Increasing Physical Activity in COPD Through Rhythmically Enhanced Music

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Please note, COVID patients were included as part of a supplement and were part of the IRB submission. References to the COVID portion are grayed out and not reported.

Introduction. Chronic obstructive pulmonary disease (COPD) is characterized by airway obstruction and limited exercise tolerance.[1,2] In COPD, hospital-based pulmonary rehabilitation can improve symptoms, functional status, and quality of life.[3-5] Hospital-based rehabilitation can also decrease unscheduled physician visits, emergency room visits, hospitalizations,[6] and possibly, mortality.[7]

Despite well documented efficacy, hospital-based pulmonary rehab remains largely underused[8,9] for various reasons: lack of access to programs, need for qualified health care professionals and equipment that demand significant costs, and limited reimbursement.[8,10] Up to 50% of eligible patients cannot participate because of transportation difficulties.[10] The success of outpatient, hospital-based programs is further hampered by suboptimal compliance with regular visits to clinics.[11] Recognition of these barriers has triggered a growing interest in home-based rehab programs.[11-15] Despite encouraging results,[11-13,15-17] however, patients enrolled in home-based programs may[15] or may not[16] benefit from training to the same degree as patients enrolled in hospital-based programs. This finding is primarily due to suboptimal exercise intensity as patients often slow their walking pace to avoid dyspnea and exercise-induced fatigue.[18] Such observations underscore the need to develop an innovative home-based program that decreases exercise-induced dyspnea and fatigue while ensuring sufficient exercise intensity to produce physiologic benefit. Recent data[19,20] suggest that rhythmically enhanced music may constitute such an innovative strategy.

Music can elicit a positive emotional reaction that lessens the fear[21] and intensity of unpleasant symptoms such as dyspnea and exercise-induced fatigue.[22,23] These data raise the possibility that diminishing the fear of dyspnea and fatigue may allow patients to tolerate more challenging physical activity and obtain a greater benefit from rehabilitation. Music also can induce entrainment of motor responses such as walking[24] (cuing gait to music).[25] Sensorimotor coupling can be optimized by embedding sonic enhancements, known as rhythmic auditory stimulation (RAS)[26] in an instrumental track[27] **(Fig. 1)**. Using RAS-enhanced music, we have been able to lengthen the distance walked by patients with COPD and peripheral artery disease (PAD).[19]

In this application, we plan to capitalize on both the sensorimotor coupling of gait with the RAS-enhanced music and the mitigating effect of music over exercise-induced dyspnea and fatigue. We reason that patients with COPD enrolled in our home exercise program augmented by patient-tailored, RAS-enhanced music will experience less dyspnea and fatigue allowing for an increase in exercise intensity and duration. Specifically, we propose to compare the efficacy of a 12-week, home-based exercise program augmented by patient-tailored, RAS-enhanced music to a 12-week traditional home-based exercise program in patients with COPD.

In May 2020 we submitted a VA Merit Review project, “Increasing Physical Activity in Patients Recovering from Prolonged Hospitalization for COVID-19 Through a Home-based, Exercise Program Utilizing Rhythmically Enhanced Music”. This study was not funded as a separate project but VA Merit Review suggested and funded an ‘Administrative Project Modification’ to this parent COPD study in which we will include patients recovering from prolonged COVID19 hospitalization. Specifically, we will use our novel RAS-enhanced music exercise program developed for the parent grant in patients recovering from COVID19. The main goal of the modified proposal for COVID19 patients is to compare the efficacy of a 12-week, home-based exercise program augmented by RAS-therapeutic music and strength training to 12-weeks usual care and strength training in patients recovering from COVID 19.

Due to the overwhelming burden on the healthcare system and high transmissibility of the virus, patients who may have typically been treated in a hospital were followed at home until absolutely necessary. These patients are suffering from longterm adverse consequences of COVID-19 and would greatly benefit from a rehabilitative intervention. Therefore, we are broadening our inclusion criteria to include any patient who visited the ED for COVID or was hospitalized for any length of time due to COVID symptoms (both typically for hypoxia and shortness of breath).

A1. Study Objectives/Hypotheses.

COPD Patients

Objective 1. *To determine the efficacy of a 12-week, home-based, patient-tailored, RAS-enhanced music exercise program in improving functional and clinical parameters in COPD.*

Hypotheses**:** Compared to patients randomized to a home-based, exercise program without music (control group), patients randomized to a home-based, exercise program augmented with RAS-enhanced music (experimental group; hereafter referred to as RAS-music group) will demonstrate greater:
1a-increase in 6-minute walking distance (primary hypothesis);
1b-greater increases in health-related quality of life (QoL).

Objective 2. *To determine whether at 12 weeks the RAS-music group will accumulate a greater volume of daily physical activity than the control group.*

Hypothesis: The RAS-music group will accumulate a greater volume of daily physical activity than the control group. This will be demonstrated by greater physical activity at 12 weeks (actigraphy).

Objective 3. *To determine whether, 24-weeks after randomization, gains in 6-minute walk distance and perceived functional improvements will be sustained to a greater extent in the RAS-music group than in the control group.*

Hypothesis: The RAS-music group will maintain improvements in measured and perceived function at 24 weeks to a greater extent than the control group.

Objective 4. *To assess impact of physiological and psychological phenotype and clinical factors on responsiveness to rehabilitation achieved with and without concurrent use of RAS-music (Exploratory Objective).*

Physiological factors of interest include: systemic inflammation, quadriceps strength, recruitment and fatigue, quadriceps function and dimension after rehabilitation. Psychological factors include: self-efficacy, anxiety, depression. Clinical factors include: adherence to the 12-week program, adherence to follow-up and number and severity of exacerbations.

COVID Patients

Objective 1. To determine the efficacy of a 12-week, home-based, patient-tailored, RAS-enhanced music exercise program and strength training in improving functional and clinical parameters in patients recovering from COVID19with a history of an emergency room and/or hospital admission..

Hypotheses**:** Compared to patients randomized to a home-based, exercise program without music (control group), patients randomized to a home-based, exercise program augmented with RAS-therapeutic enhanced music (experimental group; hereafter referred to as RAST-music group) will demonstrate greater:

1a- increase in 6-minute walking distance (primary hypothesis);
1b- greater increases in rectus femoris dimensions (ultrasound)
1c- greater quadriceps force and endurance (magnetic femoral nerve stimulation; isokinetic strength testing)
1d- increased sense of emotional investment related to the music experience
Objective 2. To determine whether at 12 weeks the RAS-music group will accumulate a greater volume of daily physical activity than the control group. (same as COPD group)

Hypothesis: The RAST-music group will accumulate a greater volume of daily physical activity than the control group. This will be demonstrated by greater physical activity at 12 weeks (actigraphy).

Objective 3. To determine whether 24-weeks after randomization, gains in 6-minute walk distance and perceived functional improvements will be sustained to a greater extent in the RAST-music group

than in the control group (same as COPD group) and whether there is any change in 6-minute walk distance and perceived functional improvements in the control group.

Hypothesis: The RAST-music group will maintain improvements in measured and perceived function at 24 weeks to a greater extent than the control group. (same as COPD)

Objective 4. *To assess impact of physiological and psychological phenotype and clinical factors including those related to music preference and history on responsiveness to rehabilitation achieved with and without concurrent use of RAST music programs (Exploratory objective).*

Specific physiological, psychological and clinical factors will include, quadriceps function and dimension after rehabilitation, self-efficacy, anxiety, depression, time of mechanical ventilation, *music preference and history* , and adherence to the program.

A.2. Impact: Using RAS-enhanced music to cue walking cadence and decrease exercise-induced dyspnea/fatigue has the potential to transform home-based pulmonary rehab. Altering the beat and tempo of music provides stimuli to speed or slow walking cadences that are imperceptible to the patient. If successful, RAS/RAST-guided exercise programs will have far reaching implications not only for COPD and COVID 19, but for rehab in other chronic diseases including interstitial lung disease, cystic fibrosis, pulmonary hypertension, cardiomyopathies and peripheral arterial disease.[19,20] If, as expected, our RAST music guided exercise program is successful, the result will also begin to finally address a critical knowledge gap on instituting music enhanced physical rehabilitation for patients recovering from COVID 19 symptoms.

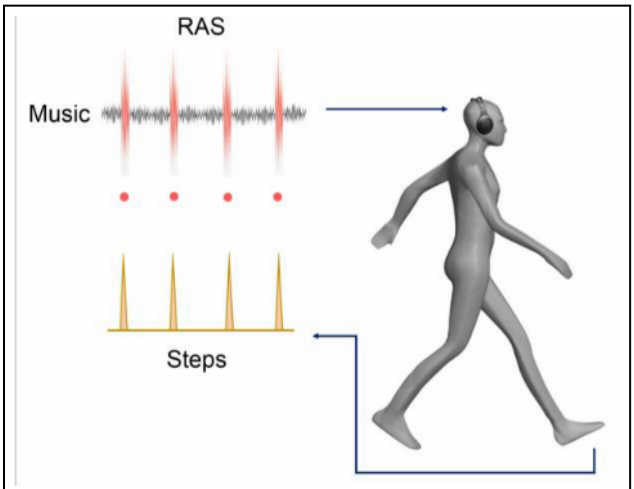


Fig 1. Rhythmic auditory stimulation (RAS) is achieved by embedding sonic enhancements in an instrumental track at fixed intervals, so that patients synchronize movements to the sonic enhancements.

A.3 Current Status of Research in this Area

A.3.1 Exercise Limitation in COPD. In patients with COPD, abnormalities in ventilatory, cardiovascular, locomotor, and neurosensory systems contribute to exercise limitation.[28] As COPD progresses, ventilatory and mechanical limitations to exercise become more prominent.[28,29] The following sections are focused overviews of current knowledge on the impact of these factors on exercise capacity in COPD.

A.3.1.1 Exercise Limitation in COPD: Dynamic Hyperinflation and Respiratory Muscles. During whole body exercise, most patients with COPD experience an increase in end-expiratory lung volume (EELV).[4,30,31] This increase results from expiratory flow limitation[32] and tachypnea.[31] The result is a progressive increase in end-inspiratory lung volume with an attendant decrease in inspiratory reserve volume (IRV).[30,33] As we[30] and others have demonstrated,[33] critical decreases in IRV elicit unsustainable dyspnea, and patients stop exercising. Unsustainable dyspnea occurs because the critical decrease in IRV is accompanied by progressive neuromechanical uncoupling between respiratory muscle effort and size of tidal volume.[29]

A.3.1.2. Exercise Limitation in COPD: Limb Muscles. Reduced muscle mass (sarcopenia) is a major systemic manifestation of COPD, and is present in up to one-third of patients.[32,34] Sarcopenia is associated with muscle weakness,[35] decreased exercise tolerance,[36] worse quality of life[36] and decreased survival.[34] Lower extremity sarcopenia is independent of body mass index (BMI),[37] highlighting the importance of direct assessment of muscle dimensions through imaging techniques such as ultrasonography, as now planned.[38,39] Additional factors contributing to decreased exercise tolerance include decrease in fatigue-resistant type 1 muscle fibers, increase in type 2 fatigue-sensitive fibers, decrease in oxidative enzymes and increase in glycolytic enzymes (quadriceps).[37] Presently, exercise training is the only strategy that can improve these structural and metabolic abnormalities in most patients with COPD.[28,37,40]

We propose to collect baseline and follow-up data on rectus femoris size (ultrasound) reasoning that these data will shed light into the impact of muscle size and function on the response to our rehabilitation program. These data will be used also to explore whether there are specific subgroups of patients who – in addition to RAS/RAST-enhanced exercise-training – could benefit from specific ancillary interventions (see sections **C.4. Alternative Outcomes** and **C6. Future Directions**).[41]

A.3.2. Exercise-training. Exercise-training is a critical intervention in the pulmonary rehab of patients with COPD[42] that can produce positive clinical outcomes.[3,4,6,7,9,43]

A.3.2.1 Exercise-Training: Impact of Locomotor Muscle Response. To obtain physiological training adaptations in a skeletal muscle, the level of load during training must be sufficient to stress the muscle and cause contractile fatigue *(muscle overload)*.[44,45] In a study by Burtin el al,[44] 29 of 46 patients with COPD developed quadriceps fatigue during a scheduled rehab visit; after 3 months of training, fatiguers achieved greater training in terms of exercise capacity and health-related quality of life than non-fatiguers. Similar results were reported by Mador et al.[45]

In the investigations of Burtin et al[44] and Mador et al,[45] quadriceps fatigue was objectively quantified by recording decreases in force of knee extension elicited by single magnetic stimulations of the femoral nerve (quadriceps twitch or Quad-Tw)**(Fig. 2)**. We have extensively used this state-of-the-art technique to evaluate strength and fatigue in healthy volunteers, patients with COPD and mechanically ventilated patients.[131]

We will collect data on quadriceps fatigability at the end of training (Quad-Tw). Specifically, we will determine whether randomization into RAS-music will increase the likelihood of quadriceps fatigue and whether quadriceps fatigue contributes to the beneficial effects of the home-based, RAS-music exercise program. These data will be used also to explore whether there are specific subgroups of patients who – in addition to RAS-enhanced exercise-training – could benefit from specific ancillary interventions (see sections **C.4. Alternative Outcomes** and **C6. Future Directions**).[41]

A.3.2.2. Exercise-Training: Hospital-Based vs. Home-Based Programs. Hospital-based pulmonary rehabilitation can produce favorable structural adaptations in the locomotor muscles and improve the clinical status of patients with COPD.[3,4,6,9] Unfortunately, less than 5% of patients who would benefit from rehab are enrolled in such a program.[46,47] Limited access of programs,[8,10] suboptimal compliance[11] and transportation difficulties[10,48] are the most common obstacles for uptake and completion of hospital programs. In addition, the gains achieved during hospital-based programs diminish progressively over time if regular physical activity is abandoned.[49] Recognition of these drawbacks has triggered interest in home rehab programs.[11-15] McGavin et al[50] were the first to report that unsupervised exercise at home (stair climbing), could reduce dyspnea and improve exercise capacity in 12 patients with COPD. Similar results were later reported by Puente-Maestu et al,[16] Strijbos et al,[15] Wedzicha et al[12] and Hernandez et al.[13] These investigations, however, have methodological limitations that hamper the generalizability of the results. In Puente-Maestu et al,[16] Wedzicha et al[12] and Hernandez et al.[13] patients received no external encouragement during exercise. Strijbos et al[15] and Wedzicha et al[12] utilized physiotherapists to supervise home-exercise training – a prohibitive resource-intensive strategy for most health care systems. As for the study of Hernandez et al,[13] the training prescription was nebulous and sample size small (20 patients in intervention group and 17 in control group completed the study). This factor raises the spectrum of Type II error. All these limitations will be overcome in the current investigation.

In a departure from previous strategies, Liu et al[11] developed a home-based program where 24 patients

with
COPD were instructed to walk keeping pace with the tempo of music loaded on a cell phone. Tempo was adjusted to coincide with the necessary walking speed for the patients' exercise training (i.e., 80% of the patient's maximal capacity). To keep the exercise target at 80% of maximal capacity the music's tempo was readjusted every four weeks during the first three months of the study (exercise training period). In the following 9 months no additional adjustments were made yet, patients were encouraged to continue exercising (self-management period). A second group of 24 patients did not receive music feedback and served as control. At the conclusion of the study, patients in the cell phone group experienced an improvement in the incremental shuttle walk test (both distance and duration) and quality of life while experiencing fewer acute exacerbations and hospitalizations than the control group.
As recognized by the investigators themselves, this small pilot study requires validation.[11] In addition, patients had no choice in selecting the music used during exercise and over the course of the trial – i.e., music never changed. That is, contrary to what we propose in our current study (see below), Liu et al[11] did not take full advantage of the capacity of music to decrease dyspnea and leg fatigue and to induce entrainment of gait.
A.3.3. Music and Exercise. Music can improve affect,[21] lessen unpleasant symptoms such as fatigue[51] and dyspnea,[22,23] and it can modulate the perceptions and ergonomics associated with physical activity.[20]
A.3.3.1. Music and Exercise: Dyspnea & Exercise-Associated Fatigue. In healthy volunteers, listening to preferred music triggers endogenous dopamine release in the caudate nucleus and the nucleus accumbens.[52] The first nucleus, part of the dorsal striatum, is involved in the *anticipatory phase* of a rewarding experience.[53] The second nucleus, part of the ventral striatum, is involved in the *consummatory phase* of a rewarding experience. This *consummatory phase* is driven by striatal coactivaton of the opioid and dopaminergic systems.[53] This striatal coativation creates a sense of pleasure and reduces pain.[54] In healthy volunteers exposed to noxious thermal stimuli, music personally selected has greater analgesic effects than no-music conditions.[55] Music-associated reduction of pain has also been reported in patients requiring physical therapy following trauma[56] or orthopedic surgery.[57]

Music-associated release of dopamine in the striatum can also enhance mood[54] and produce a sense of empowerment.[23] In patients with cancer, music interventions reduce anxiety, depression and fatigue.[51] Again, these effects are more pronounced when the patient's music preference is taken into account.[51]
The complex effects of music on the striatum are likely responsible for the reduction of ex ercised-induced dyspnea and leg fatigue in COPD (*see preliminary results*).[21-23,58] These observations raise the possibility that deconditioning patients with COPD from the unpleasant sensations of exercise-induced dyspnea and leg fatigue with self-selected music could allow them to tolerate more challenging physical activity and, thus, obtain a greater benefit from pulmonary rehab.This possibility will be tested in the experiments describe in the current proposal.
A.3.3.2 Music and Exercise: Entrainment of Gait. The ability of music to evoke a physical response is a human universal phenomenon occurring from young children to elderly patients with Alzheimer's disease.[27] A host of motor–behavioral responses such as walking, cycling, eating, and drinking can be influenced by music.[27] For example, a change in the tempo of background music in a supermarket from 70 bpm to 130 bpm can increase the pace of shopper traffic.[27] The effects of music are often implicit (individuals are not aware of being influenced by music).[59] The motor-behavioral responses to music likely result from the interaction of two mechanism: enhanced arousal and entrainment.[27] That is, music enhances arousal with resultant priming of motor behaviors while concurrently inducing an automatic synchronization between internal bodily "oscillators" and external rhythms.[27] These internal bodily "oscillators" result from the natural periodicity of neuronal activity.[27] Converging neurophysiological evidence suggests that brain regions underpinning movement production, including the cerebellum, basal ganglia, and supplementary motor areas, are also deployed during rhythm perception -- neural response to auditory rhythm denotes a preparation for movement.[27,59] Auditory stimuli can also modulate movement by altering output of the "central pattern

generators" in the spinal cord. This redundancy in neural pathways explains why period shifts in music that are not consciously perceived as such can still induce entrainment of motor responses, such as finger tapping, in patients with cerebellar lesions.[59]

Entrainment of motor responses to music can be optimized by embedding rhythmic sonic enhancements (also known as rhythmic auditory stimulation or RAS) in an instrumental track **(Fig 1)**.[20,26] For example, in Parkinson's disease RAS-enhanced music leads to significant improvements in gait velocity and stride length. Similar results have also been reported in patients with stroke and traumatic brain injury[59] and, relevant to the current proposal, in patients with COPD[58] *(please see our preliminary data,* ***Section B.6.1.****)*.

The potential benefits of personalized RAS-enhanced music in optimizing entrainment of motor responses to music has been explored in the small feasibility study by Ho et al.[58] RAS-enhanced music increased the distance walked during an incremental shuttle walking test in patients with COPD. Similarly, in a pilot study, cardiac rehabilitation patients randomized to RAS-enhanced music achieved nearly twice the volume of weekly physical activity than standard music.[20]

Taking advantage of the inherent effects of music on gait characteristics and on exercise-induced dyspnea and effort, we expect to demonstrate, for the first time and with sufficent power, that our novel home-based, patient-tailored, RAS-enhanced music exercise program will produce greater improvements in functional and clinical parameters and it will ensure greater volumes of physical activity than a home-based program with no music. These exciting possibilities will be investigated in *Objective #1* and *Objective #2* of the proposed study.

A.3.3.3. Music and Exercise: Maintenance of Pulmonary Rehabilitation Gains. Maintaining exercise benefits following hospital-based pulmonary rehab programs is challenging.[60,61] Accordingly, investigators have assessed the possibility to maintain gains obtained with hospital-based pulmonary rehab through adherence- interventions programs with weekly phone calls alone[62] or weekly phone calls plus monthly, hospital-based, exercise visits.[49] Unfortunately, weekly phone calls alone are insufficient to maintain rehab gains.[62] Weekly phone calls plus hospital-based monthly exercise visits[49] are effective yet, they are marred with all drawbacks of hospital-based programs discussed above.

In contrast to the previous studies, Strijbos et al[15] were successful in maintaining (and indeed improving) pulmonary rehab gains following 12 weeks of home-care rehabilitation. The investigators speculate that patients had become accustomed to exercise in their own domiciliary environment. This made it easier for them to continue exercising at home after the initial 12-weeks of training were over. A similar result was recently reported in the small proof-of-principle study of Ho et al.[58]

The observations of Strijbos et al[15] and Ho et al.[58] combined with our success in increasing exercise performance with RAS-enhanced music *(see preliminary results,* ***Section B.6.1.****)* lay the scientific foundation of the proposed experiments in our *Objective #3*. Specifically, these observations raise the possibility that combining RAS-music and home-based exercise training will result in greater long-term maintenance of rehabilitation gains than exercise-training alone.

A.3.4. Potential Confounders. Potential confounders to any pulmonary rehabilitation study include the patients' *physiological and psychological phenotype and clinical factors*.

A.3.4.1. Potential Confounders: Physiological Phenotype. Decreased exercise tolerance with attendant difficulty in achieving sufficient intensity of exercise during training hinders the effectiveness of rehab. [63] In addition to severity of lung disease, independent predictors of decrease exercise tolerance include quadriceps dimension, recruitment and strength, systemic inflammation (hsCRP and IL-6)[64] *(see work accomplished)*.

A.3.4.2. Potential Confounders: Psychological Phenotype. Depression,[49,60,65] anxiety[49,60,65] and overall sense of fatigue[62,66] can limit the effectiveness of pulmonary rehab as these factors may cause insufficient adherence to rehabilitation programs.

A.3.4.3 Potential Confounders: Clinical Factors. Approximately 15% of patients drop out from pulmonary rehab due to clinical factors such as COPD exacerbations,[67] cardiovascular disease (myocardial infarction, cerebrovascular accidents), or cancer.[68] Because of this, in the proposed investigation, we will assess the influence of the physiological and psychological phenotype and clinical factors on the effectives of RAS- enhanced and non RAS-enhanced home-based

rehabilitation *(Objective #4)*.

A.4. Significance and Relevance to the VA.

COPD is the third leading cause of death in the US[69]and the sixth most common chronic condition among Veterans.[70] Already in 2004, the Veterans Healthcare Administration spent annually an estimated $5.5 billion to care for the nearly one million Veterans with COPD.[71] Veterans with COPD report that their clinical condition profoundly impairs quality of life as it limits their ability to work, to carry out household chores, to maintain physical exertion and to engage in social activities.[71] In addition, these veterans have higher rates of all-cause and respiratory-related health care utilization than those without COPD.[72] Hospital-based pulmonary rehab can decrease the need for inpatient and outpatient medical care in patients with COPD[3,4,6] and can improve exercise capacity and health-related quality of life.[3,4] Unfortunately, few patients are referred to hospital-based programs or agree to attend them.[73,74] Moreover, the few who attend these programs experience a progressive loss of benefits gained after their conclusion.[49] We reason that the many limitations of hospital-based programs can be overcome by implementing our proposed home-based exercise program augmented by patient-tailored, RAS-enhanced music. Combining a home-based exercise program with the positive effects of music on dyspnea and entrainment of gait, we expect to enhance the physiologic benefits of rehabilitation. In addition, we expect to maintain these physiologic benefits by the willingness of veterans to continue using RAS-music even after the conclusion of the formal exercise program. This means that, our innovative, practical and economical program has the potential to create a paradigm shift in the care of the many veterans with COPD who have no access to pulmonary rehabilitation.

A.5. Innovation*:* Exercise training combined with RAS-enhanced music is an innovative rehab program that capitalizes on the sensorimotor coupling of gait with the rhythmicity of RAS-enhanced music[26]. Augmentation of home-based pulmonary rehab with RAS-enhanced music creates a more affordable and motivational program compared to hospital-based rehabilitation. In our proposal, we use will use rigorous techniques to study the biophysical impact of this rehab strategy on clinical outcomes *(Objectives #1)*, volume of exercise accumulated during rehab *(Objective #2)* and the potential mechanisms underpinning those gains *(Objective #4)*. In addition, we will use a careful phenotypic characterization of patients to probe the effect of RAS-enhanced rehab on maintenance of physical activity once the 12 weeks of formal exercise training are over *(Objective #3)*. Through this proposed work we expect to demonstrate, for the first time and with sufficient power, that, compared to home-based training without RAS-enhancement, our novel home-based, RAS-enhanced program will produce greater improvements in functional and clinical parameters. We also expect that this program will ensure greater volumes of physical activity in the weeks that follow formal exercise training. The latter is increasingly recognized as critical to maintain benefits of rehab and to reduce morbidity and, possibly, mortality in COPD.[7] Research such as the one proposed here is vital to advance home-based rehabilitation in veterans with COPD.

B. Background and Work Accomplished: Dr. Laghi and Dr. Collins successfully concluded studies on respiratory muscle function in patients with COPD before and after lung reduction surgery,[75,76] on the mechanisms of relief of dyspnea following administration of sympathomimetic agents[77] and enhancement of cough with electrical stimulation in spinal cord injury patients.[78] The investigators were the first to demonstrate that a ventilation-feedback technique developed in their laboratory[79] could enhance the gains in exercise capacity achieved with traditional exercise-training in COPD.[3,4] They were the first to perform a head-to-head detailed investigation of the physiologic responses to exercise in patients with severe COPD who received helium-oxygen mixtures or pressure-support ventilation.[30] Based on their visual ventilation-feedback work, they developed and tested an acoustic ventilation-feedback system to modulate the respiratory cycle during exercise and enhance pulmonary rehab in COPD. Finally, they conducted investigations on quality of life in COPD – including studies on the impact of gonadal state on respiratory muscle function, exercise capacity, depression, sexual function and survival.[80,81,82]
In summary, Dr. Laghi and Dr. Collins have extensive experience with the techniques which will be

used in the current proposal including peripheral muscle testing,[81,84,131] exercise testing,[79,81] and training,[3,4,79,80] physical activity,[85,86] use of quality of life questionnaires,[80,81,87-89] and management of large groups of participants in pulmonary and non-pulmonary rehabilitation clinical trials.[3-5,80,82,83,89-91]

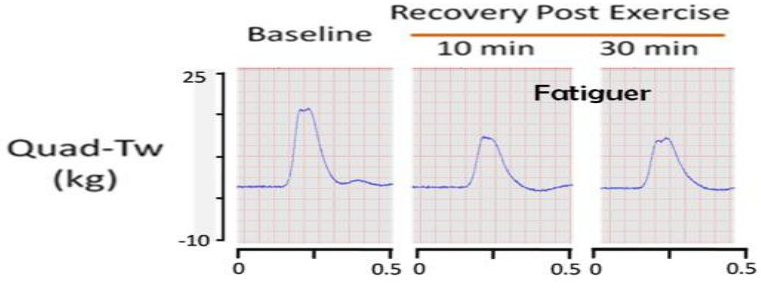
B.1. Ventilation-Feedback Training and Exercise for Patients with COPD (F2302-R). The primary objective of this study was to determine whether limiting exercise-induced dynamic hyperinflation during 12 weeks of exercise training plus ventilation-feedback training (i.e., breathing-retraining) would prolong the duration of constant-load treadmill test more than 12-weeks of exercise-training alone or breathing-retraining alone. After training, duration of the constant-load treadmill test was longer with breathing-retraining plus exercise (40±20 min) than with breathing-retraining alone (16±19 min; *P*<.0001) and tended to be longer with breathing-retraining plus exercise than exercise alone (32±17 min; *P*=.022).[4]

B.2. ***Innovative Methods for Pulmonary Rehabilitation (F3845-R)****.* The primary objective of this study was to determine whether reducing exercise-induced dynamic hyperinflation during 12 weeks of exercise training with either breathing-retraining or with helium-oxygen (heliox) would prolong the duration of constant-load treadmill test more than 12-weeks of exercise-training alone.[3] After training, exercise duration on the constant- load treadmill test increased by 11±13 min with exercise plus breathing-retraining, 8±10 min with exercise plus heliox, and 5±7 min with exercise alone.[3] Of interest, gains in exercise duration were most notable in patients with hyperinflation; those randomized to breathing-retraining showed greater gains in exercise when compared to exercise alone (12.3±13.3 vs. 4.6±7.7 min, *P*=.01).

B.3. ***Reducing Dynamic Hyperinflation through Breathing-retraining (F6955-R)****.* The purpose of this study, conducted in 205 patients with COPD, was to determine whether exercise training combined with an experimental, metronome-based auditory feedback could retrain breathing pattern and prolong exercise duration. The auditory breathing retraining plus exercise and exercise-alone groups improved time on the constant workrate treadmill test by 124% and 155%, respectively (p=.41). Unlike our previous studies, only expiratory time was greater in the feedback group than in the control group (p=.03). These results probably reflect the difficulty patients can have to entrain with a metronome reported by some investigators.[27]

B.4. Sustainability of Rehabilitation Gains in COPD (1 I01 RX001325-01). The purpose of this ongoing study, in which we have already enrolled 146 patients, is to test the hypothesis that one year after 12-weeks of pulmonary rehab, exercise gains are better maintained if the pulmonary rehab included our visual ventilation- feedback system than if it did not. This hypothesis is based on the observation that patients assigned to visual ventilation-feedback have greater improvements in mastery over dyspnea than patients not randomized to ventilation-feedback. Overall adherence to the study has been excellent (88% at one year). Analysis and data collection are ongoing as not all patients have completed the follow-up period.

B.5. Is Systemic Inflammation a Mechanism of Functional Impairment in COPD? (VA Resp-011-06F). This investigation was designed to test the hypothesis that in patients with COPD, greater functional impairment is associated with higher levels of circulating inflammatory cytokines and greater oxidative stress.



Two unique experimental modalities used in the *VA Resp- 011-06F* study that are relevant to the current proposal are: (a) assessment of quadriceps fatigue and (b) assessment of quadriceps muscle dimensions. We will separately describe preliminary results pertaining to these two modalities.

a-Quadriceps fatigue: To determine whether patients developed quadriceps fatigue after exercise, maximal voluntary contractions (MVC) and quadriceps twitch force elicited by magnetic femoral nerve stimulation (Quad-Tw) were recorded in 63 patients before and after constant-load cycle ergometry. Fatigue (decrease in Quad-Tw > 15% of baseline values, **Fig. 2**)[43] occurred in 67% of patients. Independent predictors of exercise-induced quadriceps fatigue were: less quadriceps recruitment, smaller pre-exercise Quad-Tw, greater inflammation (hsCRP, IL-6), and greater workrate ($p \leq .05$).[92]

b- Quadriceps dimensions: In the same 63 patients, the cross-sectional area of the rectus femoris using ultrasonography[39] was identified as an independent predictor of exercise capacity (VO_2 max and Watts max).

B.6.1. Pilot Study for Work Proposed-COPD: We enrolled 13 patients with COPD (age=71±57 yr, FEV_1=49±16% predicted). To assess whether RAS-music increases the distance walked during a fixed time, we measured the distance walked during three 6-minute walk tests (6MWTs) (no-music, music-as-recorded, or RAS- enhanced music) administered in random order. To minimize undue fatigue, patients rested for 30-minutes between tests. Patients were told that they would complete one walk without music and two walks while listening to self-selected music played in a continuous loop to last six minutes. During the unenhanced music walk, music was played at a tempo that matched the patient's usual cadence (steps/minute). During the RAS-enhanced walk, the music's bass was enhanced to emphasize the rhythm and the music's tempo was increased to approximately 5-10 beats/min higher than the patient's usual walking cadence. To eliminate extraneous noise, patients wore Bose® noise canceling head phones during each test. No adverse events or complications occurred. All patients successfully completed the three 6MWTs, and no patient commented that the music sounded different. Total distance walked was greater in the RAS-music walk when compared to no music (p=.038) and music without enhancement (p=.016) **(Tab.1)**. As reported by other investigators,[93] there was no difference in distance walked when the no-music walk was compared to the walk with unenhanced music. Distance walked when patients reported

Table. 1 Mean differences in walking distance based on music condition *(mean ± SD)*

	No music	Music without enhancement	RAS Music
Total distance walked (m)	461±58	452±48	470±53
Onset of dyspnea distance (m)	373±105	378±102	390±132

onset dyspnea was 372±05 m without music and 390±123 m with RAS-enhanced music. This pilot study shows that RAS music increases total distance walked and that that RAS music might delay the onset of exercise-induced dyspnea in patients with COPD.

Pilot Study 2-Peripheral Arterial Disease (PAD): We used similar methods as in **B6.1.** above to

enhance walking in a 12-week home-based, RAS-enhanced music program in 12 patients with PAD.[19] Patients in the RAS group (n=8) walked further (6MWT) than patients in the walking-only group (n=4; p=.012).

We learned some important lessons from our experience from the PAD-pilot study that we will use in our proposed COPD study: (1) Several patients did not have readily available Wi-Fi. The resultant inability to sync the Fitbit resulted in loss of data. In the proposed COPD study, we will instruct patients with no Wi-Fi to come to our Lab to sync the Fitbit and/or we will assist them in finding local hotspots to sync. (2) We will carefully track Fitbit data and call patients if Fitbit is data are missing *(see **C.1.7.**)*. (3) Helpful family members "assisted" the patients by resetting the Fitbit account making it impossible to track patients' steps. Accordingly, we developed detailed instructions for the Fitbit. (4) Patients requested more songs and playlists than we originally provided.
(5) A community advisory board advised us that patients with smartphones would prefer that the music be placed on smartphone so they would only have one device. After we changed our PAD pilot study based on these experiences, patients have been satisfied with the selection and amount of music they were given, we have been able to track Fitbit steps and we have not had issues with families resetting accounts. One patient in the PAD- pilot project requested that the music selections be placed on her smartphone.

Conclusion: The data presented in section ***D. Background and Work Accomplished*** indicate that: (a) The PIs have extensive experience with the methods to be used in the proposal; (b) The unambiguous feasibility and biological plausibility of the proposed study; and (c) The opportunity that the proposed experiments will provide unparalleled insights into home-based pulmonary rehab, sustainability of the gains achieved with pulmonary rehab and potential mechanisms that can affect such sustainability.

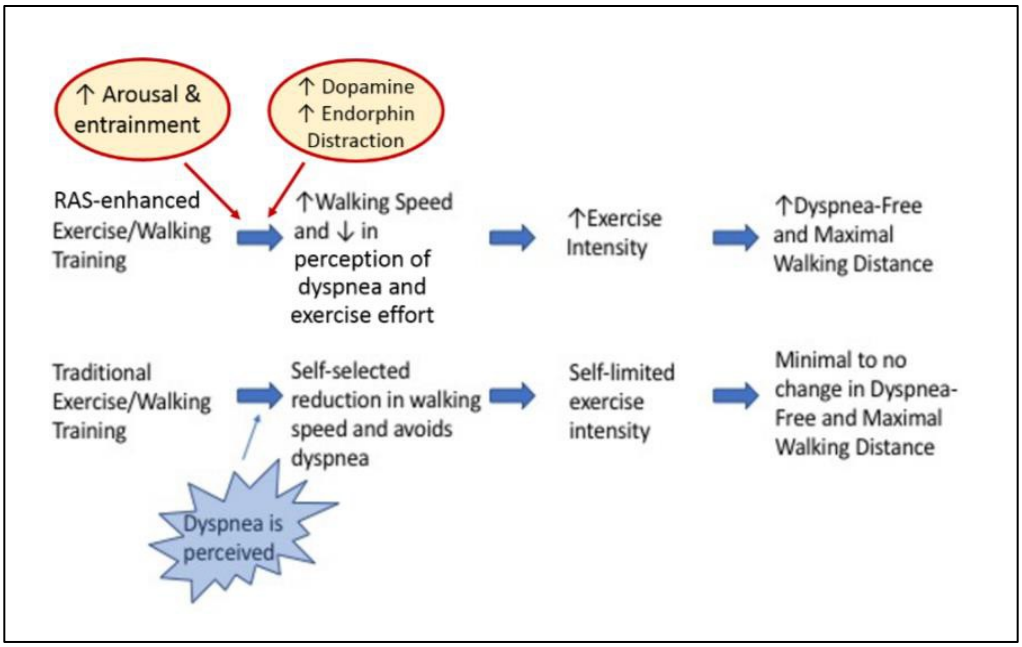
C. Work Proposed

C.1. Methods and Procedures

C.1.1 Theoretical Framework/Conceptual Model:

By embedding rhythmic sonic enhancements in self-selected music we will concurrently capitalize on the sensorimotor coupling of gait with the rhythmicity of RAS-enhanced music[26] and on the mitigating effect of music over exercise-induced dyspnea and fatigue.[52,53] The tempo of RAS-enhanced music will be adjusted to increase exercise intensity and duration **(Fig. 3)**.

Fig 3. Theoretical Framework/Conceptual Model of the work



The resulting effect of this integrated synergism will be to promote greater functional gains (primary hypothesis) at the end of 12 weeks of home- based exercise training and to promote better maintenance of the benefits of pulmonary rehab at 24 weeks than in the no-music group (secondary hypothesis).

C.1.2. General Overview of Design. The proposed study has been designed as a randomized, controlled clinical trial in which COPD patients will be randomized into an exercise program with RAS-enhanced music (RAS- music group) or in an exercise program without music (no-music group). COVID 19 patients will be randomized into an exercise program with RAST-enhanced music (RAST- music group and strength training) or in an exercise program without music (no-music but will have strength training group).Patients will complete testing procedures at pre-randomization, at 6 weeks, immediately post-rehabilitation, and 24 weeks after enrollment. Testing at 6 weeks is included to provide interim follow-up should patients not complete the 12 weeks of training.

C.1.3. Sample Size Calculation.

Sample size was estimated based on a 2-group mixed model design with baseline, 6 and 12-week measurements. Our primary goal is to compare the difference in distance walked during the *standard 6MWT* over 12 weeks between groups *(see **C.1.9.1.a.**)*. We estimate that the COPD target sample size of 68 patients per group completing 12 weeks will ensure 80% power to detect the differences between treatment arms using a two-sided significance level of 0.05, assuming a correlation of 0.70 between measurements. These estimates are based on our PAD pilot data and include similar standard deviations at baseline and at 6 weeks between groups and over time (232 feet), correlations between measurement of 0.76 to 0.86, and an increase of 87.2 feet at 6 weeks for the RAS- music group, with a slightly higher level for those completing the 12-week assessment. Based on the work of

Table. 2 COPD Study inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• ≥ 40 yr. of age	• Respiratory infection/COPD exacerbation within the previous four weeks
• FEV_1 ≤ 70%	• Exercise-limiting heart disease (Congestive heart failure – i.e., New York Heart Association Class III or IV; positive stress test or other indicators of heart disease or complaints of angina during the stress test)
• FEV_1/FVC <70%	• Exercise-limiting peripheral arterial disease (stops walking due to intermittent claudication) • Stops exercise for arthritic pain in knee or hips
• Mean SpO2 ≥ 88% at peak exercise (with or without oxygen supplementation) • Ability to hear music	• Inability to walk on the treadmill • Any unforeseen illness or disability that would preclude exercise testing or training • Participation in a formal exercise program within the previous 12-weeks

Liu et al.,[11] we estimate no change in the 6MWT in the no-music exercise training group.

COVID 19 sample size was estimated based on a 2-group design with pre- and post-test measurements. Our primary goal is to compare the difference in distance walked during the *standard 6MWT* at 12 weeks between groups. We estimate that over a two-year period we will ensure complete data collection on a total of 72 patients (36 per group). This will ensure a 58% power to detect the differences between treatment arms using a two-sided significance level of 0.05, assuming a correlation of 0.65 between measurements. Our pilot data used to support this estimate include the most conservative correlation observed between measurements (r=0.65), and an increase of 41 meters at 12 weeks for the intervention group.

According to the local IRB, enrollment is the equivalent to a patient signing an informed consent. In our three latest studies,[3,4,94] 30% of patients who signed the informed consent (i.e., enrollees) did not meet pulmonary function criteria or did not qualify for other reasons.[95] Moreover, based on our previous work, we expect an attrition 12 weeks after randomization of about 8%, and an attrition 24 weeks after randomization of 20%. Accordingly, to have complete data in 136 COPD patients as required by our power calculation *(see above)*, we plan to 'enroll' 243 COPD patients (i.e., signed informed consent) expecting to 'randomize' 170 of them, and to lose 34 of this latter group by week 24 (end of the study). We will enroll 100 patients with COVID 19 into this study.

C.1.4. Recruitment. COPD patients will be recruited from the outpatient Pulmonary Medicine Service at the Hines VA (**Tab. 2**).COVID 19 patients will be recruited from Hines outpatient Medical Services. No patient will be excluded based on gender or ethnicity. About 8 patients per month will be 'enrolled' with 5-6 of them being randomized. This will allow us to meet our target sample over 3.5 years (**Tab. 3**). Recruitment will be monitored weekly. We are confident we will meet the target number of participants *(see also section **C.5. Potential Problems**)* considering we enrolled more than 1000 patients into our various investigations[3,4,81,82,96] and that many patients with COPD attend Hines VA (4,803 unique patients with an ICD10-COPD code in FY2016, which is an underestimation of more than 1000 patients as this number does not capture patients in whom the ICD 9-COPD code has not been updated to the ICD 10-COPD code).

Table. 3 Recruitment and randomization schedule

	Year 1	Year 2	Year 3	Year 4
Number of enrolled patients	50	80	80	33
Number of randomized patients		55	55	25

C.1.5. Screening and Baseline Testing. Proposed study participants will be screened for eligibility and written informed consent will be obtained. All testing will take place at Hines VAH's Physical Performance Research Laboratory. During screening, patients will be asked about their medical history and medication use. This will be followed by physical examination, pulmonary function testing and completion of quality of life/dyspnea questionnaires **(Tab. 4)**. Eligible patients will perform additional baseline tests[4] that include a functional assessment of the quadriceps (after the completion of 12 weeks of training), quadriceps ultrasonography, two *standard 6MWT* (according to ATS recommendations, patients will be instructed to walk as fast as they can without running)[97] and two *modified 6MWT* at their usual/leisurely walk pace (*leisurely-paced 6MWT; see section **C.1.9.1**)*. Walking cadence during these tests will be used to adjust the RAS exercise prescription (RAS-music group). In addition, data from the *standard 6MWT* will be used to test the primary hypothesis that exercise training with RAS-music elicits greater increases in *standard 6MWT* distance than exercise training alone *(see sections **C.1.6.1. and C.1.9.1**)*. Patients will receive an Actigraph to measure physical activity over the course of one week.

After baseline testing is completed **(Tab. 4)** and study criteria are met, COPD patients will be randomized to exercise training with RAS-enhanced music (RAS-music group) or exercise training without music. COVID 19 patients will be randomized to exercise training with RAST-enhanced music and strength training (RAST-music group) or exercise training without music and with strength training. We chose a no-music control group as opposed to music without RAS-enhancement not to contaminate the control group. Music

can have strong bass or, when listening to music, individuals can augment the bass. Strong bass could provide an unintended RAS-like intervention. Testing and measures are described in sections ***C.1.9.1 t***

COVID 19 Inclusion/Exclusion Criteria

Inclusion Criteria

- ≥ 18 yrs. of age
- Previous hospital and/or emergency room visit for laboratory-confirmed COVID-19 diagnosis.
- Able to walk independently
- Mean $SpO_2 \geq 88\%$ at peak exercise (w/ or w/o O_2)
- Ability to hear music

Exclusion Criteria

- Able to walk more than 550 meters during a standard 6-minute walk test
- Exercise limiting heart disease (complaints of angina during the 6- minute walk distance tests or other indicators of exercise-limiting heart disease)
- Congestive heart failure (New York Heart Association Class III or IV)
- Exercise-limiting peripheral arterial disease (stops exercise due to intermittent claudication)
- Stops exercise due to arthritic pain in the knee or hips (self-report)
- Pregnancy

C1.9.5.

Randomization will be computer-generated with permuted blocks with random block sizes. This strategy is intended to preserve balance in the randomization of patients as to maintain unpredictability of the treatment assignments. Group assignment will be managed by the Hines Cooperative Studies Program Coordinating Center (CSPCC). When a patient is ready for randomization, we will contact the CSPCC to receive the randomization designation. To maintain testing integrity, Dr. Collins, Dr. Laghi or their designee will supervise patient testing and will be blinded to group assignment. When data are reviewed, the data will be void of any identifiers. Dr. Laghi (PI, pulmonologist) will remain blinded to group assignment. If patients develop medical problems during the study Dr. Laghi can request to be unblinded. When unblinded, the two physicians will not supervise further exercise testing for those given patients. The exercise physiologists, will assist with follow-up exercise, and will ask patients standardized questions regarding dyspnea, angina and ability to continue exercising.98 She will be blinded to group assignment. The project manager (Ms. O'Connell) and exercise physiologist (Ms. Jelinek) and the statistician (Dr. Reda) will be aware of patient's group assignment.

Table. 4 Testing schedule

	Measure(s)	Screen/ Baseline	6-wks	12-wks	24-wks
Eligibility/Screening					
• • $FEV_1 \leq 70\%$ $FEV_1/FVC < 70\%$	Pulmonary function test	x			
• Eligibility	History, Mini-Mental test	x			
• Co-morbidities	Charlson Index	x			
• Demographics	Demographic data information	x			
• Usual/leisurely walking cadence	Leisurely-paced 6MWT	x			
Primary Dependent Variable					
• Walking distance	Standard 6MWT	x x	x	x	x
Secondary Dependent Variables and Independent Variables					
• Dyspnea onset • E*xercise duration* (Treadmill walking time)	Constant-load treadmill test	x x	x	x x	x x
• QoL, Dyspnea, Self- efficacy, Physical Function	Questionnaires *(SF-36, CRQ, Self-efficacy for walking) COVID 19 CAS*	x	x	x	x
• Adherence	Fitbit Step Counts	x	x	x	x
• Daily physical activity	Step counts	x	x	x	x

Definition of abbreviations: 6MWT = six minutes walk test; QoL = quality of life

Exercise Prescription. Upon randomization, all patients will receive a 1-hour educational session on exercise rehabilitation.

Specifically, the clinical exercise physiologist will work with patients to: (1) set up a schedule that fits with

the patients' schedule for home-based exercise by with his/her usual daily schedule; (2) identify time-slots for exercise; (3) provide information on exercise tips; (4) address perceived barriers to exercise, (5) provide contact information, and (6) build a relationship with patients to provide support and identify health concerns.

C.1.6.1 Exercise Prescription:RAS/RAST-music group

C.1.6.1.a. Music selection*: Immediately after randomization,COPD patients in the RAS-music group will be asked to list 15 songs/music pieces within the one or more genres they most enjoy. If patients need help naming songs/music pieces, we will present them with a catalogue of "Top Twenty" songs/music within several genres . Patients will be also informed that they can choose songs/music not listed in the catalogue.*

COVID 19 patients in the RAST music group will meet with a music therapist at baseline and other timelines to complete their music assessment and music choices.

Please note that at the suggestion of the Merit Review Board we secured collaboration with music therapist: Dr Joanne V. Loewy DA, LCAT, MT-BC, Director, The Louis Armstrong Center for Music & Medicine Mount Sinai Beth Israel and Co-Editor-in-Chief, "Music and Medicine". Dr Loewy will serve as consultant to the current investigation. Dr. Loewy contributed substantively to the revisions in our application to incorporate music therapy and will work with the research team, incorporating resilience into the intervention. The music therapist will work with Dr. Loewy to assure that appropriate music therapy interventions are implemented.

C.1.6.1.b. Coaching playlist: A ***"coaching playlist"*** of 12 songs will be loaded on the patient's smartphone or iPod. *The patient's self-selected music is required to have a tempo that is within 5% of the patients' usual walking cadence* (*see **C.1.9.1.b.** Leisurely-paced 6MWT)* with brief segments of music at a faster tempo (~10 beats/minute over the leisure walking pace). (Music tempo is the speed of the underlying beat. Tempo is measured in beats per minute or BPM.) Patients will be instructed on how to access the playlist, use the headphones and maintain a cadence (steps per minute) that matches the music's tempo.

C.1.6.1.c. Personalized RAS/RAST-music visit: Patients will return to the lab one week later. During this visit *(**"personalized RAS/RAST-music visit")**,* patients will be given a playlist of the music they prefer. Each personalized playlist will include approximately 15 songs for a total of 45-60 minutes of music. The selection of songs will ensure that the music's tempo to which patients must entrain their walking cadence at home is initially slow (warm-up phase – music tempo within 5% of the walking cadence during *leisurely-paced 6MWT*), then fast (overload phase – music tempo same as during *standard 6MWT*) (*see section, standard 6MWT, **C.1.9.1.a.***) and then slow again (recovery phase – music tempo within 5% of the during *leisurely-paced 6MWT*). The first two phases will last approximately 4 minutes (i.e., two songs each). The last phase will last about 2 minutes (one song).

During the ***personalized RAS/RAST-music visit***, patients will complete one or more RAS-enhanced music cycles (i.e., warm-up, overload, and recovery) until the Research Assistant determines that the patient is comfortable with the procedure and successfully entrains his/her walking cadence with the music's tempo. (During the ***personalized RAS/RAST-music visit***, patient and research staff will concurrently listen to the music so that the research staff may give real-time music-cadence entrainment feedback to the patient).

To avoid undue burden to patients with frequent return visits to the lab, the research staff will upload in the patients' smartphone or iPod four additional playlists each with approximately 15 songs. The music's tempo in these playlists will match the required increase in walk cadence as patients progress with training -- i.e., as the weeks pass, patients will be instructed by phone to move from one playlist to the next.

During the ***personalized RAS/RAST-music visit***, patients will be instructed on the exercise prescription for the upcoming 12 weeks of exercise training. Specifically, patients will be instructed to walk while listening at the RAS-enhanced music at least 30 minutes, at least three times weekly. Compatible with perceived dyspnea (modified Borg < 3/10 [moderate dyspnea]),[3,23] patients will be encouraged to extend the period of exercise by 5 minutes every 2 weeks (not to exceed 45 minutes)[23] (Patients will be notified that the 30-to-45 minutes of three- weekly exercise session can be achieved all in one bout of exercise or in more than one bout of exercise during the exercise day). Patients will also be asked to wear the Fitbit at all times except when showering.

At the conclusion of the ***personalized RAS/RAST-music visit***, patients will be coached during 30-minutes of walking exercise to ensure that they properly understand how to conduct the RAS-music walking exercise at home and how to gauge dyspnea using the modified Borg scale.

At the end of weeks 2 and 4, 8 and 10, patients will be instructed by telephone to move to a new playlist in which RAS ensures a music tempo that is about 5% faster than in the preceding two weeks.[99] This step-up in the tempo of the RAS-enhanced music will take place only as long as dyspnea's Borg score is ≤ 3 at the conclusion of the prescribed walking exercise (modified from Collins et al).[3] Frequency and duration of exercise will be the same as described above.

At week 6, patients will return to the lab and will repeat a *standard 6MWT* to calibrate the tempo of the RAS- enhanced music that he/she will use for the following 6 weeks of training (same as ***personalized RAS/RAST-music visit*** above). At week 12, patients will return to the lab (same steps as in week 6). The purpose of this 12-week visit is to recalibrate once more the tempo of the RAS-enhanced music so that if the patient is interested in using the RAS-music during the last 12 weeks of the study he/she may do so with an updated prescription of music. At weeks 6, 12 and 24 patients will also fill out questionnaires and complete the 7-day actigraphy. At week 12 and 24, patients will also undergo a quadriceps ultrasound and Quad-Tw testing (week 12 only).

During the ***personalized RAS/RAST-music visit*** and subsequent visits to the lab, the research staff will also ensure that patients know how to use the Fitbit, will reinforce on how to use RAS-enhanced music to guide the walking cadence and will inform patients that any time during the study they can obtain different songs if they do not like or get bored with the songs provided in their personal playlist.

C.1.6.2. Exercise Prescription: No-music group. One week after randomization, patients in the no-music group will return to the lab to receive detailed instructions about the 12-week no-music exercise walking program. Specifically, they will be instructed to exercise at least 30 minutes, at least three times weekly. The exercise will consist of repeated bouts of walking, which will be slow initially for about two minutes (warm-up phase – leisurely- paced walk), then fast as they can without running for about four minutes (same as *standard 6MWT*)[97] and then slow again for about one minute (recovery phase – leisurely-paced walk). Compatible with perceived dyspnea (modified Borg < 3/10 [moderate dyspnea])[3,23] patients will be encouraged to extend the period of exercise by 5 minutes every 2 weeks (not to exceed 45 minutes).[23] (Patients will be notified that the 30-to-45 minutes of three- weekly exercise session can be achieved all in one bout of exercise or in more than one bout of exercise during the exercise day). Patients will also be asked to wear the Fitbit at all times except when showering. To conclude the visit, patients will be coached during a 30-minute walking exercise to ensure that they understood how to conduct the no-music walking exercise at home and how to gauge dyspnea using the modified Borg scale.

Of importance, the difference in exercise training between the no-music group and the RAS-music group is that the no-music exercise program **will not** be directed by RAS/RAST-enhanced music. *In addition, patients in the no-music group will be instructed to avoid listening to any music while walking.* All other methods, including phone calls at the end of weeks 2 and 4, 8 and 10 to ensure compliance and progression with home exercise, lab visits at weeks 6, 12 and 24 and encouragement to remain physically active after the first 12 weeks of training, will be same for both groups. (Patients will be scheduled so that the RAS-music and the no-music groups are not in the laboratory at the same time.)

COVID 19 Exercise and Strength Training (music and no music group)

Three times a week, patients will complete a muscle resistance/strength training session using professional grade resistance bands with handles (DYNAPRO™). Patients will complete upper, lower, and core body exercises. Training will include 9-11 exercises (e.g., shoulder press, lateral arm raises), will be progressive (i.e., bands with greater resistance will be used as participants' strength increases), and will be completed in two sets of 12-15 repetitions per exercise. Lower body exercises will include calf raises, chair sit to stands, and wall squats or squats with the resistance band. Core exercises will include basic planking exercises and abdominal work. Patients will record that they completed the strength training on their exercise log. We will focus on both upper, lower, and core body strength exercise as patients recovering from COVID 19 have generalized overall body weakness.

Usual Care Group: One week after randomization, patients in the control group will return to the lab to receive educational material on physical activity and general advice based on the 2018, *Physical Activity Guidelines for Americans* 2nd edition (U.S. Department of HHS) *(see Appendix 4*).[142] Three times a week, patients will complete a muscle resistance/strength training session using professional grade resistance bands with handles (DYNAPRO™) (same as RAS-therapeutic music group).

C.1.7. Promoting & Assessing Adherence to the Exercise Program with and without RAS/RAST-music. To promote and monitor adherence to exercise (with or without RAS-music), all patients will be provided with a 3- axis accelerometer (Fitbit).[100-102] Patients will be instructed to download (sync) data from the Fitbit into their smartphone or iPod devices. These data will be saved in the associated online "Fitbit user account" set up by the study staff. During the 12-week period of exercise training, study staff will call patients on a weekly basis to go over daily and weekly walking data saved in the Fitbit account and to answer any questions that may arise. *To enhance/ensure compliance, our study staff will take a positive approach using motivational interviewing techniques.* After week 12, weekly phone calls will stop. To maintain engagement with study staff, patients will be called again at week 18. At week 23, they will be called to be reminded of the final visit that will take place on week 24.

C.1.8. Time Summary. The two groups of patients will complete the same testing procedures at the same time intervals. In **Tab. 5**, we summarize the timeline for completion of the proposed research project.

C.1.9. Measures*:*

Table. 5 COPD Timeline for research completion

	Year 1				Year 2				Year 3				Year 4			
Finalize data collection instruments/ Purchase supplies	x															
Screen and enroll patients	x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Train and follow patients		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Data entry/Coding/Cleaning		x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Quality monitoring				x				x				x				
Data analysis/Preparation reports								x				x			x	x
Presentations/Publications *(presentations at AACVPR, ACSM, ATS, Chest)*								x				x			x	x

Definition of abbreviations: AACVPR = American Association of Cardiovascular & Pulmonary Rehabilitation; ACSM = American College of Sports Medicine; ATS = American Thoracic Society

COVID 19 timeline

~~Table 3.~~ **Timeline for research completion**

	Year 1				Year 2			
Finalize data collection instruments/ Purchase supplies	x							
Screen and enroll patients	x	x	x	x	x	x	x	x
Train and follow patients		x	x	x	x	x	x	x
Data entry/Coding/Cleaning		x	x	x	x	x	x	x
Quality monitoring				x				x
Data analysis/Preparation reports								x
Presentations/Publications *(presentations at AACVPR, ACSM, ATS, Chest)*								x

Definition of abbreviations: AACVPR = American Association of Cardiovascular & Pulmonary Rehabilitation; ACSM = American College of Sports Medicine; ATS = American Thoracic Society

C.1.9.1. Six-minute Walk Tests (6MWT): Patients will perform two 6MWT as fast as they can without running according to ATS recommendations (*standard 6MWT*)[97] and two modified 6MWT at their usual/leisurely walk pace (*leisurely-paced 6MWT*). Walking cadence during these tests will be used to adjust the RAS exercise prescription (RAS-music group). In addition, data from the *standard 6MWTs* will be used to test the primary hypothesis that exercise training with RAS-music elicits greater increases in *standard 6MWT* distance than exercise training alone. Please note that the leisurely-paced 6MWT are only completed at baseline. The standard 6MWT are repeated at all testing time points (baseline, 6 weeks, 12 weeks and 24 weeks).

C.1.9.1.a. Standard 6MWT: Patients will be instructed to walk back-and-forth a 100-foot long circuit as

fast as they can without running.[97] Standardized encouragement will be given.[97] Heart rate and blood pressure will be monitored to ensure safety. The entire test will be recorded with a camcorder to count the number of steps and, thus, calculate patient's cadence for the overload phase of RAS training (modified from Ho et al.[58] and Liu et al.[11]).

C.1.9.1b Leisurely-paced 6MWT: The purpose for this test is to identify the patient's leisurely walking cadence to set the music tempo during the warm-up and cool-down phases of the home-based exercise (RAS- music group). The test will be identical to the *standard 6MWT* with the exception that patients will be instructed to walk at their usual leisurely walking pace. We chose six minutes of observation because, in older adults, a one-minute step-count can overestimate usual walking cadence by as much as 40%.[103] The entire test will be recorded with a camcorder to count the number of steps and, thus, calculate patient's cadence for the warm-up and cool-down phases of RAS training (modified from Ho et al.[58] and Liu et al.[11]).

C.1.9.2 *Standard 6MWT* testing has been used to assess therapeutic responses in patients with COPD. This test has the potential to produce complementary information about changes in exercise performance following interventions. Accordingly, we are including this test for the following reasons: (1) The *standard 6MWT* is more reflective of activities of daily living than other walk tests and is currently the test of choice when using a functional walk test for clinical or research purposes ;[97] and (2) The *standard 6MWT* assesses the submaximal level of functional capacity. Most patients limit their own intensity of exercise and are allowed to stop and rest during the test. Because most activities of daily living are performed at submaximal levels of exertion, the *standard 6MWT* may better reflect the functional exercise level for daily physical activities;[97] (3) The *standard 6MWT* has a defined clinically important difference;[97]

***C.1.9.3. Actigraphy*:** Daily physical activity will be quantified using a lightweight (27 gm.), small (3.8 x 3.7 x 1.8 cm), triaxial accelerometer worn on the hip (actigraph GXT3). The actigraph GXT3 detects accelerations ranging from 0.05 to 2.5 Gs and it has a frequency responses ranging from 0.25 to 2.5 Hz. Motion outside human movements are rejected by a bandpass filter. The acceleration/deceleration signals are digitized by an analog - to-digital converter at 30 times/second (30 Hz) over a pre-programed epoch interval. The monitor is programmed for start time and data collection interval, and data are retrieved for analysis. The device is capable of recording up to 22 days of continuous data in one-minute epochs. The actigraph GXT3 is both reliable (Intraclass Correlation Coefficient (ICC) for activity counts of 0.97)[104] and valid in measuring physical activity[105] even in patients with low levels of overall physical activity.[106] *Since physical activity is known to vary based on the day of the week due to work and leisure activities profiles,[107] patients will be instructed to wear the sensor for 8 days, 24 hours a day.[108] At the end of day-8, patients will doff and mail the Actigraph to the lab.*

C.1.9.4. Fitbit Step Count: The Fitbit is a commercially-available motion sensor (3-axis accelerometer) designed to monitor number of steps taken, activity (sedentary, light activity, moderate activity, moderately vigorous), distance walked and sleep.[30] Specific Fitbit devices can be worn at the hip, pocket and writs.[109] The Fitbit device worn at the waist is highly accurate in step counting[101] – i.e., high correlation with observed step counts (r= 0.97 to 0.99)[101] and high ICC (0.97).[111] Fitbits worn at the wrist are not as accurate as those worn at the hip[101,111] – the Fitbit worn on the wrist can underestimated step counts by 16% for slow walking and by 11% for moderately fast walking.[101] Relevant to our proposal, however, is the fact that most patients are very receptive to wear wristband Fitbits for long periods of time.[109] Accordingly, we will use the wristband Fitbit as a source of general information on daily level of physical activity during the 12 weeks of exercise training and will use that information to monitor adherence to the program and to motivate patients to exercise. We will use hip actigraph recordings[100] to accurately quantify physical activity (see ***C.1.9.3.)***.

C.1.9.5. Questionnaires: Self-reported physical function and quality of life will be evaluated using eight questionnaires *(see* **C.*1.9.5.a.*** *to* **C.*1.9.5.e.****)*.

C.1.9.5.a. Chronic Respiratory Disease Questionnaire (CRQ). This questionnaire is designed to determine how the lives of patients with chronic airflow limitation are affected by the illness and the perceived impact of symptoms and limitations on quality of life.[112] Test-retest reliability and validity of the CRQ are well established.[112] Patients will not be informed of their previous responses on the questionnaire when the CRQ is administered at week 6 and 12 and 24. CRQ scores will be used as covariates in the final analysis if appropriate *(see* ***C.2 Statistical Analysis****)*.

C.1.9.5.b. Short Form-36 Health Survey (SF-36): This is a general health-related quality of life

instrument to quantify perceived physical function and mental health.[8] The SF-36 will be used to describe the sample and to have a comparator measure to published clinical pulmonary rehabilitation programs.[113]
C.1.9.5.c. Charlson Comorbidity Index. This validated[114] and widely utilized index[80,82] will be used to determine whether comorbidities influence study outcomes *(see **C.2 Statistical Analysis**).*
C.1.9.5.d. Depression and Anxiety. To control for the influence of ongoing depression and anxiety on adherence, the Center for Epidemiologic Studies Depression Scale (CES-D)[115] and the State-Trait Anxiety Inventory (STAI)[116] will be administered at baseline and at major data collection time-periods. CES-D and STAI scores will be used as covariates in the final analysis as appropriate.
C.1.9.5.e. Self-Efficacy. The Self-Efficacy for Walking[117] and the Self-Efficacy for Shortness of Breath questionnaires[118] will be used to measure self-efficacy at all time periods.[117] These are reliable and valid[118] instruments designed to assess a patient's confidence in keeping shortness of breath from interfering from walking or from doing what they want to do.
C.1.9.5.f. COPD Assessment Test The COPD Assessment Test (CAT) measures the impact COPD has on patient's well-being and daily life.
C.1.9.5.g Coronavirus Anxiety Scale (CAS) Assesses dysfunctional anxiety associated with the COVID19
C.1.10. Exacerbations. Approximately 25% of patients with moderate-severe COPD are expected to experience an exacerbation over the course of 24 weeks.[119] Exacerbations negatively impact adherence to exercise programs and quality of life.[119] Exacerbations will be monitored weekly throughout the study. Acute exacerbations are defined by changes in sputum color, volume or consistency and are accompanied by an increase in dyspnea.[31] Acute exacerbations are classified as mild (the need for increased use of inhaled bronchodilators only), moderate (the need for systemic corticosteroids and/or antibiotics), or severe (the need for hospitalization).[31] Since moderate exacerbations usually resolve in approximately two weeks,[120] patients who experience an exacerbation within two weeks of testing will have their testing deferred until the exacerbation has resolved. If patients report an exacerbation (or have signs of exacerbation), the research team will notify Dr. Laghi for assessment and treatment if needed. In the final analysis, occurrence and severity of exacerbations will be included as potential covariates.
C.1.11. Data Management, Quality Control. All data will be cleaned using frequency distributions to identify errors in data entry. In addition, 10% of the data will be hand-checked for accuracy. If the coding/entry error rate is > 2% for any test/instrument, we will check 25% of the data. If the error rate is still > 2%, all of the data for that test/instrument will be hand-checked. Monitoring logs will be maintained for (a) patients screened for participation [demographic information and reason for non-participation (for non-participants only)]; (b) patient entry into the study; (c) timeliness of data collection; and (d) missing data.
C.1.12. Treatment Fidelity. We will employ treatment fidelity strategies recommended by the NIH.[121] Dr. Bronas will conduct a blinded review of the exercise prescription and music for patients assigned to the exercise groups. He will evaluate the initial exercise prescriptions and exercise progression. He will also review a selection of music assure that appropriate adjustments for tempo and beat have been made. Moreover, we have a detailed operations manual. To prevent group contamination, patients in the two groups will be seen/tested at different times.[3,4]

C.2. Statistical Analysis. Descriptive statistics will be used to summarize baseline characteristics of patients.

C.2.1. **Statistical Analysis: Primary Hypotheses**

H1A: IN PATIENTS WITH COPD, IMPROVEMENTS IN 6-MINUTE WALKING DISTANCE WILL BE GREATER AFTER COMPLETING 12 WEEKS OF A HOME-BASED, EXERCISE PROGRAM WITH RAS-ENHANCED MUSIC THAN AFTER A HOME-BASED, EXERCISE PROGRAM WITHOUT MUSIC.
The analysis of the primary outcome (improvements in 6-minute walking distance) is based on all data collected during the intervention period—baseline, 6 and 12-weeks. We will use a mixed-model analysis that includes treatment, time and treatment-by-time interaction terms. Specifically, we will test whether the treatment- by-time interaction differs from 0. This model will automatically account for missing data where missing at random is assumed. We will conduct a sensitivity analysis[129,130] based on the results of the mixed model analysis to determine whether other assumptions regarding the missing data may produce different results. One component of the sensitivity analysis will also include adjustment for

baseline demographic and health covariates.

C.2.2. Statistical Analysis: Secondary Hypotheses

Statistical analysis for H_{1c} will parallel that of H_{1a}.
H_1D: THE RAS-ENHANCED MUSIC GROUP WILL DEMONSTRATE GREATER INCREASES IN HEALTH-RELATED QUALITY OF LIFE (QOL) THAN THE CONTROL GROUP.

Statistical analysis for H_{1d} will parallel that of H_{1a}.
H_2: THE RAS-ENHANCED MUSIC GROUP WILL ACCUMULATE A GREATER VOLUME OF DAILY PHYSICAL ACTIVITY THAN THE CONTROL GROUP. THIS WILL BE DEMONSTRATED BY GREATER PHYSICAL ACTIVITY AT 12 WEEKS (ACTIGRAPHY).

Statistical analysis for H_2 will parallel that of H_{1a}.
H_3: THE RAS-ENHANCED MUSIC GROUP WILL MAINTAIN IMPROVEMENTS IN MEASURED AND PERCEIVED FUNCTION AT 24 WEEKS TO A GREATER EXTENT THAN THE NO-MUSIC CONTROL GROUP.

In the statistical analysis of H3, we will use independent t-tests to compare the changes in measured function (distance walked in the 6MWT and perceived function (questionnaires) between 12 and 24-weeks between the RAS-music and the no-music groups. We will also conduct paired t-tests within each group to determine whether values at 24 weeks are worse than those at 12 weeks. These computations will be based on those patients with 12 and 24-week data. To assess whether patients included in the H3 analysis are representative of the original randomized groups, we will also compare demographic and health measures (i.e., FEV_1 percent predicted, comorbidities, depressive symptoms and exacerbations) of patients included in the H3 analysis to patients who were not.

C.2.3. Statistical Analysis: Exploratory objective: [exploratory objective not reported]

TO ASSESS IMPACT OF PHYSIOLOGICAL AND PSYCHOLOGICAL PHENOTYPE AND CLINICAL FACTORS ON RESPONSIVENESS TO REHABILITATION ACHIEVED WITH AND WITHOUT CONCURRENT USE OF RAS-MUSIC. PHYSIOLOGICAL FACTORS INCLUDE: SYSTEMIC INFLAMMATION (HSCRP), QUADRICEPS STRENGTH, RECRUITMENT AND FATIGUE, QUADRICEPS FUNCTION AND DIMENSION AFTER REHABILITATION. PSYCHOLOGICAL FACTORS INCLUDE: SELF-EFFICACY, ANXIETY AND DEPRESSION. CLINICAL FACTORS INCLUDE: ADHERENCE TO THE 12-WEEK PROGRAM, ADHERENCE TO FOLLOW-UP AND NUMBER AND SEVERITY OF EXACERBATIONS.

To assess the impact of the above confounders two separate analyses will be conducted: (a) A linear regression model with changes from baseline to 12 weeks of training as the dependent variable, and assigned treatment group, physiologic and psychologic phenotype and clinical factors as the independent variables, and
(b) A mixed model ANOVA with baseline, and 12 and 24 weeks measurements as dependent measures and assigned group, physiologic and psychologic phenotype and clinical factors as the independent variables.

C.3. Expected Outcome: We expect to demonstrate that improvements in 6-minute walking distance from baseline to 12 weeks will be greater after completing 12 weeks of a home-based, exercise program with RAS- music than after a home-based, exercise program without music.

C.4. Alternative Outcomes. Our primary hypothesis will be rejected if, at 12 weeks, improvements in 6-minute walking distance are not greater with exercise-training plus RAS-music than with exercise-training without music. In this case, at least three alternative outcomes will be considered.

C.4.1. Alternative Outcome #1: Improvements in 6-minute walking distance are greater after exercise-training without music. If this occurs, at least three possibilities must be considered.

One, despite efforts to optimize randomization (*see* ***C.1.5.***), the RAS-music group experienced less severe quadriceps fatigue or other confounders than the exercise-alone group (e.g., imbalance in the randomization at baseline of fitness or history/likelihood of exacerbations) (see *Explorative Objective*). If this occurs, we will conduct a future study focused on patients with more severe COPD who have smaller

quadriceps and develop less fatigue during exercise and who are stratified according to baseline fitness and history/likelihood of exacerbations.

Two, patients paid more attention to the RAS-music than to the assigned exercise (inadequate exercise intensity during training). Less exercise intensity would reduce potential gains obtainable with rehab. Although we consider this possibility very unlikely,[11,58] we will objectively test for sub-optimal challenge of the leg muscles (lack of contractile fatigue; *see section* ***A.3.2.1.***) by recording Quad-Twitches at the end of training.[44]

C.4.2. Alternative Outcome #2. If improvements in 6-minute walking distance are similar in the two groups at least three possibilities must be considered.

One, the RAS-music group did not comply with RAS during training. To monitor and optimize adherence with RAS-music plus exercise we developed a very rigorous protocol *(see section* ***C.1.7.)***. If, despite our adherence protocol, compliance remains poor we will investigate possible barriers to poor compliance and plan future studies to address barriers (see ***C.4.3. Alternative Outcome #3)***.

Two, RAS-music adds nothing to gains achieved with exercise-training alone. Two mechanisms could cause this unlikely[11,58] result: (1) insufficient stress on muscles and (2) suboptimal entrainment. The first possibility would be supported if prevalence of exercise-induced quadriceps fatigue elicited by a typical exercise-training session in the two groups is the same. The second possibility would be supported if less gains are related to greater failure to entrain gait during teaching sessions (*poor entrainers*). If that happens, we plan future studies where RAS-music in *poor entrainers* will optimized – i.e., in the subgroup of *poor entrainers* we will increase the volume of RAS music and augment the entraining pulse (strongly emphasized beat) to facilitate music-motor synchronization.[27]

Three, the positive impact of RAS-music is smaller than predicted – i.e., Type II error.

C.4.3. Alternative Outcome #3. Neither group experiences improvement in 6-minute walking distance. If this occurs at least three possibilities must be considered.

One, neither group engaged in home-based exercise training. Several factors, including psychological phenotype (i.e., anxiety, depression)[122] are known to reduce acceptance and adherence to rehab.[7,8,12,57,58] If our data demonstrate that psychological factors interfere with acceptance and adherence to home rehab (see *Explorative Objective*), we will plan a future investigation that will include formal psychological interventions (i.e., cognitive behavioral therapy) to address those factors.[123]

Two, physiological/clinical factors decreased exercise tolerance thereby curbing intensity of exercise during training.[63] These factors could include frequency of exacerbations, severity of lung disease, quadriceps dimension, recruitment and strength, systemic inflammation (hsCRP) (see *Explorative Objective*).[64] If the negative results of our study parallel these physiological/clinical factors, we will explore the possibility of combining pulmonary rehab with the administration of novel anti-inflammatory agent(s). This strategy is based on the mounting evidence that systemic inflammation may contribute to local and systemic manifestations of COPD.[124] Additional ancillary interventions could include strategies to enhance muscle anabolism,[125,126] to enhance muscle recruitment by the central nervous system,[127] and strategies to promote muscle overload (fatigue) during training.[41,128]

Three, limited adherence to home-based exercise: please see point One, section **C.4.2.**

C.4.4. Miscellaneous limitations and alternative methods

C.4.4.1. Medications: Medications may be adjusted throughout the study; such adjustments may affect outcome variables including exercise endurance. *Proposed Action*: Patients must be on stable therapy before enrollment. From our previous experience, we expect that several patients will require minor adjustments of their anti-hypertensive medication throughout the study. Medication lists and doses will be documented at each evaluation period. If patients require significant medication changes as judged by Drs. Laghi (Pulmonary) or Budinger (Data Safety Monitoring), appropriate statistical adjustments will be made.

C.4.4.2. Patients withdrawal: Patients may withdraw from the study at a higher rate than anticipated. *Proposed Action*: Since we use intent-to-treat analysis, any patient completing at least six weeks of training will be included in the analysis. If more than 20% of patients withdraw - or have to be withdrawn - prior to the sixth week of training, we will increase the number of randomized patients accordingly.

C.4.4.3. Lack of internet access: Some patients have no internet access. (Patients need internet access to sync the Fitbit). *Proposed Action*: Patients without internet access will be provided with a list neighborhood locations with Wi-Fi hotspots. Alternatively, patients will be free to come to the lab to sync

the Fitbit.

C..4.4.4. Music in the control group: Some patients in the control group may be used to listening to music while walking. *Proposed Action: Throught the study, patients in the no-music group will be instructed to avoid listening to any music while walking.* In addition, at the end of the study, we will ask patients in the control group whether they listened to music while walking. Appropriate statistical adjustments will be made if needed.

C.5. Potential Problems.

C5.1. Insufficient patient enrollment. This is a very unlikely considering the large number of patients with COPD cared for at Hines VAH and our excellent track record.[3,4,80,94] In addition, we could enroll patients from the Jesse Brown VA located 10 miles east of Hines. We could advertise in local newspapers and on Chicago Transit Authority busses.[96]

C5.2. Exacerbations. Exacerbations can cause functional impairment and decreased peripheral muscle function *(see sections **A.3.4** and **C.2.3. Exploratory Objective**).* Exacerbations will be tracked as part of our data safety monitoring.

C.5.3. Adherence to the home-based program. In our studies, patient compliance to training has ranged from 90 to 95%.[3,4,94] In this proposal we will take several steps to ensure high compliance with training ***(see C.1.7.)***.[139] All patients will receive at weekly phone calls. In addition, they will be called if they do not sync their Fitbit or do not exercise for three consecutive sessions. Additionally, patients will receive $20 to cover travel expenses for each visit to the lab.

C.6. Future Directions. If, as we hypothesize, RAS-music plus exercise-training improves exercise capacity at the conclusion of a 12-week home-based rehab program and, thereafter, it promotes the maintenance of physical activity, three questions for future studies will arise: (1) What is the effect of RAS-music plus exercise on the systemic manifestations of COPD including depression, osteoporosis, and coronary artery disease? (2) Could RAS-music plus exercise decrease the staggering heath care cost for veterans and non-veterans with COPD?

(3) What is the effect of RAS-music plus exercise on survival? To address these questions, we will pursue a multi-center randomized clinical trial. In addition, we will consider additional studies tailored to specific subgroups of patients. For example, if we find that to achieve and maintain benefits from home-based, RAS-music rehab patients must also develop quadriceps fatigue,[44,45] we will design an investigation where in *"non-fatigures"* we will combine RAS-music plus a one-leg exercise-training[41,128] or RAS-music plus neuromuscular electrical stimulation of the quadriceps, gastrocnemius and tibialis anterior muscles.[126]

Risk to Subjects

a. *Human Subjects Involvement and Characteristics.* Patients recruited for this study will be adults with chronic obstructive pulmonary disease (COPD). Most patients with COPD that we recruited in the past[1-3] were in their late 60's or early 70's. Accordingly, we anticipate that patients who will participate the proposed study will be of similar age. We expect to enroll 243 patients and randomize 170 of them. Patients with COPD often have several comorbidities[4,5] and require careful screening prior to enrollment and randomization. To enroll the required 243 COPD patients and the 100 COVID patients, we expect to screen about 6000 patients via electronic chart review. More information about recruitment follows in the *Recruitment Section* below. Patients' fulfilment of inclusion/exclusion criteria (Table 2 above) will be evaluated during the screening and baseline testing phase of the study. Non- veterans will be enrolled in the study. We recruit non-veterans to ensure that an adequate number of women participate in the study.

b. *Sources of Materials.* Most of our research data are collected from the research participants and used for research purposes. We do use medical record information as part of our medical history review. We also use pulmonary function test results if they have been completed within the previous year and there have been no exacerbations or reasons to believe that the patient's condition has changed.

c. *Potential Risks.* There are potential risks associated with this study. There is the risk that unknown cardiovascular or other clinical conditions may be uncovered as a result of participation in the study. In our ongoing study, 30 patients were excluded from participation due to medical comorbidities. These

included cardiovascular disease, cancer, hypertension, and diabetes. There are also other risks such as falling, muscle soreness, lightheadedness or dizziness that may occur with exercise training. These are extremely rare occurrences. Patients may choose to not participate in the research program or withdraw from the research program at any time. There is a clinical pulmonary rehabilitation program that they can enroll in at the Hines VA Hospital if they so choose.

Adequacy of Protection from Risk

a. Recruitment and Informed Consent. Patients are identified from the Pulmonary Clinic, their ICD-9CM code (ICD-9CM 496, 491.21), clinic stop (pulmonary clinic or pulmonary function testing laboratory), outpatient medical clinics, or self-referral. Recruitment flyers, brochures, and posters will be displayed in key areas of the hospital and outpatient clinics. A brief electronic chart review (CPRS) is conducted. A HIPAA waiver and an informed consent waiver will be sought to screen electronic medical records (CPRS) of potential patients for eligibility in the study. Patients are excluded if they do not meet inclusion/exclusion criteria (Table 1). All other potential participants are sent a recruitment flyer and letter inviting them to join the study. A short survey and return envelope is enclosed for them to return. Patients may choose to be contacted by the study staff or not to be contacted by the study staff. If they choose not to be contacted, no more contact is made. If they do not respond, a second letter of invitation is sent. If patients respond positively, they are contacted by the project manager (S. O'Connell RN, MBA). The study is briefly explained and if the patient is still interested and no exclusionary criteria have been uncovered an in-person visit is scheduled. In the interim, a copy of the informed consent is mailed to the potential participant to review with their family or physician. We believe that informed consent is a process that begins at the letter of invitation and/or when patients inquire about the study and does not end until they have completed the study.

When the initial in-person visit takes place, research staff will explain the purpose of the study, study procedures, benefits, risks, confidentiality and privacy, and the subject's rights. Since this study involves a substantial time commitment on the part of the patient, time commitment is emphasized during the consenting process. The written consent is reviewed in detail and is used as a guide for the person obtaining the consent. Patients are encouraged to ask questions throughout this process. The informed consent procedure generally takes 30-60 minutes to complete. Patients are encouraged to take the consent home and review it with their family and/or their doctor before signing. Some patients insist on signing the consent the same day that the study is explained. If this occurs, the patient is given a copy of the consent to bring home and informed again that he/she is free to withdraw from the study at any time. patients will be paid $20 for each visit to the laboratory. The payment is intended to defray travel costs and supplement the cost of appropriate walking shoes. The amount of reimbursement is not excessive and will not be emphasized during the recruitment process.

Ms. Susan O'Connell RN, MBA and Dr. Laghi will be responsible for obtaining the informed consent from study participants. Ms. O'Connell has been a research study nurse and project manager for the past 22 years and has been a member of the Hines/Lovell IRB. She is very experienced in obtaining informed consent and in HIPAA authorizations. She has worked in the Physical Performance Laboratory for the past 17 years and is extremely familiar with the study procedures, risks, and benefits of participation. Ms. O'Connell will be primarily responsible for the informed consent process. Dr. Laghi has been conducting research for over 20 years and is very familiar with the consenting process. He has a commitment to and an appreciation for the informed consent process. All staff have attended IRB and HIPAA training.

Consent for picture and voice recording will also be obtained prior to videotaping the six- minute walks for step counts. We will explain to the patients that the recording will only be used to count steps. Once the steps are counted and then confirmed by another staff member, the recording will be deleted. If a patient refuses to consent to be recorded, steps will be counted by a separate research assistant throughout the six-minute walk test.

a. Protection Against Risk

Six-minute walk testing: The six-minute walk is a submaximal test. McDermott (2014) reports only one

adverse event during >7900 six-minute walk tests (this was a fall with a fractured forearm). We have completed >2000 six-minute walk tests on patients with COPD without incident.

Exercise training: Training sessions will be completed in the patient's home environment. Investigators and research staff will discuss places to exercise and plans for walking with the subject. Patients will be provided with alternative safe places for exercise as well areas to exercise in lieu of inclement weather. If patients are having difficulty finding places to walk, the staff will assist them in finding a place that is close their home. Those assigned to the RAS-entrainment group will walk with headphones on.

Burden: Given that much of the intervention will be completed at home or in the community, burden should not be an issue. Also, patients will be paid $20 for each visit to the laboratory. The compensation is intended to pay for travel and time for participation.

Uncovering unknown illness: At the time of consent, patients will be informed that there is a chance that an illness will be uncovered during the study. Coronary artery disease was the primary disease discovered during our previous studies. It will be made clear to patients that study staff will assist them in seeking resolution to problems discovered throughout the course of the study, but financial obligations associated with this follow-up treatment will not be paid for by the research study.

Confidentiality: All research data will be coded for data entry so that a patient's identity cannot be determined (e.g., COPD001, COPD002). All computerized files will be password protected and available only to those involved with the research project. All data are stored on a secure VA Hospital Network Drive (our laboratory has 7 GB of storage space allocated to us on the research network drive). Dr. Collins does have an encrypted VA laptop that she uses to analyze data and to write manuscripts. Drs. Laghi and Collins both have encrypted Ironkey flashdrives for transferring data when needed. Since data are transferred from the VA network drive to the encrypted laptop, special precautions have been taken. First, an approved encrypted thumb drive is always used to transfer data (this is generally not done as a first choice for transferring data; VPN connections are used with the encrypted laptop and data are moved behind the firewall). Next, identifiable data (i.e., screening logs), are kept separately from the study data files. These files are never removed from the VA network drive. Thus, any files transferred to the laptop are identified only by study number (COPD1, COPD2). Lastly, we do not enter social security numbers into our databases.

Login and passwords will be created for the Fitbit devices. This will allow the research staff to monitor step counts from the Fitbit on the Fitbit website. No Protected Health Information (PHI) will be entered into the Fitbit website. The patient's name entered in the Fitbit will be the participant's study number. Once the study has ended, the logins will be reconfigured so that patients can use whatever name they wish and log into the Fitbit site to monitor their progress if they so choose.

Hard copies of the patient study files and source documentation will be maintained in locked research offices in the Physical Performance Laboratory at all times. These data and access to these rooms are available to study personnel only. We retain records according to the new records retention policies (6 years after cut-off time). EKGs from the exercise stress tests will be discarded when patient follow-up is completed. We are connected to the Cardiology EKG network and the EKGs are stored there indefinitely. If patients provide written permission and request that their test be sent to a treating physician, these data and tests will be given or sent to others. Release of information procedures are followed. These procedures will be explained to patients at the time of completing the informed consent.

Potential Benefits of the Proposed Research to the Subjects and Others. The risks to patients are low when compared to the potential benefits of participation. Since there is no non-exercising control group, all patients have potential to increase their physical function. In addition to decreased breathlessness and improved quality of life[2,7,8] and, possibly, decreased COPD-related hospitalizations, emergency department visits and unscheduled physician visits[9] patients may gain cardiovascular benefit from participation such as improved lipid profiles and generalized fitness and functional status.[2,7,8] Patients also benefit from improved coordination of care. Our project manager (S. O'Connell, RN, MHA) actively

works with clinicians to coordinate appointments efficiently.

Importance of the Knowledge to be Gained. Increasingly, cardiac rehabilitation efforts are being moved to the home environment. These trends are the same for pulmonary rehabilitation. Finding ways to keep patients involved in home-based rehabilitation programs is critically important. We reason that our innovative home-based exercise program augmented by patient-tailored, rhythmically enhanced music will successfully lessen patients' perception of exercise-induced dyspnea and exercise-induced effort while concurrently increasing intensity and duration of walking.

Data Safety Monitoring/Adverse Events. Data Safety Monitoring will be ongoing throughout the study. Dr. Scott Budinger (Northwestern University) will be responsible for reviewing our data safety monitoring reports yearly. Data collection methods and forms will be reviewed initially. Dr. Budinger will be notified of all study-related serious adverse events within 48 hours of discovery. He will decide if further action beyond what the research team has proposed is warranted. The following information will be included in the yearly reports to Dr. Budinger: study event update (e.g., changes in personnel, recruitment strategies, testing procedures), study enrollment and randomization data (actual vs. expected), baseline data on patients by randomization group, recruitment and retention flow diagram (i.e., CONSORT diagram), patient retention data (deaths, loss to follow up, withdrawals) and adverse event monitoring log. Adverse events will be split in study related and non-study related. Specific adverse events to be monitored include: exacerbations, falls, emergency room visits, hospitalizations and deaths. Subject group assignment will be blinded for the above reports.

Women and Minority Inclusion: We actively recruit veterans to participate in our studies. We expect at least 20% of our patients to be minority patients (our current study consists of 11% minority patients). To boost the number of women participants, we will request permission to the local IRB to enroll non-veterans with COPD.
Vulnerable patients will not be recruited in this study.

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