Abbreviated Title: Exercise and COVID-19

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Title: COVID-19, Chronic Adaptation and Response to Exercise (COVID-CARE): A Randomized Controlled Trial

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council for Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

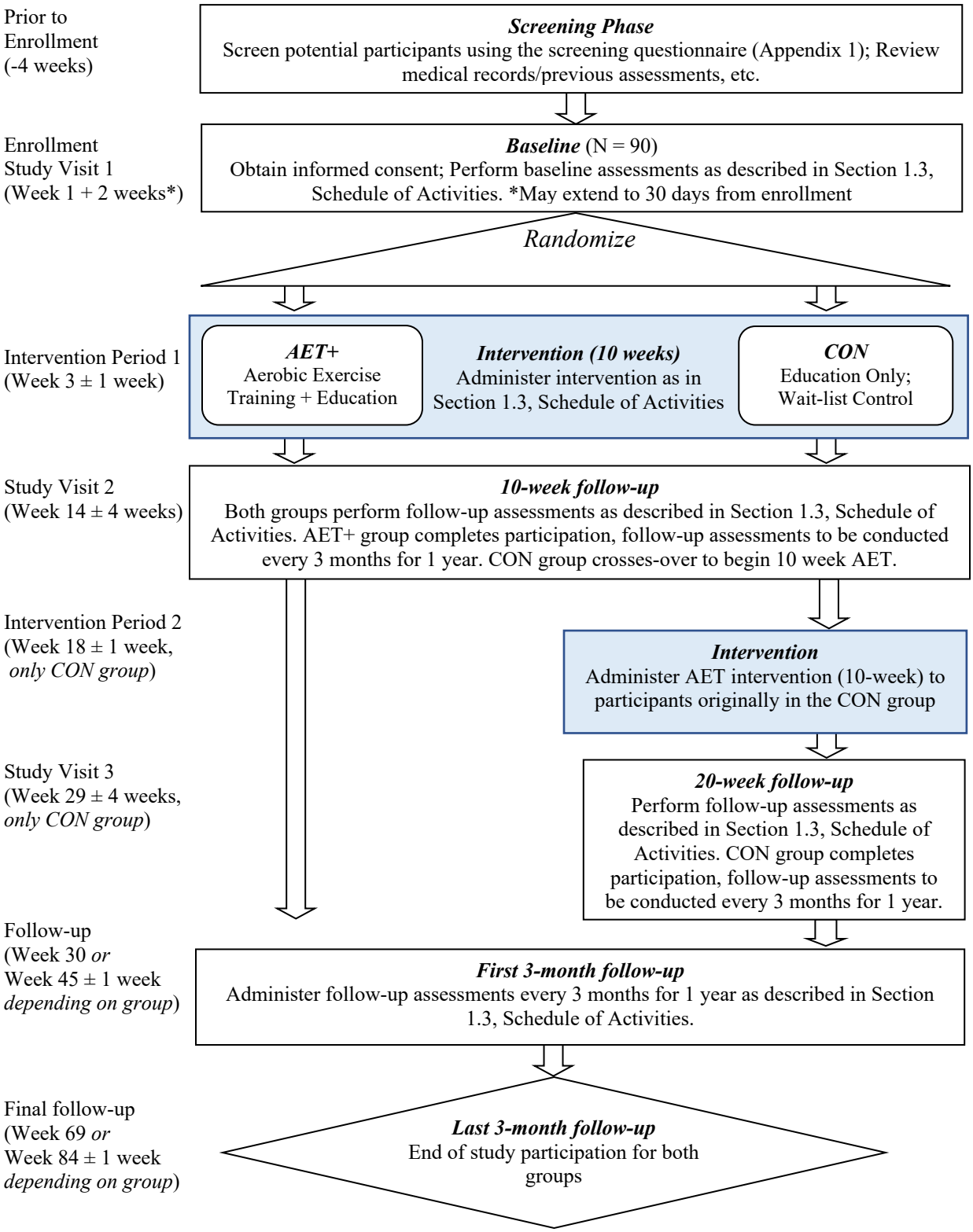
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	COVID-19, Chronic Adaptation and Response to Exercise (COVID-CARE): A Randomized Controlled Trial
Study Description:	This randomized controlled trial will determine whether aerobic exercise training has a beneficial effect on physical function, health-related quality of life, free-living physical activity and sleep quality among survivors of COVID-19. Participants will be randomized to either an aerobic exercise training and education (AET+) group or a control education only group (CON) for 10 weeks. Assessments for physical function, self-reported health outcomes for quality of life (QOL), free-living physical activity and sleep quality will be measured at baseline and following the 10-week intervention period. Participants in the CON group will then crossover and perform AET after the 10-week follow-up visit. All participants will be monitored for one year to capture free-living physical activity, sleep quality and health-related QOL outcomes over time. It is hypothesized that following 10 weeks, physical function, health-related QOL, free-living physical activity and sleep quality will show greater improvement with AET+.
Objectives:	Primary Objective: To examine the effect of aerobic exercise training on physical function in participants recovering from COVID-19. Secondary Objectives: To examine the effect of aerobic exercise training on patient reported outcomes and other health-related QOL components in participants recovering from COVID-19; To examine the effect of aerobic exercise training on free-living physical activity and sleep quality in participants recovering from COVID-19. Exploratory Objectives: To explore the effect of aerobic exercise training on clinical outcomes, cardiorespiratory function, cognition, biomarkers, metabolomics, ultrasound-based muscle measurements, and vascular function in participants recovering from COVID-19; To explore the feasibility of conducting the AET program remotely in the crossover CON group of participants recovering from COVID-19; To explore follow-up physical activity, sleep quality and health-related QOL outcomes over 1 year in participants recovering from COVID-19.
Endpoints:	Primary Endpoints: Physical function as measured by distance walked during the 6 minute walk test after 10 weeks post-randomization with AET+ and CON. Secondary Endpoints: Patient-reported outcomes and other health-related components after 10 weeks post-randomization with AET+ and CON; Free-living physical activity and sleep quality after 10 weeks post-randomization with AET+ and CON. Exploratory Endpoints: Clinical outcomes, cardiorespiratory function, cognition, biomarkers, metabolomics, ultrasound-based muscle measurements, and vascular function after 10 weeks post-randomization with AET+ and CON; Collection of initial feasibility data to conduct exercise sessions remotely; Explore relationships between the physiological variables and post-study health outcome variables over time.

Study Population:	Ninety male and female adults (18 to 80 years old) recovering from COVID-19, from the greater Washington DC metropolitan area.
Phase:	N/A
Description of Sites/Facilities Enrolling Participants:	Single-site study (NIH Clinical Center)
Description of Study Intervention:	Aerobic Exercise Training: Participants will perform aerobic exercise, 3 times a week for 10 weeks, with supervision by credentialed RMD staff members. Participants will be encouraged to target 30 minutes of continuous aerobic exercise. The intensity of exercise will be gradually increased from light-moderate to moderate-high as safely tolerated by the participant and guided using heart rate targets. Education: Participants will have weekly education sessions for 10 weeks. All sessions are ~1 hour and will be conducted remotely by credentialed RMD staff members. Participants randomized to AET+ will perform both exercise training and education during the 10 week intervention period. Participants randomized to CON will perform education only during the first 10 weeks, followed by exercise training during the second 10 weeks (crossover).
Study Duration:	36 months
Participant Duration:	Up to 17 months if randomized to AET+, and up to 21 months if randomized to CON

1.2 SCHEMA


Prior to Enrollment (-4 weeks)
Screening Phase
Screen potential participants using the screening questionnaire (Appendix 1); Review medical records/previous assessments, etc.
Enrollment Study Visit 1 (Week 1 + 2 weeks*)
Baseline (N = 90)
Obtain informed consent; Perform baseline assessments as described in Section 1.3, Schedule of Activities. *May extend to 30 days from enrollment
Randomize
Intervention Period 1 (Week 3 ± 1 week)
AET+
Aerobic Exercise Training + Education
Intervention (10 weeks)
Administer intervention as in Section 1.3, Schedule of Activities
CON
Education Only; Wait-list Control
Study Visit 2 (Week 14 ± 4 weeks)
10-week follow-up
Both groups perform follow-up assessments as described in Section 1.3, Schedule of Activities. AET+ group completes participation, follow-up assessments to be conducted every 3 months for 1 year. CON group crosses-over to begin 10 week AET.
Intervention Period 2 (Week 18 ± 1 week, only CON group)
Intervention
Administer AET intervention (10-week) to participants originally in the CON group
Study Visit 3 (Week 29 ± 4 weeks, only CON group)
20-week follow-up
Perform follow-up assessments as described in Section 1.3, Schedule of Activities. CON group completes participation, follow-up assessments to be conducted every 3 months for 1 year.
Follow-up (Week 30 or Week 45 ± 1 week depending on group)
First 3-month follow-up
Administer follow-up assessments every 3 months for 1 year as described in Section 1.3, Schedule of Activities.
Final follow-up (Week 69 or Week 84 ± 1 week depending on group)
Last 3-month follow-up
End of study participation for both groups

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	**Screening Phase** - 4 weeks	**Study Visit 1** (Enrollment/Baseline) Week 1 +/- 2 weeks*
Screening Questionnaire	X	
Review Medical Records	X	
Demographics	X	
Informed consent		X
History and Physical Exam, Cardiology Evaluation		X
Concomitant medication review		X
Vital signs		X
ECG, Echo, PFT, Chest CT, Neuromuscular Ultrasound		X
Biospecimen Collection (blood and urine)[a]		X
Physical Assessment (6MWT, SPPB/Mini-BEST, CPET)		X
VAS-CFS and Qualitative interviews[b]		X
Patient-reported Outcomes and QOL		X
Physical activity and sleep quality monitoring		X
Other assessments (e.g. neurology, vascular function)		X
Optional assessments (brain MRI, skin biopsies)		X
Randomization		X
Adverse event review and evaluation		X
Complete Case Report Forms (CRFs)		X
[a]Including urine pregnancy test (women of childbearing potential); [b]Repeated before and up to 72 hours after the CPET		
*May extend to 30 days from enrollment		

Continued: SOA for AET+ group

Procedures	**Intervention Period 1** Week 3 +/- 1 week	**Study Visit 2** (10-week follow-up) Week 14 +/- 4 weeks	**3-month follow-up 1** Week 30 +/- 1 week	**3-month follow-up 2** Week 43 +/- 1 week	**3-month follow-up 3** Week 56+/- 1 week	**3-month follow-up 4** Week 69 +/- 1 week
History and Physical Exam, Cardiology Evaluation		X				
Concomitant medication review		X				
Vital signs	X	X				
ECG, Echo, PFT, Chest CT, Neuromuscular Ultrasound		X				
Biospecimen Collection (blood and urine)[a]		X				
Physical Assessment (6MWT, SPPB/Mini-BEST, CPET)		X				
VAS-CFS and Qualitative interviews[b]		X				
Patient-reported Outcomes and QOL		X	X	X	X	X
Physical activity and sleep quality monitoring	X	X	X	X	X	X
Other assessments (e.g. neurology, vascular function)		X				
Optional assessments (skin biopsies)		X				
Supervised Exercise Session (thrice weekly)	X					
Education Sessions (weekly)	X					
Adverse event review and evaluation	X----------X					
Complete Case Report Forms (CRFs)	X----------X					

[a]Including urine pregnancy test (women of childbearing potential); [b]Repeated before and up to 72 hours after the CPET

Continued: SOA for CON group

Procedures	**Intervention Period 1** Week 3 +/- 1 week	**Study Visit 2** (10-week follow-up) Week 14 +/- 4 weeks	**Intervention Period 2** Week 18+/-1 week	**Study Visit 3** (20-week follow-up) Week 29 +/- 4 weeks	**3-month follow-up 1** Week 45 +/- 1 week	**3-month follow-up 2** Week 58 +/- 1 week	**3-month follow-up 3** Week 71 +/- 1 week	**3-month follow-up 4** Week 84 +/- 1 week
History and Physical Exam, Cardiology Evaluation		X		X				
Concomitant medication review		X		X				
Vital signs		X	X	X				
ECG, Echo, PFT, Chest CT, Neuromuscular Ultrasound		X		X				
Biospecimen Collection (blood and urine)[a]		X		X				
Physical Assessment (6MWT, SPPB/MiniBEST, CPET)		X		X				
VAS-CFS and Qualitative Interviews[b]		X		X				
Patient-reported Outcomes and QOL		X		X	X	X	X	X
Physical activity and sleep quality monitoring	X	X	X	X	X	X	X	X
Other assessments (e.g. neurology, vascular function)		X		X				
Optional assessment (skin biopsies)		X		X				
Supervised Exercise Session (thrice weekly)			X					
Education Sessions (weekly)	X							
Adverse event review and evaluation	X ----------							---------- X
Complete Case Report Forms (CRFs)	X ----------							---------- X

[a]Including urine pregnancy test (women of childbearing potential); [b]Repeated before and up to 72 hours after the CPET

2 INTRODUCTION

2.1 STUDY RATIONALE

The emergence of SARS-CoV-2 as a novel coronavirus at the end of 2019 (COVID-19) resulted in a pandemic that has affected millions of people worldwide. Although clinicians and scientists are gaining an understanding of the various presentations and manifestations of COVID-19, limited reports are available on the recovery trajectory and long-term outcomes faced by survivors. With the increasing number of COVID-19 cases being reported in the United States and worldwide, many people will require follow-up care related to acute respiratory distress syndrome (ARDS), critical illness and prolonged hospitalization (1). Persons recovering from ARDS and ICU stays typically experience a multitude of negative health outcomes that include physical and mental deficits, reduced life satisfaction and social health (2). Effective use of aerobic exercise training as a cardiorespiratory, rehabilitative intervention could have a high degree of impact on patient functional and quality of life outcomes.

This randomized controlled clinical trial will examine the effect of a 10 week aerobic exercise training program on physical function, health-related quality of life outcomes, free-living physical activity and sleep quality among persons recovering from COVID-19. Recruitment will occur during the phase of long-term recovery and when participants are no longer infectious. The use of a crossover control group in the study design will allow examination of the spontaneous recovery for physical function, quality of life outcomes, free-living physical activity and sleep quality among survivors of COVID-19.

2.2 BACKGROUND

By July 2020, the 2019 coronavirus outbreak had affected over 12 million people and resulted in over 570,000 deaths worldwide (3). While these numbers continue to grow, they are likely underestimations due to delayed reporting and limited test availability (4). In early July, overall cumulative hospitalization rates in the United States was 104.1 per 100,000 among confirmed COVID-19 cases, with higher rates affecting adults over 65 years of age (5). Yet even among hospitalized individuals between 18 and 49 years of age, 24.3% were severe cases of COVID-19 (i.e., requiring ICU admission) (5), indicating that young and working-aged adults are not immune to this pandemic.

Following the surge of hospitalization and critical care needs, post-acute care and rehabilitation will be required in many persons recovering from COVID-19 (6). However, the relatively short period since the emergence of COVID-19 and the immediate focus centered on management of acute cases has resulted in few reports regarding recovery and longer-term issues faced by COVID-19 survivors. Initial reports suggest symptoms persist for months among patients hospitalized with COVID-19 (7), and even weeks in those with only milder symptoms (8). Over 1,100 observational or natural history studies are currently underway worldwide (on clinicaltrials.gov as of 7/13/2020), however, it will take months to years to fully understand the long-term sequelae of COVID-19.

Early rehabilitation guidelines for COVID-19 are now available (9), along with recommendations by physiatrists with early experience with this disease (10, 11). Conditions similar to COVID-19, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), may also help inform future rehabilitation needs (12). In addition, the relatively high incidence among hospitalized COVID-19 patients requiring ICU

admission (20.3%) and further developing ARDS (32.8%) (13), suggest rehabilitation approaches for critical illness and prolonged hospitalization as being appropriate.

Previous experience regarding recovery post-SARS and ARDS suggests physical and mental limitations affecting quality of life. Physical capacity is reduced following recovery from ARDS (14), even in adults that are relatively young (ages 20 to 40 years) (15). Similar impairments in physical function have also been observed among previously healthy medical staff recovering from SARS (16). However, impairments can persists for years, as seen in physical and psychological issues at 5 years post-ARDS (17), and physical impairments, lower quality of life (18) and mental health problems (19) at 1 year post-SARS are still being observed. The persistent health problems experienced by survivors of ARDS/SARS, even in younger working-aged adults, makes it imperative that programs are incorporated early to improve quality of life and facilitate return to work (20). A recent Cochrane Review found no studies that looked at fitness to return to work at 12 months post-ARDS and concluded that "the potential long-term consequences of ARDS are important to survivors, [therefore] future research should incorporate a longer follow-up to measure the impacts on quality of life." (21).

Physical exercise is often utilized in both general (22) and clinical populations (23, 24) to improve physical and mental well-being, and is an integral part of pulmonary rehabilitation (25). To our knowledge, there has only been one study that utilized exercise training in persons recovering from SARS (26). This RCT reported improved physical function in the group that exercised, however no difference in health-related quality of life was found when compared to the control group that had educational sessions regarding exercise (26). A limitation of this study was that it failed to report whether patients in the exercising group had adhered to the exercise program as intended. While attendance was monitored (and was >85%), only 40% of the sessions were supervised which has important consequences if patients did not perform the exercise sessions as prescribed. Nevertheless, this study did not report any adverse events and achieved a completion rate of 100% (26), suggesting that patients were able to safely perform exercise training post-SARS. Although this RCT did not include a follow-up period beyond the 6-week intervention, exercise was implemented early in the recovery process from SARS (within 2 weeks of hospital discharge), suggesting the recovery trajectory may be affected with early exercise intervention.

While our knowledge about COVID-19 grows every day, much remains unknown regarding the sequela from this novel disease. Although COVID-19 mainly manifests as a respiratory illness, it is increasingly recognized that other organ systems may be affected including cardiac, renal, neurologic, gastrointestinal, endocrine, and hematologic (27). The multitude of neurological symptoms repeatedly reported during acute COVID-19 infection has medical experts fearing that the viral outbreak may trigger other diseases such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (28). Indeed, personal observation and communication with health professionals actively treating persons recovering from COVID-19, report excessive fatigue (beyond what would be expected from hospitalization), which persists for weeks beyond hospital discharge. This has since been supported by other recent reports (7, 29). Post-Exertional Malaise (PEM), a feature of ME/CFS has been reported among individuals post-COVID (30), and described as "worsening of symptoms following even minor physical or mental exertion, with symptoms typically worsening 12 to 48 hours after activity and lasting for days or even weeks."(31). Relevant to this discussion, exercise training has been widely used to combat

fatigue associated with chronic illnesses including multiple sclerosis (32), cancer (33) and CFS (34). Further, disuse muscle atrophy and/or weakness are known to occur following even relatively brief periods of physical inactivity (35), and the effects of critical illness and/or the use of paralyzing agents in the ICU also increases the risk of muscle and nerve dysfunction and may be associated with prolonged weakness and disability (36). Exercise is a frequently proposed therapy for critical illness myopathy and neuropathy (37).

Our lack of knowledge for this novel disease coupled with the rapidly evolving nature of this pandemic makes specific rehabilitation recommendations challenging. Further, the growing number of survivors with sequela post-COVID-19 makes the need for an immediate rehabilitation approach apparent. By capitalizing on past experience with similar diseases, staying up to date with current findings, and paying attention to our colleagues in the field, honing in on an appropriate intervention is possible. Regular exercise is well recognized for preventing diseases and promoting health benefits in the general population, yet it is also widely used in chronic illnesses in the form of cardiac and pulmonary rehabilitation. Exercise does not fall under FDA regulations, and may be applied as soon as the safety and efficacy of treatment has been demonstrated. This makes exercise an attractive and much needed rehabilitative strategy for battling long-term sequelae of COVID-19, and could have immense impact at the personal and public health level.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 Known Potential Risks

2.3.1.1 Blood Draws

Routine venipuncture for blood draws usually does not cause any serious problems, however risks of the procedure include pain, bleeding, bruising, hematoma formation, nerve damage, and infection. These risks will be minimized by having trained and credentialed NIH CC personnel perform the procedure and obtain the blood samples. On occasion, some participants may become dizzy, nauseous, or faint at the sight of their own blood. We will instruct participants to face a different direction during the procedure if they are prone to these reactions. If these reactions do occur, participants will be given appropriate instructions for managing them by the trained technician acquiring the sample.

2.3.1.2 Electrocardiogram (ECG)

There is no clinically significant risk associated with this procedure. There may be minor discomfort, when the ECG electrodes are removed from the chest. In rare instances, a reaction to the electrodes may cause redness or swelling of the skin.

2.3.1.3 Echocardiogram (Echo)

The use of diagnostic transthoracic ultrasound is not associated with significant risk. There is however, the possibility of an allergic response to the gel used to optimize contact of the ultrasound transducer with the skin in a few people. This allergic reaction may present as a rash and/or itching localized to the area of contact, and will subside after a few hours to a few days.

2.3.1.4 Pulmonary Function Testing (PFT) with DLCO

Serious risks are not associated with pulmonary function tests or lung diffusion tests. Participants may experience perceptions associated with exertion on the PFT and may feel dizzy and short of

breath for a short time after completion of the test. Participants may also experience slight dizziness and shortness of breath during and shortly after the DLCO procedure. Bronchodilator administration may also cause transient increase in heart rate, blood pressure, arrhythmias and nervousness. In all cases, these symptoms are not specific to any emergent condition, unless severe and persistent, and should only last a few minutes following the tests.

2.3.1.5 Brain Magnetic Resonance Imaging (MRI)

The brain MRI is an optional assessment and performed only once at baseline. People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, some types of dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye. All participants will be screened for these conditions prior to the study, and if they have any, they will not receive an MRI scan.

It is not known if MRI is completely safe for a developing fetus. Therefore, all participants who are physically able to become pregnant will have a pregnancy test performed no more than 24 hours before an MRI scan. The scan will not be done if the pregnancy test is positive.

People with fear of confined spaces may become anxious during an MRI. Those with back problems may have back pain or discomfort from lying in the scanner. The noise from the scanner is loud enough to damage hearing, especially in people who already have hearing loss. Everyone having a research MRI scan will be fitted with hearing protection. If the hearing protection comes loose during the scan, they will be instructed to let the technologist know right away. Participants will be asked to notify the investigators if they have hearing or ear problems. Participants will be asked to complete an MRI screening form for each MRI scan they have. There are no known long-term risks of MRI scans.

The MRI system and the coils to be used in this study are FDA cleared. However, the study uses the MRI system in research mode which is investigational. While in research mode, the MR system operates below the limits that the FDA deems to present significant risk as defined in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices. In addition, research image processing is used that is not cleared by the FDA. This is in addition to the standard diagnostic data that is generated by the MR system. There is no potential for serious risk to the health, safety, or welfare of the subjects using the MRI scanner in these ways.

The use of gadolinium with MRI is optional. Gadolinium is a contrast agent approved for use with MRI by the FDA. Symptoms from the contrast infusion are usually mild and may include feeling hot, burning, or coldness in the arm during the injection, a metallic taste, headache, allergic reactions and nausea. In an extremely small number of individuals, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Unless specifically allowed by the protocol, participants will not receive gadolinium-based contrast agents for research purposes if they have previously had an allergic reaction to them. Individuals with a history of anaphylaxis to other agents or chronic asthma requiring treatment will not receive gadolinium under this protocol unless they have previously

received gadolinium and tolerated it well. Participants will be asked about such allergic reactions and history of asthma before a contrast agent is administered.

People with kidney disease are at risk for a serious reaction to gadolinium contrast called "nephrogenic systemic fibrosis," which has resulted in a very small number of deaths. If subjects are 60 years old or greater or have diabetes, kidney disease or liver disease, blood work to assess kidney function will be performed within 2 weeks before any MRI scan with gadolinium contrast. Participants may not receive gadolinium for a research MRI scan if kidney function is not normal. There is no evidence for the potential of gadolinium-related toxicity in people with normal kidney function. This protocol follows NIH Clinical Center guidelines for kidney-function screening related to gadolinium administration.

Most of the gadolinium contrast is eliminated in the urine. However, recent studies have found very small amounts of residual gadolinium in the body, including the brain, by imaging and at autopsy. Macrocyclic gadolinium-containing contrast agents are substantially less likely to leave gadolinium behind than linear agents. Only macrocyclic agents are used in this study. There is presently no evidence that the retained gadolinium is associated with any adverse effects.

2.3.1.6 Computed Tomography (CT)

This research study involves exposure to radiation from up to 3 CT scans, and would expose the participant to 0.48 rem per year based on a conventional high resolution chest CT on 3 occasions (0.16 rem x 3 = 0.48) per year. This total radiation exposure is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil.

While there is no direct evidence that the amount of exposure received in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer. It is also best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults. All participants who are physically able to become pregnant will have a pregnancy test performed no more than 24 hours before the CT scan. The scan will not be done if the pregnancy test is positive. Participants that are breast feeding will also not perform this scan.

2.3.1.7 Neuromuscular Ultrasound

Ultrasound imaging is widely used in clinical practice and has an excellent safety profile. The sound waves produced during diagnostic ultrasound imaging (B-mode, shear wave elastography, microvascular flow, M-mode) are considered safe when used and applied by trained health care providers. The energy produced by ultrasound has the potential to produce biological effects on the body including mild warming or heating of tissues under the transducer. In rare instances, ultrasound can produce cavitation (small pockets of gas in body fluids or tissues). The long-term consequences of these effects are unknown.

2.3.1.8 Cardiopulmonary Exercise Test (CPET)

The risks of this study are those associated with participation in vigorous aerobic exercise. The general risks of exercise include sudden cardiac arrest, myocardial infarction, angina, electrocardiographic abnormalities, shortness of breath, dizziness, early fatigue onset and exhaustion, joint or muscle pain or soreness. These risks are slight and the likelihood of their

occurrence is small even in high risk individuals with known coronary atherosclerosis or chronic heart failure during maximal exercise testing. In studies that include patients with known heart disease as well as patients in whom the presence of heart disease is unknown, morbidity and mortality during maximal exercise testing remains low at 0.0 to 8.3 per 100,000 and 0.0 to 1.0 per 100,000 respectively (38-47). Pre-screening minimizes the risk to almost negligible levels.

Specific to post-COVID infection, PEM may develop within hours and last for several days after the CPET in certain individuals. Among those displaying significant post-COVID symptoms and PEM, muscle tissue damage have been reported in samples taken the day following a CPET (48). It is unknown whether prolonged or irrevocable muscle damage may be caused by the CPET or which individuals may be affected. Therefore, potential participants reporting PEM on the DSQ-PEM during the pre-screen phase will not be included.

To minimize risk and maximize safety, participants will be evaluated by NIH cardiology, perform medical history and physical examination, ECG, Doppler cardiac echocardiography, and pulmonary function tests with DLCO, to exclude those with contraindications to exercise prior to the CPET. During the CPET, participants will be monitored by continuous 12-lead ECG. Prior to beginning the test, participants will be informed of the signs and symptoms of heart disease and questioned frequently during the test regarding their presence. As recommended by the American Heart Association and the American College of Sports Medicine (ACSM), exercise will be overseen by personnel appropriately trained in clinical exercise testing (49). In addition, a licensed independent practitioner (LIP) will be present during all exercise tests. The investigators and clinical exercise training and testing staff in our laboratory are highly experienced in cardiopulmonary exercise testing, even in high-risk patients such as those with pulmonary artery hypertension and interstitial lung disease. As PEM may develop even among those reporting no PEM on enrollment, the presence of significant symptoms consistent with PEM may be captured during the qualitative interviews. These interviews were specifically developed to detect the presence of PEM and are performed by LIPs and/or persons with experience and skill conducting interviews for identifying the presence of PEM. The impact of exercise on post COVID-19 condition and PEM is still unresolved, therefore the clinical team will monitor for possible development of PEM symptoms throughout the study and manage participants accordingly.

Risk of injury also includes those related to falling on a moving treadmill belt, such as abrasions, contusions, cuts, sprains, and fractures. The likelihood that any of these injuries would occur is small and preventive measures will be enforced to ensure that the risks remain at a minimum.

The treadmill is equipped with handrails for aiding balance and providing increased stability. The treadmill also is equipped with a “hot” switch that is easily within the reach of the participant while walking on the treadmill. When the switch is activated, the treadmill stops and ends the test immediately. Under this circumstance, the treadmill cannot be restarted unless both the treadmill itself and the computer control are reset. Participants are instructed in treadmill safety and the use of the hot switch before beginning the test protocol. Participant response to the test is monitored visually, electronically, and by verbal interaction between the participant and the testing staff.

Participants with diabetes will be monitored before and after exercise testing for glucose levels and glycemic responses to exercise. Physical activity generally reduces glycemic levels and intense activity can cause transient blood glucose derangements in individuals with diabetes.

Thus, the risks of hypoglycemia and hyperglycemia are associated with exercise in individuals with diabetes. The acute risks of exercise for individuals with diabetes must be weighed against the potential long-term benefits such as a reduction in cardiovascular disease risk and improved hemodynamic function. In order to reduce risks and avoid the onset of diabetic symptoms during participation in the study, glucose monitoring will be performed per standard of care.

2.3.1.9 6 Minute Walk Test (6MWT)

The major risks associated with this test are stumbles and falls, which could result in sprains, strains, fractures, contusions, and concussion. Additional risks include heart attack, cardiac arrest and sudden death similar to the CPET.

To maintain participant safety during this test, the 6MWT will be conducted by credentialed RMD staff members with expertise in exercise testing. Participants will be screened for evidence of pre-existing cardiovascular disease and subsequently monitored for the development of signs and symptoms that could indicate complications such as hypoxia, chest pain, shortness of breath, nausea, pallor and diaphoresis. Additionally, they will be instructed to sit immediately following the test to avoid falling in the event they should become dizzy after strenuous exercise.

2.3.1.10 Neuropsychological Test and Questionnaires

The neuropsychological tests are not harmful, but may be frustrating or stressful. Filling out the questionnaires may be perceived as boring.

All participants will be informed prior to consent that they will be asked multiple questions that relate to their emotional and psychological health, and they will be told that they can refuse to answer any or all questions that they are not comfortable with. They may also stop the testing at any time for any reason.

2.3.1.11 Olfactory Testing

There are minimal anticipated medical risks associated with the olfactory test (UPSIT).

2.3.1.12 Autonomic Nervous System Testing

There are minimal anticipated medical risks associated with the Quantitative Sudomotor Axon Reflex Test (QSART) for recording sweat volume. Participants may feel a tingling sensation when the electric current is on. Some participants may experience brief lightheadedness associated with breathing deeply and the Valsalva maneuver. During the tilt table test, some participants may feel lightheaded or weak or may faint. Should participants have symptoms or large changes in blood pressure or heart rate related to the tilt test, they will be immediately brought back to the supine position and monitored until their symptoms improve and blood pressure and heart rate are back to baseline values.

2.3.1.13 Vascular Function Testing

Vascular Function Testing comprise of several different assessments involving different risks and discomforts. For the pulse wave analysis (PWA), cardio-ankle vascular index (CAVI), peripheral arterial tonometry (PAT) and ankle-brachial index (ABI), these procedures are very well tolerated. Other than potential transient minimal discomfort with the blood pressure cuff, no side effects are expected. Subjects with fragile skin may suffer minor trauma.

For the near-infrared spectroscopy (NIRS) occlusion reperfusion test, this test is generally well tolerated. Some individuals will experience discomfort in the occluded limb, while the cuff is inflated. If that occurs, we will attempt distraction of the participant. If discomfort continues and the participant wishes to stop the test, we will deflate the cuff before the specified time is completed. Near-infrared light does not ionize biological tissue and poses no significant health risk. Since water absorption is low within this spectral range, local heating of the tissue is also minimal. Burns and heat damage are highly unlikely. The optical powers we will use in this study are all far less than those used with surgical lasers meant to incise, ablate, and coagulate tissue. The measurement itself is painless, and should not cause significant discomfort. Nevertheless, should any participant show signs of stress, the measurement will be suspended or cancelled.

For other optical imaging modalities, all are non-invasive and associated with risk due to the use of non-ionizing radiation such as visible, ultraviolet and infrared light. This includes nail capillaroscopy, infrared imaging (IR), Laser Speckle Contrast imaging (LSCI), in conjunction with assessment of oxygenation by Laser Doppler probes, temperature skin patches, continuous monitoring of blood pressure and main vital signs. Most people tolerate the skin patches for temperature monitoring well but it is possible for the subject to develop a mild allergy to the adhesive used on the patches.

For lower extremity ultrasound, no adverse effects have been described with this imaging technique.

2.3.1.14 Skin Biopsies

An optional procedure is skin biopsies. This procedure is performed using local anesthetic and a 4 mm or smaller piece of skin is removed aseptically by punch procedure. Discomfort at the biopsy site is usually mild and transient. This can be treated with minor analgesics. Most common risks include a reaction to the local anesthetic and the slight possibility of local bleeding or infection. Scarring always occurs at the biopsy site.

2.3.1.15 Exercise Training

The risks are those associated with aerobic exercise in general. Exercise leads to expected physiologic responses such as an increase in breathing rate, sensations of warmth, sweating, and varying degrees of muscle fatigue. Individuals who are unfamiliar with exercise or those who are deconditioned sometimes find these sensations uncomfortable. Participants will be trained to use the Borg scale to rate their perceived exertion which will help supervising staff to assess the participant's response to training (both immediately and over time) and adjust the exercise intensity or dose as necessary. Any form of exercise has the potential to result in muscle or joint injuries, or present a risk for falls, but these risks will be minimized through close supervision of exercise training sessions by trained staff. Upright aerobic exercise such as walking or stepping can lead to overuse injuries to the hips, knees, ankles, and/or feet. While these can occur in anyone, they are more likely to develop in those who are unaccustomed to exercise and those with obesity, osteoarthritis, or connective tissue or rheumatologic disease. Participants will be assessed for the presence of pain before and after each session. Those who develop new or worsening pain or pain associated with exercise will be evaluated by a LIP. Participants may also experience immediate or delayed muscle soreness due to initiating an exercise training program especially if they were previously sedentary. The onset of muscle soreness typically occurs

immediately or within 48 hours and lasts a few days to a week. Many participants may also experience increased levels of fatigue that are sustained for up to 24 hours following the exercise sessions. This fatigue will typically subside after one to three weeks. Rarely, heart attack and sudden death can occur in the setting of exercise. To mitigate these risks participants will be thoroughly screened prior to enrollment for the presence of existing heart disease or excessive cardiac risk, have exercise intensities increased gradually (both within each session and over time), be monitored closely during exercise for the development of cardiovascular signs and symptoms (e.g. chest pain, dyspnea, dizziness, lightheadedness, or nausea), and be instructed in lifestyle changes such as reducing obesity and controlling comorbid conditions to decrease their cardiac risk factors over time. Exercise may cause PEM to develop in certain individuals, however the type, severity and onset of symptoms differ widely among individuals. Supervising staff will assess tolerance of their previous exercise session before each session and adjustments to the exercise intensity or dose will be made as necessary.

In order to determine that the participants' individualized exercise training regimen is within a safe and effective range as determined by ACSM guidelines, participants will undergo a CPET prior to beginning exercise training. The intensity of training will be well below that which was attained during the CPET and participants who develop clinical signs and symptoms on the CPET will be excluded from the study. All participants will be pre-screened and approved for participation by a medical staff member before beginning participation. Participants' exercise training sessions will be monitored by staff specifically credentialed for the supervision of exercise in clinical populations.

As mentioned above (2.3.1.8), participants with diabetes will be monitored before and after exercise training for glucose levels and glycemic responses to exercise. Glucose monitoring will be performed per standard of care to reduce risks and avoid the onset of diabetic symptoms.

Participants in the CON group will have the option of performing their exercise sessions on-site at NIH CC or remotely (exploratory objective #5). Those that participate in remote exercise training sessions will have additional inherent risks when exercising in different environments such as the home. This includes confined or cluttered spaces, and exercising near furniture, decorations or devices, that may result in trips or falls causing sprains, strains, fractures, contusions, and concussion. To minimize these risks, participants will be requested to use an open space for conducting the exercise sessions and common trip hazards will be identified during the first remote session, prior to conducting exercise. Participants will also be asked to familiarize themselves with the equipment provided for communication and monitoring of physiological responses, in order to minimize the risks of equipment failure, loss of visual/voice contact with study staff, or data loss. All remote sessions will be supervised by credentialed RMD staff members with experience in exercise rehabilitation. Participants will also be asked to confirm their location, contact information and presence of any other person(s), prior to the start of all sessions to ensure RMD staff members have the information at their disposal should an emergency call be needed. Participants who are deemed unsuitable for remote monitoring due to safety concerns (e.g. those who have no suitable exercise space, have a high risk of injury from falls, are unwilling or unable to perform glucose monitoring, demonstrate impulsive or unsafe behaviors, lack the technologic skills, connectivity or bandwidth required for remote monitoring) will not participate in remote exercise sessions.

2.3.1.16 Use of Accelerometer

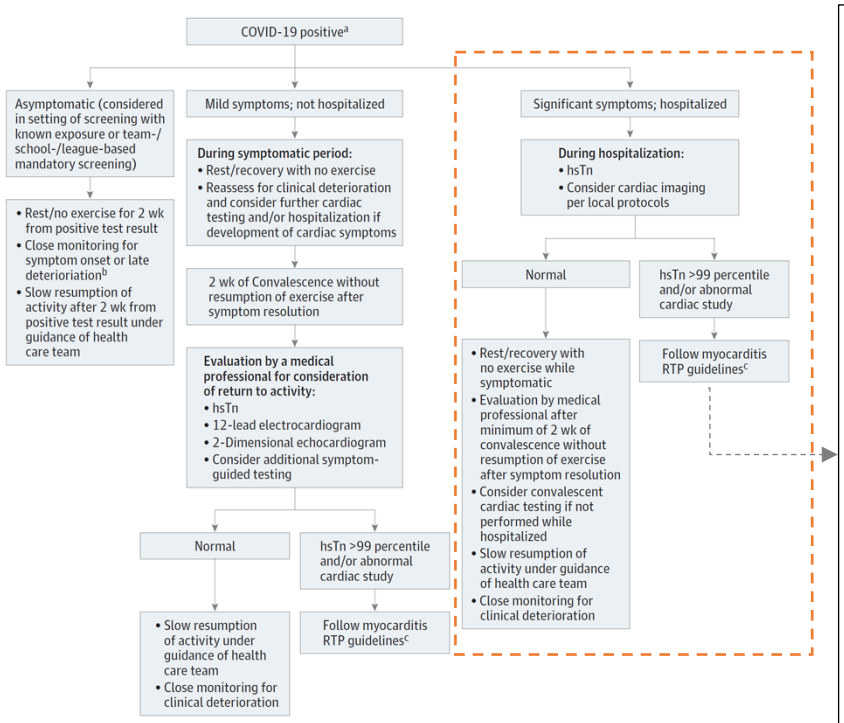
There are no known medical risks associated with wearing an accelerometer. Similar to most smartwatches on the market, some participants may experience slight discomfort associated with wearing this device on the wrist for extended periods of time.

2.3.2 Known Potential Benefits

Participants in this protocol have the potential to receive direct benefit from participating in this research. The exercise prescription used in this study is consistent with recommendations for patients with obstructive lung disease (49) and for improving cardiorespiratory fitness among the general population (22). A previous study found that participation in a similar aerobic exercise training program improved 6MWT distance and predicted peak VO_2 among individuals recovering from SARS (26). Participants recovering from COVID-19 may directly benefit from aerobic exercise training, where improvements in cardiorespiratory fitness enables individuals to accomplish functional activities or work at a lower percentage of their peak capacity and with less fatigue. Further, exercise participation has been shown to be beneficial in the reduction of all-cause mortality and morbidity in certain subsets of the population and is generally recommended for all who are physically able to participate (22).

2.3.3 Assessment of Potential Risks and Benefits

Cardiac complications associated with COVID-19 infection have been reported (50), with myocarditis potentially resulting in cardiac dysfunction, arrhythmias or sudden death with vigorous exercise (51) being a primary concern. A gradual return to sports or exercise is suggested in athletes or previously active people who have survived COVID-19. Additionally, specific assessments based on risk stratification of severity of symptoms and hospitalization due to COVID-19 are shown below (51):



Myocarditis Return-to-Play Guidelines from American College of Cardiology/American Heart Association

1. Before returning to competitive sports, athletes who initially present with an acute clinical syndrome consistent with myocarditis should undergo a resting echocardiogram, 24-hour Holter monitoring, and an exercise ECG no less than 3 to 6 months after the initial illness
2. It is reasonable that athletes resume training and competition if all of the following criteria are met:
   - Ventricular systolic function has returned to the normal range
   - Serum markers of myocardial injury, inflammation, and heart failure have normalized
   - Clinically relevant arrhythmias such as frequent or complex repetitive forms of ventricular or supraventricular ectopic activity are absent on Holter monitor and graded exercise ECGs

   At present, it is unresolved whether resolution of myocarditis-related late gadolinium enhancement should be required to permit return to competitive sports.
3. Athletes with probable or definite myocarditis should not participate in competitive sports while active inflammation is present. This recommendation is independent of age, gender, and LV function.

The recommendations for participants in this study are those contained in the dashed box above (51) with the myocarditis return-to-play guidelines (52). These were taken into consideration to minimize risk among patients recovering from COVID-19 in this study as follows:

- Inclusion of participants ≥ 7 days since symptom resolution
- Exclusion of participants with cardiac disease or conditions deemed unsafe for participation upon cardiology evaluation
- All participants will be evaluated prior to participation in exercise by credentialed NIH medical staff, including an evaluation at baseline (e.g., ECG, echocardiogram, cardiac imaging, cardiac biomarkers as appropriate) by NIH Cardiology
- All participants will perform the CPET with 12-lead ECG at the CC that is monitored by credentialed RMD staff members experienced with clinical exercise testing
- Gradual exercise progression with supervision by RMD staff members specifically credentialed for the supervision of aerobic exercise in clinical populations
- Thrice weekly check-ins to include monitoring of vital signs and symptoms before and after exercise during the 10 week AET intervention

Considerable overlap has been observed between the constellation of persisting symptoms in the post COVID-19 condition and ME/CFS (53). Featured among them is PEM, which was self-reported in 59% of surveyed participants reporting sequelae post COVID-19 (30). The distinguishing nature of PEM is the wide variety of worsening symptoms that may occur among individuals (from physical/mental fatigue to cold-like symptoms) and the onset or duration of symptoms (from hour to days) (54). Triggers of PEM not only include physical activity, but also mental effort and emotional stressors (54). It was recently observed that individuals identified as having PEM and post-acute sequelae of SARS-CoV2 (PASC) showed a multitude of abnormalities following a CPET, compared to a control group of individuals that had no lingering symptoms post COVID-19 (48). These abnormalities included compositional changes in skeletal muscle fibers, metabolic dysfunction, and muscle tissue damage in samples taken the day after the CPET (48). However, repeated muscle biopsies may have affected some of these findings, as the control group also showed these changes and interactions for group and time were not significant. Further, the PASC group averaged 17.9 months since initial infection, which was almost 4 times longer than the control group at 4.7 months. This extended duration of living with PASC may also account for some of the observed differences.

Specifically for PASC patients experiencing PEM, exercise recommendations "…*should follow a slow, progressive approach and be regularly evaluated in regard to symptom severity and the health status of patients*" (55). The following considerations are in place to minimize risk for patients that have or develop PEM during the study:

- Screening prior to enrollment to exclude potential participants that are identified as having PEM
- Perform assessment of PEM during H&Ps, and as needed throughout the study, by NIH medical staff for management of participants.
- Perform qualitative interviews before, during and after the CPET to monitor the development of significant symptoms consistent with PEM. Interviews are performed by LIPs and/or persons with experience and skill conducting interviews for identifying the presence of PEM.

- Gradual exercise progression with supervision by RMD staff members specifically credentialed for the supervision of aerobic exercise in clinical populations
- Assess and monitor symptoms and tolerance of previous exercise sessions by RMD staff members to adjust exercise sessions as necessary.

In general, health risks during exercise are very small. These risks are considered to be even smaller when maximal exercise evaluations are performed under supervised and safe clinical conditions, and additional medical tests and examinations related to defining the seriousness of the patients' conditions are performed. Improvement in cardiorespiratory fitness enables individuals to accomplish a given amount of activity or work at a lower percentage of their peak capacity and with less fatigue. Moreover, improvement of exercise tolerance generally increases quality of life by permitting individuals to engage more easily in daily physical activities. Specifically as it pertains to COVID-19, "…there is a strong rationale for incorporation of exercise prescription in management of Long COVID based on cardiac deconditioning as a major contributor to symptom burden and the well-described physiologic responses (and benefits) of exercise on the cardiovascular system"(56). Early reviews of the available literature on exercise training post-COVID suggest improved physical functioning and quality of life among non-hospitalized (55) and hospitalized (57) individuals. It is anticipated that the potential benefits of participating in an aerobic exercise conditioning program outweighs the minimal risks associated with exercise in patients recovering from COVID-19. Thus, this protocol involves greater than minimal risk to study participants, with the prospect of direct benefit to individual participants.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
#1. To examine the effect of aerobic exercise training (AET) on physical function in participants recovering from COVID-19	Physical function is represented by the distance walked (in meters) during a 6 minute walk test (6MWT) as the primary outcome. Other measures of physical function include the time to exhaustion on the CPET and the SPPB/Mini-BEST score. All physical function outcomes will be measured at baseline and after the AET and CON regimens, and after crossover in the CON group.	The 6MWT distance has been used to reflect longitudinal changes in physical function among patients with ARDS (17, 58) and SARS (18, 59), and to detect changes due to exercise participation in patients recovering from SARS (26). In the only study found to date that utilized a training intervention in patients with COVID-19, the 6MWT was used in the RCT to examine changes in exercise capacity following 6 weeks of respiratory training (60).

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		A minimal important difference (MID) has yet to be established among survivors of COVID-19. We will consider 30 meters as the MID for this study based on reported ranges of 20 to 30 meters in patients with idiopathic pulmonary fibrosis (61, 62) and ARDS (63).
Secondary		
#2. To examine the effect of AET on patient reported outcomes and other health-related quality of life (QoL) components in participants recovering from COVID-19	Patient reported outcomes related to fatigue, sleep, post-exertional malaise, post-traumatic stress disorder, depression, anxiety, general and COVID-19 specific QOL outcomes. These outcomes are measured at baseline and after the AET and CON regimens, after crossover in the CON group, and every 3 months for 1 year.	There are currently no studies available regarding the effect of exercise on these outcomes on recovery from COVID-19. It is expected that QOL will be improved with AET as aerobic exercise has been associated with improvements in patient-reported outcomes and health-related QOL in the lung disease population (64-66).
#3. To examine the effect of AET on free-living physical activity and sleep quality in participants recovering from COVID-19	Quantification of free-living physical activity and sleep quality using wearable accelerometer device. These outcomes are captured upon study entry, throughout the AET and CON regimens, and throughout crossover in the CON group. Outcomes will also be captured every 3 months for 1 year.	Physical activity has been reported to be lower as a result of the COVID-19 pandemic due to public health guidance and governmental measures implemented worldwide (67), and poor sleep quality have been observed among the general population (68) and healthcare workers (69). There are currently no studies available regarding the effects of exercise on these measures on recovery from COVID-19. It is expected that both physical activity and sleep quality will be improved with AET as aerobic exercise is

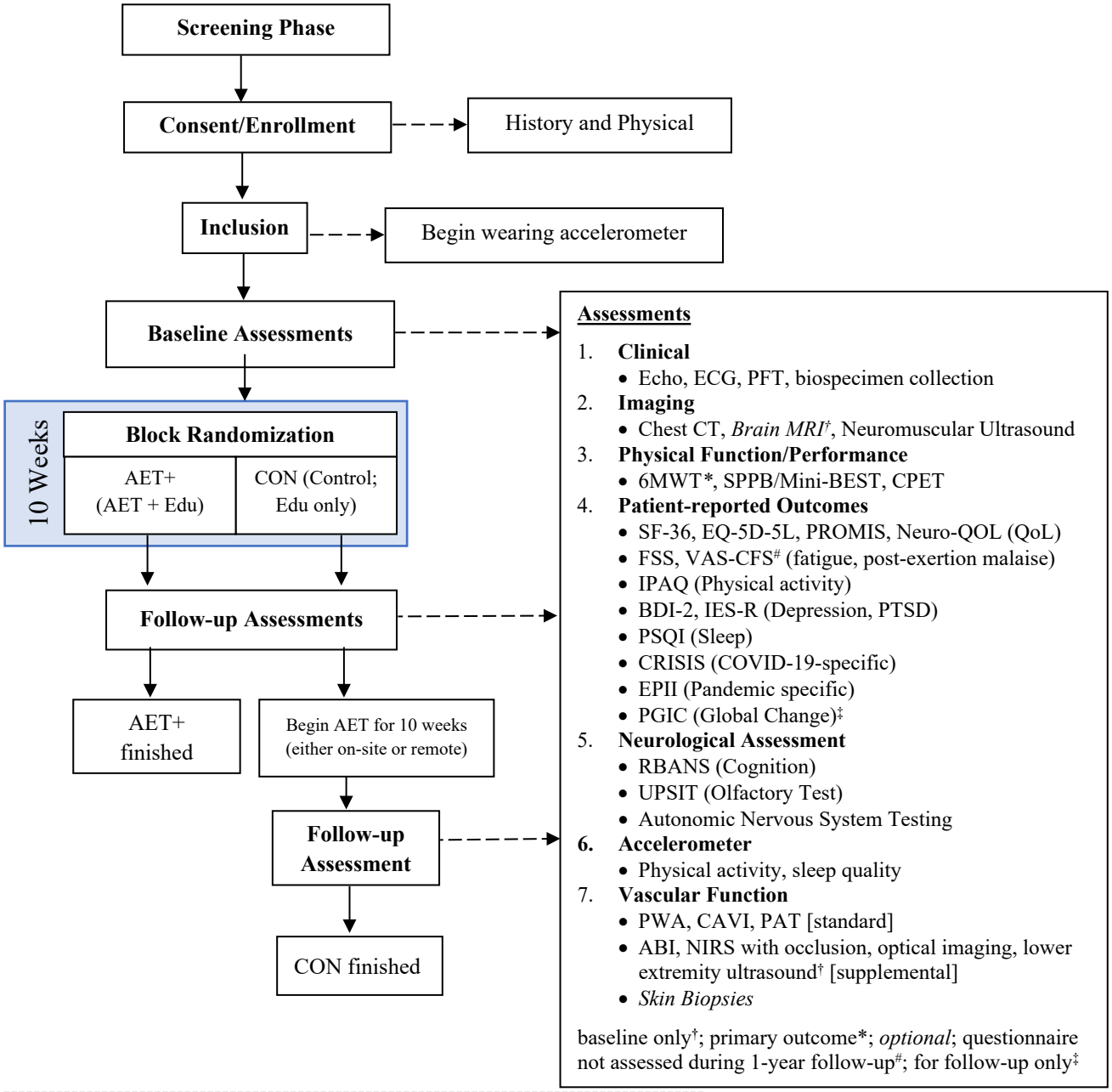
OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
		associated with greater physical activity (64) in patients with lung disease, and better sleep quality (70) in older adults.
Exploratory		
#4. Explore the effect of AET on clinical outcomes, cardiorespiratory function, cognition, biomarkers, metabolomics, ultrasound-based muscle measurements, vascular and autonomic function in participants recovering from COVID-19	Clinical outcomes (such as cardiac and lung function), cardiorespiratory function, cognition, biomarkers, metabolomics, ultrasound-based muscle measurements, vascular and autonomic function. These outcomes are measured at baseline and after the AET and CON regimens, and after crossover in the CON group.	It is unknown to what degree COVID-19 affects these exploratory outcomes and there are currently no studies available regarding the effect of exercise on recovery from COVID-19. It is likely that AET will result in improvements for these exploratory outcomes based on findings in other populations that demonstrate improved clinical outcomes (71), cardiorespiratory function (64), cognition (72), biomarkers (73), metabolomics (74), muscle measurements (75) and vascular (76) and autonomic (77) function with exercise training.
#5. Explore the feasibility of conducting the AET program remotely in participants recovering from COVID-19 that were randomized to the CON arm	Measure retention, safety, exercise adherence and participant experience in the CON group that crossed over to exercise.	Collection of data to examine feasibility of conducting exercise sessions remotely in this population. It is expected that remotely conducted exercise sessions will be feasible based on effectiveness of remotely conducted pulmonary rehabilitation in patients with chronic obstructive pulmonary disease (78).
#6. Explore follow-up free-living physical activity,	Free-living physical activity, sleep quality, and health-	There are currently no studies available for changes in physical

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
sleep quality, patient reported outcomes and other health-related QoL components in participants recovering from COVID-19	related QOL are measured every 3 months for 1 year in both groups.	activity, sleep quality and QOL after COVID-19 over an extended period of time. It is expected that benefits from exercise training will be maintained at 1-year follow-up, based on long-term studies in patients with lung disease following PR programs (79, 80).

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-site randomized controlled trial with a wait-list (cross-over) design. The study will be led by the Rehabilitation Medicine Department (RMD) at the NIH Clinical Center, in collaboration with other NIH institutes. An overview of the study is as follows:



1-year Follow-up: Following completion of exercise training, participants are mailed an accelerometer and contacted every 3 months for 1 year to examine continued free-living physical activity, sleep quality and QOL changes over time.

The overall aim of this RCT is to determine whether AET is beneficial for improving functional outcomes and recovery among survivors of COVID-19. All participants will perform baseline assessments (Study visit 1) including physical, cognitive testing, patient-reported outcomes, and vascular function as listed in **Section 8, Study Assessments and Procedures**. Thereafter, participants will be randomized to either one of 2 arms for 10 weeks: 1) an aerobic exercise training with education (AET+) group, or 2) a wait-list control group (CON) provided with education only. After 10 weeks, both groups will repeat the same assessments as performed at baseline (Study Visit 2; 10-week follow-up). Following this visit, participants in the CON group will crossover and perform 10 weeks of AET either on-site or remotely, followed by a third assessment visit (Study Visit #3; 20-week follow-up). Participants will also begin wearing a wristwatch accelerometer at the baseline study visit and through to the follow-up time point (10 weeks for AET+, 20 weeks for CON), for continuous collection of free-living physical activity and sleep quality. In addition, all participants will be monitored periodically over one year to capture physical activity, sleep quality and health-related QOL outcomes over time.

4.2 Scientific Rationale for Study Design

The CON arm is an important comparison to the AET+ arm as little is currently known regarding the rate and magnitude of spontaneous recovery from COVID-19. In addition, the CON arm is of a "wait-list" design and participants randomized to CON will have an opportunity to receive the "active" exercise intervention, albeit after a delay of 10 weeks. The CON arm also involves weekly education sessions with the research team over the 10 weeks, which are the same as the AET+ group. Therefore, the only difference between the groups is the addition of exercise training, which is the intervention being studied. Lastly, the sequential crossover design for the CON group also provides a sub-study that allows collection of pilot feasibility data to conduct exercise sessions remotely.

This RCT design has been successfully carried out by our research team in high-risk patients with pulmonary hypertension (65) and is currently used in an ongoing RCT in patients with interstitial lung disease (14-CC-0027). Our research team is uniquely qualified to undertake this research, and is one of the few teams possessing the experience and background necessary for performing this type of rehabilitation research.

4.3 Justification for Dose

COVID-19 is a viral infection that primarily affects the respiratory system, leading to minor respiratory illness in most people or major lung complications in others. Chest computed tomographic (CT) data from patients with COVID-19 have revealed abnormalities suggestive of lung disease (81), even in hospitalized patients that did not develop severe pneumonia (82). Pulmonary fibrosis has also been reported to develop among certain survivors of COVID-19, especially in those that were older and had severe illness (83).

Previous coronavirus outbreaks have been associated with lasting pulmonary dysfunction among SARS (59) and MERS (84) survivors, and a preliminary study in patients recovering from COVID-19 also reported functional impairment of the lung (85). Among laboratory confirmed patients with COVID-19 discharged from the hospital, almost half of the sample (47%) had deficits in carbon monoxide diffusion capacity (DLCO) during pulmonary function testing (85), suggesting residual pulmonary vascular disease with this latest coronavirus outbreak.

Pulmonary rehabilitation (PR) is a comprehensive intervention for those with chronic respiratory disease. A major component of PR is exercise training, specifically endurance or aerobic-type of exercise. PR is considered standard recommendations for patients with chronic obstructive lung disease, however patients with other lung diseases such as interstitial lung disease, pulmonary hypertension, cystic fibrosis and asthma, are also believed to benefit from PR (86). Recent rehabilitation guidelines for patients post COVID-19 with pulmonary sequelae include PR programs (9).

The exercise intervention and education used in this study are consistent with current PR programs. Current PR guidelines recommend that aerobic exercise be performed continuously for 20 to 60 minutes on 3 to 5 days a week at an intensity which is perceived as moderate to somewhat hard (rating of perceived exertion of 4 to 6 out of 10) for at least 10 weeks (86). Further, our lab has conducted similar education and aerobic exercise training interventions among patients with pulmonary hypertension (65) and interstitial lung disease (87), with high adherence and no serious adverse events. Improvements in physical function and self-reported fatigue were observed (64, 65), demonstrating patients with advance lung disease were able to gain benefits from this exercise training regimen.

It is also increasingly recognized that a small proportion of patients with COVID-19 may present with atypical manifestations to include gastrointestinal, hematologic or neurologic organ systems (27, 88, 89). Reports of persistent symptoms among those having recovered from COVID-19 include fatigue, dyspnea, joint and chest pain (7). Physical exercise, more specifically aerobic exercise, has been shown to be beneficial in those with neurological disorders (90-92) and may support neuroimmune function by reducing neuroinflammation (93). Exercise training is also widely used for chronic conditions that have associated fatigue such as multiple sclerosis (32), cancer (33) and CFS (34). The exercise intervention used in this study also meets current physical activity recommendations by the ACSM for the general population (22).

In summary, patients recovering from COVID-19 are likely to have residual symptoms that negatively impact their quality of life. Aerobic exercise is recommended as part of PR for persons with advance lung disease, yet is also a therapeutic option for persons with neurological disorders and those that experience severe and chronic fatigue. Exercise was also included in a recent consensus statement for post COVID-19 rehabilitation recommendations (9). The use of aerobic exercise as a rehabilitation strategy for survivors of COVID-19, is therefore appropriate and justified.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Screening procedures will be performed as part of this study, as specified in Section 8.1.

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Male or female, aged 18 to 80 years
2. Previous infection with SARS-CoV2 at least 4 weeks prior to enrollment, confirmed by laboratory or a healthcare provider. Participants with a documented positive home antigen test will need confirmation of positive COVID-19 antibodies (positive anti-

Nucleocapsid antibody test, OR positive anti-Spike antibody test if unvaccinated at the time of the antibody test) to be considered.

3. Presence of physical limitations or significant fatigue since COVID-19 as demonstrated by:
    a. Total score ≤ 19 on the PROMIS short form for physical function *or* total score ≥ 9 on the PROMIS short form for fatigue, ***AND***
    b. Score ≥ 1 on the Patient Global Rating of Flu Severity *and* Patient Global Assessment of Interference with Daily Activities
4. Absence of post-exertional malaise (PEM) as identified on the DSQ-PEM where:
    a. Items 1 to 5 has no score ≥ 2 for frequency *and* no score ≥ 2 for severity, occurring in the same row, ***AND***
    b. Item 7 or 8 is "No", ***AND***
    c. Item 9 is ≤ 13 hours
5. Able to read, speak and understand English or Spanish
6. Able to understand and willing to sign a written informed consent document
7. Willing and able to complete study procedures

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Above normal performance (i.e, ≥100% predicted) in the 6MWT based on normative data for gender and age (94, 95)
2. History or cardiac condition as determined by NIH cardiology to be unsafe for exercise participation (e.g. ischemic heart disease, right- or left-sided heart failure, cor pulmonale or pulmonary hypertension, dilated or hypertrophic cardiomyopathy or non-idiopathic cardiomyopathy)
3. Significant hepatic or renal dysfunction
4. Cancer diagnosis with evidence of metastasis or a life expectancy of less than one year
5. History of stroke resulting in impairments in functional mobility that limits safe participation
6. Active substance abuse including EtOH
7. Severe psychiatric disease, not responsive to treatment or medication
8. History of diabetes *and* on insulin pump therapy, *or* uncontrolled diabetes with HbA1c > 9.0%
9. Pregnancy
10. Acceptance onto a lung transplant waiting list
11. Extreme obesity with BMI > 40 kg/m^2
12. On medications that would influence exercise performance such as beta blockers or antiretroviral therapy
13. Ongoing tobacco and/or nicotine product use
14. Enrolled in another interventional clinical research trial
15. Any other medical or health condition(s) that unduly increases the risk of exercise testing or training, affects the normal physiologic response to exercise testing or training, and/or would otherwise interfere with the ability to interpret the data as determined by the PI

5.3 INCLUSION OF VULNERABLE PARTICIPANTS

5.3.1 Participation of NIH Staff or family members of study team members

NIH staff and family members of the study team members may be enrolled in this study when this population meets the study entry criteria. Neither participation nor refusal to participate as a participant in the research will have an effect, either beneficial or adverse, on the participant's employment or position at NIH.

Every effort will be made to protect participant information, but such information may be available in medical records and may be available to authorized users outside of the study team in both an identifiable and unidentifiable manner.

The *NIH Frequently Asked Questions (FAQs) for Staff Who are Considering Participation in NIH Research* and *Leave Policy for NIH Employees Participating in NIH Medical Research Studies (NIH Policy Manual 2300-630-3)* will be provided to participants for them to review. Please see section 10.1.2 for consent of NIH Staff.

5.4 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Fast (nothing to eat or drink besides water) up to 8 hours as needed for specific clinical blood draws
- Abstain from caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 1 hour before the start of exercise testing/training.
- Abstain from caffeine products, strenuous exercise and fast at least 6 to 8 hours prior to performing the vascular function tests
- Hold all medications (including vasodilators, antihypertensives, statins) on the morning of the vascular function tests, but bring their medication with them so they may resume right after completion of the tests.
- Refrain from strenuous exercise at least 24 hours prior to performing the ultrasound muscle test
- Refrain from caffeine products, strenuous exercise and certain medications prior to performing the autonomic function tests
- Refrain from starting up other structured exercise training programs
- Comply with current NIH CC guidance for visitors and out-patients during the COVID-19 pandemic (e.g., requiring face coverings, symptom self-assessments, admission and pre-procedure SARS-CoV2 PCR testing, surveillance, etc.)

5.5 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of negative COVID-19 antibody blood test results, timing of COVID-19 diagnosis, tobacco/nicotine use, BMI cut-off, stability of previous medical concern, present PEM, present myocarditis or absence of significant fatigue or physical limitations may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.6 STRATEGIES FOR RECRUITMENT AND RETENTION

- The target number of enrolled adults aged 18 to 80 years is 76. There are no limits related to gender, race or ethnicity. It is anticipated that up to 90 participants will be required to attain the target enrollment.
- The recruitment rate is expected to be 4 – 8 persons each month
- Participants will be primarily recruited from the greater Washington DC capital area
- Recruitment of participants from other NIH studies may also occur (e.g., 20-CC-0113: Cardiopulmonary Inflammation and Multi-System Imaging During the Clinical Course of COVID-19 Infection in Asymptomatic and Symptomatic Persons, 18-H-0011: Technical Development of Cardiovascular Magnetic Resonance Imaging (CMR) Using a Low Specific Absorption Rate (SAR) Scanner System; 14-H-0188: Prospective Evaluation of Next Generation CT Reconstruction, 000089-N: Natural History of Post-Coronavirus Disease 19 Convalescence at the National Institutes of Health)
- Direct patient referrals from physicians and clinics in the greater Washington DC capital area such as Inova Fairfax Hospital, Suburban Hospital, etc.
- The recruitment strategy offered by the NIH/CC Office of Patient Recruitment, including sample recruitment messages and advertisements in the form of study flyers will be used. IRB-approved flyers may be left with clinics for interested treating physicians to refer participants to this study with approval of the venue or in accord with their policy; self-referral is also permitted. Study flyers and physician letters may be sent using commercially available mailing lists via direct mail. Recruitment flyers may also be given directly or sent electronically to those requesting study information. Flyers may be made available at outreach exhibits, speaking engagements, support group meetings, professional meetings or association/trade meetings with approval of the venue or in accord with their policy.
- IRB approved flyers may also be posted in the community at venues such as grocery stores, community centers, universities, bookstores and libraries or placed in possible venues such as advocacy group offices, in doctor's office waiting rooms, places of worship, public libraries and retail establishments with approval of the venue or in accord with their policy.
- IRB approved sample recruitment messages, flyers and advertisements may be placed on websites such as those of advocacy groups, local newspapers, local magazines, neighborhood blogs, or radio stations, or Facebook pages.
- IRB-approved sample recruitment messages, flyers and advertisements may be posted on listservs with the permission of the moderator and may include organizations such as civic community groups, and advocacy or professional groups. These materials may also be shared with users that are authorized to post and send messages to the group.
- We will also utilize NIH CC-sponsored digital and social media resources such as Twitter, Instagram, Facebook, CC Radio, CC TV, Photo Gallery; databases such as NIH

Search the Studies, ClinicalTrials.gov, and Research Match; and local newspapers such as the Washington Post to disseminate information about the study to potential participants and their healthcare providers.

- Recruitment efforts may also include speaking engagements at support groups, advocacy groups, community advisory board meetings, forums and events for "long COVID" or associated post-COVID conditions in the greater Washington DC capital area.

5.6.1 Costs

There are no costs to participants for participation in this study. NIH does not bill health insurance companies or participants for any research related procedures or clinical care that the participants receive at the NIH CC. If a participant has an emergent issue which is outside the scope of NIH, then that individual will be transferred to an outside hospital.

5.6.2 Compensation

- There is no compensation for participants that perform the COVID-19 antibody testing only.
- Participants will receive compensation for research activities and interventions, based on research-related inconveniences and time. Participants may receive up to the following amounts, depending on the study arm, assessments performed and optional procedures completed:

	AET+	**CON**
Study Visit 1 (+ optional measures)	$ 880 (+$ 90)	$ 880 (+$ 90)
Study Visit 2 (+ optional measures)	$ 860 (+$ 40)	$ 860 (+$ 40)
Study Visit 3 (+ optional measures)	N/A	$ 780 (+$ 40)
30 Exercise Training Visits at $30/session	$ 900	$ 900
10 Education sessions at $10/session	$ 100	$ 100
Four 3-month follow-ups ($60/follow-up)	$ 240	$ 240
MAX TOTAL (+ OPTIONS)	*$ 2980 (+$ 130)*	*$ 3840 (+$ 170)*

- Payment will be processed after completion of the study visits and each 3-month follow-up period
- Should participants be unable to finish the study, they will be paid for parts completed
- No travel reimbursement will be provided
- For NIH staff participants, please refer to NIH HRPP Policy 404

6 STUDY INTERVENTION

6.1 STUDY INTERVENTIONS ADMINISTRATION

6.1.1 Study Intervention Description

Participants in the AET+ arm will receive both exercise and education during the 10-week intervention period, while participants in the CON arm will receive exercise after completing 10 weeks of education.

6.1.1.1 Educational Sessions

The education portion will comprise of 10 separate weekly lectures, lasting approximately 1 hour. Sessions will be conducted by credentialed RMD staff members and participants in both the CON and AET+ arm will receive the same educational lectures remotely within the 10-week intervention period. Educational topics to be covered will be related to exercise programming, safety and well-being such as considerations for benefits and adaptations of exercise, relevant anatomy and physiology, nutrition and lifestyle considerations, managing co-morbid conditions, forms of exercise training, home recommendations, and locating community resources.

6.1.1.2 Aerobic Exercise Training Sessions

The AET regimen will consist of 10 weeks of aerobic exercise. Vital signs and review of cardiac-related signs or emerging symptoms will be performed before and after every session. Following a brief warm-up period, participants will be encouraged to target 30 minutes of aerobic exercise, followed by a brief cool-down. The sessions will be continuous unless the participant cannot tolerate the regimen, in which case the exercise bouts will be alternated with rest intervals until the total time of the exercise bouts equals the 30 minutes. The intensity of exercise will be guided using heart rate (HR), and gradually increased from light-moderate to moderate-high intensity as safely tolerated by the participant.

The frequency of the sessions will be 3 times per week, unless make up sessions are needed in the 10 weeks. The target endpoint for each session will be completion of the prescribed training time, however symptomatic endpoints for stopping the training session will be those recommended by the ACSM, or as needed for the safe management of participants.

For participants in the AET+ group, the exercise sessions will be conducted as out-patient visits to the NIH CC under direct supervision by credentialed RMD staff members. To explore and collect pilot feasibility data for conducting remote monitoring of exercise sessions, participants in the CON group may perform the exercise sessions outside NIH with real-time remote supervision by credentialed RMD staff members. It is anticipated that some participants may need to perform initial exercise sessions as out-patient visits to the NIH CC for familiarization and safe exercise participation. Other participants may be deemed unsuitable for remote monitoring due to safety concerns (e.g., no suitable exercise space, high risk of injury from falls, unwilling or unable to perform glucose monitoring, demonstrate impulsive or unsafe behaviors, or lack the technologic skills, connectivity, or bandwidth required for remote monitoring) or refusal. There may also be participants that prefer or opt to perform the exercise sessions on-site at NIH. Participants will be provided and taught how to use the necessary equipment (e.g., pulse oximetry, blood pressure monitor, HR monitor, tablet, etc.) to enable vital sign measurement and remote monitoring of sessions off-site. Additional precautions that will be taken for participants exercising off-site include reviewing and identifying common trip hazards at the remote site,

requesting an open and flat space for conducting the exercise sessions and confirming their location, contact information and presence of any other person(s) prior to the start of all sessions. The credentialed RMD staff member conducting the session will review all this information prior to the start of all sessions and have the participants' medical history immediately available during the session.

6.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized to either education (CON arm) or exercise + education (AET+ arm). Due to the nature of the intervention, participants will not be blinded to their treatment allocation. Study personnel will be blinded through initial baseline screening/testing and randomization, however following randomization, due to the nature of exercise training and the time points involved in this study, the blinding process will no longer be possible.

We will use random block-size randomization (with block sizes randomly varying between 4 and 6) to keep groups as equal in number as possible and to avoid early filling of one of the groups. To minimize bias, an independent randomizer who is not affiliated with this study in any other way, will perform randomization of participants.

6.3 STUDY INTERVENTION COMPLIANCE

We will monitor compliance and attendance with the exercise and education sessions, as well as adherence to the prescribed intensity and duration of exercise during the exercise training sessions in both groups, whether on-site at NIH CC or off-site (remotely). These include recording exercise heart rate, ratings of perceived exertion and number of exercise minutes in the exercise training log. For participants in the CON group, outcomes related to retention and feasibility such as number of exercise sessions conducted remotely, satisfaction with exercise and reason(s) for not participating in remote exercise sessions will also be captured.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Participants in the AET+ arm who are unable to complete at least 80% of the exercise sessions, will be withdrawn from the study. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Participants are free to withdraw from participation in the study intervention at any time upon request.

An investigator may discontinue or withdraw a participant from the study intervention for the following reasons:

- Disease progression which requires discontinuation of the study intervention
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Investigator discretion
- Positive pregnancy test

- Participant unable to perform exercise training for 2 consecutive weeks

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Prior to removal from the study, efforts will be made to have participants complete a safety visit within 14 days of the last exercise session.

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant study intervention non-compliance
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Concurrent enrollment in other interventional clinical trials
- Death
- Screen Failure

The reason for participant discontinuation or withdrawal from the study will be documented. Participants who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Participants who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for the scheduled study visit and is unable to be contacted by the research study staff.

The following actions will be taken if a participant fails to return to the NIH CC for a required study visit:

- We will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, at least 3 attempts by phone call, text or email). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 SCREENING PROCEDURES

8.1.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the participant has signed a consent include the following:

- Email, written, in person or telephone communications with prospective participants.
- Review of existing medical records to include but not limited to H&P, laboratory studies, SARS-CoV2 test results, hospitalization records, etc.
- Review of existing MRI, x-ray, or CT images.
- Review of previous assessment results to include but not limited to 6MWT, PFT, ECG, Echo, etc.
- Completion of screening questionnaire (Appendix 1)

All screening tests and procedures will be performed within 30 days prior to enrollment. Data collected from the screening questionnaire will not be used for research purposes.

8.1.2 Screening activities performed after a consent for the study has been signed

The following screening activities will be performed only after the participant has signed the consent for this study:

- History and Physical Exam
- Clinical Evaluations as in section 8.2 below (e.g., ECG, echo, imaging, urine and blood tests)
- 6MWT

Assessments performed at outside facilities or on another NIH protocol may also be used to determine eligibility once a participant has signed the consent. All remaining screening tests and procedures must be performed within 30 days of enrollment.

In order to participate in this study, potential participants that used home-based COVID-19 antigen test kits may decide to undergo COVID-19 antibody testing to confirm past COVID-19 infection. Informed consent for this blood test will be obtained by telehealth, in person, or telephone. Participants will come to the NIH and have the blood drawn onsite. Approximately 7 mL of blood is required for this test. These participants will require a positive anti-SARS nucleocapsid antibody test to be eligible for the full study.

8.2 CLINICAL EVALUATIONS

The following clinical evaluations are performed to establish eligibility and safe participation of the participants in the study. Should current NIH clinical evaluations be available, these may not be repeated to reduce subject burden and unnecessary testing. Any clinical assessment or imaging considered as part of the clinical evaluation may be added for research use.

8.2.1 History and Physical Examination

A comprehensive clinical assessment will be performed by a credentialed NIH medical staff member. This exam will include vital sign measurements (e.g., temperature, pulse, respirations, blood pressure, oxygen saturation), anthropometric measurements (height and weight), detailed medical/social/surgical history, medication review, physical examination and other assessments (such as PEM assessment, balance/motor assessment, vision/hearing assessment and other functional abilities) as appropriate.

A brief physical exam at follow-up study visits will be performed by a credentialed RMD medical staff member to ensure continued inclusion and safe participation of the participants in the study.

Telehealth visits may also be performed by a credentialed and authorized NIH medical staff member, as necessary, for further review and follow-ups with the participant. All platforms utilized during the telehealth visit will meet all NIH information security requirements. During a telehealth visit, the credentialed NIH medical staff member will be in a closed and private environment to ensure privacy for the participant. The participant will be instructed to conduct the encounter in a private environment, free of distraction.

8.2.2 Cardiac Evaluation

Survivors of COVID-19 may have cardiac complications (50) and the presence of myocarditis may lead to cardiac dysfunction, arrhythmias or sudden death with vigorous exercise (51). An initial cardiac evaluation will be performed by NIH Cardiology for all participants and clearance will be obtained prior to the performance of any exercise testing. If necessary, additional diagnostic tests may be performed as part of the cardiac evaluation.

Additional cardiac reviews will be performed by NIH Cardiology at each study visit to ensure continued inclusion and safe participation of the participants in the study.

8.2.3 Biospecimen Collection and Laboratory Evaluations

8.2.3.1 Urine Collection

Urine specimens will be collected from all study participants at the NIH Outpatient Phlebotomy for clinical evaluations for inclusion/exclusion, and to examine participants' safety risk for exercise participation. Participants hospitalized with COVID-19 are more likely to have co-morbidities that affect the kidneys such as diabetes and hypertension. Therefore, urine will be collected from all participants for urinalysis and an albumin/creatinine ratio (microalbumin) to assess for kidney disease or urologic abnormalities. Urine samples will not be stored. Follow-up urine collection for clinical assessment may be repeated at subsequent study visits as deemed necessary for continued inclusion and safe participation of the participant in the study.

In addition, female participants of childbearing potential will undergo urine dip-stick pregnancy testing at the NIH Outpatient Phlebotomy for study inclusion and within 24 hours prior to MRI and CT. In order for a female participant of childbearing potential to be enrolled, this test must be negative. Urine samples will not be stored. Follow-up pregnancy tests will be performed at subsequent study visits and within 24 hours prior to CT. For continued participation in the study, this test must be negative.

8.2.3.2 Blood Collection

Venous blood samples via a standard blood draw technique will be collected from study participants by a trained phlebotomist at the NIH Outpatient Phlebotomy. During this study, up to 300ml of blood will be collected from participants at each study visit for research and clinical purposes. Part of the blood sample collected will be used for clinical evaluations for inclusion/exclusion, and to examine participants' safety risk for exercise participation. These may include:

- Acute care panel[a]

- Mineral panel
- Complete Blood Count with Differential (CBC with Diff)
- Hepatic panel
- Lipid panel[a]
- D-dimer, Lactate dehydrogenase (LDH), Creatine Kinase (CK), C-reactive Protein (CRP)
- Prothrombin time/International Normalized Ratio (PT/INR)
- Partial Thromboplastin Time (PTT) Test
- Iron, Ferritin, Transferrin and Iron-binding Capacity (TIBC)
- Thyroid Stimulating Hormone (TSH)
- Hemoglobin A1C: To evaluate glycemic control in those with diabetes mellitus as part of the exclusion criteria
- Cardiac troponin (Troponin-I) to assess for acute myocardial injury
- Pro-brain natriuretic peptide (ProBNP): To objectively monitor for potential myocardial damage and indicate acute heart failure. This test is used as a standard of care in many emergency departments when patients exhibit symptoms of heart failure such as shortness of breath and fatigue
- Other blood testing as clinically indicated to investigate for underlying systemic illnesses

[a]Fasting labs.

Blood collected for clinical assessments will not be stored. Follow-up blood collection for clinical assessments may be repeated at subsequent study visits as deemed necessary for continued inclusion and safe participation of the participants in the study.

8.2.4 Radiographic or other imaging assessments

Clinical imaging (such as coronary computer tomography angiogram (CTA), cardiovascular magnetic resonance (CMR) or chest x-ray), as well as functional testing with or without imaging may be performed under specific protocols (e.g., 18-H-0108: Vascular Disease Discovery Protocol; 20-H-0099: Data Collection of Standard Care and Evaluation of NHLBI Patients and Donors) as deemed necessary by medical staff to establish risk for exercise participation, inclusion and safe participation in the study by the participant.

8.2.5 Electrocardiograms (ECGs)

All participants will be screened for signs/symptoms of coronary artery disease, cardiomyopathy or any other underlying cardiovascular diseases that may increase the participant's risk of performing an exercise-based intervention by screening all participants with a 12-lead ECG. This will be performed in the NIH Electrocardiography Laboratory. Participants will be required to lay supine on an examination table while 12 electrodes are placed on the participant's chest and then connected to an electrocardiogram by an ECG technician. A cardiologist will interpret all electrocardiograms prior to the performance of any exercise testing.

Repeat resting 12-lead ECGs will be performed at follow-up study visits for safety, prior to the performance of any exercise testing.

8.2.6 Pulmonary Function Testing (PFT) with Diffusion Capacity (DLCO)

Participants will perform PFT for assessing Lung Volume, Forced Spirometry, Maximal Voluntary Ventilation (MVV) and Diffusion Capacity (DLCO). These tests will be performed at

the NIH Pulmonary Function Laboratory. Forced Vital Capacity (FVC) is used to evaluate the degree of obstructive and restrictive lung disease, if present. MVV is used to evaluate the participant's ventilatory limitation. Both tests will be obtained while the participant is at rest. We will determine whether participants' exercise capacity is limited by ventilation by computing the ratio between expired minute ventilation (Ve) measured at the end of CPET and MVV (Ve/MVV must be 0.90 or greater). To perform the FVC and the MVV test, the participant will be instructed to sit, plug his or her nose with their free hand (or wear a nose clip) and create an airtight seal over the mouth piece. For the FVC, the participant will be asked to take in three regular breaths, followed by a deep inhalation and a quick and complete exhalation, blowing air until there is nothing left to expire. This test will be repeated at least 3 times. For the MVV, the participant will be asked to breathe in and out normally three times followed by breathing in and out rapidly (90-100 breaths·min^{-1}) for 12-15 seconds. Baseline bronchodilator responsiveness testing will also be performed according to the American Thoracic Society (ATS) standards and guidelines (96) to detect the presence of an obstructive ventilatory defect, and may be repeated at follow-up testing as appropriate.

Pulmonary fibrosis has been reported to develop among certain survivors of COVID-19 (83), which may suggest impaired ability for the interstitial lung tissue to exchange gases across the respiratory membrane wall. Therefore, a DLCO test will be used to determine the lungs' ability to exchange gases across this respiratory membrane wall. Using a mouthpiece and nose clip, the participant will exhale fully and be required to inhale rapidly and maximally air containing a small amount of carbon monoxide, hold their breath for 10±2 seconds, and then exhale at moderate speed. Exhaled air is then measured to determine the amount of carbon monoxide that was absorbed by the lung tissue and as such determine the participant's diffusion capacity.

PFTs with DLCO will also be performed following completion of the exercise training for the AET+ group, and following both the education phase and exercise training phase for the CON group.

8.2.7 Echocardiogram (Echo)

COVID-19 infection has been associated with cardiac complications, including myocarditis and myocardial injury (50, 97). Therefore, all participants will undergo a cardiac echocardiogram for screening and safe participation in the study. Doppler echocardiograms will be performed at the NIH Echocardiogram Laboratory. A transducer placed on the participant's chest will allow evaluation of regional and global ventricular function, valvular function, as well as right and left ventricular size/thickness and systolic pressure.

Repeat echocardiograms may be performed at follow-up study visits to ensure continued inclusion and safe participation of the participants in the study.

8.3 Safety and Research Assessments

The following assessments are performed for research purposes and will be conducted at all study visits to the NIH (i.e., study visit 1, 2 and 3), unless specified otherwise or performed recently at the NIH. Assessments performed for safety (i.e., vital signs and review of signs/symptoms) will be performed as described. It is anticipated that participants in this study may not complete the entire list of assessments (e.g., questionnaires, vascular tests, etc.).

Omissions such as these will be considered expected provided they are not the primary outcome, not related to determination of the exercise training range and do not include data needed to assess safety for a procedure.

8.3.1 Vital Signs

Vital signs (e.g., temperature, pulse, blood pressure, oxygen saturation) will be obtained at every study visit, and prior to and following exercise testing and training sessions. For study visits, exercise tests and training sessions performed at the NIH CC, a credentialed RMD staff member will obtain vital signs. For exercise training sessions performed outside NIH (i.e. remotely), participants will perform and read out their measures to a credentialed RMD staff member, using equipment provided to the participant for this purpose.

8.3.2 Review of Cardiac-related Signs/Symptoms

The presence of cardiac-related signs/symptoms and/or pain will be reviewed by a credentialed RMD staff member prior to and following all exercise testing and training sessions. These may be conducted in-person (when the participant is at the NIH CC) or remotely (for exercise sessions performed outside the NIH CC).

8.3.3 Blood Specimen Collection and Laboratory Evaluation

At each study visit, venous blood samples via a standard blood draw technique will be collected from study participants by a trained phlebotomist at the NIH Outpatient Phlebotomy. Up to 300ml of blood will be collected from participants at each study visit, and part of the collected blood sample will be used for research purposes to include markers for exercise-specific adaptations (e.g. pro-brain-derived neurotrophic factor (BDNF), mature BDNF, insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF)), inflammatory markers (e.g. CRP, IL-6, D-dimer), metabolites (e.g. C-peptide, glucose-dependent insulinotropic polypeptide, glucagon like peptide, glucagon, insulin, leptin, and pancreatic polypeptide), immunology (e.g., C3/C4, IgE), lung injury or function (e.g. HGF, KGF, N-PCP-III), endothelial function (e.g., Von Willebrand factor activity/antigen, fibrinogen degradation/split products, plasminogen activator inhibitor-1, lupus AC, soluble P-selectin, factor VIII, VWF-cleaving protein, soluble thrombomodulin, antithrombin III activity), and neuronal injury (e.g., neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP)).

8.3.4 Radiographic or other imaging assessments

8.3.4.1 Chest computed tomography (CT)

Lung abnormalities on CT scans have been observed to persists for years among survivors of SARS (98), however it is unknown how recovery evolves for patients with COVID-19. Participants will perform an initial chest CT scan, unless one has been performed recently at NIH. Repeated CT scans may be performed at each follow-up study visits.

CT scanning uses x-rays to obtain an image of the lungs. The CT scanner is shaped like a metal cylinder, and participants will lie on a table that slides in and out of the scanner. Participants will be in the scanner for up to 20 minutes and will be able to communicate with the CT staff at all times.

8.3.4.2 Brain Magnetic Resonance Imaging (MRI)

It is increasingly recognized that COVID-19 may also manifest as neurological complications (99), and abnormal brain imaging has been reported among severe cases of COVID-19 infection (100, 101). It is unknown if abnormalities continue to be present and may be detected among those recovering from COVID-19.

Considering the extensive evidence for central nervous system involvement in COVID-19 patients that has been already described in the literature (102), optional brain imaging at baseline has the potential of delineating potential structural abnormalities and may shed more light on the rehabilitation responses among participants in this study.

Participants will have the option to undergo brain MRI at baseline, unless they have had one performed recently at NIH. The MRI scanner is a cylinder surrounded by a strong magnetic field. MRI of the brain will be done with field strengths of up to 3 Tesla at the NIH CC. The MRI scan session will take 60 to 120 minutes. Participants will be able to communicate with the MRI staff at all times during the scan.

MRI scans will include various multiplanar imaging sequences, including T1, T2, FLAIR, diffusion weighted and susceptibility weighted sequences, among others. Imaging will cover the brain and orbits. Special sequences targeting the olfactory pathways will be obtained. Other sequences for structural may include diffusion tensor imaging and resting state functional connectivity. Intravenous administration of an FDA-approved, macrocyclic, gadolinium-based MRI contrast agent may be performed and post-contrast imaging will be compared to pre-contrast imaging to assess for any abnormal meningeal or parenchymal enhancement. Contrast agents will be used at FDA-approved doses. NIH CC Radiology and Imaging Sciences guidelines for gadolinium administration will be followed.

The MRI system and the coils to be used in this study are FDA cleared. However, the study uses the MRI system in research mode which is investigational. While in research mode, the MR system operates below the limits that the FDA deems to present significant risk as defined in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices. In addition, research image processing is used that is not cleared by the FDA. This is in addition to the standard diagnostic data that is generated by the MR system. There is no potential for serious risk to the health, safety, or welfare of the subjects using the MRI scanner in these ways. The use of the MRI in research mode and the research image processing represent a Non-Significant Risk device study subject to the abbreviated requirements in 21 CFR 812.2(b).

Participants will be screened for MRI safety using the Screening Questionnaire used by the Radiology and Imaging Sciences Program of the CC. All women of childbearing potential will provide a urine sample for a pregnancy test performed no more than 24 hours before each MRI scan. Women who are discovered to be pregnant will no longer be eligible to participate in this study and will not perform any further imaging or study procedures.

8.3.4.3 Neuromuscular Ultrasound Imaging

Newly developed myopathies have been reported among patients with COVID-19, which may be associated with the coronavirus infection or drug therapies, however muscular weakness also accompanies critical illness and prolonged hospitalization (103). Diaphragmatic dysfunction is

also present in a high percentage of critically ill patients, and is associated with increased morbidity and mortality (104, 105). It is unknown whether COVID-19 affects neuromuscular recovery or the extent of ventilatory dysfunction associated with COVID-19.

Measurement of muscle properties with MRI and ultrasound are increasingly utilized to characterize or assess muscle structure and function (106-108). Ultrasound imaging also offers a non-invasive assessment of the diaphragm (compared to electromyography and nerve conduction testing) (109), with published data available for healthy controls and patients with diaphragm dysfunction (110-112). In patients with COVID-19 related illness, qualitative and quantitative neuromuscular ultrasound will provide additional information related to the presence of muscle pathology or ventilatory dysfunction that may contribute to exercise intolerance and disability. Repeat measurements post exercise intervention may provide insight into changes post exercise at the body function/structure level (muscle) that may contribute to improved function, as well as additional insights into potential factors contributing to ventilatory dysfunction affecting this population.

Neuromuscular imaging measures will be performed at every study visit. Ultrasound measures will be obtained in the following muscles: biceps, triceps, quadriceps (rectus femoris, vastus lateralis), hamstrings (semitendinosus, semimembranosus) and diaphragm (including accessory muscles of respiration). Measurements at each visit will include:

- B-mode ultrasound measurement of muscle thickness in short and long axis at the mid-belly, and zone of apposition (attachment to the ribcage) for the diaphragm.
- Heckmatt scale rating (113) from a representative B-mode image.
- Shear wave elastography in long axis including speed of sound and shear modulus (kPa). Nine measurement points will be obtained in each muscle (3 superficial, 3 mid, 3 deep).
- Microvascular flow measurements in short and long axis
- M-mode ultrasound measurement of the diaphragm from an anterior subcostal view of the hemi diaphragm motion during inspiration.

Participant and limb position will be standardized for this protocol.

8.3.5 Physical Function and Performance

8.3.5.1 6 Minute Walk Test (6MWT)

The 6MWT will be obtained at every study visit. The 6MWT will be conducted on room air, unless the participant has been prescribed supplemental O_2, in which case, the delivery device and O_2 flow will be the same at each test to maintain consistency. Participants will rest in a seated position and asked about specific symptoms (e.g., shortness of breath, pain, etc.) prior to the test. Resting blood pressure, heart rate and O_2 saturation will be recorded in the seated position. The participant will then be given standardized instructions to walk at their own pace but to cover as much distance as possible in 6 minutes along a pre-measured corridor/course. Once the participant is ready to begin, the participant will be asked to stand and informed when to start and when to stop. Oxygen saturation, heart rate and ECG will be measured and recorded throughout the test using portable devices. Rating of perceived dyspnea and rating of perceived exertion will also be asked before and after the test. Distance covered will be recorded at 1.5

minutes and the end of 6 minutes. The Fatigue/Fatigability Scale (114) will be completed before the test begins and immediately after. At the end of the test, the participant will be asked to stop and instructed to rest quietly in a seated position with recovery heart rate and oxygen saturation being recorded for up to ten minutes to evaluate the participant's ability to recover from intense activity. The ECG will also be continuously monitored before, during and after the test.

Fatigue Scale Items (Use before Walking Test)	Score	Fatigability Scale Items (Use After WalkingTest)
Extremely Tired	7	Extremely More Tired
Somewhat Tired	6	Somewhat More Tired
A Little Tired	5	A Little More Tired
Neither Tired Nor Energetic	4	Neither More Tired Nor More Energetic
A Little Energetic	3	A Little More Energetic
Somewhat Energetic	2	Somewhat More Energetic
Extremely Energetic	1	Extremely More Energetic

Schnelle, et al. J Am Geriatr Soc 60:1527–1533, 2012.

The target endpoint for this test is the completion of the six minutes of walking, however symptomatic endpoints recommended by the American Thoracic Society (ATS) (115) for stopping a 6MWT will be followed. The participants may be instructed to stop at any time during the test for any adverse response to the test. Should the participant's O_2 saturation fall to <85%, the participant will be instructed to stop and rest. The participant will be allowed to resume the test if their O_2 saturation rises >85%, however the timer will continue while the participant rests. Should the participant's O_2 saturation fall to <80%, regardless of dyspnea or other signs or symptoms, the test will be terminated and the participant allowed to rest. Supplemental O_2 may be applied ad lib if the O_2 saturation fails to return to baseline with rest alone. For participants performing the 6MWT on room air and SpO_2 falls <88%, the participant will be referred for a pulmonary consultation, and the 6MWT will be repeated with the prescribed level of supplemental O_2. Blood glucose of diabetic participants will be monitored before testing, and after as clinically necessary. Testing will be performed by qualified staff using an NIH glucometer.

The primary outcome variable is the 6MWT distance. The distance-saturation product (DSP) will be calculated as the ratio between total distance walked and lowest SpO_2 value, in those that performed the 6MWT on room air (116). The performance fatigability index will be calculated as the ratio of the 1.5-minute walking speed to the walking speed calculated over the entire 6 minutes of the test divided by the total distance covered on the test. The perceived fatigability index will be calculated by having the participant rate their feeling of tiredness prior to the 6MWT and measuring the change in tiredness after the 6MWT. The change in tiredness divided by the total distance walked will be computed as the perceived fatigability index (114). Heart rate variability will also be examined using the ECG data.

8.3.5.2 Short Physical Performance Battery (SPPB) and the Mini Balance Evaluation Systems Test (Mini-BEST)

The SPPB is a battery of assessments to evaluate lower extremity function and includes balance, gait speed and chair stand tests. While designed for older adults, it has also been used in chronic conditions such as pulmonary disease (117) and survivors of acute respiratory failure (118). It is a recommended COVID-19 core outcome measure of physical function by the American Physical Therapy Association (APTA) (119).

The Mini-BEST is a battery of performance measures that evaluates balance deficits in areas such as anticipatory postural adjustments, reactive postural control, sensory orientation and dynamic gait. It has been used to detect balance disorders across various neurologic conditions, and recommended as a research outcome measure by the Academy for Neurologic Physical Therapy (ANPT) (120).

The SPPB and the mini-BEST may be utilized for assessing lower mobility strength, gait and balance in participants. The SPPB may be more appropriate for those with more severe physical deficits and the Mini-BEST for higher functioning individuals. Participants scoring high on these assessments at the baseline visit may not need to perform these at follow-up study visits.

8.3.5.3 Cardiopulmonary Exercise Test (CPET)

The CPET will be obtained at every study visit. Participants will complete an incremental ramp protocol on the treadmill or cycle ergometer where the work rate will be gradually increased until volitional fatigue is reached by the participant. The ramp rate used will be based on participants' responses to their current physical activity habits. Participants will perform the CPET on room air, unless they were prescribed O_2, in which case, supplemental O_2 will be provided during the test using the same delivery device and flow at each test to maintain consistency. Rating of perceived dyspnea and rating of perceived exertion will be asked and recorded throughout the test.

This is a symptom-limited test in which the target endpoint is exertional intolerance defined as the participants expressed desire to stop exercising despite strong verbal encouragement from the testing staff. Other symptomatic endpoints for stopping the exercise test will be those recommended by the ACSM. Additionally, should any participant's O_2 saturation decrease to <80%, the test will be terminated with or without the presence of symptoms of severe dyspnea. Blood glucose of diabetic participants will be monitored before and after testing, and as clinically necessary. Testing will be performed by qualified staff using an NIH glucometer.

The CPET will be performed on a treadmill or cycle ergometer interfaced with the Medgraphics Cardio2 Ultima® CPX system for automatic increment of the work rate. A facemask placed over the lower portion of the participant's face (mouth and nose) or a mouthpiece and nose-clip will house the interface for pulmonary gas exchange measurements. For participants prescribed O_2, this test may be performed without collecting gas exchange as modified oxygenation may produce inaccurate gas exchange variables (121). Heart rate will be obtained in all participants from ECG recordings and electrodes will be placed on the participants' chests in the standard Mason-Likar exercise testing configuration. ECG will be monitored and recorded continuously throughout the test and recovery.

Key variables measured by the CPET include peak O_2 uptake (VO_2), the "gold standard" index for global cardiorespiratory function, and the anaerobic threshold (AT), which denotes the point that additional energy sources are required to supplement aerobic metabolism if exercise is to continue. Other gas exchange variables such as CO_2 output (VCO_2), ventilation, respiratory rate, and end-tidal partial pressure of CO_2 and O_2 allows analysis of respiratory and ventilatory responses to exercise. Other variables such as peak respiratory exchange ratio and peak heart rate from ECG will also be measured and recorded to facilitate data analysis. Pulse oximetry and

blood pressure will also be monitored during the CPET. Heart rate variability may also be examined using the ECG data.

8.3.6 Patient-reported Outcomes and Questionnaires

The patient-reported outcomes and questionnaires will be obtained at every study visit, as well as every 3 months for up to 1 year following the completion of the last study visit, unless otherwise specified. Completion of the self-reported outcome and questionnaires may be completed digitally and/or by paper format.

8.3.6.1 Short-Form Health Survey (SF36v2)

The SF36v2 is widely used throughout the world as an instrument to measure general health-related QOL in eight domains and yields physical and mental component summary scores. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group (122). SF36 has already been used among survivors of COVID-19 (60) and is a recommended outcome during the rehabilitation period (123) after COVID-19. This instrument is validated in Spanish.

8.3.6.2 EuroQoL 5-Dimension 5-Level (EQ-5D-5L)

The EQ-5D-5L is a health-related QOL questionnaire consisting of 5 questions and 1 visual analog scale. It has been validated in patients with chronic obstructive pulmonary disease and found to be responsive to changes following pulmonary rehabilitation (124). It is a recommended COVID-19 core outcome measure of QOL by the American Physical Therapy Association (APTA) (119). This instrument is available in Spanish.

8.3.6.3 Patient-Reported Outcomes Measurement Information System (PROMIS)

PROMIS is a self-reported set of measures to characterize health related quality of life for the general population and those with chronic conditions. Specifically, the PROMIS-57 is a profile instrument consisting of 57 questions, spanning 7 domains including physical function, depression, anxiety, pain interference, fatigue, sleep disturbance and ability to participate in social roles/activities. Other PROMIS scales such as dyspnea severity and functional limitations may also be used. These instruments are validated in Spanish.

8.3.6.4 Quality of Life in Neurological Disorders (Neuro-QoL)

Neuro-QOL is a set of self-report measures to assess health-related quality of life in those with neurological disorders. Specifically, the Neuro-QOL Cognitive Function v2.0 is a single short-form consisting of 8 questions that assesses adult cognitive function in 2 domains related to executive function and general concerns. This instrument is validated in Spanish.

8.3.6.5 Fatigue Severity Scale (FSS)

The FSS is used to monitor change in fatigue in response to therapeutic interventions. This scale is composed of nine items with a seven-point response format. A response of one indicates strong disagreement and a response of seven indicate strong agreement with statements regarding how fatigue affects physical and social functioning. Clinical improvement in fatigue is associated with reductions in scores on the FSS. The FSS is also a practical measure due to its brevity and ease of administration and scoring (125). It has been used to detect changes in fatigue severity with exercise intervention among patients with advance lung disease (64). This instrument is available in Spanish.

8.3.6.6 Visual Analogue Scale for Chronic Fatigue Syndrome Symptoms (VAS-CFS Symptoms)

The VAS-CFS consists of 12 items related to physical fatigue, mental fatigue or mental fog, muscle aches, muscle weakness, headache, join aches, lightheadedness, "flu-like" symptoms, sore throat, gastrointestinal discomfort, shortness of breath, and environmental sensitivity. This questionnaire takes about 2 minutes to administer. This instrument has not been validated in Spanish.

The VAS-CFS will be used to capture changes associated with post-exertional malaise, and will be repeated up to seven times around the CPET to include prior to the CPET, ~15 minutes after the CPET, ~60 minutes after the CPET, ~ 4 hours after the CPET, ~24 hours after the CPET, ~48 hours after the CPET, and ~72 hours after the CPET. The VAS-CFS will only be obtained at every study visit, and not during the 1-year follow-up.

The VAS-CFS may be accompanied by a brief qualitative interview to capture unique experiences of participants before and after the CPET. An interviewer guide will structure and direct the interviews so that participants are prompted to explain their experiences in detail, but interviewers will have discretion to modify as appropriate. The interviewing guide will include the following basic questions: 1) I am interested in how you feel right now, physically, cognitively, and emotionally; 2) What symptoms are bothering you the most right now?; 3) Is how you feel right now typical for how you feel on an average day (since you were infected with COVID-19?); 4) Is how you feel right now different from how you used to feel after exertion before you were infected with COVID-19?; 5) Is there anything else you would like to add about how you are feeling right now?. Data collected during qualitative interviews will consist of audio recordings. Persons who decline to be audio-taped will not be included in the qualitative portion of the study.

An in-depth qualitative analysis process, thematic analysis, will be used to systematically code and categorize the textual data. Investigators will read over the transcripts several times to allow immersion into the data, and then construct a preliminary categorical structure or "coding scheme." They will then independently "code" all the transcripts (i.e. the textual data), which involves identifying salient categories, collating those categories into overarching themes, and assigning names to the themes. Codes will be compared to identify disagreements and meetings will be conducted to discuss coding differences at-length and reach consensus. A qualitative software package (such as MAXQDA) will be used to highlight text within the transcripts and create categories and sub-categories electronically.

8.3.6.7 Beck's Depression Index-2 (BDI-II)

A self-report tool that measures the severity of depression and its interaction with other mood states. The BDI-II is a frequently used tool in clinical studies of depression and mood and in clinical evaluation. It has also been used to detect changes in depressive symptoms among patients with chronic obstructive pulmonary disease following pulmonary rehabilitation (126). This instrument is validated in Spanish.

Should a participant indicate severe depressive symptoms and/or suicidal ideation, the study coordinator or research staff member will remain with the participant and the PI will be notified. The PI or RMD medical staff will assess any issues that arise such as suicidal ideation. Other emergent psychiatric evaluation and treatment will be performed under the guidance of the

NIMH Psychiatry Consultation Service. The participant will be offered referral as appropriate for psychiatric or other evaluation with a clinician and/or for psychiatric assistance with a provider in their home community along with follow up by phone to assure that psychiatric intervention was obtained. For medical problems or conditions that occur outside of the NIH CC, participants will need to seek care and treatment from their primary care physician or a local emergency room.

8.3.6.8 Impact of Events Scale – Revised (IES-R)

A self-report questionnaire that assesses symptoms of post-traumatic stress disorder (PTSD). The IES-R may be repeated to detect changes over time, and has been used to examine changes in post-traumatic stress among survivors of SARS at 1 and 3 months after hospital discharge (127). This instrument is available in Spanish.

Scores ≥ 24 indicate that PTSD may be a clinical concern. Participants meeting this threshold will undergo a structured interview by a qualified on-site professional and referred for appropriate medical care by their clinical care provider. Other emergent psychiatric evaluation and treatment will be performed under the guidance of the NIMH Psychiatry Consultation Service. Care will be provided until the participant is stable, can continue research participation or until care can be transferred to the participant's own health care providers. For medical problems or conditions that occur outside of the NIH Clinical Center, participants will need to seek care and treatment from their primary care physician or a local emergency room.

8.3.6.9 Pittsburg Sleep Quality Index (PSQI)

A self-report instrument that assesses the duration, depth, number of arousals, latency, and restfulness of sleep. The PSQI has been used to assess sleep quality in clinical populations (128), as well as ARDS survivors (129). This instrument is validated in Spanish.

8.3.6.10 International Physical Activity Questionnaire (IPAQ)

The IPAQ short form is a commonly used questionnaire to monitor daily physical activity with recall over the previous 7 days. This instrument provides information regarding performance of daily physical activities as well as a quantitative score based on the known energy requirements of the activities performed by the participants. It has been used to capture changes in physical activity in patients with lung disease following a PR program (130). This instrument is available in Spanish.

8.3.6.11 The CoRonavIruS Health Impact Survey (CRISIS)

A COVID-19 specific questionnaire that measures the health impact over the past 2 weeks and may be used to capture changes over time. This instrument is available in Spanish.

8.3.6.12 Epidemic – Pandemic Impacts Inventory (EPII)

A new measure that examines the impact of disease pandemics on aspects of life such as work/employment, education/training, home life, social activities, physical distancing and quarantine and emotional health/well-being. This instrument is available in Spanish.

8.3.6.13 Patient Global Impression of Change (PGIC)

A one item questionnaire that evaluates the patients' overall assessment of their improvement or decline in status over time. This instrument is available in Spanish. As this instrument assesses changes from the start of the study, it will not be administered at the baseline visit.

8.3.7 Neurological Assessment

8.3.7.1 Repeatable Battery for the Assessment of Neuropsychological Status-Update (RBANS Update)

The RBANS will be obtained at every study visit. THE RBANS is a brief neurocognitive battery with alternate forms to minimize practice effects for repeated testing. Cognitive domains measured include immediate memory, delayed memory, attention, language and visuospatial skills. The RBANS-update has two alternate forms in Spanish.

8.3.7.2 University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT will be obtained at every study visit. The UPSIT is a quantitative assessment of olfaction and therefore of cranial nerve I function. This test comprises 40 questions with accompanying scratch and sniff strips, and is available in Spanish.

8.3.7.3 Autonomic Nervous System (ANS) Testing

Dysfunction of the ANS have been observed among individuals following COVID-19 infection (131, 132). In particular, autonomic dysfunction is suggested to be contributing to COVID-19 morbidity and mortality (133) and long-term sequelae experienced by survivors (134). There are currently no studies reporting on the effect of exercise on autonomic function in survivors of COVID-19.

We aim to perform ANS testing at every study visit, however, participants demonstrating normal function may not need to perform them at subsequent study visits.

i) The Quantitative Sudomotor Axon Reflex Test (QSART) is a measurement of sympathetic post-ganglionic cholinergic function. It is performed on the Q-Sweat Device (WR Medical Electronics Co., Maplewood, MN) using standard iontophoresis methodology and 10% acetylcholine. Iontophoresis chambers are placed on four sites, the forearm, proximal lateral calf and medial ankle, and foot, and sweat volume is recorded (µl/mm2).

ii) Using beat-to-beat blood pressure and heart rate monitoring (WR Medical Electronics, Inc, Maplewood, MN), the following measure are performed: 1) Heart rate-deep breathing is a parasympathetic test performed by having the subject take 6-8 slow deep breaths with 10 seconds per respiratory cycle and measuring the heart rate variability; 2) Valsalva maneuver is a test that involves the sympathetic and parasympathetic system and performed with a forced expiration at 40 mm Hg for 15 seconds and measuring heart rate and blood pressure response; 3) Tilt table testing is performed with a head-up tilt of 70 degrees for 10 minutes after at least 20 minutes in the supine position. Changes in heart rate and blood pressure are continuously recorded during head up tilt and after return to supine position. Published normative values will be used (135). The hemodynamic criteria for postural orthostatic tachycardia syndrome is a sustained increase of ≥30 beats per minute from baseline

heart rate when transitioned from supine to upright position for 10 minutes and in absence of orthostatic hypotension (systolic blood pressure drop of > 20 mm Hg or diastolic blood pressure drop of > 10 mm Hg (136).

8.3.8 Vascular Function

Patients with severe COVID-19 are observed to have endothelitis in various organs (137) and it has been speculated that vascular dysfunction may be involved (138). Currently, there are no studies reporting on vascular function in patients following COVID-19 or the effect of exercise in survivors of COVID-19.

Standard Vascular Function Assessments:

The following vascular function assessments are considered standard and will be obtained at every study visit. It is recommended that participants fast 6 to 8 hours before these vascular tests, as well as refrain from caffeine products and strenuous exercise. Participants will also be requested to hold all medications (including but not limited to all vasodilator, anti-hypertensive and statin), on the morning of the test. Participants will be asked to bring their medications with them on the day of the vascular tests, and will resume their medications right after completion of the procedures. This avoids any possible confounding variables from interfering with the readings of the vascular measurements. Prior to starting the tests, participants are resting for at least 10 minutes to acquire values for resting vitals. Testing is also conducted in a temperature-controlled quiet room, with the participant in the supine position.

8.3.8.1 Pulse wave Analysis (PWA)

The SphygmoCor system is a set of non-invasive tools used to determine central blood pressures and arterial stiffness. It derives the pressure wave from the ascending aorta to the carotid artery, and gives an accurate measurement of pressure at the heart, brain, and kidneys as Pulse Wave Velocity (PWV). This system cannot be used on participants who may suffer from heart arrhythmias or arterial stenosis.

8.3.8.2 Cardio-ankle vascular index (CAVI)

CAVI provides an index of overall arterial stiffness. ECG electrodes are placed on both wrists, a microphone for phonocardiograph is placed on the 2nd intercostal space, and 4 blood pressure cuffs are wrapped around 4 extremities. Arterial stiffness is calculated following specified formulas. Advantages of this procedure for measuring arterial stiffness is that it is not altered by blood pressure and is simple to perform.

8.3.8.3 Peripheral arterial tonometry (PAT)

An EndoPAT device quantifies the endothelium-mediated changes in vascular tone. It is elicited by a 5-minute occlusion of the brachial artery (using a standard blood pressure cuff). When the cuff is released, the surge of blood flow causes an endothelium-dependent flow mediated dilation. This dilation is captured by EndoPAT as an increase in the PAT Signal amplitude. A post-occlusion to pre-occlusion ratio is calculated by the EndoPAT software, providing a Reactive Hyperemia Index (RHI). The test is easy to perform, and is both operator and interpreter independent. It is a noninvasive test, providing automatic analysis, office-based procedure. It is an accepted standard test to cause reactive hyperemia (the increase of blood flow after a temporary restriction in blood supply) for the assessment of endothelial function.

Supplemental Vascular Function Assessments:

In addition, some or all of the following supplemental vascular function assessments may be administered to better characterize the vasculature in this population. These will be performed at every study visit, unless specified, and may be used in combination with other assessments and procedures as appropriate to reduce participant burden.

8.3.8.4 Ankle-brachial Index (ABI) and Digit Measurements

The ABI may be performed to investigate functional consequences of potential abnormalities of vascular anatomy. Waveforms and systolic blood pressures will be measured using Doppler ultrasound on both brachial, posterior tibial and anterior tibial arteries using a blood pressure cuff inflated over the upper extremity or lower extremity. We may check the pressure and waveforms of the digits (fingers and/or toes) as well. Measurements will be performed during resting steady-state conditions and in some participants after standardized treadmill or bike exercise. The ABI for each limb represents the ratio of the highest arterial (tibial or dorsalis pedis) pressure for each lower limb to the highest arterial (brachial) pressure of the two upper limbs.

8.3.8.5 Non-invasive tissue oxygenation using near-infrared tissue spectroscopy (NIRS)

Near-infrared spectroscopy (NIRS) can provide continuous assessment of the oxygen saturation of hemoglobin in arterial, venous and capillary beds, providing an aggregate measure of tissue oxygenation both at rest and in response to a physiologic challenge. Such methods are routinely used in both pediatric and adult cardiac intensive care units as a non-invasive means of measuring critical organ perfusion and cardiac function. NIRS light penetrates biological tissues, including skin, bone, and muscle. Like other optical methods, light is applied to the region of interest and undergoes scattering and absorption before being detected by a photosensor. There are numerous FDA cleared clinical instruments as well as research technology using a variety of methodologies that measure the proportion of oxygenated and deoxygenated hemoglobin in the tissue one to four centimeters below the skin surface. Baseline oxygenation may be measured above major arm and leg muscle groups throughout the body. These measures may be repeated following transient (3-5 minutes) cuff inflation proximal to the monitored muscle group. Technologies can be used to precisely and accurately characterize tissue perfusion, metabolism, and composition in both normal and diseased states. Subsequent studies may also repeat these measures during or following light exercise (hand-grip, or foot tap, etc.).

8.3.8.6 Optical Imaging for Circulation Evaluation

Optical imaging tests (including nail capillaroscopy, infrared imaging (IR), laser speckle contrast imaging (LSCI), vein imaging, in conjunction with assessment of oxygenation by laser Doppler probes, temperature skin patches, continuous monitoring of blood pressure and main vital signs) are non-invasive methods to assess function and thermodynamics of the peripheral vasculature. As such, optical imaging provides complementary data to static imaging methods such as angiography and PET scans with the additional advantage of having no risk of radiation exposure.

The rationale for these tests is to dynamically assess vascular flow, microcirculation, vascular reactivity to temporary ischemia and the thermodynamics of vascular inflammation in patients. Angiography often reveals irreversible pathology with changes in the microcirculation (i.e. “collateral artery formation”) occurring over time in response to impaired vascular flow. Optical

imaging of these vessels may lead to the discovery of novel non-invasive imaging biomarkers that could be used to assess response to therapy via assessment of dynamic changes in vascular flow and the microcirculation. A combination of some or all of the tests described below may be performed depending on the participant's status and as needed.

- Nailfold Video Capillaroscopy: Nailfold capillary changes are thought to reflect underlying vasculopathy in several pathological conditions. Capillaroscopy is a technique used to determine the extent of microcirculatory flow obstruction in humans. Briefly, we will measure periungual microvascular perfusion with an advanced computer using video capillaroscopy operating at low (90X) and higher (200-500X) magnifications. Measurements will capture capillary density, tortuosity, dimensions of individual capillary loops and allow for the quantification of capillary blood flow and velocity. Measurements will be performed in 1-10 fingers depending on the patient's disease status. Measurements performed at rest may be quantified and correlated with clinical measures. After an initial baseline capillaroscopy video at rest, two additional functional tests may be performed: the sigh test and the venous occlusion test. The sigh test is done to observe peripheral vasoconstriction in response to a respiratory sigh. During the test, the participant will be instructed to sigh, defined as a deep inspiration. For the occlusion test, a blood pressure cuff will be inflated to venous occlusion (~15 - 30 mmHg) for 5 minutes on the whole arm or finger to enhance image contrast by increasing the amount of blood retained in the capillaries. Video capillaroscopy will be performed during both functional tests to observe the effect of sigh and venous occlusion on capillary quantitative measures. Results will assess the presence of microvascular obstruction and the functional health of the microcirculation in participants.
- Laser Doppler Flowmetry: Laser Doppler flowmetry measurements will be made on forearm surfaces before, during and after post occlusion reactive hyperemia (PORH) to assess local and targeted blood flow. The probes of this device are smaller than one centimeter in diameter and are placed against the skin while secured with an adhesive pad. A laser signal is emitted from the probe onto the skin and the signal refracted from moving red blood cell is detected as a shift in frequency.
- Laser Speckle Contrast Imaging (LSCI): Assessment of blood flow perfusion with LSCI (Moor Instruments) will provide semi-quantitative information of microvascular blood perfusion. LSCI will be used to create a blood flow image map. Skin measurements can reflect blood flow in capillaries, arterioles, venules and dermal vascular plexuses. Comparison of these measures with IR photography will show increased sensitivity to more superficial nutritional blood supply. LSCI measurements may be made on volar or dorsal surface of the forearm as well as on frontal lobe areas at rest and during and after exercise and at the same time as Laser Doppler flowmetry probe measurements, IR photography, continuous BP and other vital measurements. In addition, it may be performed in other areas of interest as appropriate. LSCI allows for very fine spatial resolution of blood flow within 0.5 mm from the skin surface, while laser Doppler flowmetry has higher signal-to-noise ratio within up to 2 mm from the skin surface for oxygen content and blood flow measures from the same area. Simultaneous use of these tests allows for complementary and more comprehensive data to be obtained.
- Passive IR Photography for Blood Flow Distribution and Vasomotion: Passive IR photography is a non-invasive, real-time, in vivo imaging system that has been developed

for determining spatial distributions of blood flow. This method passively measures natural IR emission from the skin in a non-invasive way (no contact with the participants' skin). Prior data in over 20 patients with sickle cell disease showed that IR forearm imaging is sensitive to alterations in blood flow [NHLBI Protocol 07-H-0196]. This test will be administered to observe spatial distributions of blood flow and response to ischemic pain in participants at rest and during, and after a blood pressure cuff will be inflated above the systolic pressure to occlude the limb for 3 to 5 minutes. The cuff will then be instantly released and response to blood flow occlusion will be measured with IR photography. In addition, IR photography may be performed in targeted areas to assess for vascular flow at rest and during and after exercise.

- Lower Extremity Ultrasound: This is a standard clinical test performed in Radiology and will be used to evaluate the venous systems of the lower extremities for the presence of deep vein thrombosis (DVT). This is an important observation because of the finding of a hypercoagulable state associated with COVID-19. This test will be performed only once at entry to the study.

8.3.8.7 Skin Biopsies

Endothelial cell dysfunction have been reported among patients with COVID-19 (137), with increased vascular permeability, hypercoagulability, hyperinflammation and inhibition of fibrinolysis being observed in tissue samples taken from patients that had COVID-19 infection (139, 140). Biochemical and molecular studies on skin biopsy specimens allow elucidation of the pathological role of SARS-CoV-2 on blood vessels, with particular focus on regulation of ACE2, ANGII, and ANG1-7(141), which are known to be implicated in SARS-CoV-2 infection.

The procedure for skin biopsies is optional and the participant will consent at the time of the procedure which will be documented in the patient record. Skin biopsy consent is included in the initial consent document. If the participant refuses the optional skin biopsy at that time, the refusal will be documented in the medical record and in the research record. Up to two 4 mm or smaller skin punch biopsies may be obtained per visit using a small skin punch under local anesthetic with a bandage to dress the wound. Skin biopsies will be cultured for the isolation of distinct cell populations for subsequent biochemical, cell biological and molecular analyses. We will use immunohistochemistry and in situ hybridization to evaluate endothelial cell dysfunction in multiple vascular beds. We may also use skin biopsy specimens for electron microscopy evaluation to characterize the effect of SARS-CoV-2 on endothelial cells, pericytes and vascular smooth muscle cells.

8.3.9 Accelerometer

Participants will be provided with a small, non-invasive, portable wristwatch accelerometer (Actigraph Inc., Pensacola, FL), to be worn continuously (i.e., 24 hours, 7 days a week) on the participants' non-dominant wrist for collection of free-living physical activity and sleep quality during the course of the study. Participants will begin wearing the accelerometer during the baseline study visit and through to the follow-up assessment time-point (i.e., 10-week follow-up visit for AET+ group or 20-week follow-up visit for CON group). In addition, all participants will be mailed the monitors to be worn for approximately 2 weeks, to coincide with repeated 3-month follow-up periods for one year to capture free-living physical activity and sleep quality outcomes over time.

These small activity monitors have been widely used in large epidemiological studies (NHANES, UK BioBank, etc.) as normative population datasets, and in clinical trials to monitor both population patterns and changes in physical activity, function, and sleep outcomes. Accelerometry signals will be extracted, and overall physical activity levels and sleep duration and quality will be examined using established predictive equations and compared to normative datasets. The device is an FDA 510(k) cleared Class II medical device.

8.4 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse events (AE) and serious adverse events (SAE) are defined as described in NIH HRPP SOP Policy 801. All research events will be monitored by the clinical research staff and reported according to NIH IRB as per Policy 801.

8.4.1 Definition of Adverse Event (AE)

Adverse event means any untoward medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in research, whether or not considered related to the participant's participation in the research.

8.4.2 Definition of Serious Adverse Events (SAE)

A serious adverse event (SAE) is any AE that:

- results in death,
- is life-threatening (places the participant at immediate risk of death from the event as it occurred,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in a persistent or significant disability/incapacity,
- results in a congenital anomaly/birth defects, OR
- based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse)

8.4.3 Classification of an Adverse Event

8.4.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.4.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.4.3.3 Expectedness

Clinical research staff will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

8.4.4 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Clinical research staff will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 14 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable.

8.4.5 Adverse Event and Serious Adverse Event Reporting

Reporting of AEs and SAEs that do not meet the definition of an Unanticipated Problem (UP) will be reported at the time of Continuing Review (CR) to the NIH IRB as specified in NIH HRPP SOP Policy 801.

Death of a research participant that is possibly, probably or definitely related to the research must be reported within 24 hours of the investigator becoming aware of the death to NIH IRB.

8.5 UNANTICIPATED PROBLEMS

Unanticipated problems (UPs) are defined as described in NIH HRPP SOP Policy 801.

8.5.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and

- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

8.5.2 Unanticipated Problem (UP) Reporting

The NIH PI/designee will report unanticipated problems (UPs) to the NIH IRB as per Policy 801. A UP must be reported within 7 calendar days of an investigator becoming aware of the actual or suspected UP. Reporting of UPs will also be reported at the time of Continuing Review (CR) to the NIH IRB as specified in NIH HRPP SOP Policy 801.

8.6 NON-SIGNIFICANT RISK (NSR) DEVICE STUDY

We believe this study is a non-significant risk (NSR) device study subject to the abbreviated IDE requirements of 21 CFR 812.2(b). The device, as used in this study, does not meet the definition of a significant risk (SR) device per 21 CFR 812.3(m) because:

(1) it is not intended as an implant and does not present a potential for serious risk to the health, safety, or welfare of a subject;

(2) it will not be used in supporting or sustaining human life, and does not present a potential for serious risk to the health, safety, or welfare of a subject;

(3) it will not be used of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and does not present a potential for serious risk to the health, safety, or welfare of a subject because the Magnetic Resonance in research mode operates below the limits that the FDA deems to present significant risk as defined in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices; and

(4) it does not otherwise present a potential for serious risk to the health, safety, or welfare of a subject because the Magnetic Resonance in research mode operates below the limits that the FDA deems to present significant risk as defined in the FDA guidance document, Criteria for Significant Risk Investigations of Magnetic Resonance Diagnostic Devices.

Per regulations, abbreviated IDEs (NSR device studies) do not require an application to the FDA as the IRB acts as FDA's surrogate for review, approval, and continuing review of these type of device studies.

8.6.1 Sponsor Reporting for NSR Device Study

The PI will report all unanticipated adverse device effects (UADEs) to the Sponsor within 10 working days. This should be submitted to the ORSC RSS by a MedWatch Form (Form 3500A), which should be sent ENCRYPTED to the REGSupportORSC@nih.gov inbox with a cc to the CD/CMO/designee. The Sponsor will immediately conduct an evaluation, with the PI, to determine if the UADE presents unreasonable risk to subjects. If the Sponsor determines that the UADE presents unreasonable risk, part of the study presenting the risk or all of the study will be

terminated within 5 working days of the determination, and no later than 15 working days after the Sponsor received notice of the UADE. For non-significant risk device investigations terminated due to an UADE, a sponsor may not resume a terminated investigation without IRB and FDA approval.

All AEs will be sent to the Sponsor quarterly, or at minimum annually. For non-significant risk device studies, this information should be included in the continuing review to the IRB.

In addition, the PI will report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. The Sponsor will notify the FDA of withdrawal of IRB approval.

The PI will report to the Sponsor, within 5 working days, if the device is used without obtaining informed consent. The Sponsor will notify the FDA of use of the device without informed consent.

The PI will report to the Sponsor any request to return, repair, or otherwise dispose of any units of a device. The Sponsor will notify the FDA within 30 working days.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESIS

- Primary endpoints

For Objective #1, we will test the hypothesis that AET will improve physical function, as measured by the 6MWT distance. The 6MWT distance is the primary outcome variable for this RCT and thus our project is powered on the sample size estimated to achieve a significant change in this outcome (See Sample Size section below). Outcome variables will be measured at baseline (study visit 1) and following the 10-week intervention (study visit 2).

- Secondary Endpoints

For Objective #2, we will test the hypothesis that AET will improve patient reported outcomes and other health-related QoL components. For Objective #3, we will test the hypothesis that AET will improve free-living physical activity and sleep quality. All outcome variables will be measured at baseline (study visit 1) and following the 10-week intervention (study visit 2).

9.2 SAMPLE SIZE DETERMINATION

The sample size is calculated based on the primary outcome of 6MWT distance. Based on findings from an RCT of similar exercise interventions in participants recovering from SARS (26), the mean improvement of the 6MWT distance in the AET+ group over the CON group is expected to be 56.7 meters (20.7 ± SD=98.6 meters for the control group and 77.4 ± SD=71.3 meters for the exercise group). With a significance level of 0.05, 80% power and 1:1 randomization to two groups, a sample size of 38 in each group is adequate to detect such a difference. Sample size was determined by the Power Analysis and Sample Size (PASS) program for a two-sample t-test with unequal variance.

Our recruitment goal was therefore set at 76 participants, however, 85% of randomized participants are expected to complete at least the second study visit. Therefore, 90 participants

need to be randomized in order to achieve 76 completed participants. Recruitment will remain open until 38 participants in each of the AET+ and CON cohorts have completed at least the second study visit (i.e., 10-week time point).

It is expected that approximately 4 to 8 participants will be enrolled each month, such that target enrollment may be reached within 1.5 to 2 years.

9.3 POPULATIONS FOR ANALYSES

A Per-Protocol analysis will be used where participants that complied with the protocol sufficiently to ensure that their data will likely represent the effects of exercise (i.e., participants who participated in at least 80% of the exercise sessions) are included in the dataset.

9.4 STATISTICAL ANALYSES

9.4.1 General Approach

For descriptive statistics, continuous data will be presented as means with standard deviation and categorical data as percentages. The study will be powered under the assumption that no informative covariates are identified and using 6MWT as the primary outcome. We will include the baseline outcome measure in the model (i.e., the value of the dependent variable at baseline). Assumptions for normality will be assessed as appropriate.

9.4.2 Analysis of the Primary Endpoints

The primary endpoint for this study is physical function, as measured by 6MWT distance after 10 weeks post-randomization. An analysis of covariance (ANCOVA) will be used for objective #1, with the 6MWT distance after the 10-week intervention (study visit 2) as the dependent variable, baseline 6MWT distance (study visit 1) as the covariate and treatment group as the fixed factor. Other factors related to participant characteristics such as timing (e.g., early vs. late study entry) and those related to COVID-19 severity (e.g., age, comorbidities, hospital admission, duration of hospitalization, ventilator use, drug treatments, etc.) may have potential effects on the primary outcome and may be included as covariates in the model. The association between these baseline (i.e., pre-randomization) patient characteristics and the primary outcome will be tested in bivariate and multivariable analyses, and the optimal set of predictors will be included in the final model to account for baseline participant characteristics that may affect recovery.

9.4.3 Analysis of the Secondary Endpoints

A secondary endpoint for this study is the patient-reported outcomes and other health-related components, as well as free living physical activity and sleep quality. An analysis of covariance (ANCOVA) will be used for objective #2 and #3, with the variables of interest after the 10-week intervention (study visit 2) as the dependent variable, baseline variables (study visit 1) as the covariate and treatment group as the fixed factor. Other factors related to participant characteristics such as timing (e.g., early vs. late study entry) and those related to COVID-19 severity (e.g., age, comorbidities, hospital admission, duration of hospitalization, ventilator use, drug treatments, etc.) may have potential effects on secondary outcomes and may be included as covariates in the model. The association between these baseline (i.e., pre-randomization) patient characteristics and secondary outcomes will be tested in bivariate and multivariable analyses,

and the optimal set of predictors will be included in the final model to account for baseline participant characteristics that may affect recovery.

Analyses of secondary endpoints are not dependent on findings of the primary endpoints.

9.4.4 Safety Analyses

Not Applicable

9.4.5 Baseline Descriptive Statistics

Demographics and other baseline characteristics will be presented by treatment group and with both treatment groups combined. For continuous baseline variables, percentiles (median, 25th and 75th), means and standard deviations will be presented. For categorical baseline variables, frequencies and percentages will be presented.

Since randomization is expected to produce balance between treatment groups with respect to baseline characteristics, inferential statistics to compare the two treatment groups on baseline characteristics are not recommended, and will not be used.

9.4.6 Planned Interim Analyses

No interim analysis is planned.

9.4.7 Sub-Group Analyses

Per NIH policy, sex differences will be statistically tested. It is expected however that this subgroup analysis will be underpowered to detect sex differences.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

9.4.9 Exploratory Analyses

An exploratory endpoint for this study is the clinical outcomes, cardiorespiratory function, cognition, biomarkers, metabolomics, ultrasound-based muscle measurements, and vascular and autonomic function. An analysis of covariance (ANCOVA) will be used for objective #4, with the variables of interest after the 10-week intervention (study visit 2) as the dependent variable, baseline variables (study visit 1) as the covariate and treatment group as the fixed factor. Other factors related to participant characteristics such as timing (e.g., early vs. late study entry) and those related to COVID-19 severity (e.g., age, comorbidities, hospital admission, duration of hospitalization, ventilator use, drug treatments, etc.) may have potential effects on exploratory outcomes and may be included as covariates in the model. The association between these baseline (i.e., pre-randomization) patient characteristics and exploratory outcomes will be tested in bivariate and multivariable analyses, and the optimal set of predictors will be included in the final model to account for baseline participant characteristics that may affect recovery.

We are also interested in the feasibility of conducting the AET program remotely in participants recovering from COVID-19 that were randomized to the CON arm (objective #5). Outcomes related to feasibility such as retention, safety, exercise adherence and participant experience will be reported. A paired samples t-test will be used to examine changes in variables of interest (Study Visit 2 and 3) in those participants that participated in remote exercise monitoring.

We are also interested in examining relationships between various outcomes (functional, physiological variables, health outcome variables, etc.) on longer-term follow-up. Therefore, we will explore (objective #6) relationships between physiological variables and post-study health outcome variables obtained during the 1 year follow-up period. These will be analyzed using Pearson product moment correlations and appropriate nonparametric procedures.

10 REGULATORY AND OPERATIONAL CONSIDERATIONS

10.1 INFORMED CONSENT PROCESS

10.1.1 Consent Procedures and Documentation

The informed consent document will be provided as a physical or electronic document to the participant for review prior to consenting. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the consent form and ask questions regarding this study prior to signing.

A signed consent document will be obtained before any study procedures are conducted. Only study investigators designated as able to obtain consent, will obtain informed consent. All study investigators obtaining informed consent will have completed the NIMH Human Subjects Protection Unit (HSPU) “Elements of Successful Informed Consent” training.

If the investigator feels the individual’s capacity to consent to research participation is questionable, the NIH HSPU will be requested to determine whether the individual has the capacity to provide consent. If the individual is determined to not have the capacity to provide consent to research, they will not participate in the study.

The consent form contains all required elements and will be used for all participants. The initial consent process as well as re-consent, when required, will take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed. If the consent process is occurring remotely, participants and investigators may view individual copies of the approved consent document on screens at their respective locations, or the same screen may be used when both the investigator and the participant are co-located but this is not required. If required, the witness signature will be obtained similarly as described for the investigator and participant below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to the participant) or on the electronic document. The process for documenting signatures on an electronic document is described below.

When a hand signature on an electronic document is used for the documentation of consent, this study will use the iMedConsent platform (which is 21 CFR Part 11 compliant) to obtain the required signatures. Both the investigator and the participant will sign the electronic document

using a finger, stylus or mouse. Electronic signatures (i.e., the "signature" and a timestamp are digitally generated) will not be used.

10.1.2 Considerations for Consent of NIH staff, or family members of study team members

If the potential participant is a member of the research team where this research is taking place, procedures outlined in NIH HRPP Policy 404 will be followed. Consent for NIH staff will be obtained as detailed above with the following additional protections:

Consent from staff members will be obtained by an individual independent of the staff member's team whenever possible. Otherwise, the consent procedure will be independently monitored by the CC Department of Bioethics Consultation Service to minimize the risk of undue pressure on the staff member.

10.1.3 Consent of Adults who lack, or lose, decision-making capacity to consent to research participation

Adults unable to consent to research are excluded from enrolling in the protocol. However, it is possible that participants enrolled in the protocol may permanently lose the capacity to consent for themselves during the course of the study. In the event this occurs, participants will be withdrawn from the study.

The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for an independent assessment of whether an individual has the decision-making capacity to provide consent to research participation.

10.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and Clinical Director, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

10.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, and their staff. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the IRB, and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study.

The study participant's contact information will be securely stored at the NIH CC for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB or Institutional policies.

The data entry and management system used for this study is the Clinical Informatics System for Trials and Research (CiSTAR). This NIH database stores data in encrypted-fashion in a dedicated server located within the NIH NINDS data center and is protected according to federal standards. Data transmissions are secured by encryption and access to CiSTAR will be limited to the Principal Investigator and designated Associate Investigators, and be password protected.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10.4 Storage, Use and Sharing of Specimens and Data for Secondary Research

Data and samples kept at the NIH will be stored for future use in a coded fashion in a locked room or secure Institute freezers of the study investigators, until they are no longer of scientific value or if a participant withdraws consent for their continued use, at which time they will be destroyed.

Data and samples may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases.

10.5 Safety Oversight

Data and safety will be monitored by the Principal Investigator, in conjunction with an independent medical monitor (IMM). We have enlisted the assistance of Matthew N. Bartels, MD, MPH, Chairman of the Department of Physical Medicine and Rehabilitation at the Montefiore Medical Center/Albert Einstein College of Medicine, New York, as the IMM for this study. He will be apprised of all significant adverse events, and will also have access to the study data.

10.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council for Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by the Office of Research Support and Compliance (ORSC).

Monitoring will be conducted through a combination of remote and on-site visits as needed. The frequency and extent of the monitoring visits will be based on the site's performance and enrollment rate, typically every 6 to 12 months.

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.Research study staff will meet on a regular basis when participants are actively receiving an intervention to discuss each participant. Study investigators will evaluate the safety of study participants throughout the conduct of the study and respond to AEs in a timely manner. The PI in collaboration with IMM and study investigators will review any cases associated with serious adverse outcomes and advise on whether or not any changes in the research plan are warranted.

10.7 Quality Assurance and Quality Control

The NIH CC's Quality Assurance Program will conduct study monitoring at least annually or more frequently as required for open studies. Monitoring visits will include a review of participant consent documents, primary outcome and safety laboratory results which will be monitored for accuracy, correct dating, and agreement between case report forms and source documents. All regulatory reports, reviews and amendments, adverse events and problem reports related to the study, along with investigator credentials, training records and the delegation of responsibility log will also be reviewed during monitoring visits. Any major findings will be summarized in writing and reported to the study PI who will be responsible for submitting the monitoring report to the IRB.

Research study staff will perform internal quality management of study conduct, data collection, documentation and completion, throughout the study.

10.8 Data Handling and Record Keeping

10.8.1 Data Collection and Management Responsibilities

Data will be collected using appropriately calibrated computer-assisted instrumentation, commercial software programs, data collection sheets and self-reported outcome questionnaires. The Patient Self Report (PSR) module in CiSTAR will be used to manage data collection of the self-reported outcome questionnaires electronically.

Upon enrollment, all participants will be assigned a sequential code that will be used as the participant identifier for all participant files, biological samples and data collection sheets. Data and samples will be stored in secured areas, using codes that we assign. The study investigators will have access to the code key.

Data will be kept in password-protected computers. Data collected during qualitative interviews will consist of audio recordings, which will be sent to a professional service for transcription via a secure website or transcribed locally to restricted access folders on the NIH CC network. Data, recordings, and transcriptions will be stored in locked cabinets and restricted access folders on the NIH CC network. Transcriptions will not contain any identifying information and will be labeled with a number only. Blood samples will be stored in secured Institute freezers of the

study investigators until they are ready for batch analysis. Computer software used for gas exchange data collection are kept on password-protected computers that are off-network and stored in a locked laboratory with restricted access. Electronic data collected in the laboratory will be transferred to a restricted access folder on the NIH CC network with appropriate firewall protection. Only study investigators will have access to this folder. A password protected USB device will be used to transfer electronic data. Paper data collection sheets will be kept in de-identified participant folders in locked filing cabinets in secure areas. Participant consent forms and other relevant medical records with patient names and other identifiable data are kept in separate folders and locked in separate filing cabinets. No information will be kept in either folder that could be used to link a participant's medical record file to a participant's study data file. Only study investigators will have access to the stored data and samples.

Data collection is the responsibility of the research staff under the supervision of the PI. All study investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All electronic forms captured by PSR will be considered source documentation.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs) and concomitant medications) and clinical laboratory data will be entered into a secure database, such as CiSTAR, or captured by Clinical Research Informatics System (CRIS) or Biomedical Translational Research Information System (BTRIS). All these data capture systems are provided by the NIH. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

10.8.2 Study Records Retention

Study documents will be retained as per the NIH Intramural Records Retention Schedule.

10.9 PROTOCOL DEVIATIONS AND NON-COMPLIANCE

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the NIH Institutional Review Board as per Policy 801. All deviations must be addressed in study source documents. The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.9.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the IRB-approved research protocol.

- Major deviations: Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact the rights, welfare or safety of the participant, or to substantially negatively impact the scientific integrity or validity of the study.
- Minor deviations: Deviations that do not have the potential to negatively impact the rights, safety or welfare of participants or others, or the scientific integrity or validity of the study.

10.9.2 NIH Definition of Non-Compliance

Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human participants in research, or the requirements or determinations of the IRB, whether intentional or not.

- Serious non-compliance: Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the participant. Non-compliance that materially affects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research participants.
- Continuing non-compliance: A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to participants or otherwise materially compromise the rights, welfare and/or safety of participants, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different non-compliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB.

10.10 Publication and Data Sharing Policy

10.10.1Human Data Sharing Plan

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers after the completion of the primary endpoint by contacting the PI or his designee.

Participants enrolled in this protocol may be directly referred and/or cross-enrolled in other NIH studies. When permissible, data and samples collected under this protocol may be shared with other NIH protocols to include:

- 20-CC-0113: Cardiopulmonary Inflammation and Multi-System Imaging During the Clinical Course of COVID-19 Infection in Asymptomatic and Symptomatic Persons
- 18-H-0011: Technical Development of Cardiovascular Magnetic Resonance Imaging (CMR) Using a Low Specific Absorption Rate (SAR) Scanner System
- 14-H-0188: Prospective Evaluation of Next Generation CT Reconstruction
- 000089-N: Natural History of Post-Coronavirus Disease 19 Convalescence at the National Institutes of Health
- 19-NR-0098: Patient-Centered Assessment of Symptoms and Outcomes
- 18-H-0108: Vascular Disease Discovery Protocol

Samples and data may be shared with other NIH protocols, other investigators, or databases/repositories, under the following guidelines:

- Data and samples may be shared with collaborating laboratories at NIH or outside of NIH and/or submitted to NIH-designated repositories and databases.
- Samples and data will be stripped of identifiers and may be coded ("de-identified") or unlinked from an identifying code ("anonymized"). When coded data is shared, the key to the code will not be provided to collaborators, but will remain at NIH. Data and samples may be shared with investigators and institutions with a Federalwide Assurance (FWA) or operating under the Declaration of Helsinki (DoH) and reported at the time of continuing review. Sharing with investigators without an FWA or not operating under the DoH will be submitted for prospective IRB approval. Submissions to NIH-sponsored or supported databases and repositories will be reported at the time of Continuing Review. Submission to non-NIH sponsored or supported databases and repositories will be submitted for prospective IRB approval.
- Required approvals from the collaborating institution will be obtained and materials will be shipped in accordance with NIH and federal regulations.
- Applicable identified data (e.g., generated via CRIS) will be shared following standard NIH CC operating procedures including BTRIS data access policies. Data to be shared include baseline characteristics as well as key study outcome variables in a tabulated format, after adequate data cleaning, processing, and quality control. Data sharing will be performed at or prior to the time of publication.

10.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIH CC has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 ABBREVIATIONS

6MWT	Six minute Walk Test
ABI	Ankle-Brachial Index
ACSM	American College of Sports Medicine
AE	Adverse Event
AET	Aerobic Exercise Training
AET+	Aerobic Exercise Training + Education Group
AI	Associate Investigator
ANCOVA	Analysis of Covariance
ANS	Autonomic Nervous System
APTA	American Physical Therapy Association
ARDS	Acute Respiratory Distress Syndrome
BDI-II	Beck's Depression Index-2
BMI	Body Mass Index
BTRIS	Biomedical Translational Research Information System
CAVI	Cardio-Ankle Vascular Index
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CiSTAR	Clinical Informatics System for Trials and Research
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
CMR	Cardiovascular Magnetic Resonance
COC	Certificate of Confidentiality
CON	Control Group (Education Only)
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus-2019
CPET	Cardiopulmonary Exercise Test
CR	Continuing Review
CRF	Case Report Form
CRISIS	CoRonavIruS Health Impact Survey
CRIS	Clinical Research Informatics System
CT	Computed Tomography
CTA	Computer Tomography Angiogram
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DLCO	Diffusion Capacity
DSMB	Data Safety Monitoring Board
DSQ-PEM	DePaul Symptom Questionnaire – Post Exertional Malaise
DRE	Disease-Related Event
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiogram

eCRF	Electronic Case Report Forms
EPII	Epidemic – Pandemic Impacts Inventory
EQ-5D-5L	EuroQoL 5-Dimension 5-Level
EtOH	Ethyl alcohol
FDA	Food and Drug Administration
FSS	Fatigue Severity Scale
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practices
GWAS	Genome-Wide Association Studies
HAP	Human Activity Profile
HbA1c	Hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
HSPU	Human Subjects Protection Unit
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IES-R	8.3.6.7 Impact of Events Scale – Revised
ILD	Interstitial Lung Disease
IMM	Independent Medical Monitor
IND	Investigational New Drug Application
IPAQ	International Physical Activity Questionnaire
IR	Infrared Imaging
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSCI	Laser Speckle Contrast Imaging
LVEF	Left Ventricular Ejection Fraction
ME/CFS	Myalgic Encephalomyelitis/Chronic Fatigue Syndrome
MERS	Middle East Respiratory Syndrome
Mini-BEST	Mini Balance Evaluation Systems Test
MOP	Manual of Procedures
MRI	Magnetic Resonance Imaging
MVV	Maximal Voluntary Ventilation
Neuro-QOL	Quality of Life in Neurological Disorders
NIH	National Institutes of Health
NIH CC	NIH Clinical Center
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NIRS	Near-Infrared Spectroscopy
OHRP	Office for Human Research Protections

PAT	Peripheral Arterial Tonometry
PEM	Post Exertional Malaise
PFT	Pulmonary Function Test
PI	Principal Investigator
PORH	Post Occlusion Reactive Hyperemia
PR	Pulmonary Rehabilitation
PROMIS	Patient-Reported Outcomes Measurement Information System
PSQI	Pittsburg Sleep Quality Index
PSR	Patient Self Report module
PTSD	Post-Traumatic Stress Disorder
PWA	Pulse wave Analysis
PWV	Pulse wave Velocity
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
QSART	Quantitative Sudomotor Axon Reflex Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomized Control Trial
RHI	Reactive Hyperemia Index
RMD	Rehabilitation Medicine Department
RPE	Ratings of Perceived Exertion
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SF36v2	Short Form 36 Health Survey Version 2
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SpO2	Saturation of peripheral O_2
SPPB	Short Physical Performance Battery
UP	Unanticipated Problem
UPSIT	University of Pennsylvania Smell Identification Test
US	United States
USB	Universal Serial Bus
VAS-CFS	Visual Analogue Scale for Chronic Fatigue Syndrome Symptoms
VO_2	Oxygen Consumption

12 REFERENCES

1. McNeary L, Maltser S, Verduzco-Gutierrez M. Navigating Coronavirus Disease 2019 (Covid-19) in Physiatry: A CAN Report for Inpatient Rehabilitation Facilities. PM&R. 2020;12(5):512-5.

2. Oliveira RPd, Teixeira C, Rosa RG. Acute respiratory distress syndrome: how do patients fare after the intensive care unit? Rev Bras Ter Intensiva. 2019;31(4):555-60.

3. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4.

4. Richterich P. Severe underestimation of COVID-19 case numbers: effect of epidemic growth rate and test restrictions. medRxiv. 2020:2020.04.13.20064220.

5. COVID-NET: COVID-19-Associated Hospitalization Surveillance Network, Centers for Disease Control and Prevention [Available from: https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html.

6. Grabowski DC, Joynt Maddox KE. Postacute Care Preparedness for COVID-19: Thinking Ahead. JAMA. 2020.

7. Carfì A, Bernabei R, Landi F, Group ftGAC-P-ACS. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020.

8. Tenforde MW, Kim S, Lindsell C, Rose E, Shapiro N, Files DC, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network—United States, March–June 2020. MMWR Morb Mortal Wkly Rep. 2020.

9. Barker-Davies RM, Sullivan O, Senaratne KPP, Baker P, Cranley M, Dharm-Datta S, et al. The Stanford Hall consensus statement for post-COVID-19 rehabilitation. Br J Sports Med. 2020;54(16):949.

10. Kiekens C, Boldrini P, Andreoli A, Avesani R, Gamna F, Grandi M, et al. Rehabilitation and respiratory management in the acute and early post-acute phase. "Instant paper from the field" on rehabilitation answers to the Covid-19 emergency. Eur J Phys Rehabil Med. 2020.

11. Zhao HM, Xie YX, Wang C. Recommendations for respiratory rehabilitation in adults with COVID-19. Chin Med J. 2020.

12. Sheehy LM. Considerations for Post-acute Rehabilitation for Survivors of COVID-19. JMIR Public Health Surveill. 2020.

13. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

14. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, et al. One-Year Outcomes in Survivors of the Acute Respiratory Distress Syndrome. N Engl J Med. 2003;348(8):683-93.

15. Jadhav AR, Shinde SB. Functional exercise capacity in young survivors of acute respiratory distress syndrome. Indian J Tuberc. 2019.

16. Su MC, Hsieh YT, Wang YH, Lin AS, Chung YH, Lin MC. Exercise capacity and pulmonary function in hospital workers recovered from severe acute respiratory syndrome. Respiration. 2007;74(5):511-6.

17. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional Disability 5 Years after Acute Respiratory Distress Syndrome. N Engl J Med. 2011;364(14):1293-304.

18. Hui DS, Joynt GM, Wong KT, Gomersall CD, Li TS, Antonio G, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. Thorax. 2005;60(5):401-9.

19. Tansey CM, Louie M, Loeb M, Gold WL, Muller MP, de Jager J, et al. One-Year Outcomes and Health Care Utilization in Survivors of Severe Acute Respiratory Syndrome. Arch Intern Med. 2007;167(12):1312-20.

20. Dodoo-Schittko F, Brandstetter S, Blecha S, Thomann-Hackner K, Brandl M, Knüttel H, et al. Determinants of Quality of Life and Return to Work Following Acute Respiratory Distress Syndrome. Dtsch Arztebl Int. 2017;114(7):103-9.

21. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. Cochrane Database Syst Rev. 2019(7).

22. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59.

23. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, et al. Aerobic exercise and neurocognitive performance: A meta-analytic review of randomized controlled trials. Psychosom Med. 2010;72(3):239-52.

24. Zheng G, Xia R, Zhou W, Tao J, Chen L. Aerobic exercise ameliorates cognitive function in older adults with mild cognitive impairment: a systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2016;50(23):1443-50.

25. Ries AL. Pulmonary Rehabilitation: Summary of an Evidence-Based Guideline. Respir Care. 2008;53(9):1203.

26. Lau HM-C, Ng GY-F, Jones AY-M, Lee EW-C, Siu EH-K, Hui DS-C. A randomised controlled trial of the effectiveness of an exercise training program in patients recovering from severe acute respiratory syndrome. Aust J Physiother. 2005;51(4):213-9.

27. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020.

28. Hornig M. What does COVID-19 portend for ME/CFS? https://solvecfs.org/wp-content/uploads/2020/04/COVID19-MECFS_Sci_Review.pdf2020 [

29. O'Connor C. COVID-19 Fatigue: Not So Fast2020. Available from: https://heartfailure.onlinejacc.org/content/jhf/8/7/592.full.pdf.

30. Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG. Chronic Fatigue and Postexertional Malaise in People Living With Long COVID: An Observational Study. Physical Therapy. 2022;102(4).

31. Centers for Disease Control and Prevention. Treating the Most Disruptive Symptoms First and Preventing Worsening of Symptoms [Available from: https://www.cdc.gov/me-cfs/healthcare-providers/clinical-care-patients-mecfs/treating-most-disruptive-symptoms.html.

32. Latimer-Cheung AE, Pilutti LA, Hicks AL, Martin Ginis KA, Fenuta AM, MacKibbon KA, Motl RW. Effects of exercise training on fitness, mobility, fatigue, and health-related quality of life among adults with multiple sclerosis: A systematic review to inform guideline development. Arch Phys Med Rehabil. 2013;94(9):1800-28.

33. Meneses-Echávez JF, González-Jiménez E, Ramírez-Vélez R. Supervised exercise reduces cancer-related fatigue: a systematic review. J Physiother. 2015;61(1):3-9.

34. Larun L, Brurberg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database Syst Rev. 2019(10).

35. Atherton PJ, Greenhaff PL, Phillips SM, Bodine SC, Adams CM, Lang CH. Control of skeletal muscle atrophy in response to disuse: clinical/preclinical contentions and fallacies of evidence. Am J Physiol Endocrinol Metab. 2016;311(3):E594-604.

36. Piva S, Fagoni N, Latronico N. Intensive care unit-acquired weakness: unanswered questions and targets for future research. F1000Res. 2019;8.

37. Mehrholz J, Pohl M, Kugler J, Burridge J, Mückel S, Elsner B. Physical rehabilitation for critical illness myopathy and neuropathy. Cochrane Database Syst Rev. 2015(3):Cd010942.

38. Atterhog JH, Jonsson B, Samuelsson R. Exercise testing: a prospective study of complication rates. Am Heart J. 1979;98(5):572-9.

39. Franklin B, Hellerstein H, Gordon S, Timmis G, editors. Exercise Testing: Basic Principles. New York, NY: Churchill Livingstone; 1992.

40. Gibbons L, Blair SN, Kohl HW, Cooper K. The safety of maximal exercise testing. Circulation. 1989;80(4):846-52.

41. Gibbons LW, Mitchell TL, Gonzalez V. The safety of exercise testing. Prim Care. 1994;21(3):611-29.

42. Hamm LF, Crow RS, Stull GA, Hannan P. Safety and characteristics of exercise testing early after acute myocardial infarction. Am J Cardiol. 1989;63(17):1193-7.

43. Modesto KM, Møller JE, Freeman WK, Shub C, Bailey KR, Pellikka PA. Safety of Exercise Stress Testing in Patients With Abnormal Concentrations of Serum Potassium. Am J Cardiol. 2006;97(8):1247-9.

44. Squires RW, Allison TG, Johnson BD, Gau GT. Non-Physician Supervision of Cardiopulmonary Exercise Testing in Chronic Heart Failure: Safety and Results of a Preliminary Investigation. J Cardiopulm Rehabil Prev. 1999;19(4):249-53.

45. Stuart JRJ, Ellestad MH. National survey of exercise stress testing facilities. Chest. 1980;77(1):94-7.

46. Vacanti LJ, Sespedes LB, Sarpi Mde O. Exercise stress testing is useful, safe, and efficient even in patients aged 75 years or older. Arq Bras Cardiol. 2004;82(2):151-4, 47-50.

47. Young DZ, Lampert S, Graboys TB, Lown B. Safety of maximal exercise testing in patients at high risk for ventricular arrhythmia. Circulation. 1984;70(2):184-91.

48. Appelman B, Charlton BT, Goulding RP, Kerkhoff TJ, Breedveld EA, Noort W, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. Nature Communications. 2024;15(1):17.

49. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 10th ed. Philidelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins Health; 2018.

50. Kochi AN, Tagliari AP, Forleo GB, Fassini GM, Tondo C. Cardiac and arrhythmic complications in patients with COVID-19. J Cardiovasc Electrophysiol. 2020;31(5):1003-8.

51. Phelan D, Kim JH, Chung EH. A Game Plan for the Resumption of Sport and Exercise After Coronavirus Disease 2019 (COVID-19) Infection. JAMA Cardiol. 2020.

52. Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NA, 3rd, et al. Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities: Task Force 3: Hypertrophic Cardiomyopathy, Arrhythmogenic Right Ventricular Cardiomyopathy and Other Cardiomyopathies, and Myocarditis: A Scientific Statement From the American Heart Association and American College of Cardiology. Circulation. 2015;132(22):e273-80.

53. Sukocheva OA, Maksoud R, Beeraka NM, Madhunapantula SV, Sinelnikov M, Nikolenko VN, et al. Analysis of post COVID-19 condition and its overlap with myalgic encephalomyelitis/chronic fatigue syndrome. Journal of Advanced Research. 2022;40:179-96.

54. Stussman B, Williams A, Snow J, Gavin A, Scott R, Nath A, Walitt B. Characterization of Post–exertional Malaise in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Front Neurol. 2020;11:1025.

55. Sick J, König D. Exercise Training in Non-Hospitalized Patients with Post-COVID-19 Syndrome—A Narrative Review. Healthcare. 2023;11(16):2277.

56. Edward JA, Peruri A, Rudofker E, Shamapant N, Parker H, Cotter R, et al. Characteristics and Treatment of Exercise Intolerance in Patients With Long COVID. Journal of Cardiopulmonary Rehabilitation and Prevention. 2023;43(6):400-6.

57. Ahmadi Hekmatikar AH, Ferreira Júnior JB, Shahrbanian S, Suzuki K. Functional and Psychological Changes after Exercise Training in Post-COVID-19 Patients Discharged from the Hospital: A PRISMA-Compliant Systematic Review. International Journal of Environmental Research and Public Health. 2022;19(4):2290.

58. Ruhl AP, Huang M, Colantuoni E, Lord RK, Dinglas VD, Chong A, et al. Healthcare Resource Use and Costs in Long-Term Survivors of Acute Respiratory Distress Syndrome: A 5-Year Longitudinal Cohort Study. Crit Care Med. 2017;45(2):196-204.

59. Ngai JC, Ko FW, Ng SS, To K-W, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology. 2010;15(3):543-50.

60. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: A randomized controlled study. Complement Ther Clin Pract. 2020;39:101166.

61. Nathan SD, du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, et al. Validation of test performance characteristics and minimal clinically important difference of the 6-minute walk test in patients with idiopathic pulmonary fibrosis. Respir Med. 2015;109(7):914-22.

62. Swigris JJ, Wamboldt FS, Behr J, du Bois RM, King TE, Raghu G, Brown KK. The 6 minute walk in idiopathic pulmonary fibrosis: longitudinal changes and minimum important difference. Thorax. 2010;65(2):173-7.

63. Chan KS, Pfoh ER, Denehy L, Elliott D, Holland AE, Dinglas VD, Needham DM. Construct Validity and Minimal Important Difference of 6-Minute Walk Distance in Survivors of Acute Respiratory Failure. Chest. 2015;147(5):1316-26.

64. Keyser RE, Christensen EJ, Chin LM, Woolstenhulme JG, Drinkard B, Quinn A, et al. Changes in fatigability following intense aerobic exercise training in patients with interstitial lung disease. Respir Med. 2015;109(4):517-25.

65. Chan L, Chin LMK, Kennedy M, Woolstenhulme JG, Nathan SD, Weinstein AA, et al. Benefits of Intensive Treadmill Exercise Training on Cardiorespiratory Function and Quality of Life in Patients With Pulmonary Hypertension. Chest. 2013;143(2):333-43.

66. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2015(2):Cd003793.

67. Ammar A, Brach M, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, et al. Effects of COVID-19 home confinement on physical activity and eating behaviour Preliminary results of the ECLB-COVID19 international online-survey. medRxiv. 2020:2020.05.04.20072447.

68. Casagrande M, Favieri F, Tambelli R, Forte G. The enemy who sealed the world: Effects quarantine due to the COVID-19 on sleep quality, anxiety, and psychological distress in the Italian population. Sleep Med. 2020.

69. Jahrami H, BaHammam AS, AlGahtani H, Ebrahim A, Faris M, AlEid K, et al. The examination of sleep quality for frontline healthcare workers during the outbreak of COVID-19. Sleep Breath. 2020.

70. Tseng T-H, Chen H-C, Wang L-Y, Chien M-Y. Effects of exercise training on sleep quality and heart rate variability in middle-aged and older adults with poor sleep quality: a randomized controlled trial. J Clin Sleep Med. 2020:jcsm.8560.

71. Grace A, Chan E, Giallauria F, Graham PL, Smart NA. Clinical outcomes and glycaemic responses to different aerobic exercise training intensities in type II diabetes: a systematic review and meta-analysis. Cardiovasc Diabetol. 2017;16(1):37.

72. Northey JM, Cherbuin N, Pumpa KL, Smee DJ, Rattray B. Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. Br J Sports Med. 2018;52(3):154-60.

73. Negaresh R, Motl RW, Zimmer P, Mokhtarzade M, Baker JS. Effects of exercise training on multiple sclerosis biomarkers of central nervous system and disease status: a systematic review of intervention studies. European Journal of Neurology. 2019;26(5):711-21.

74. Kuhl J, Moritz T, Wagner H, Stenlund H, Lundgren K, Båvenholm P, et al. Metabolomics as a tool to evaluate exercise-induced improvements in insulin sensitivity. Metabolomics. 2008;4(3):273-82.

75. Zenith L, Meena N, Ramadi A, Yavari M, Harvey A, Carbonneau M, et al. Eight Weeks of Exercise Training Increases Aerobic Capacity and Muscle Mass and Reduces Fatigue in Patients With Cirrhosis. Clin Gastroenterol Hepatol. 2014;12(11):1920-6.e2.

76. Green DJ, Smith KJ. Effects of Exercise on Vascular Function, Structure, and Health in Humans. Cold Spring Harb Perspect Med. 2018;8(4).

77. Mohammed J, Derom E, Van Oosterwijck J, Da Silva H, Calders P. Evidence for aerobic exercise training on the autonomic function in patients with chronic obstructive pulmonary disease (COPD): a systematic review. Physiotherapy. 2018;104(1):36-45.

78. Liu X-L, Tan J-Y, Wang T, Zhang Q, Zhang M, Yao L-Q, Chen J-X. Effectiveness of Home-Based Pulmonary Rehabilitation for Patients with Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Randomized Controlled Trials. Rehabilitation Nursing. 2014;39(1):36-59.

79. Perez-Bogerd S, Wuyts W, Barbier V, Demeyer H, Van Muylem A, Janssens W, Troosters T. Short and long-term effects of pulmonary rehabilitation in interstitial lung diseases: a randomised controlled trial. Respir Res. 2018;19(1):182.

80. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: A prospective cohort study. Respir Med. 2014;108(1):203-10.

81. Li M. Chest CT features and their role in COVID-19. Radiology Infect Dis. 2020:10.1016/j.jrid.2020.04.001.

82. Pan F, Ye T, Sun P, Gui S, Liang B, Li L, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology. 2020;295(3):715-21.

83. Wei J, Lei P, Yang H, Fan B, Qiu Y, Zeng B, et al. Analysis of thin-section CT in patients with coronavirus disease (COVID-19) after hospital discharge. Clin Imaging. 2020.

84. Park WB, Jun KI, Kim G, Choi J-P, Rhee J-Y, Cheon S, et al. Correlation between Pneumonia Severity and Pulmonary Complications in Middle East Respiratory Syndrome. J Korean Med Sci. 2018;33(24):e169-e.

85. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020:2001217.

86. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188(8):e13-64.

87. Keyser RE, Woolstenhulme JG, Chin LM, Nathan SD, Weir NA, Connors G, et al. Cardiorespiratory function before and after aerobic exercise training in patients with interstitial lung disease. J Cardiopulm Rehabil Prev. 2015;35(1):47-55.

88. Abobaker A, Raba AA, Alzwi A. Extrapulmonary and atypical clinical presentations of COVID-19. J Med Virol. 2020:1-7.

89. Lopez M, Bell K, Annaswamy T, Juengst S, Ifejika N. COVID-19 Guide for the Rehabilitation Clinician: A Review of Non-Pulmonary Manifestations and Complications. Am J Phys Med Rehabil. 2020:10.1097/PHM.0000000000001479.

90. Flach A, Jaegers L, Krieger M, Bixler E, Kelly P, Weiss EP, Ahmad SO. Endurance exercise improves function in individuals with Parkinson's disease: A meta-analysis. Neurosci Lett. 2017;659:115-9.

91. Panza GA, Taylor BA, MacDonald HV, Johnson BT, Zaleski AL, Livingston J, et al. Can Exercise Improve Cognitive Symptoms of Alzheimer's Disease? J Am Geriatr Soc. 2018;66(3):487-95.

92. Vogel JS, van der Gaag M, Slofstra C, Knegtering H, Bruins J, Castelein S. The effect of mind-body and aerobic exercise on negative symptoms in schizophrenia: A meta-analysis. Psychiatry Res. 2019;279:295-305.

93. Spielman LJ, Little JP, Klegeris A. Physical activity and exercise attenuate neuroinflammation in neurological diseases. Brain Res Bull. 2016;125:19-29.

94. Enright PL, Sherrill DL. Reference Equations for the Six-Minute Walk in Healthy Adults. Am J Respir Crit Care Med. 1998;158(5):1384-7.

95. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference Values for a Multiple Repetition 6-Minute Walk Test in Healthy Adults Older Than 20 Years. J Cardiopulm Rehabil Prev. 2001;21(2):87-93.

96. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88.

97. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. Am J Emerg Med. 2020.

98. Wu X, Dong D, Ma D. Thin-Section Computed Tomography Manifestations During Convalescence and Long-Term Follow-Up of Patients with Severe Acute Respiratory Syndrome (SARS). Med Sci Monit. 2016;22:2793-9.

99. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. Lancet Neurol. 2020.

100. Kremer S, Lersy F, de Sèze J, Ferré J-C, Maamar A, Carsin-Nicol B, et al. Brain MRI Findings in Severe COVID-19: A Retrospective Observational Study. Radiology. 2020:202222.

101. Fitsiori A, Pugin D, Thieffry C, Lalive P, Vargas MI. Unusual Microbleeds in Brain MRI of Covid-19 Patients. J Neuroimaging. 2020.

102. Koralnik IJ, Tyler KL. COVID-19: A Global Threat to the Nervous System. Ann Neurol. 2020;88(1):1-11.

103. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. Neurology. 2020;94(22):959-69.

104. Boon AJ, Sekiguchi H, Harper CJ, Strommen JA, Ghahfarokhi LS, Watson JC, Sorenson EJ. Sensitivity and specificity of diagnostic ultrasound in the diagnosis of phrenic neuropathy. Neurology. 2014;83(14):1264-70.

105. Supinski GS, Morris PE, Dhar S, Callahan LA. Diaphragm Dysfunction in Critical Illness. Chest. 2018;153(4):1040-51.

106. Fujiwara K, Asai H, Toyama H, Kunita K, Yaguchi C, Kiyota N, et al. Changes in muscle thickness of gastrocnemius and soleus associated with age and sex. Aging clinical and experimental research. 2010;22(1):24-30.

107. Cadore EL, Izquierdo M, Conceição M, Radaelli R, Pinto RS, Baroni BM, et al. Echo intensity is associated with skeletal muscle power and cardiovascular performance in elderly men. Exp Gerontol. 2012;47(6):473-8.

108. Mah JK, van Alfen N. Neuromuscular Ultrasound: Clinical Applications and Diagnostic Values. Can J Neurol Sci. 2018;45(6):605-19.

109. Dubé B-P, Dres M. Diaphragm Dysfunction: Diagnostic Approaches and Management Strategies. J Clin Med. 2016;5(12):113.

110. Vetrugno L, Guadagnin GM, Barbariol F, Langiano N, Zangrillo A, Bove T. Ultrasound Imaging for Diaphragm Dysfunction: A Narrative Literature Review. J Cardiothorac Vasc Anesth. 2019;33(9):2525-36.

111. Ricoy J, Rodríguez-Núñez N, Álvarez-Dobaño JM, Toubes ME, Riveiro V, Valdés L. Diaphragmatic dysfunction. Pulmonology. 2019;25(4):223-35.

112. Boon AJ, Harper CJ, Ghahfarokhi LS, Strommen JA, Watson JC, Sorenson EJ. Two-dimensional ultrasound imaging of the diaphragm: quantitative values in normal subjects. Muscle Nerve. 2013;47(6):884-9.

113. Heckmatt JZ, Pier N, Dubowitz V. Real-time ultrasound imaging of muscles. Muscle Nerve. 1988;11(1):56-65.

114. Schnelle JF, Buchowski MS, Ikizler TA, Durkin DW, Beuscher L, Simmons SF. Evaluation of two fatigability severity measures in elderly adults. Journal of the American Geriatrics Society. 2012;60(8):1527-33.

115. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.

116. Lettieri CJ, Nathan SD, Browning RF, Barnett SD, Ahmad S, Shorr AF. The distance-saturation product predicts mortality in idiopathic pulmonary fibrosis. Respir Med. 2006;100(10):1734-41.

117. Medina-Mirapeix F, Bernabeu-Mora R, Llamazares-Herrán E, Sánchez-Martínez MP, García-Vidal JA, Escolar-Reina P. Interobserver Reliability of Peripheral Muscle Strength Tests

and Short Physical Performance Battery in Patients With Chronic Obstructive Pulmonary Disease: A Prospective Observational Study. Arch Phys Med Rehabil. 2016;97(11):2002-5.

118. Gandotra S, Lovato J, Case D, Bakhru RN, Gibbs K, Berry M, et al. Physical Function Trajectories in Survivors of Acute Respiratory Failure. Ann Am Thorac Soc. 2019;16(4):471-7.

119. Martin R, Botkin R, Campbell A, Faucheux C, Kegelmeyer D, Kendig T, et al. COVID-19 Core Outcome Measures: APTA Academies and Sections Consensus Statement 2020 [updated 7/29/2020. Available from: https://www.apta.org/contentassets/1a6e0ee7cd25403888d2959c1c8476cd/covid-19-core-outcome-consensus-statement-june-2020.pdf.

120. Academy for Neurologic Physical Therapy. ANPT Outcome Measures Recommendations 2018 [Available from: https://www.neuropt.org/practice-resources/neurology-section-outcome-measures-recommendations.

121. Radtke T, Crook S, Kaltsakas G, Louvaris Z, Berton D, Urquhart DS, et al. ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. Eur Respir Rev. 2019;28(154):180101.

122. Hawthorne G, Osborne RH, Taylor A, Sansoni J. The SF36 Version 2: critical analyses of population weights, scoring algorithms and population norms. Qual Life Res. 2007;16(4):661-73.

123. Jin X, Pang B, Zhang J, Liu Q, Yang Z, Feng J, et al. Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (COS-COVID). Engineering. 2020.

124. Nolan CM, Longworth L, Lord J, Canavan JL, Jones SE, Kon SSC, Man WD-C. The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. Thorax. 2016;71(6):493-500.

125. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989;46(10):1121-3.

126. Tselebis A, Bratis D, Pachi A, Moussas G, Ilias I, Harikiopoulou M, et al. A pulmonary rehabilitation program reduces levels of anxiety and depression inCOPD patients. Multidiscip Respir Med. 2013;8(1):41.

127. Wu KK, Chan SK, Ma TM. Posttraumatic stress after SARS. Emerg Infect Dis. 2005;11(8):1297-300.

128. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213.

129. Dhooria S, Sehgal IS, Agrawal AK, Agarwal R, Aggarwal AN, Behera D. Sleep after critical illness: Study of survivors of acute respiratory distress syndrome and systematic review of literature. Indian J Crit Care Med. 2016;20(6):323-31.

130. Gaunaurd IA, Gómez-Marín OW, Ramos CF, Sol CM, Cohen MI, Cahalin LP, et al. Physical Activity and Quality of Life Improvements of Patients With Idiopathic Pulmonary Fibrosis Completing a Pulmonary Rehabilitation Program. Respir Care. 2014;59(12):1872-9.

131. Blitshteyn S, Whitelaw S. Postural orthostatic tachycardia syndrome (POTS) and other autonomic disorders after COVID-19 infection: a case series of 20 patients. Immunologic Research. 2021;69(2):205-11.

132. Shouman K, Vanichkachorn G, Cheshire WP, Suarez MD, Shelly S, Lamotte GJ, et al. Autonomic dysfunction following COVID-19 infection: an early experience. Clinical Autonomic Research. 2021;31(3):385-94.

133. Del Rio R, Marcus NJ, Inestrosa NC. Potential Role of Autonomic Dysfunction in Covid-19 Morbidity and Mortality. Front Physiol. 2020;11:561749-.

134. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, Lim PB. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clin Med (Lond). 2021;21(1):e63-e7.

135. Low PA, Denq JC, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. Muscle Nerve. 1997;20(12):1561-8.

136. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Auton Neurosci. 2011;161(1-2):46-8.

137. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;395(10234):1417-8.

138. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020:1-4.

139. McGonagle D, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. Lancet Rheumatol. 2020;2(7):e437-e45.

140. Escher R, Breakey N, Lämmle B. Severe COVID-19 infection associated with endothelial activation. Thromb Res. 2020;190:62-.

141. Li Y, Cao Y, Zeng Z, Liang M, Xue Y, Xi C, et al. Angiotensin-converting enzyme 2/angiotensin-(1-7)/Mas axis prevents lipopolysaccharide-induced apoptosis of pulmonary microvascular endothelial cells by inhibiting JNK/NF-κB pathways. Scientific reports. 2015;5:8209-.