their symptoms; on bad days their energy level is lower and PA is limited by the symptoms. In our preliminary studies, some people reported being afraid of PA and at the first sign of an exacerbation they immediately went to bed. This fear-based response contributes to physical deconditioning and difficulty reestablishing PA patterns.

We propose to test the Active-Life intervention, both its direct effects on total PA and sedentary time and its indirect effects mediated by barriers-efficacy (self-efficacy for overcoming barriers to PA) and outcome expectations for PA. In addition we will examine effects of Active-Life on physical frailty.

INNOVATION

The proposed Active-Life intervention is novel in the following ways:

1) The focus on LPA is novel. Physical activity guidelines (CDC, AHA) and most intervention studies target MVPAs that are too strenuous and not feasible for long-term maintenance in many people with COPD.
2) The laboratory-based exercise employs functional circuit training (FCT), designed for people with COPD. Although the effects of FCT have not yet been examined in COPD, except for one small study of two weeks of circuit training,[58] it is promising because it engages muscle groups that are commonly used in activities of daily living. We combine FCT with walking, the most common PA, because this will prepare people to increase their day-to-day activities.
3) We have optimized the theory-based behavioral component of the Active-Life intervention by including the use of self-efficacy enhancing strategies, previously used in an earlier study, and adding implementation intentions, a self-regulatory strategy that, to date has not been used for this population.
4) The combined use of two objective measures of PA (ActivPAL and ActiGraph accelerometers) contributes to the novelty of this study. The ActivPAL measures *PA behavior 24 hours a day* (time spent stepping, standing, and sitting/lying), while the ActiGraph measures the *intensity of PA during waking hours*. This comprehensive measurement approach is one that we have not seen in other research. Subjects do not have to apply the ActivPAL monitor every day and this minimizes the loss of data that is seen with most other devices. The ActivPAL produces a reliable and valid measure of time spent in sedentary behavior; it is the gold standard. Reliable and valid data for sedentary behavior cannot be obtained from ActiGraph.[59]

APPROACH

Scientific Premise and Feasibility.

The Active-Life and Chair-HE (active control) will be delivered over 10 weeks with 2 visits/week for the first 8 weeks and 1 visit/week for weeks 9-10 (see Table 1). After completion of the 10 week structured intervention we will provide 8 5-minute phone coaching sessions and two booster sessions. Phone coaching and booster sessions will be used to support long-term maintenance of PA.

Table 1. Key Elements Intervention & Control

Active-Life	Exercise	• Functional Circuit training • Walking • Stretching
	Behavioral	• PA specific self-efficacy enhancement
	PA Education	• Principles of exercise • Benefits of LPA & MVPA • Negative effects of too much sedentary time • Breathing problems action plan
Active control	Exercise	• Chair exercises and stretching, emphasize arms and shoulders
	Behavioral	• Imagery, used to promote relaxation
	Health Education	• Includes basic lung physiology, healthy eating, travel issues, common medications, energy conservation, review of CDC PA guidelines, etc.

Active-Life Intervention. Justification is discussed below and further details of the intervention are described under research design.

Functional circuit training and walking. The FCT and walking were designed so that people would practice the types of activities required to perform daily activities at home, thereby facilitating the transfer of skills to the home setting (Appendix A). Although circuit training has been successfully used to promote mobility, strength, and endurance in people with heart failure, the frail elderly, and after stroke,[60-62] we found only one preliminary study of a 2-week circuit training program for people with COPD.[58] In this study, COPD patients tolerated relatively high-intensity exercise without dyspnea and hypoxemia and demonstrated improvements in functional status and lower extremity strength.[58] Rest periods between exercise stations allow subjects to recover from dyspnea and muscle fatigue before moving to the next station and engaging a different set of muscles. When we employed similar rest periods in a study of upper body resistance training, it worked well, allowing people to socialize with each other and making the exercise session fun.[63] Because circuit training provides a variety of activities, it minimizes the risk of boredom, and requires minimal equipment making it easy to perform in the home setting. The FCT will be

combined with walking, because walking is a common activity of daily living.

Behavioral: PA-specific self-efficacy enhancing intervention. Self-efficacy is a form of "situation specific self-confidence." Self-efficacy expectations, which have profound effects on multiple elements of behavior, reflect individuals' beliefs in their capabilities to successfully meet the challenge at hand. The expectations influence the choice of activities in which people engage, the effort they put forth during the activity, and how long they persist in the activity when faced with difficulties and/or challenges.[64-66] Substantial evidence suggests that perceived self-efficacy is an important and consistent determinant of the initiation and maintenance of health-promoting behaviors such as exercise. Those with a high sense of self-efficacy for PA are more likely to engage in PA, work hard at it, and persist despite setbacks. Self-efficacy is especially important during the initial adoption of exercise and PA, [67] but it also plays a role in the maintenance stage of exercise and PA.[68,69] Dr. Larson and her team developed and tested an exercise-specific self-efficacy enhancing intervention[70,71] to promote both adherence to upper body resistance training and an active lifestyle that included adherence to national PA guidelines. Results were positive and are described in the preliminary data.[72] In the current application she modified the intervention to focus on increasing LPA and decreasing sedentary time.

Pedometer. Pedometers are affordable, provide a simple, easy-to-understand output for the user, and provide immediate feedback, which can be motivational.[73] When combined with goal setting, pedometer-based interventions have been successful in promoting increased walking.[74,75] A meta-analysis of studies with older adults reported a moderate effect size, 0.53.[76]

Goal setting. *SMART goals* and *implementation intentions* are self-regulatory strategies that have been successfully used to increase PA in the home setting.[77,78] SMART goals help subjects establish goals that are **S**pecific, **M**easurable, **A**ttainable, **R**ealistic and **T**imely. Implementation intention is a self-regulatory strategy that facilitates the implementation of goals for behavior change. Using principles described by Gollwitzer,[79] subjects create "IF THEN" plans describing when, where, and how the PA will be performed. When an individual encounters the critical situation, the goal-directed behavior is immediate because the decision has already been made. For example, someone might say "IF it is 9AM on Monday, Wednesday or Friday morning THEN I will walk for 20 minutes, outside in good weather and at the local mall in bad weather." Formulating such behavioral intentions makes it easier for an individual to identify, attend to, and recall situations for enacting goal-directed behavior such as PA.[80] In a recent meta-analysis, implementation intentions were effective in increasing PA with small to medium effect sizes, and the effect was sustained during no-contact follow-up periods, making it a promising strategy for promoting long-term maintenance of PA.[81,82] Further, implementation intentions were shown to have a stronger effect in clinical populations when combined with barriers management programs, such as the self-efficacy enhancing intervention described here.[81]

Education: PA education and breathing problems action plan. The *PA education* component of Active-Life focuses on the principles of exercise, the benefits of LPA, and the negative effects of too much sedentary time, because many people with COPD do not understand the importance of increasing LPA and decreasing sedentary time. The *breathing problems action plan* is refined from an earlier action plan used in Dr. Larson's upper-body resistance training study.[63] The goal of this component of the Active-Life intervention is to support help-seeking behavior at the onset of an acute exacerbation of COPD, to minimize the duration of illness, to minimize the attendant decrease in PA, and to support the early return to usual levels of PA.

Potential mediators of PA. For the Active-Life intervention, potential theoretically-based mediators include barriers-efficacy for PA and outcome expectations for PA.

Barriers-efficacy for PA. Support for the importance of self-efficacy for overcoming barriers to PA was presented above. People with COPD must overcome numerous barriers to being active.

Outcome expectations for PA. Outcome expectations, which include physical, social, and self-evaluative domains, reflect an individual's beliefs about the probability that a given behavior will produce a set of specific outcomes.[66] For example, if people with COPD expect that an increase in PA would not improve their health, this could influence their PA behavior. Outcome expectations is a core construct in social cognitive theory, but has not been studied as much as self-efficacy. However, it is a potentially important construct, because interventions could be designed to change outcome expectations, as seen in the educational component of our intervention. To date, the empirical evidence for the role of outcome expectations is conflicting, especially for its effects on PA in older adults.[83-85] The effects of outcome expectations have not been examined in COPD.

Effects on physical frailty. Increasing PA will decrease the risk of frailty in older people with chronic disease. Frailty is important because it leads to adverse outcomes such as disability, increased health care utilization and death.[44,86] While there is no well-accepted definition of frailty, it is widely acknowledged that a *low level of*

PA contributes to frailty and a decrease in PA is frequently used as an indicator of physical frailty.[36,44,86] Other indicators of physical frailty include a decline in strength, endurance, physical function, balance, and walking speed.[44,86] While this is not a comprehensive list of frailty indicators, it does reflect factors that are most likely to be influenced by a PA intervention.

Other factors that influence PA in people with COPD and could influence response to the Active-Life intervention include affective states, dyspnea and fatigue, history of PA, social support for PA, and disease-related factors such as the frequency of acute exacerbations of COPD.

Affective state. Research findings suggest that people with COPD have an increased risk of depression:[87-90] a higher prevalence of depression[91-94] and depressed mood[95] has been reported in some but not all studies of people with COPD.[96,97] Depression in COPD can have a negative influence on PA.[98,99] Increases in PA can have a positive effect on anxiety and depression, but it is not clear if LPA is sufficient to produce this effect.[100]

Symptoms of dyspnea and fatigue. Dyspnea and fatigue are the most common symptoms reported by people with COPD. Dyspnea correlates weakly to moderately with PA, from r=-0.21 to -0.46.[101-104] Less is known about fatigue, but one study reported a weak correlation between fatigue and PA, r=-0.16.[101] The consensus is that symptoms contribute to the decline in PA, but the magnitude of the effect is not known.

History of PA. Evidence for the relationship between previous PA and current activity comes from the exercise adherence literature. People who are physically active and have participated in exercise training are more likely to adhere to a new exercise program.[105] This has been demonstrated in many groups including middle-aged[106] and older-aged adults.[67,68,107]

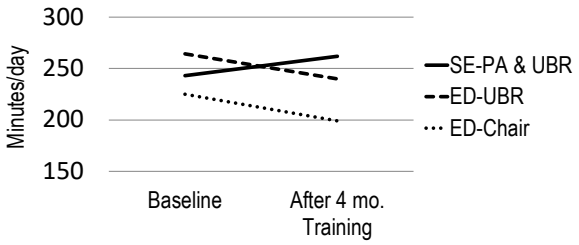
Social Support. Social interactions play an important role in physical and psychological health,[108] but such interactions are known to decrease with aging. Substantial evidence suggests that social support contributes to exercise adherence in older men and women,[109-113] and that the relationship between social support and PA is mediated by self-efficacy.[114]

Acute exacerbations of COPD. For purposes of this research an acute exacerbation of COPD is defined as "a complex of respiratory symptoms (increased or new onset) of at least two of the following: cough, sputum, wheezing, dyspnea, or chest tightness lasting 3 or more days, requiring a course of treatment with antibiotics or systemic steroids."[115] An increase in symptoms is known to trigger a decrease in PA.[26,116,117]

Preliminary Studies. Dr. Larson has conducted multiple randomized controlled trials in people with moderate to very severe COPD.[63,72,118-120] She is experienced in recruiting and retaining subjects, delivering exercise interventions in a systematic manner, tracking fidelity of the interventions, and measuring outcomes such as aerobic capacity, strength and objectively measured PA in people with COPD. Dr. McAuley was co-investigator on Dr. Larson's most recent clinical trial[63,72] and Dr. Han was co-investigator on the preliminary studies for this application. This research team has collaborated for several years.

Exercise specific self-efficacy enhancing intervention for COPD. Dr. Larson and her team tested the effects of a self-efficacy enhancing intervention to promote MVPA in people with COPD.[63] It was combined with upper-body resistance training over 16 weeks to achieve two goals: to promote adherence to upper-body resistance training and to establish an active lifestyle by increasing MVPA. Physical activity was measured with ActiGraph uniaxial accelerometers (Model 7164). At the end of the 16-week intervention, the self-efficacy enhancing group increased time spent in LPA by +20.68 (29.30) min/day, while the two active control groups decreased time spent in LPA by -22.43 (47.88) and -25.73 (51.76) min/day (see Figure 1).[72] The effect size (Cohen's d) for change in time spent in PA was large for LPA (1.14) and very small for MVPA. Changes in LPA were not sustained at 12-months.

Figure 1. Actigraph Data, Time Spent in LPA and MVPA



SE-PA & UBR=Self-Efficacy for Physical Activity and Upper Body Resistance Training;
ED-UBR=Health Education and Upper Body Resistance;
ED-Chair=Health Education and Chair Aerobics.

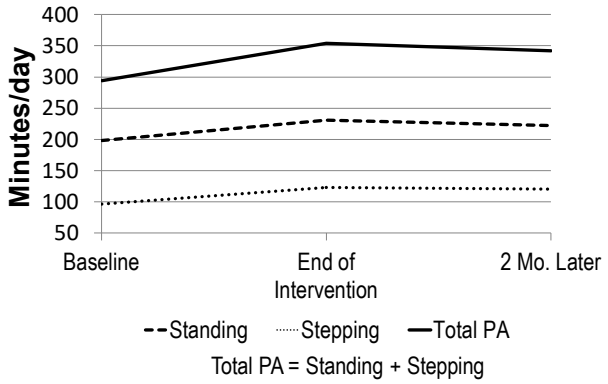
Although subjects in the self-efficacy enhancing group were encouraged to increase MVPA to meet national PA guidelines, they instead increased their LPA. The lack of an increase in MVPA is plausibly explained by the fact that their pulmonary symptoms limited their ability to sustain higher volumes of MVPA on a day-to-day basis. This RCT demonstrated the research team's ability to implement a self-efficacy enhancing intervention and the potential effects of this intervention when the focus was on MVPA. The Active-Life intervention is a modification and refinement of the exercise specific self-efficacy enhancing intervention for COPD and it places greater emphasis on long term maintenance of PA.

Active-Life development. The 10-week Active-Life intervention was designed by Dr. Larson and her team to focus on LPA as a more realistic target for people with moderate to very severe COPD. Additional refinements include: (a) the addition of pedometers to provide objective day-to-day feedback, (b) the addition of SMART goals and implementation intentions to facilitate the accomplishment of PA goals, (c) refinement of PA education to establish the importance of LPA and the negative effects of too much sedentary behavior, and (d) phone coaching to facilitate the transition from laboratory to home and long term maintenance.

In the early phase of pilot testing we compared the effects of a 6-week intervention to the same intervention delivered over 10 weeks. All subjects indicated that a 6-week program was too short and they recommended a 10- or 14-week program. The majority recommended 10 weeks.

Active-Life pilot. We pilot tested the 10-week Active-Life intervention in 10 subjects and the observed changes in PA behavior are promising (see Figure 2). Physical activity was measured with ActivPAL and ActiGraph GT3X accelerometers. ActivPAL measures the time spent in PA (standing and stepping) 24 hours/day and the ActiGraph measures the intensity of PA during waking hours.

Figure 2. Time spent in physical activity before and after active-life intervention, ActivPal Data, N=10



Total PA = Standing + Stepping

ActivPAL data demonstrated that subjects increased their total PA time at the end of the intervention by a mean of 60 (SD=78) min/day and 80% of the gains were maintained at 2-month follow-up. Repeated measures ANOVA demonstrated significant increases in the time spent in total PA (P = 0.029). A similar improvement was seen for the time spent sitting/lying (sedentary time).

The ActiGraph data demonstrated that the combination of LPA and MVPA increased by 30%, +47.5 (SD=57.3) min/day from baseline to end of training, and a total of +34.9 (SD=60.8) min/day from baseline to 2-month follow-up. The Actigraph does not capture standing time, an important component of LPA and this accounts for the differences in total PA time documented by ActivPAL.[30] In addition the ActiGraph is worn only during waking hours and wear time is not as consistent as it is with ActivPAL. The increases in PA from baseline to end of the intervention were 72% LPA and 26% MVPA. The breakdown was similar for increases in PA maintained at 2 mo. follow-up. Similar increases in PA were observed for triaxial data (vector magnitude counts/day) (P = 0.047) and step counts from the ActiGraph accelerometer (P = 0.008). The triaxial data reflect movement in three planes and the activity counts reflect movement in the vertical plane.

Taken together, these data suggest that the intervention was successful in increasing time spent in PA and decreasing time spent in sedentary activities. It was more successful than previously published interventions. Importantly, the high level of PA at 2 months after the completion of the intervention is very promising. It suggests that the proposed PA goals are realistic and the Active-Life intervention supports long term maintenance of PA.

Table 2. Uptake of Active-Life Intervention, Repeated Measures ANOVA (N=10)

Measure	Baseline M (SD)	End of Intervention M (SD)	2 mo. Follow-up M (SD)	P
6MWD (ft.)	1357 (352)	1474 (285)	1421 (342)	.034
BE light PA	66.2 (21.9)	74.6 (17.6)	72.0 (26.6)	.384
PASR (n=7)	23.7 (9.0)	40.3 (12.0)	35.1 (12.1)	.025
MOEES	49.8 (3.6)	--	59.4 (11.0)	.014

6MWD = Six-minute walk distance; BE light PA = Barriers-efficacy for light physical activity; PASR = Physical activity self-regulation; MOEES = Multidimensional outcome expectations for exercise scale (total)

Relationships between ∆PA and social-cognitive variables. There is strong evidence for the uptake of the intervention as demonstrated by increases in six-minute walk distance, barriers-efficacy for light PA, the use of self-regulation strategies for PA and outcomes expectations for exercise (Table 2).

The sample size in this preliminary study was too small to examine mediation and to ensure stable correlations. Given these limitations we observed positive relationships between *changes* in the time spent in PA (standing/stepping) and self-efficacy for overcoming barriers to light PA (barriers-efficacy for light PA) (Table 3) and this is consistent with the hypothesis for aim 2. The observed relationship for outcome expectations and PA are less clear, but will be clarified in the proposed research using a larger sample that allows for controlling relevant variables.

Potential effects on frailty. To demonstrate a positive effect on frailty, *an intervention should either produce an increase or prevent decline in frailty indicators*. For this research that would mean an improvement in function or a slower rate of decline in function. In a 3 year longitudinal study of people with COPD we

demonstrated a 3% yearly decline in self-reported physical functional,[121] reflecting a gradual relinquishing of activities.[122] In the pilot study of Active-Life we demonstrated an increase in PA, an important frailty indicator. In addition other indicators of physical frailty were measured including the six-minute distance walk and Short Physical Performance Battery (SPPB). By the end of the intervention, the six-minute distance walk had increased by 116 (SD=128) feet. At the 2–month follow-up, however, a decrease of 53 (SD=129) feet had occurred, leaving an overall increase of 63 (SD=129) feet from baseline to follow-up (Table 2). This is consistent with an overall increase in frailty indicators and/or a decrease in the rate of decline, but in the one-group research design it was not possible to determine if Active-Life slowed the rate of decline. The proposed research will clarify this by comparing the effects of the Active-Life to an active control condition. Since a ceiling effect was observed with the SPPB (data not shown) the proposed study will measure isometric strength of the lower extremities to avoid the possibility of a ceiling effect. The SPPB will still be useful in documenting the presence or absence of declines in balance and walking speed (two frailty indicators).

Table 3. Bivariate Correlations: Social Cognitive Variables vs. Change in Physical Activity (baseline to 2 mo. follow-up, N=10)

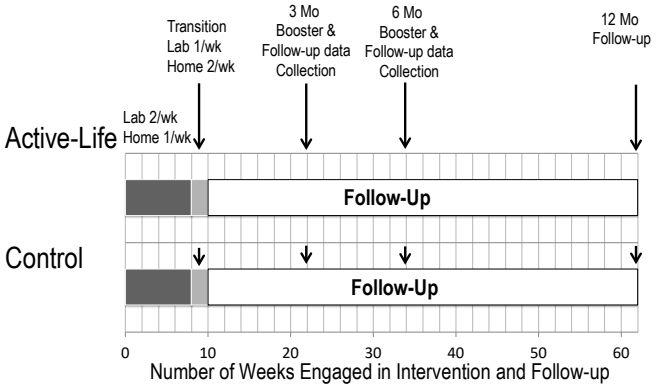
Social Cognitive Variables	Δ[a] Standing/Stepping (min./day)	P
Barriers-efficacy for Light PA (baseline)	*r* = .556	.095
Barriers-efficacy for Light PA (end of intervention)	*r* = .496	.145
Barriers-efficacy for Light PA (2 mo. follow-up)	*r* = .515	.128
MOEES (baseline)	*r* = -.193	.593
MOEES(2 mo. follow-up)[b]	*r* = -.401	.250

Δ[a] = 2-mo. follow-up minus baseline measure; [b]Note data from end of intervention is not available for this measure; BE-PA = barriers-efficacy for physical activity; MOEES = multidimensional outcome expectations for exercise scale.

Research Design.

This is a randomized controlled trial with an active control group. Data collectors will be blinded to group assignment and because of the nature of the intervention it is not possible to blind subjects. The final sample will be 128 subjects with moderate to very severe COPD, randomly assigned to either Active-Life (experimental) or Chair-HE (active control) with blocking for COPD severity. Randomization will be performed by Dr. Yang, the statistician. He will use the blockrand function from the blockrand package of the R software to generate and produce randomization cards with equal number of cases and controls. The assignments are put into sequentially numbered opaque envelopes and opened only when a patient is ready to be assigned. Active-Life and Chair-HE will be conducted in groups of 10. The Active Life groups and Chair-HE groups will be conducted separately and sessions will be scheduled so that subjects in the two groups do not meet each other. We will try to recruit enough subjects so that we can schedule 10 subjects in each group.

Figure 3. Timeline for intervention and follow-up boosters



Follow-up = weekly phone coaching for 2 weeks, every other week coaching until 3 months, monthly phone coaching until 6 mo. follow-up.

Outcomes will be measured at baseline; end of the structured intervention; and at 3, 6, and 12 months after completion of the intervention, total of 5 visits to measure outcomes (Figure 3). The components of the intervention and the duration of each are summarized in the table below.

The Active-Life intervention and Chair-HE include a total of 18 laboratory sessions,11 5-minute phone coaching sessions (weekly for 2 weeks, every other week for 2 ½ months and monthly for 3 months) and 2 in-person booster sessions. ***Follow-up phone coaching*** is designed to promote long term maintenance. Staff will review PA goals and accomplishments, provide appropriate feedback to enhance self-efficacy for PA. A case report form will be completed after each interaction for purposes of documenting the intervention. Each ***booster session*** will consist of one full laboratory session with the exercise, behavioral and educational components of the experimental and/or control group interventions. The booster sessions will be performed at the 3 month and 6 month visits, immediately after the completion of all outcome measures. The experimental and control interventions will be delivered by kinesiology trained research specialists and both interventions are scripted to facilitate a systematic delivery.

Summary of Activities								
Testing visits	Visit 1	Visit 2	Week 1-10	Week 11	Week 12-21	Week 22	Week 34	Week 62
Screening	X							
Testing visit #1-5		X		X		X	X	X
Activity monitoring (7 days)		X		X		X	X	X
Structured intervention elements			**Week 1- 10**	**Week 11-21**		**Week 22**	**Week 34**	
Lab-based exercises, with behavioral/ educational program			two visits a week for 8 weeks, then one visit/week for 2 weeks.					
Coaching phone calls (5 minutes)					Total of 8 phone calls during the first 6 months of follow-up.			
Booster session (one full lab-based session)						X*	X*	

Active-Life intervention*.* Key components are described below and in Table 4. The details of the intervention are documented in a manual for the staff to use, session-by-session, making it easy to implement in a systematic manner (Appendix A section 44.1).

Structured exercise training includes two laboratory-based sessions and one home-based session per week for 8 weeks, followed by a 2-week transition to home training that includes one laboratory-based session and two home-based sessions a week. Minimal equipment is required for the FCT (elastic bands, small balls and a chair) and the laboratory and home-based exercises are the same. Each session includes (1) walking, (2) functional circuit training, and (3) stretching. *Structured walking.* Each exercise session starts with 20 minutes of walking. Subjects set goals and establish a walking path with guidance from staff. *Functional Circuit Training* includes 13 structured activities designed to be performed in both the laboratory and home setting. The circuit includes diagonal wall touch, rolling squat, lateral pull down, chair balance, alternating side leg lift, wall push-ups, alternating back leg lifts, arm curls, oblique twist, supported hamstring curl, triceps kickbacks, seated leg extension and lateral (arm) raise. Posters are mounted in the laboratory at each of the 13 stations demonstrating the exercises (at 3 different levels) for that station and the kinesiology specialist guides subjects in the use of good form for each exercise. Subjects spend 60-90 seconds at each station and repeat the circuit 1-2 times during an exercise session. They rest between sets and between circuits until recovered from breathlessness. The intensity of the exercises and the speed of execution is adjusted to attain a rating of perceived exertion equal to somewhat hard to hard at the end of each circuit, or 13 to 15 on the 20 point Borg scale.[123] The circuit has three levels of intensity; subjects progress from one level to the next based on their rating of perceived exertion. *Stretching.* Sessions end with stretching the major muscle groups. *Home training sessions. S*light modifications of the exercises are required for the home training. Subjects are taught how to perform the exercises at home and are given a booklet that demonstrates each exercise. They are also encouraged to use mall walking or a similar strategy if they cannot walk at home because of weather.

Behavioral (Self-efficacy enhancing) and educational components are conducted for 20-30 minutes at each laboratory visit. The intervention is designed to maximize each of the four sources of self-efficacy: mastery, social modeling, social persuasion, and interpretation of physiological and psychological dimensions. Table 4 describes the activities that target each of the four sources of self-efficacy. Appendix A provides an example of two sessions. Space limitations prohibit the inclusion of all sessions.

The program challenges subjects to increase their total PA (combined LPA and MVPA) by at least 60 minutes a day. *Note we focus on LPA, but do not discourage MVPA for those who can tolerate it.* The previously tested self-efficacy intervention is optimized by the addition of self-regulatory strategies to support

mastery. This includes (a) monitoring PA with a pedometer to provide objective day-to-day feedback, and (b) SMART goals and implementation intentions to facilitate accomplishment of PA goals.[79] We refined the PA educational to establish the importance of LPA and the negative effects of too much sedentary behavior. After completion of the structured intervention subjects will receive follow-up with 11 5-minute phone coaching sessions and two booster sessions as scheduled in Figure 3. At this point subjects should have reached the maintenance stage of behavior change, but to confirm this we will take final measurements at 12-months of follow-up.

Table 4. BEHAVIORAL AND EDUCATIONAL COMPONENTS OF ACTIVE-LIFE INTERVENTION

SELF-EFFICACY ENHANCING COMPONENT OF ACTIVE-LIFE INTERVENTION	
Sources of Self-Efficacy	**Activities used to optimize each source of self-efficacy**
Mastery	**Subjects complete detailed exercise logs in the laboratory.** • Research staff graph results and interpret for subjects to demonstrate progress. **Exercise specialists conduct sessions and focus on progress with the following activities**. Even small gains are highlighted. • FCT & walking - gains in performance (level 1, 2 & 3) and the reduced effort required for a given level of training. • Adherence - attendance and performance of FCT & walking, emphasizing small triumphs in overcoming barriers to adherence. • Pedometers – Fitbit pedometers are used to provide objective daily feedback about the volume of walking. Fitbit data are not used to test hypotheses. **Setting Goals:** Staff will assist subjects to establish personal goals for FCT, walking and other physical activities of interest. Staff guide subjects in the development of SMART goals and provide structured feedback weekly. **Implementing Goals**: Implementation intentions strategies – staff will assist subjects with the development of IF ___ THEN ____ statements that support the accomplishment of activity goals. **Staff employ cognitive rehearsal activities to assist recall and retention of gains that have been accomplished**
Social modeling	**Mount large posters on the walls illustrating older people performing exercises.** • Illustrate that exercise and PA are enjoyable. • Make the training sessions fun (music, post photographs of subjects exercising). • Subjects observe their peers exercising.
Social persuasion	**Staff will frame performance feedback appropriately to enhance self-efficacy.** **Subjects participate in a buddy system of 2-3 people who train together.** • Buddies train together, call each other when one does not show up for training, provide assistance and encouragement to each other as it relates to overcoming barriers to exercise and PA
Physiological and psychological feedback system	**Staff teach subjects to understand physiological responses to exercise with an emphasis on elements unique to people with COPD.** • Teach subjects about how the body responds to the stress of exercising and reassure them that their responses are normal. Emphasize that muscle soreness, fatigue and dyspnea are normal responses to exercise training. • Teach subjects to assess and interpret their respiratory symptoms of dyspnea and fatigue
EDUCATIONAL COMPONENTS OF ACTIVE-LIFE INTERVENTION	
PA education: Principles of exercise including individuality, specificity, progression, overload, adaptation, recovery and reversibility. Health benefits of LPA, MVPA and negative health effects of sedentary behavior and bedrest. Strategies for overcoming barriers to PA.	
Relapse Prevention for PA: • Teach subjects to differentiate between lapse, relapse and collapse. Strategies include group activities, role modeling and reflection. • Structured problem solving for overcoming lapses, relapses and collapses in PA behaviors.	
Breathing Problems Action Plan: The nurse teaches subjects to assess the severity of an exacerbation and to modify their exercise accordingly. Structured problem solving includes the use of successful strategies identified by other people with COPD. • Teach subjects how to *modify PA during an exacerbation* of COPD by maintaining frequency, decreasing intensity, increasing rest periods and decreasing the duration of exercise/PA. Teach to avoid bedrest until it is required by symptoms. • Teach subjects how to *re-establish PA after an exacerbation* of COPD by maintaining frequency, gradually increasing intensity and gradually increasing the duration of exercise/PA. Resume PA immediately and gradually, according to ability.	
FOLLOW-UP ACTIVITIES TO SUPPORT LONG-TERM MAINTENANCE	
• Phone coaching, 11 5-minute calls (see figure 3 for schedule) • Booster sessions, 1 at 3 mo. and 1 at 6 mo. follow-up.	

Active Control Group. Chair-HE will be performed 2/week in the laboratory and 1/week at home for 8 weeks

and then 1/week in the laboratory and 2/week at home for weeks 9-10 (transition). This serves as an active treatment to control for the attention that subjects receive with Active-Life. The time spent with subjects in the active control group is the same as the time spent with the experimental group. Chair exercises do not produce changes in strength or aerobic capacity or cause changes in resting heart rate or blood pressure.[124] When we used this same active control for another study of resistance training in COPD, very few subjects recognized it as an active control treatment and no increases in objectively measured PA occurred.[63]

Chair-HE includes stretching of all major joints with an emphasis on arms and shoulders, and massage of muscles that can be reached from the chair (scalp, neck, shoulders, lower back, abdomen and thighs). In addition, fantasy is used during the exercises to enhance enjoyment. For example, the fantasy of conducting an orchestra is used for some of the arm exercises. The chair exercises are based on the video "Armchair Fitness: Gentle Exercise".[125] Each session includes 5 minutes of slow stretching, 20 minutes of faster paced exercises, 5 minutes of slower paced stretches, followed by 5-10 minutes of massage and imagery.

Behavioral. Guided imagery is used during the Chair-HE sessions to promote relaxation.

Health Education. Health education, delivered in the lab setting, is modeled after the patient education program used in two of Dr. Larson's earlier studies.[63,119] Health education classes include topics of interest to people with COPD, including basic lung physiology, pathophysiology of COPD, commonly used medications, breathing techniques, healthy eating and PA, relaxation, travel considerations, and energy conservation. Health education will include one session that reviews of CDC PA guideline, much like the typical pulmonary rehabilitation program. The teaching plan for health education will be implemented during 20 minutes of each laboratory session, just prior to the chair exercises. While the content of this health education is totally different from the education in the experimental group, the subjects in our previous studies reported that it was nonetheless valuable; thus, the risk of disenchantment about group assignment is reduced.

Follow-up phone calls will be implemented with the same frequency as with the experimental group and focus on coaching for adherence to chair exercises and stretching. Booster session will be performed at 3 and 6 months follow-up and will include a full laboratory session with all elements.

Procedures for an intervention sessions (weeks 1 - 10)

1. Subjects arrive in the laboratory and a member of our research team (nurse, respiratory therapist or exercise specialist) measures their blood pressure, heart rate and oxygen saturation (pulse oximetry) and questions them about how they are feeling.
2. Subjects perform 20 minutes of hall walking under the direct supervision of the exercise specialist.
3. They return to the laboratory and are seated for a behavioral intervention session where the nurse or the exercise specialist leads them in a variety of activities to build their confidence in their ability to be physically active and/or delivers educational material.
4. Next subjects perform the exercises appropriate for the group assignment (Active Life group exercises together and Chair HE group exercises together). The two groups are scheduled at different times and do not come in contact with each other. This component is directly supervised by the exercise specialist. We have photos on the wall that illustrate the exercises (lab-bases exercises (photo) uploaded to section 44.1) and the exercise specialist moves around the group guiding people and giving them feedback to make sure that they are performing the exercises correctly using good form. Subjects are told to take their time as they do the exercises to minimize dyspnea.
5. The research team member measures blood pressure, heart rate and oxygen saturation (pulse oximetry) before each subject leaves the laboratory.
6. This sessions takes approximately 2 hours.

Procedures for a phone call (for additional details see coaching phone protocol in section 44.1)

1. The research staff schedule phone calls with subjects. During the phone call the staff member
    a. assesses the extent to which a subject is meeting his/her exercise goals,
    b. problem solves with the subject to help him/her overcome barriers to being active,
    c. provides support and reinforces progress,
    d. works with the subject to re-evaluate and set new goals.
2. The phone call takes approximately 5 minutes.

Procedure for booster sessions

1. Boosters sessions are scheduled concurrently with the testing sessions at weeks 22 and 34. This is to

minimize the number of trips that subjects make to the laboratory.

2. The booster session is an intervention session that is the same as the intervention sessions during weeks 1-10. These sessions are designed to support people in their efforts to be physically active, to help them remember how to do the exercises and to get them re-energized about being physically active.
3. Each booster sessions takes approximately 2 hours. Since the booster will be combined with testing visits the total time will be 4 hours (booster = 2 and testing = 2).

Measures for Aim 1. The primary dependent variables are the time spent in PA and sedentary behavior. ActivPAL data will be used for hypothesis testing and ActiGraph data will be used to describe the intensity of PA. PA will be measured for 7 consecutive days at each measurement.

A substantial body of literature supports the reliability and validity of the ActivPAL.[126,127] The *ActivPAL3 accelerometer* will be used to measure the time spent standing/stepping and sitting/lying. The ActivPAL3 accelerometer is a small (15g) rectangular device (53 x 35 x 7 mm) taped to the anterior aspect of the thigh. The sampling frequency is 10 Hz and the recording interval is 0.1 second. The proprietary software classifies free-living activity into time spent lying/sitting, standing and stepping. ActivPAL is waterproofed by wrapping it in a barrier film that does not have to be removed for bathing. First applied in the laboratory, it is then worn 24 hours a day for a 7-day period to capture each measurement, and then removed in the laboratory. This greatly reduces the loss of data that occurs when subjects wear a monitor during waking hours but forget to put it on when they wake up each morning. In our pilot work we have had no missing ActiPAL data. We will report time spent sitting/lying, time spent standing/stepping (separately and combined) and the number of transitions from sitting to standing per day. Time spent standing and stepping and sitting/lying will be used for hypothesis testing (Aim 1).

Complimentary measures of PA. Both uniaxial and triaxial data from the *ActiGraph GT9X Link accelerometer* (ActiGraph, Pensacola, Florida) will be used to further describe changes in PA. Actigraph data will be used to measure the intensity of PA, specifically the time spent in LPA and MVPA and stepcount. The Actigraph Link accelerometer is a small lightweight device worn at the waist. ActiGraph Link contains a gyroscope, magnetometer and accelerometer. It samples at a rate of 30 Hz, has 4 GB of memory and a 14-day battery life. It measures acceleration in 3 axes and includes an inclinometer to determine the wearer's position. The Link is a newer product, but it builds on an earlier uniaxial accelerometer that is considered to be a reliable and valid measure[128,129] in the rapidly evolving science of measuring PA. The uniaxial accelerometer was used in an NHANES study and the same uniaxial data can be downloaded from the newer Link device for purposes of validation. Subjects will wear the ActiGraph accelerometer during waking hours and we will report time spent in LPA and MVPA using valid cutpoints for elderly people: 100-1951 counts per minute for LPA and ≥ 1952 counts per minute for MVPA. [51,130,131] In addition we will report triaxial data, total vector magnitude counts per day; this captures a wider range of PA than the uniaxial data. There are no uniformly accepted cutpoints for analyzing uniaxial and triaxial accelerometry data. We are using the best information available for older people and will refine our strategy if new information emerges. In addition to the above we will report total steps/day. We will use ActiGraph software to set appropriate parameters for cleaning data, deleting non-wear time and spurious activity counts, determining number of valid days of monitoring and for summarizing results according to industry standards.[132,133]

Table 5. MEASURES

MEASURES	Screen	Base-line	Wk. 2	Wk. 10	Mo. 3, 6	Mo. 12
PRIMARY OUTCOME - PA						
-Time spent in PA and sedentary behavior ActivPAL and ActiGraph monitoring (7 days)		X		X	X	X
HYPOTHESIZED MEDIATORS						
-Barriers Efficacy Scale			X	X	X	X
-Multidimensional Outcome Expectations Scale			X	X	X	X
SECONDARY OUTCOMES - FRAILTY INDICATORS						
-6-Minute walk test		X		X	X	X
-Isometric strength (knee flexors & extensors)		X		X	X	X
-PROMIS Physical Function (CAT)		X		X	X	X
-Short Physical Performance Battery		X		X	X	X
OTHER FACTORS THAT INFLUENCE PA (COVARIATES)						
Symptoms						
Chronic Respiratory Disease Questionnaire -SA		X		X	X	X
PROMIS Fatigue(CAT)		X		X	X	X
Negative Affect						
PROMIS Anxiety (CAT)		X		X	X	X
PROMIS Depression (CAT)		X		X	X	X
Historical PA		X				
Historical PA Questionnaire						
Social Support for PA						
Positive and Negative Social Influences on PA in Older Adults (PNSIPA)		X		X	X	X
Self-Regulation of PA						
PA self-regulation scale (PASR12)		X		X	X	X
Measures used to describe the sample						
-Functional Comorbidity index	X					
-Frequency of acute exacerbations over the past year (**since enrollment)	X			X**		X
-Spirometry	X					X

Measures at week 2 will be taken during the second week of the intervention to give subjects time to establish realistic expectations.

Measures at week 10 will be taken after completing the 10 week intervention, and measures at 3, 6 and 12 months will be taken at 3, 6, and 12 months after completion of the intervention. Computerized Adaptive Testing (CAT), Chronic Respiratory Questionnaire Self-Administered (CRQ-SA).

Measures for Aim 2. Mediator variables include Barriers-Efficacy for PA and Outcome Expectations for PA.

Barriers-Efficacy for PA. Self-efficacy for overcoming barriers to PA will be measured to document subjects' perceived ability to follow through and continue with PA when faced with common barriers to exercise (*Barriers Efficacy Scale: COPD version*). This is a form of self-regulatory efficacy. The Barriers Efficacy Scale: COPD, which we used in one of our earlier studies of COPD,[63] was modified from the well-established barriers efficacy scale published by McAuley.[134,135] It includes 14 items, 11 original and 3 specific to people with COPD. The reliability and validity of both the original scale and the COPD version are supported.[71,114,134-137]

Outcome Expectations for PA. The *Multidimensional Outcome Expectations for Exercise Scale (MOEES)* will be used to measure outcome expectations for PA.[138] The MOEES is constructed of 15 items organized into three subscales (physical, self-evaluative and social). Using data from a large group of older subjects, construct validity was supported by factor analysis and significant associations in the predicted direction for PA and self-efficacy.[138] Internal consistency reliability was demonstrated for each scale with Crobach's alphas from 0.81 to 0.84.[138]

Measures for Secondary Aim. Physical activity is an important frailty indicator. In addition to PA we will measure strength, endurance, physical function, balance and walking speed as indicators of frailty.

Strength and endurance will be measured with two widely used field tests of physical performance: isometric strength and the six-minute walk. All tests will be administered using standardized instruction.

Isometric strength of the knee extensors and flexors will be measured with a hand-held dynamometer (Lafayette Manual Muscle Testing System, Model 01165). The system includes an adjustable strap for stabilization of the limb during testing. Measures will be taken with the leg flexed at 90^0, with the subject seated for knee extension and standing for knee flexion. This device uses precise load cell technology for measuring peak force within a 0-300 lb. range with 1% accuracy. Standard testing procedures will be followed, whereby the tester meets the effort of the participant during a 4-6 second maximal voluntary contraction. This is a "make" test, not a "break" test (i.e., there is no attempt to overcome or break the subject's resistance). Measures taken with hand-held dynamometers are highly reliable and appropriate for measuring change over time.[139-141] Because this device is portable, training and testing subjects in community settings is possible.

Six-minute walk test (6MWT) will be conducted according to the American Thoracic Society guidelines.[142] Support for validity and reliability of the 6MWT is well established.[143]

Physical function will be measured with the PROMIS Physical Function scale with computerized adaptive testing (CAT). PROMIS Physical Function CAT includes a bank of 121 items reflecting perceived capability to perform physical activities (upper and lower extremities, central core and instrumental activities of daily living). Internal consistency is high (0.99) and there is support for its validity when used in people with COPD. [144] The computerized administration was equivalent to paper and the pencil method in people with COPD. [145,146]

Balance and walking speed will be measured with the *Short Physical Performance Battery (SPPB)*.[147] It includes balance tests (side-by-side stand, semi-tandem stand, tandem stand), gait speed (timed 4 meter walk) and chair stand (time required to perform 5 rises). Performance on each test is rated and the composite score ranges from 0-12. The SPPB is a valid and reliable test[147] and is sensitive to change.[148]

Other variables that influence PA for people with COPD are described in the scientific premise and measures are described below. These variables are important given their potential to influence subjects' response to the intervention. They will be used as covariates as appropriate. Three PROMIS instruments will be employed (fatigue, anxiety and depression) with computerized adaptive testing to reduce subject burden. All three have high internal consistency (0.97 – 0.99), evidence to support their validity in people with COPD[144] and have demonstrated equivalent scores for computerized forms of administration and paper and pencil form in people with COPD. [145,146]

Symptoms of dyspnea and fatigue will be measured with the Chronic Respiratory Disease Questionnaire Self-Administered (CRQ-SA) [149] and the PROMIS Fatigue CAT. The CRQ-SA reflects the intensity of dyspnea experienced with daily activities and is widely used in research. There is strong evidence of its reliability and validity.[149,150] The PROMIS Fatigue CAT is generated from a bank of 95 items and reflects fatigue from mild feelings of tiredness to a sense of exhaustion.

Negative Affective will be measured with the PROMIS Anxiety and PROMIS Depression scales using CAT. The PROMIS Anxiety CAT and PROMIS Depression CAT are generated from item-banks, with 29 and 28 items respectively. PROMIS Anxiety reflects a range from perceived fear, hyperarousal to somatic symptoms of arousal. PROMIS Depression reflects a range from perceived negative moods to a decrease in positive affect and engagement; it does not include somatic symptoms.

Historical PA will be measured with the Historical PA questionnaire.[151] Subjects report their volume of activity at three different ages: 15 years, 30 years, and 50 years of age. Test-retest reliability of this instrument is strong.[152]

Social Support for PA will be measured with the Positive and Negative Social Influences on PA in Older Adults (PNSIPA).[153] The PNSIPA measures the frequency of social influences from the subject's social network that encourage or discourage PA. Reliability and validity of this instrument are well established.[153]

Self-Regulation for PA will be measured with the Self-Regulation for PA Scale to quantify the uptake of self-regulatory strategies from the Active-Life intervention. It measures use of self-regulation strategies (goal setting, self-monitoring, etc.) to support PA adoption and adherence.[154-156] The Self-Regulation for PA scale has strong reliability and validity.[154-156]

Number of COPD exacerbations in the last year or since enrollment will be obtained by interview using the definition that was described earlier. Medical records will be checked as needed to clarify self-reported data.

Measures used to describe the sample. Demographic and clinical history will be collected by interview. *Comorbidity* will be assessed with the Functional Comorbidity Index (FCI),[157] an 18-item interviewer administered questionnaire developed to assess comorbidities that predict physical function. The FCI is a

stronger predictor of physical function than the Charlson comorbidity index.[158] *Disease Severity.* Spirometry[159] will be measured using a portable spirometer that meets ATS standards (ML3500S MicroLab Spirometer; Micro Direct, Inc., Lewiston, ME). Research staff will be trained to perform these measures on site, using ATS guidelines for spirometry. This eliminates the need to travel to Ann Arbor for testing.

Sample. A total of 128 subjects will be studied, 64 in each of two groups. We will recruit up to 250 subjects to allow for attrition.

Inclusion criteria.

- Subjects must have moderate to very severe airflow limitation. The forced expiratory volume in 1 second (FEV1) compared to predicted (% predicted)must be FEV1 <80% predicted according to GOLD standards (moderate, 50%, ≤ FEV1 < 80% predicted; Severe 30% ≤ FEV1 < 50%; very severe, FEV1 < 30% predicted).[160]
- Subjects must be ≥ 50 years of age,
- COPD must be their major pulmonary problem,
- can have no other major health problems that limit PA and/or walking,
- must be clinically stable at the time of enrollment,
- must be sedentary with less than 30 minutes of moderate PA 5 days a week,
- must provide written medical clearance with permission to participate in the research.

Exclusion criteria.

- People will be excluded if they have participated in a structured exercise program or pulmonary rehabilitation within the last year.
- Major health problem that limits PA
- Will be excluded if unable to meet all the above inclusion criteria.

To insure a similar severity of disease and gender mix in each group, subjects will be randomly assigned to groups that are stratified according to gender and severity of airflow obstruction (i.e., stratified randomization). Screening will include pulmonary function tests, brief history and physical exam, 6-minute walk test and permission of their physician.

Subject recruitment is one of the most challenging components of this research. We have been successful in the past and we build on this experience by establishing a multifaceted and robust plan for recruitment. Subjects will be recruited from the following sources, see letters of support.

Table 6. Recruitment location and plan	**Size of potential subject pool**
UM Health System. We will screen medical records and mail recruitment letters to potentially qualified people. For those who respond we will conduct an initial phone screening to determine preliminary eligibility, followed by in-person screening to determine final eligibility.	1800 patients with COPD documented by pulmonary function tests
Clinical Trial Prospects (CTP) opt-in data base. A direct mail campaign will be used to compliment regional recruitment from pulmonary rehabilitation programs. CTP will mail recruitment letters to the people in their database with COPD. Screening will occur through an interactive voice response or interactive web response (respondent's choice). Our research staff will follow up with in-person screening as appropriate. We piloted the CTP recruitment strategy and with a single mailing received 31 responses from qualified people.	People with COPD in the CTP database within 25 mile radius: 2,644 Flint, MI

Recruitment from CTP databases will yield people with more moderate forms of the COPD while recruitment from Flint area will help with racial and ethnic diversity in subject recruitment. Both are required to support generalizability of results to the broader population of people with COPD.

Attrition. We expect to retain 70% of subjects at the end of the intervention. Our subjects are older adults with chronic disease and in our experience the most common reasons for attrition will be serious acute exacerbations and other health problems that occur over the 12 months of follow-up.

Power Analysis. The power and sample size were calculated based on the inference of mediators. We adopted the sample size calculation proposed by Vittinghoff[161] according to the insight that, under the condition that the intervention and the mediator were correlated, testing the existence of the mediator was equivalent to testing the independent effect of the mediator. The formula of sample size calculation for the linear model was $n = \frac{(Z_\alpha + Z_\beta)^2 \sigma_e^2}{(\gamma\sigma)^2(1-\rho^2)}$, where Z_α and Z_β were the quantiles of the standard Gaussian distribution corresponding to the type I and Type II error rates, σ_e^2 was the residual variance, γ was the effect size of the mediator, σ was the

standard deviation of the mediator, and ρ was the correlation between the intervention and the mediator. We set type I error rate α at 0.05, type II error rate β at 0.2 (power = 0.8), the residual variance at 1, mediator variance at 1, and correlations between intervention and mediator range from 0.1 to 0.5. The effect size γ was determined using Cohen's definition of effect size from small (0.14) to medium (0.39)[162]. Evaluating our previous study, we expected to detect small to medium effect size ($\gamma = 0.26$). Therefore, when the correlation between the intervention variable and mediator was 0.3, we required 128 patients to reach 80% power. Because our past experience indicated 30% attrition, we proposed to enroll 183 patients at baseline to provide enough power to infer intermediate variables.

Data Analysis Plan. Data on all patients who are randomly assigned to Active-Life intervention group and active control group will be analyzed on an intention-to-treat basis. Deviations from randomized allocation will be reported. Summary statistics will be used to characterize the sample distribution at each time period. Proper transformations will be investigated and taken if the sample distributions violate the normality assumption. For **Aim 1** of determining the Active-Life intervention effect on PA and sedentary behavior at 10 weeks, and 3, 6, and 12 months, Analysis of Covariance (ANCOVA) will be used at each time period to adjust for the baseline PA measurements and other baseline covariates.[163] The dependent variable for the ANCOVA is PA and sedentary behavior described in the Research Design section. The adjusting covariates include age, gender, COPD severity, and variables listed in the "other factors that influence PA" section. The Active-Life intervention is claimed to be effective if the marginal *p*-value of the intervention variable is < 0.05. For **Aim 2** of identifying intermediate variables (or mediators) between the Active-Life intervention and PA, we will calculate the average causal mediation effects (ACME).[164,165] The potential mediators include variables barriers-efficacy for PA, and outcome expectations for PA. The significant non-zero causal mediation effect indicates that the intervention on the PA goes through the mediator. The analysis will be carried out using the R mediation package.[164] Since we anticipate having missing values at 10 weeks, we plan to deal with them via standard multiple imputations. More specifically, we will run mediation analysis on multiple imputed data sets. A confidence interval is used to summarize the ACME. Finally, since the mediation analysis assumes the sequential ignorability assumption[161,166] we will evaluate this assumption by conducting sensitivity analysis.
Secondary Aim. To evaluate the short term and sustained effects of the Active-Life intervention, the linear mixed model (LMM) with a random intercept will be used to model the effect of the intervention. The random intercept in the LMM takes into account that the frailty indicators measured at baseline, 10 weeks; and 3, 6, and 12 months are correlated within the same individual. A number of response variables characterizing the effects of the intervention are considered, based on strength, endurance, physical function, balance, and walking speed. In addition to the binary indicator variable representing intervention or control, the demographic variables such as age, gender, and race will be added as covariates in the LMM to improve the precision of estimation. The intervention is claimed to be statistically significant if the p-value of the intervention variable is < 0.05.

Strategies to address potential limitations.

Recruitment. We have used our state wide connections to establish a robust plan for subject recruitment. Travel distance is an important predictor of program completion,[63] so we will establish regional data collection sites in Grand Blanc, and Flint in addition to Ann Arbor. We require only a small space for training and all equipment is portable so all interventions and data collection can be performed on site. This will reduce the need for subjects to travel long distances for testing.

Retention activities. (a) At enrollment all subjects will be told that if they wish, they can participate in the alternative intervention after completing their assigned intervention and follow-up. This is to minimize subjects' disenchantment based on group assignment and to minimize attrition. We have taken this approach with two previous intervention studies and it dispels subjects' concerns about random assignment to groups. We will not conduct any data collection during the alternative intervention. In our experience a few people will take us up on this offer. (b) We will provide financial incentives for each data collection visit ($25) and for each 7-days of PA data ($50), but not for intervention visits because a financial incentive for training would limit generalizability of results. (c) To minimize the loss at follow-up, we will tell subjects that it is just as important that we study those who stop being active as those who continue with their PA.

Fidelity of the intervention. (a) All elements of the intervention and control group activities are scripted to facilitate delivery in a systematic manner. (b) We will use checklists to regularly monitor fidelity of intervention sessions and retrained staff as necessary to maintain quality. (c) We will regularly review subjects' records of laboratory activities, home-based activities, goal setting and case report forms for follow-up phone coaching. (d) We will examine uptake of the intervention by summarizing data from the self-regulation of PA scale.

Future Directions. This research advances the field by establishing a method of increasing PA that is potentially sustainable on a long-term basis. If successful next steps will be to (a) examine multiple health outcomes and (b) modify the intervention to target people with other chronic diseases, such as heart failure.

Timetable. Subject recruitment and training will be done in groups of 10. We will train new staff and recruit and enroll 40 subjects in year 1, enroll and follow-up 50 subjects/year in years 2 & 3, enroll and follow-up 43 subjects in year 4, and finish follow-up data collection, finalize data analysis and publish manuscripts in year 5.

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