

Protocol

Exploratory Study of Different Doses of Endurance Exercise in People with Parkinson Disease



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SYNOPSIS

Title: Exploratory Study of Different Doses of Endurance Exercise in People with Parkinson Disease

Study Objectives

The overall objective of this Phase II study is to determine the futility or non-futility of conducting a Phase III randomized controlled trial to determine the effects of exercise on the progression of PD symptoms. The primary aim is to determine whether individuals with de novo Parkinson's disease (naïve to drug treatment) can achieve the randomly assigned levels of mean exercise intensity (60-65% HRmax or 80-85% HRmax) and adhere to the exercise protocol.

The secondary aims are to determine: 1) whether moderate- or high-intensity endurance exercise [or both] warrants further investigation as a therapeutic intervention for motor symptoms in the treatment of de novo Parkinson's disease by conducting a futility trial, and 2) the incidence of adverse events and 6-month attrition associated with endurance exercise for each exercise arm (i.e., mean 60-65% HRmax and mean 80-85% HRmax groups).

Design and Outcomes

This will be a Phase II, multisite, randomized, evaluator-blinded, no exercise controlled, and exploratory clinical trial of the effects of 26 weeks of endurance exercise on the ability of patients with Parkinson's disease to exercise at the assigned heart rates. Outcome variables include:

- * Exercise intensity
- * Change in UPDRS motor
- * Adherence to exercise
- * Attrition
- * Adverse events

Interventions and Duration

One hundred twenty-six patients will be randomly assigned to 3 groups: 1) 80-85% HRmax; 2) 60-65% HRmax; 3) no-exercise control (42 patients per group). The entire intervention period is 12 months, with the primary end point at 6 months. After 6 months, the control group^{1,2} will be randomized to exercise for 6 months and the intervention groups will continue to exercise at their prescribed dose for 6 additional months. The endurance exercise will be 4 days per week for approximately 50 minutes per session (including warm up and cool down).

Evaluations will take place using the following schedule:

- * Baseline, 6 and 12 months: Unified Parkinson's Disease Rating Scale (UPDRS and MDS UPDRS), HR average during exercise, days per week of exercise, attrition, quality of life (PDQ-39 and RAND), sleep (Epworth and PDSS-2) fatigue (Modified Fatigue Impact Scale), and health status (HSU) will be assessed.

If participants have initiated dopaminergic therapy prior to the 6 or 12 month assessments, subsequent UPDRS evaluations will be conducted in the off-medicated state after overnight (12 hour) withdrawal from medication. (These data will be used for secondary analysis).

Self-reported depression (BECK) and cognitive function (MoCA) will be assessed at screening visits, 6 and 12 months, but not at baseline.

- * Each Month: Physical activity level and general health status (including initiation of dopaminergic therapies) will be documented.

Should subjects require dopaminergic therapy within the first 6 months of the study, they will be tested immediately prior to initiating the drug therapy (evaluations should be the same as the month 3 assessment involving UPDRS and MDS UPDRS only).

- * Month 3: UPDRS and MDS UPDRS

If a participant initiates dopaminergic therapy prior to the 3 month assessment, subsequent UPDRS evaluations will be conducted in the off-medicated state after overnight (12 hour) withdrawal from medication. (These data will be used for secondary analysis)

¹ Participants are encouraged to continue to exercise as they have been prior to enrollment in the study

² When talking to participants we will refer to the control group as usual-care.

- * Continuously: Falls, adverse events (AEs), and Serious Adverse Events (SAEs)

Sample Size and Population

Our target population is 126 persons diagnosed with de novo Parkinson's disease. Randomization will be stratified by site.

1. STUDY OBJECTIVES

1.1 Primary Objective

The Primary Aim (PA1), on which this exploratory Phase II clinical trial is powered, and the primary Hypothesis (H1) is:

- PA1: To test whether individuals with de novo Parkinson's disease (naïve to dopaminergic drug treatment) can achieve the randomly assigned levels of mean exercise intensity (60-65% average HRmax or 80-85% average HRmax) and adhere to the exercise protocol.
- H1: Patients assigned to the 80-85% HRmax group will exercise at a 20% higher relative intensity than those in the 60-65% HRmax group and both groups will demonstrate adherence levels of at least 3 days per week.

1.2 Secondary Objectives

Secondary Aims (SA) are:

- SA2: To determine if intense endurance exercise warrants further investigation as a therapeutic intervention for motor symptoms in the treatment of de novo Parkinson's disease by conducting a futility trial. In an efficacy trial, the null hypothesis is that treatments are equivalent and rejection of the null hypothesis indicates one treatment is more effective than the other. In contrast, in a futility trial the null hypothesis is that the treatment has promise and will produce results exceeding a meaningful threshold. The alternate hypothesis in a futility trial is that treatment is not sufficiently different from control to warrant further investigation and is therefore futile.
- H2: The exercise groups will demonstrate potential for therapeutic efficacy using a futility threshold of $\theta=3.5$ points ($\theta=\Delta\text{UPDRS control}-\Delta\text{UPDRS exercise}$) on the UPDRS motor scale at 6 months or last visit prior to dopaminergic therapy being initiated within 6 months, when compared with wait-listed no exercise control group.
- SA3: To estimate the incidence of adverse events and 6-month attrition associated with endurance exercise for each exercise arm (i.e., mean 60-65% HRmax and mean 80-85% HRmax groups).
- H3: For each treatment arm, there will be a low incidence of exercise-related adverse events (10%) and 6-month attrition (<15%).

2. BACKGROUND

2.1. Rationale

- Subjects will be individuals with primary PD who have not yet begun dopaminergic pharmacological interventions (de novo PD).
- The intervention regimens consist of endurance exercise performed at either moderate (60-65% HRmax) or high (80-85% HRmax) intensity. The exercise will be delivered via treadmill training, 4x per week for 26 weeks. Subjects then will be encouraged to continue to exercise for an additional 26 weeks at the prescribed training level. The control subjects will not exercise for the first 26 weeks but will be offered the exercise intervention for the second 26 weeks. Controls will be randomly assigned to one of the two exercise intensities.
- The rationale for the two exercise intensities include: 1) the ranges are within the guidelines for safe endurance exercise for older adults; 2) they have been chosen to detect a minimum difference of 15% in average exercise HR between the groups and a mean difference of 20% (82.5% - 62.5% = 20%); and 3) The highest intensity (80-85% HRmax) has been demonstrated to be feasible in our preliminary work.
- Data from primate models of PD indicate HR demand may be important for symptomatic change and potential neuronal plasticity.¹ The frequency investigated in animal studies ranged from several times a week to every day to multiple times per day.²⁻⁵ Findings from our investigation will establish if there

are differences in symptom modifying responses to moderate (60-65% HRmax) and high (80-85% HRmax) intensity.

- v. The necessary intensity cannot yet be inferred from the animal literature. Intensity is not reported in terms of HR demand in rodent models, nor can it be discerned how HR demand in a rodent model relates to humans. However, with respect to exercise in older adults generally and people with PD specifically:
- In 1991 Kohrt and colleagues⁶ showed that individuals aged 60-71 benefitted from an exercise program in which the intensity averaged 80±5% HRmax with increases in VO₂max of ~25%. This adaptation was independent of sex, age, and initial level of fitness. The proposed high-intensity exercise intervention is modeled after this study.
 - In 2008 Fisher and colleagues⁵ compared high-intensity activity (75% age-appropriate maximal heart rate but with a range from 50% to 75%) with low-intensity (50% or less) on several measures including the UPDRS and altered cortical excitability in patients with Parkinson's disease. They found small changes in the UPDRS total score but performed no statistical analyses. They did show that the cortical silent period was lengthened in the high-intensity group. Because the late part of the silent period duration is thought to reflect long-lasting cortical inhibitory processes, the idea is that high-intensity exercise may restore these inhibitory processes.
 - In 2009, Ridgel and colleagues⁷ compared forced exercise (high pedaling rate forced by a trainer on a tandem bike) with voluntary exercise in individuals with PD. Both groups exercised at 60-80% of HRmax. The forced group reduced their motor UPDRS score by 12 points (35%) whereas the other group did not. This study was an important 'proof of concept' study to demonstrate the potential PD-specific benefits of exercise, but the exercise mode is not clinically practical. Nevertheless, the clinical effect was striking and, if reproduced using treadmill training, would change clinical practice.
 - In 2010 Mehrholz and colleagues⁸ conducted a meta-analysis of exercise interventions in patients with PD and concluded that: "Patients with Parkinson's disease who receive treadmill training are more likely to improve their impaired gait hypokinesia. However, the results must be interpreted with caution because there were variations between the trials in patient characteristics, the duration and amount of training, and types of treatment. Additionally, it is not known how long these improvements may last."
- vi. In summary, the literature suggests that: 1) older adults respond well to intense exercise; 2) changes in cortical excitability in patients with PD suggest a generalized response to exercise that is consistent with the animal studies; and 3) changes in gait hypokinesia in response to exercise training are consistent with specificity of training principles.
- vii. Issues that remain to be determined include the extent to which endurance exercise can mitigate the symptoms of PD, the mechanism by which such benefits occur, and whether there is a dose-response effect of exercise. In 2011, Speelman and colleagues⁹ concluded that: "In rodent models of Parkinson disease, which rely on administration of neurotoxins (6-OHDA or MPTP) to induce parkinsonian symptoms, exercise attenuates the degree of injury to midbrain dopaminergic neurons, and restores basal ganglia function through adaptive mechanisms of dopamine and glutamate neurotransmission." However, to the best of our knowledge the intensity of exercise has not been explicitly manipulated using relative heart rate or oxygen consumption levels. Furthermore, the physiological mechanism by which changes in PD symptoms are improved in response to exercise are not well understood, but one possibility is increased cortical vascularity. It will be impossible to determine the mechanism(s) by which exercise mitigates symptoms of PD in humans until the dose of exercise is established and beneficial effects of exercise are confirmed in a Phase III clinical trial.
- viii. To summarize the relevance of this proposed investigation, we quote from Speelman et al⁹ who stated that "Accumulating evidence suggests that patients with PD might benefit from physical activity and exercise in a number of ways, from general improvements in health to disease-specific effects and, potentially, disease-modifying effects (suggested by animal data). Many issues remain to be addressed, including the need to **perform clinical trials** to demonstrate these **presumed benefits** of physical activity and exercise **in patients with PD.**"

2.2. Supporting Data

- i. Exercise can both regulate brain function¹⁰⁻¹³ and modify the symptoms of PD.¹⁴ There is mounting evidence that it also protects against neurological damage in animal models. Both symptom- and disease-modifying effects of exercise are important to understand. In this exploratory trial, we are focusing on symptom-modifying effects because this is the necessary first step in understanding the dose-response effects of endurance exercise. Once the dose-response effects on PD symptoms are known, further studies can investigate protection against neurological damage. We are aware that the recent Physical Activity Guidelines Advisory Committee Report (<http://www.health.gov/PAGuidelines/Report/membership.aspx>) provided strong evidence for the multiple health benefits of moderate-intensity physical activity (i.e., 65% HR max). The Executive Summary of the Report further indicated that there is strong evidence that vigorous-intensity exercise (i.e., 80% HR max) is associated with greater improvements for some health outcomes compared to those observed with moderate-intensity exercise. Additionally, disease-modifying effects of exercise may require high-intensity exercise. The proposed protocol will investigate the potential benefits of moderate vs vigorous-intensity exercise on PD symptom modification.
- ii. The premise for the study was based on the growing evidence for neuronal plasticity following brain damage.¹⁵ Several principles have emerged for modifying the symptoms of neurological insult including the following: specificity of training is important, repetition is critical, and **exercise intensity matters**. Investigators have applied these principles to animal models of PD with attempts to reduce the parkinsonian symptoms resulting from neurochemical damage.^{4, 16, 17} Two approaches have been used: emphasis on skill development¹⁷ or on gait.^{1, 4, 16} The mechanism by which exercise modifies brain function is not well understood but one possibility is increased cortical vascularity.¹⁰ It will be impossible to determine the mechanism(s) by which exercise mitigates symptoms of PD in humans until the dose of exercise is established and beneficial effects of exercise are confirmed in a Phase III clinical trial.
- iii. We have chosen to use treadmill exercise to challenge gait for 3 reasons: 1) with respect to specificity, impaired gait is one of the critical symptoms associated with PD; 2) repetition is a required part of training; and 3) it is easy to control intensity of exercise. The necessary intensity cannot yet be inferred from the animal literature. Intensity is typically not measured using HR in rodent models, nor can it be discerned how HR demand in a rodent model relates to humans. With respect to endurance exercise **in people with PD**, a number of investigators have examined changes in PD symptoms and functional performance in response to increasing levels of exercise and, in some cases increasing intensity.^{5, 18-23} To date, none of these studies were designed to provide definitive data.
- iv. The major risk from this exercise intervention is that subjects may develop muscle soreness or strains. These adverse events are common with exercise for adults of any age. The occurrence of such events will be minimized by gradually increasing the exercise intensity and duration to the target levels during the first 8 weeks of training. In a study of 34 people in stages 1-3 of PD who participated in an endurance exercise program at 65-80% HRmax, there were 2 reports of sprains 11 reports of soreness in the first 4 months of supervised treadmill exercise. All of these events resolved without the need for the subject to leave the study.
- v. There is also a possibility that exercise will lead to an increase in falls. Although falls are common among people with PD^{24, 25}, subjects with *de novo* PD are in the earliest stages of PD, before falls become problematic. Additionally, in a study of 34 people in later stages of PD (i.e., already on dopamine replacement therapies, Stages 1-3 of Hoehn and Yahr) who exercised for 16 months using a similar protocol, only 1 non-injurious fall occurred during treadmill exercise (Schenkman, unpublished results).
- vi. There is a potential risk of cardiac events during high-intensity exercise. The risk of death from an exercise test has been estimated to be 1 in 10,000.²⁶ The risk of a heart attack is about 4 in 10,000 and the risk of a problem that would require hospitalization (for example, chest pain) is about 2 in 10,000.²⁶ We will minimize the likelihood of this happening by having each patient carefully screened prior to entry into the study. See section 4.1.2.b. for further details.

3. STUDY DESIGN

- i. This is a Phase II, multisite, randomized, evaluator-blinded, no-exercise controlled, exploratory clinical trial of the effects of 26 weeks of endurance exercise on the ability of patients to exercise at the assigned

target heart rate ranges. Subjects in the exercise arms will be encouraged to continue to exercise for an additional 26 weeks (52 weeks total). Outcome variables include the following:

- * Exercise intensity
 - * Change in UPDRS motor
 - * Adherence to exercise
 - * Attrition
 - * Adverse events
- ii. A futility analysis will determine whether changes in the UPDRS are sufficient with either or both of the exercise intensities to warrant a Phase III clinical trial. If so, the subsequent trial may include assessment of the mechanisms of such changes.
 - iii. Figure 1 summarizes the overall study design. See below:

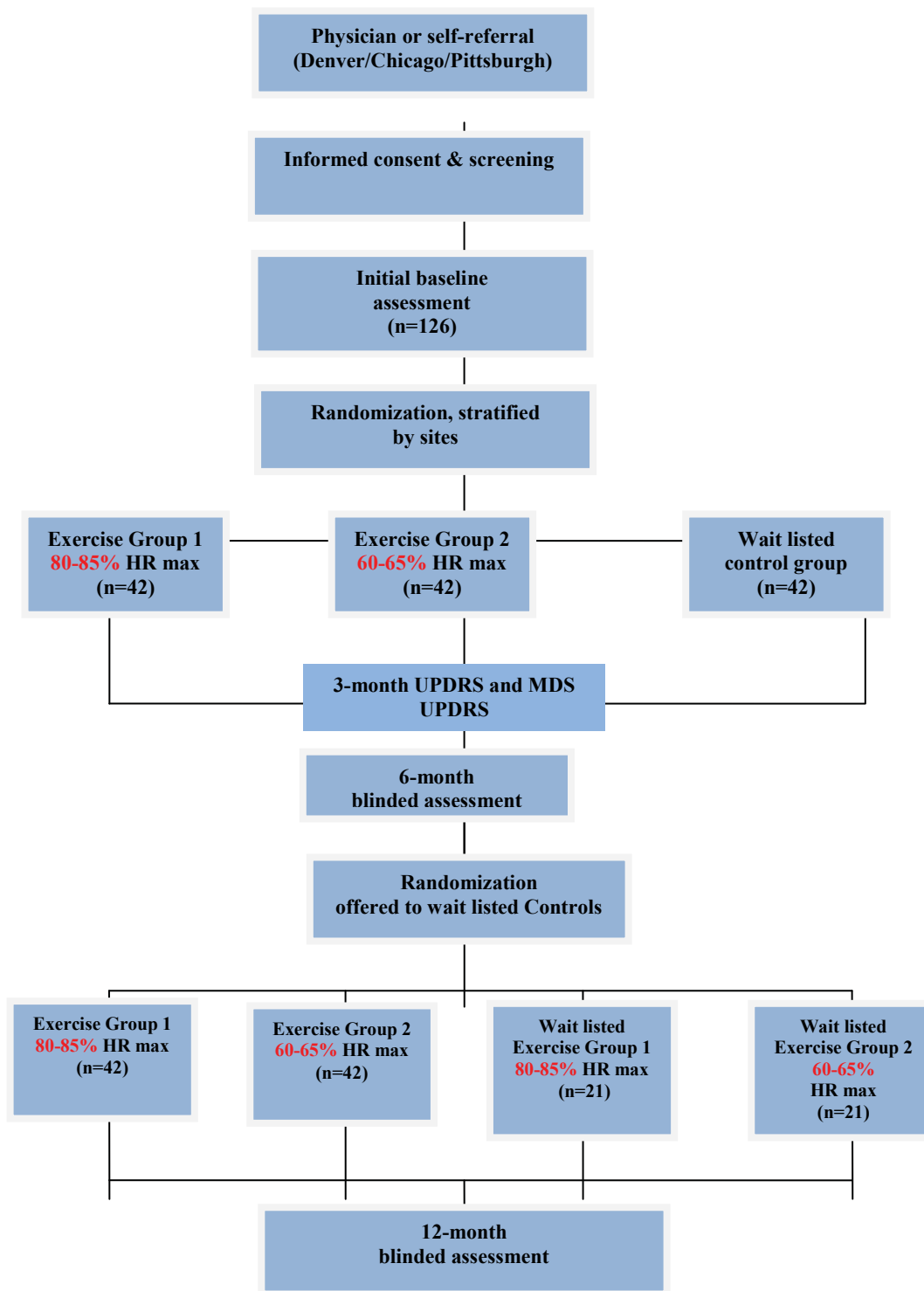


Figure 1: Phase II clinical trial design

4. Selection and Enrollment of Subjects

4.1 Primary Inclusion/Exclusion Criteria

4.1.1. Inclusion Criteria

- i. Primary PD diagnosed by a neurologist who is a movement disorders specialist, using UK Brain Bank Criteria
- ii. The UK Parkinson's disease Society Brain Bank clinical diagnostic criteria are a three-step process as listed below. We are listing all criterion but will not be using those related to levodopa.
 - *Step 1 Diagnosis of Parkinsonian Syndrome*
 - Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
 - And at least one of the following:
 - a) Muscular rigidity
 - b) 4-6 Hz rest tremor
 - c) Postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
 - *Step 2 Exclusion Criteria for Parkinson's Disease*
 - History of repeated strokes with stepwise progression of parkinsonian features
 - History of repeated head injury
 - History of definite encephalitis
 - Oculogyric crises
 - Neuroleptic treatment at onset of symptoms
 - More than one affected relative
 - Sustained remission
 - Strictly unilateral features after three years
 - Supranuclear gaze palsy
 - Cerebellar signs
 - Early severe autonomic involvement
 - Early severe dementia with disturbances of memory, language and praxis
 - Babinski sign
 - Presence of cerebral tumor or communicating hydrocephalus on CT scan
 - Negative response to large doses of levodopa (if malabsorption excluded)
 - MPTP exposure
 - *Step 3 Supportive prospective positive criteria for Parkinson's disease (Three or more required of definite Parkinson's disease)*
 - Unilateral onset
 - Rest tremor present
 - Progressive disorder
 - Persistent asymmetry affecting side of onset most
 - Excellent response (70-100%) to levodopa
 - Severe levodopa-induced chorea
 - Levodopa response for 5 years or more
 - Clinical course of ten years or more
- iii. Age 40-80

4.1.2. Exclusion Criteria

- i. Makuna
- ii. Use of any PD medication within 60 days prior to the baseline visit including levodopa, direct dopamine agonists, amantadine, Rasagiline (Azilect), Selegiline (Eldepryl), Artane (trihexyphenidyl).
- iii. Duration of previous use of medications for PD that exceeds 90 days.
- iv. Expected to require such treatments in the next 6 months.
- v. Regular use of neuroleptics/dopamine receptor blockers. Occasional previous neuroleptic use as an antiemetic is allowed if not within six months prior to baseline visit.

- * Poorly controlled or unstable cardiovascular disease.
 - * Resting blood pressure >150/90 mmHg.
 - * CBC: out of range and physician's judgment
 - * Beck depression score > 16, indicating depression that precludes ability to exercise. Any subject with such a score will be referred to a PCP or physician for further evaluation and management of depression.
- vi. Stable doses of psychotropic medications are allowed (e.g., anxiolytics, hypnotics, benzodiazepines, antidepressants) if the dose has been stable for 28 days prior to screening. Investigators will strive to avoid or minimize changes in such medications; however, if clinical situations require a dosage change, introduction, or discontinuation of psychotropic medications, these changes will be recorded, and the subject will be permitted to remain in the trial.
- * Hypo- or hyperthyroidism (TSH <0.5 or >5.0 mU/L), abnormal liver function (AST or ALT more than 2 times the upper limit of normal), abnormal renal function (serum creatinine >2 mg/dL).
- vii. Montreal Cognitive Assessment (MoCA) score of <26/30 (mild cognitive impairment (MCI)).²⁷
- * Disorders that interfere with ability to perform endurance exercises (e.g., stroke, respiratory problems, traumatic brain injury, or neuromuscular disease)
 - * Any clinically significant medical condition, psychiatric condition, drug or alcohol abuse, or laboratory abnormality that would, in the judgment of the physician, interfere with the ability to participate in the study.
 - * Regular participation in vigorous endurance exercise, defined as >2 days/week for at least the past 4 months at moderate to vigorous exercise (e.g., > 65% HR MAX).
 - * Evidence of serious arrhythmias or ischemic heart disease using a graded exercise test (GXT). The test will be administered by a health care professional trained to interpret blood pressure and ECG responses to exercise. Individuals with a positive treadmill test will require a follow-up diagnostic evaluation by a cardiologist to rule-out cardiovascular disease before they can be enrolled.

4.2 Secondary Inclusion / Exclusion Criteria

4.2.1. Disorder

- * Subjects will be included who have primary Parkinson disease as determined by a neurologist who is a movement disorders specialist using the UK PD brain bank criteria (e.g., bradykinesia and at least one of tremor, rigidity, or postural instability).²⁸⁻³⁰ Primary PD refers to parkinsonism not due to secondary causes such as cerebrovascular event or supranuclear palsy. They will be in Hoehn and Yahr stage less than stage III, and disease duration less than 5 years and will not be likely to require dopaminergic therapies within 6 months.

4.2.2. Clinical Indicators of Current Status

- * Clinical indicators of current status will include screening tests to rule out cardiovascular or other disorders that preclude exercise at 80%-85% HRmax. Failed screening tests (e.g., high blood pressure) can be remediated. If the issue is resolved in time to reach randomization within 8 weeks from signing of the informed consent, the subject will continue through screening and baseline testing. If the remediation is outside of the 8 week window, the subject will be re-screened by the neurologist.

4.2.3. Screening Procedures

- * Subjects will be assessed for severity of Parkinson disease.
- * A blood draw will screen for medical conditions that could contradict exercise training or influence the adaptive response to exercise.
- * A graded exercise test will be performed to screen for conditions that could contradict exercise training (e.g., serious arrhythmias, ischemic heart disease).
- * The sample will be between ages 40 and 80. Parkinson's disease typically affects men to women at a ratio of 2:1. Therefore, we anticipate enrolling subjects in this ratio at all three sites.

4.2.4. Serious Illness

- * Serious illness (requiring systemic treatment and/or hospitalization) will preclude enrollment until subject either completes therapy or, in the opinion of the site investigator, is clinically stable on therapy for at least 4 weeks prior to study entry. Should a subject have a serious illness during the screening period, s/he will be referred back to the neurologist to determine whether the screening can continue.

4.3. Study Enrollment Procedures

Figure 2, pp. 19-20 outlines all study procedures and time frames.

4.3.1. Subjects will be:

- 1) referred from the Movement Disorders Center at each site, 2) referred by community neurologists and movement disorders specialists, or 3) self-referred.
- * The majority of subjects interested in participating in the study are expected to be current patients in the Movement Disorder clinics. Others will be referred by community neurologists or may self-refer in response to advertisements or posting on Clinicaltrials.gov. Origin of the referral will be documented. Subjects who do not meet the eligibility criteria will be recorded. Subjects who qualify for the study and decline participation will be asked to indicate their reasons for refusal to participate and these will be recorded. Each site will collect the same information in the screening log. Individual sites will monitor recruitment on a weekly basis. The Steering Committee will monitor study recruitment at least on a monthly basis and based on those data will determine whether alternate recruitment strategies should be instituted.

4.3.2. Screening Procedures

- * Subjects must provide written informed consent prior to implementation of any study procedures. This will take place in a quiet, private room. Once the subject has read over the document, a member of the investigative team will review the entire document to be sure that the procedures and time commitments are understood. Comprehension and autonomy will be assessed by asking subjects to explain in their own words what the study is about. The subject will sign the consent form, complete a Demographic questionnaire and Beck's depression Inventory, and then the member of the investigative team will administer the Montreal Cognitive Assessment (MoCA).
- * The neurologist will complete a neurological examination, to confirm eligibility (e.g., primary PD) and a physical examination to evaluate eligibility for the study.
- * A metabolic panel, complete blood count and TSH will be obtained to evaluate health status.
- * Under the supervision of a clinician, a GXT to volitional exhaustion will be performed to assess blood pressure and ECG responses to exercise. VO₂ Max will be determined during the graded exercise test.
- * The research assistant will enter all eligibility information into the electronic database. Once the data for these screening procedures are fully entered and the subject is deemed eligible, the site neurologist will sign off on the medical exclusions and the site PI will sign off on eligibility. The subject then will complete all baseline data collection.
- * Control participants who wish to exercise will be rescreened for metabolic panel, complete blood count and TSH, the physical and neurologic exam and a GXT at the end of six months and within two weeks of beginning exercise.

4.3.3. Baseline Testing

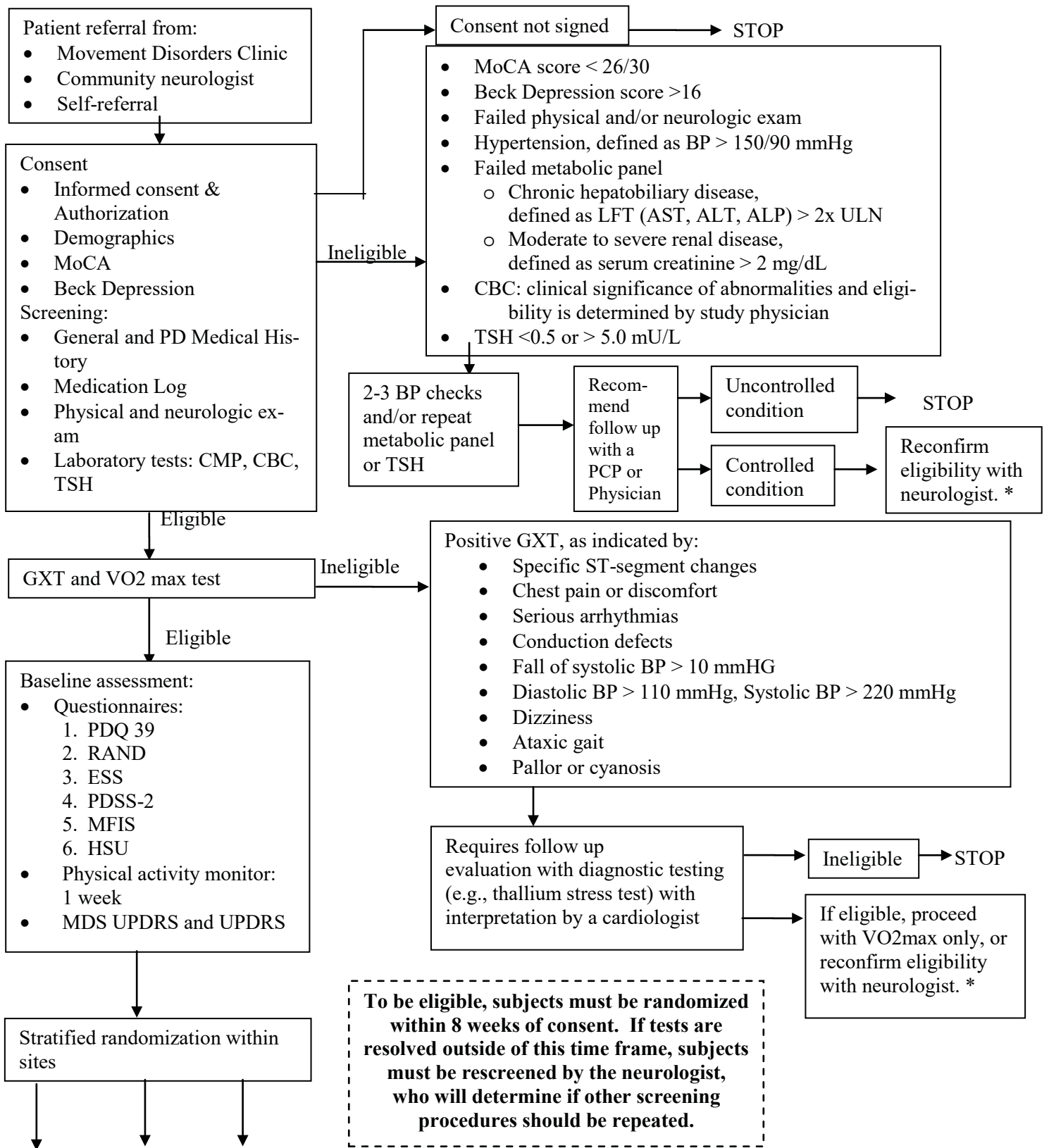
- * UPDRS and MDS UPDRS will be administered by a neurologist who is a movement disorders specialist.
- * Physical activity will be monitored for one week, using the ActiGraph GT3X+ activity monitor for data collection. (Subjects will receive the physical activity monitor at the beginning of data collection and will return the physical activity monitor one week later).
- * The following questionnaires will be completed:
 - Health Status Update (HSU)
 - Parkinson's Disease Questionnaire-39 (PDQ 39)
 - Veterans RAND 36-Item Health Survey (RAND)
 - Parkinson's Disease Sleep Scale-2 (PDSS-2)
 - Epworth Sleepiness Scale (ESS)

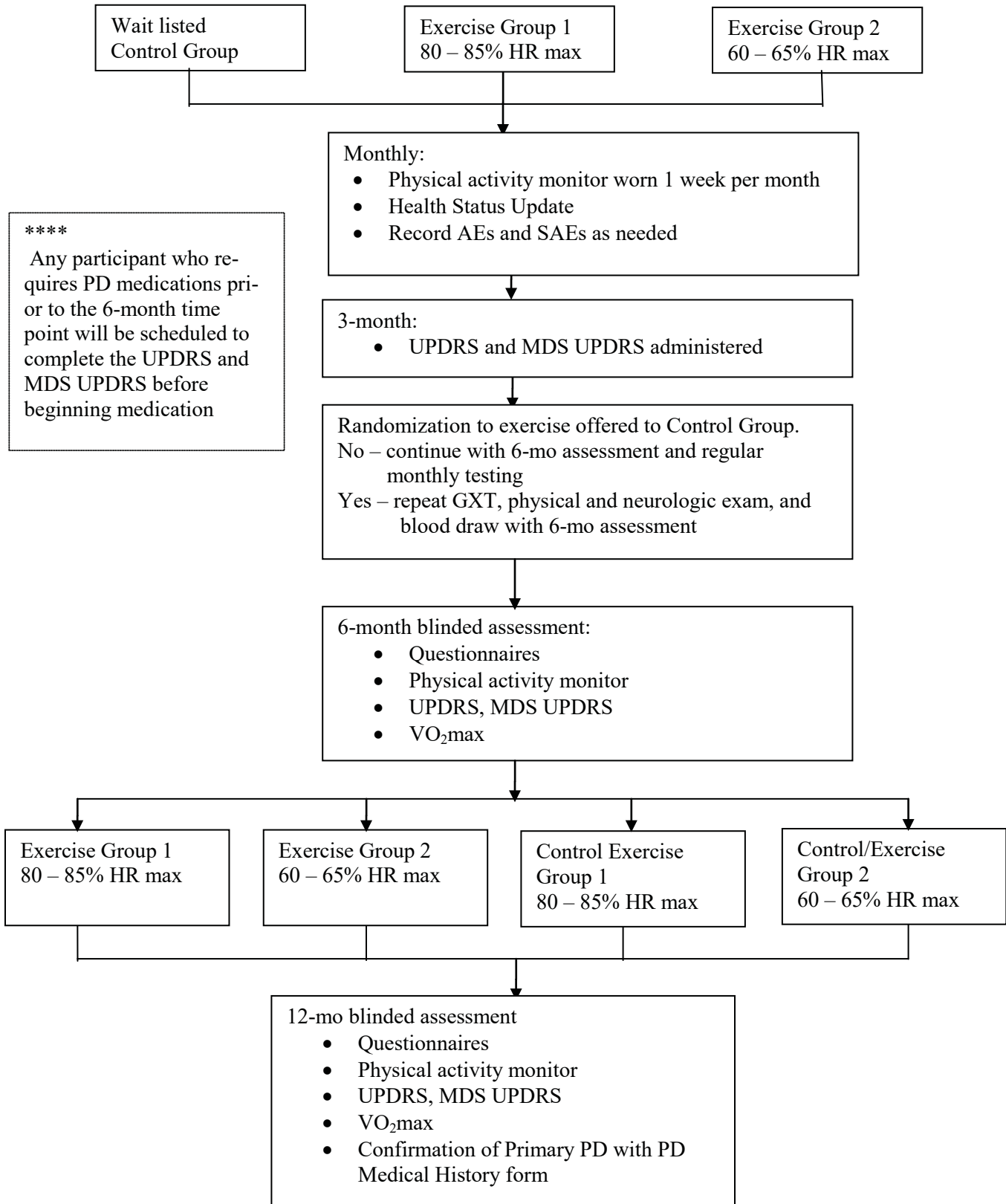
- Modified Fatigue Impact Scale (MFIS)
- * Once these data have been obtained, the research assistant will randomize the subject. The group assignment will be provided on the screen. Allocations for subsequent subjects will remain concealed.

4.3.4. Randomization

- * Subjects will be randomized to 1) no-exercise control (i.e., usual care); 2) exercise 4x per week at 60-65% HRmax; or 3) exercise 4x per week at 80-85% HRmax. The study biostatistician will generate the randomization sequences for each site in SAS version 9.2 using permuted block randomization with random block sizes. The University of Pittsburgh Center for Research on Health Care Data Center systems analyst will load the randomization list into the web-based data management system such that allocation concealment will be preserved for consecutively enrolled subjects.
- * Figure 2 provides a detailed summary of the study procedures. See below:

Figure 2: Overview of Study Procedures





5. Study Interventions

5.1. Interventions, Administration and Duration

- 5.1.1. Subjects will exercise on a treadmill using procedures we have used over the past two decades.³¹⁻³³ The regimen will include 5-10 min of warm up, 30 min of exercise at target HR and 5-10 min of cool down. They will exercise 4 days per week. The two intervention groups will be given a HR range to achieve during exercise sessions: 60-65% or 80-85% of HRmax. This will lead to a mean HR for the groups of $62.5 \pm 2.5\%$ and $82.5 \pm 2.5\%$ of HRmax respectively. In this way, the difference in mean HR between the groups should be 20% of HRmax while the minimum and maximum differences should be 15 and 25. During the first 8 weeks of training, exercise duration and intensity will be gradually increased to the target levels. Subjects will be instructed on monitoring HR and adjusting the exercise to remain in the target HR range (i.e., by changing treadmill speed and/or incline). During exercise, subjects will wear a heart rate monitor that captures and stores HR throughout the exercise bout. The exercise Research Assistant (RA) will electronically transfer the HR file from each exercise session (supervised and unsupervised) into the study database.
- 5.1.2. During the first 2 weeks, subjects must exercise at a main study site under supervision of an Exercise training RA. All 'on-site' exercise sessions will be supervised by an exercise RA. After 2 weeks, the RA will determine whether the subjects may exercise off-site at a community fitness facility or at home to maximize the likelihood of compliance. If the subjects are exercising in their target HR range for the prescribed duration and have demonstrated to the exercise RA that they are able to operate the HR monitor, the subjects will exercise 2X/wk at the main site for 2 weeks and then 1X/wk for 2 weeks. Thereafter, if cleared by the RA, subjects will be expected to exercise on-site at least 2 x/month at the main site. Other exercise sessions will take place at the approved off-site facility. HR monitors must be worn for all sessions. HR data will be downloaded once weekly by an approved person at the facility or brought to a main site to be downloaded by the RA. In addition, the subject will be given an exercise diary log to document his/her were time sessions on a weekly basis. The RA will check adherence to their prescription each week and will work with the participant as needed to assure appropriate adherence to the protocol.
- 5.1.3. The intent of allowing exercise off site is to enhance recruitment, retention, and long-term adherence to exercise. Cardiovascular safety is assured by the screening GXT. Safety with respect to treadmill exercise will be established for each subject during the first two weeks of exercise at the main study site and also has been established in our previous work for by 34 subjects with PD, Stages 1.5-3 of H&Y who exercised for up to 16 months without incident (Schenkman, unpublished data). Additionally, many of the designated health clubs we work with are affiliated with hospitals and specialize in exercise programs for people with PD.
- 5.1.4. The exercise training RA will assure exercise fidelity for each subject by comparing exercise sessions, duration and mean HR to the subject's target on a weekly basis and by working with the subject to make necessary adjustments.
- 5.1.5. At the completion of the 6-month exercise intervention, subjects will be encouraged to continue to exercise, using the same protocol as for the first 6-months. Adherence will be assessed after the first six months (primary end point) and again after an additional 6 months (12 months).
- 5.1.6. Control group: Subjects will be asked not to change their usual exercise habits for 6 months. On completion of the control period, subjects will be randomly assigned to 60-65% HRmax or 80-85% HRmax for six months of follow up.
- 5.1.7. At the completion of 6 and 12 months from enrollment in the study, all outcome data (VO₂ MAX, UPDRS and MDS UPDRS, and questionnaires) will be repeated for all subjects.

5.2. Handling of Study Interventions

- 5.2.1. Each subject will, of necessity, be aware of group assignment. However, study personnel who collect the following outcome measures (i.e., UPDRS, exercise intensity [HR and duration]) will be blinded to the subject's group assignment as will the site P.I., Co-Is, including the statistician. The site P.I., Co-Is, including the statistician will be blinded to other outcome measures (e.g., HR at which subjects exercise; adherence). These data are collected electronically by the treating RA, and are used by the RA to assist subjects to adhere to their prescribed exercise regimen.

5.3. Concomitant Interventions

5.3.1. Subjects are precluded from enrolling in other studies or interventions that could affect their UPDRS motor score or VO₂ MAX (e.g., drug trials, exercise studies.)

5.4. Adherence Assessment

5.4.1. Compliance will be assessed by documenting number of days of exercise as well as actual exercise duration and HR intensity for each exercise session. Subjects will wear a Polar Heart Rate Monitor during each exercise session. These monitors store HR during the session as well as the time exercised.

6. CLINICAL AND LABORATORY EVALUATIONS

6.1. Schedule of Evaluations

	Before Study (All screening and baseline data should be completed within 8 weeks from consent)			Start of exercise within 1 wk	Month											
	Screening visit	Baseline testing; completed within 10 days of GXT	Immediately after baseline		1	2	3	4	5	6	7	8	9	10	11	12
SCREENING																
Informed consent	X															
Medical history ¹	X															X
Neurological examination	X															
Physical examination	X															
MoCA and Beck	X								X							X
Blood draw: CMP, CBC, and TSH	X															
Exercise stress test (GXT) with VO ₂ Max	X															
Controls only: repeat blood draw, GXT, physical and neurologic exam									X							
BASELINE																
Wear physical activity monitor for 1 week		X				X	X	X	X	X	X	X	X	X	X	X
Health Status Update		X				X	X	X	X	X	X	X	X	X	X	X
UPDRS and MDS UPDRS		X					X		X							X
VO ₂ Max									X							X

¹ PD Diagnosis will be reconfirmed at 12 months using the medical history assessment, specifically the PD medical history. The medical history includes both general and PD specific history.

- * This trial follows an intention-to-treat design. Subjects who discontinue intervention will be followed and evaluated as if they were still taking part in the exercise protocol. The study coordinator will contact the subjects who elect to discontinue on a monthly basis and will make every effort to retain such subjects in the study. When practical, the subjects will be encouraged to resume the study intervention. They will be encouraged to resume at their specified level but, if exercise intensity is an issue, will be encouraged to take part at whatever level they can. Subjects in the control group who start to exercise during the control period will be encouraged to maintain their previous activity level during the control period.

6.2.7. *On Study/Off-Intervention Evaluations*

- * Since this study is intention to treat, all evaluations will continue even if the subject is no longer following the treatment regimen.

6.2.8. *Final On-Study Evaluations*

- * Final On-Study evaluation will take place within three weeks of the 12 month end point. The evaluation will include the following:
 - Confirmation of primary PD
 - Repeat of the UPDRS, MDS UPDRS and VO₂ MAX
 - Questionnaires
 - Activity Monitors

6.2.9. *Off-Study Requirements*

- * Primary and secondary outcomes will be ending at 6 months.
- * Subjects in the two intervention arms will be encouraged to continue on the exercise protocol until 12 months. The final study visit will be at the end of 12 months from initial exercise. The control group can exercise past the assessment, but the UPDRS must be done at 26 and 52 weeks.
- * Wait listed controls will begin to exercise after the 6 month outcomes assessment and will continue on their exercise protocol until 12 months. Their final study visit will be at 6 months following the beginning of their exercise.

6.3. Special Instructions and Definitions of Evaluations

6.3.1. *Informed Consent*

- * Informed consent will be obtained at the initial screening visit before the neurological examination and UPDRS are completed. A model informed consent is in the Appendix.

6.3.2. *Medical History*

- * A check list will be used during the medical examination to make sure that all conditions for which subjects might be excluded are assessed.
- * Treatment History: Medical status and pharmacological interventions will be monitored on a monthly basis throughout the study.

6.3.3. *Concomitant Treatments*

- * We will document all concomitant treatments and the condition for which the subjects are being treated. These will be documented monthly using the Health Status Update questionnaire.

6.3.4. *Study Intervention Modifications*

- * The goal of this study is to determine futility / non-futility of high and moderate aerobic endurance exercise. There is sufficient evidence for the safety of endurance exercise at the planned intensities, both for people with and without specific disorders, hence there are no stopping rules. Should subjects experience adverse events (e.g., muscle soreness that inhibits or prevents exercise in a normal manner) during the exercise phase; the program will be modified as necessary and then gradually increased back to the prescribed training level.

6.3.5. *Clinical Assessments*

- * A maximal graded exercise test (GXT) will be performed under the supervision of a clinician during screening to determine whether exercise generates serious arrhythmias or changes in the ECG consistent with ischemia and to measure HRmax. A resting 12-lead ECG will be recorded in the recumbent and upright positions immediately prior to the exercise test. If the findings on the resting ECG do not contraindicate exercise, the exercise test will be performed.

- * Contraindicators include the following: (a) ST-segment depression of more than 0.2 mV that is either horizontal, downsloping, or slowly upsloping (less than 1 mV/sec) and lasts for 0.08 sec, or ST-segment elevation greater than 0.1 mV; (b) chest pain or discomfort; (c) serious arrhythmias, including multifocal PVCs, ventricular tachycardia, frequent (>10/min) PVCs or couplets, or sustained atrial tachyarrhythmias; (d) A-V block or other conduction defects; (e) a fall of systolic blood pressure of 10 mmHg or greater from the peak level with increasing exercise intensity; (f) diastolic blood pressure above 110 mmHg or systolic above 220 mmHg; (g) dizziness; (h) ataxic gait; and (i) pallor or cyanosis. False positive GXTs are not uncommon in middle-aged and older adults. Subjects who have a positive GXT will be required to pursue a follow-up diagnostic evaluation and clearance by a cardiologist if they want to continue to be considered for enrollment in the study.
- * Maximal aerobic power (VO₂max) will be measured by indirect calorimetry (TruMax 2400, ParvoMedics, Sandy, UT) during the GXT. A warm-up period on the treadmill will be used to identify the walking speed that generates a HR that is 65-70% of the age-predicted HRmax; for fit individuals, this may require increasing the elevation of the treadmill. After a brief rest interval to initiate the indirect calorimetry, the test will start at the designated walking speed (and grade). The treadmill grade will be increased by 2% every 2 minutes to volitional exhaustion or until the proctor stops the test because of abnormal responses to exercise.
- * Unified Parkinson's Disease Rating Scale (UPDRS) and Movement Disorder Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) will be used to assess severity of symptoms of Parkinson's disease, daily activities, motor skills and mental capacity. These scales will be administered at baseline, 3 months, 6 and 12 months.

6.3.6. *Additional Evaluations*

- * Activity Monitors. These will be used to assess physical activity level monthly.

6.3.7. *Questionnaires*

- * PDQ-39 and RAND will be used to assess quality of life at baseline and at each follow up time (6 and 12 months).
- * A Health Status Update questionnaire will be used monthly to assess changes in health condition, including medication changes.
- * PDSS-2 and Epworth sleep scales will be administered to assess sleep at baseline and at each follow up time (6 and 12 month).
- * MFIS will be used to assess fatigue at baseline and at each follow up time (6 and 12 month).
- * BECK depression scale will be used to screen and assess changes in self-reported depression a screening and at each follow up time (6 and 12 month).
- * Montreal Cognitive assessment (MoCA) will be used to assess changes in cognitive function at screening and at each follow up time (6 (v. 2) and 12 (v. 3) month).
- * PD Therapy Warranted Survey will be completed by the neurologist should complete at 3, 6 and 12 months and also at any UPDRS/MDS UPDRS related visit just prior to initiation of PD related therapy. This survey is to capture the subjects status at the time of the assessments.
- * "A feedback survey will be used to assess study experience at each follow up time (6 and 12 month)
- * 24 month Exercise Habit Feedback Survey – "this survey is to query the participants' exercise habits 1 year after completion of the study."

6.3.8. *Adherence Assessments*

- * Adherence will be documented in terms of the following: (1) number of sessions exercised per week; (2) length of exercise sessions; (3) average HR during exercise sessions; (4) percent time and minutes within target HR zone.

7. MANAGEMENT OF ADVERSE EXPERIENCES

- * Muscle soreness and strains are common with exercise and it is anticipated that some subjects will experience these events during the course of the study. Management and modification of the exercises will be managed on a case-by-case basis.

- * It is possible that falls will occur. Should a fall occur during treadmill testing or exercise, the fall will be reported as a SAE or AE (depending on the outcomes of the fall). Specific causes will be determined and appropriate strategies will be instituted to minimize fall risk. For example, if the subject has exhibited unsafe behavior that can be changed (e.g., turning head to talk to person on the adjacent treadmill), safety procedures will be emphasized. If necessary, a harness will be used for safety with future exercise.
- * Should an individual experience an adverse health event during exercise testing or training, emergency response procedures (for on-site events) will be followed by staff members certified in CPR and trained to respond to urgent and emergent situations. The subject will be required to undergo follow-up evaluation by the primary care provider, or appropriate specialist, and cleared for continuation in the study.
- * Reporting: AEs and SAEs will be documented by the research assistant, to whom they are divulged, as indicated below and their relatedness to the study will be indicated as appropriate in the electronic data base. Determination of relatedness will be made by site PI and will be confirmed by the SMC.
- * AEs will be documented in the electronic data base for AEs within two days.
- * SAEs will be reported within 24 hours as follows:
 1. RA enters data into the electronic data base for SAEs
 2. Electronic data base automatically contacts:
 - a. PIs (Corcos and Schenkman)
 - b. Tony Delitto if at Pittsburgh
 - c. Medical officer of the SMC
 - d. NINDS
 - e. Research Subject Advocate (Barb Hammack)
 3. Site PI notifies site IRB
 - ♦ Note that the study personnel may not know of SAEs that are not study related until the monthly follow-up. If such events occur, they will be documented as above as soon as the study personnel are aware of their occurrence.

8. CRITERIA FOR INTERVENTION DISCONTINUATION

- * A subject would be discontinued from the study intervention if a medical condition develops that precludes the continuation of exercise. In such events as much follow-up data will be obtained as possible.

9. STATISTICAL CONSIDERATIONS

9.1. General Design Issues

9.1.1. *The **Primary Aim (PA1)**, on which this exploratory Phase II clinical trial is powered, and the **primary Hypothesis (H1)** is:*

- * **PA1:** To test whether individuals with de novo Parkinson's disease (naïve to dopaminergic treatment) can achieve the randomly assigned levels of mean exercise intensity (60-65% average HRmax or 80-85% average HRmax) and adhere to the exercise protocol.
- * **H1:** Patients assigned to the 80-85% HRmax group will exercise at a 20% higher relative intensity than those in the 60-65% HRmax group and both groups will demonstrate adherence levels of at least 3 days per week.
- * The primary outcome for exercise intensity is derived from the average heart rate during the exercise sessions from weeks 9 to 26. The primary outcome for adherence is determined by the average number of days per week exercised and duration in minutes of exercise at the target HR. The heart rate and adherence (date of visit) data will be uploaded directly from heart rate monitors.

9.1.2. *The **Secondary Aims (SA)** are:*

- * **SA 2:** To determine if intense endurance exercise warrants further investigation as a therapeutic intervention for motor symptoms in the treatment of de novo Parkinson's disease by conducting a futility trial. In an efficacy trial, the null hypothesis is that treatments are equivalent and rejection of the null hypothesis indicates one treatment is more effective than the other. In contrast, in a futility trial the null hypothesis is that the treatment has promise and will produce results exceeding a meaningful threshold. The alternate hypothesis in a futility trial is that treatment is not sufficiently different from control to warrant further investigation and is therefore futile.
- * **H2:** The exercise groups will demonstrate potential for therapeutic efficacy using a futility threshold of $\theta=3.5$ points ($\theta=\Delta\text{UPDRS}_{\text{control}}-\Delta\text{UPDRS}_{\text{exercise}}$) on the UPDRS motor scale at 6 months or last visit prior to dopaminergic therapy being initiated, when compared with wait-listed no exercise control group. The primary outcome of the secondary aim is the change in the Unified Parkinson's Disease Rating Scale (Motor Score) from baseline to either 6 months or last off medication study visit (if initiating dopaminergic therapy prior to 6 months). The UPDRS Motor Score measures the severity of the symptoms of disease most appropriate for our study and is the gold standard in other PD trials.
- * **SA 3:** To estimate the incidence of adverse events and 6-month attrition associated with endurance exercise for each exercise arm (i.e., mean 60-65% HRmax and mean 80-85% HRmax groups).
- * **H3:** For each treatment arm, there will be a low incidence of exercise-related adverse events (10%) and 6-month attrition (<15%).
- * The primary outcomes of the third aim are adverse events defined as exercise-related discomforts, minor injuries, and , and falls and attrition defined as the number of subjects who discontinued exercise with no 6 month efficacy data or are otherwise lost to follow-up. These outcomes are very relevant in determining the feasibility of a larger Phase III trial for exercise in PD.
- * Adverse events and attrition will be monitored by the Steering Committee on a biweekly basis masked to the subjects exercise intervention assignment.
- * At the initiation of the study an independent reviewer will monitor the heart rate and adherence data and will compare these data across the three sites to assure that there are no site specific discrepancies in adherence to the protocol.
- * This trial is a randomized controlled Phase II futility trial to test the feasibility, potential efficacy, and safety of intense exercise in Parkinson's disease patients. Subjects will be randomized to three parallel groups: (1) usual care (2) exercise 4xper week at 60-65% HRmax (3) exercise 4x per week at 80-85% HRmax.
- * *Justification for concurrent control group:* The Phase II futility design will guide our decisions about future larger trials involving intensive exercise in Parkinson's disease. Futility designs derived from cancer research have recently been used in the study of therapeutic interventions in PD^{34,35} but mainly in drug trials.^{36,37} Even in well defined drug trials, there is debate on whether to rely on historical placebo control treatment from such trials as DATATOP³⁸ versus using concurrent controls in conjunction with historical data (calibration controls). The placebo effect in PD drug therapy trials is widely recognized and does not reflect natural disease progression in de novo patients. Placebo controls from drug trials are not appropriate controls for exercise intervention studies because of the modality of the intervention; therefore, a concurrent wait-list control group is necessary for us to conduct the futility component of our study.³⁹ The same approach has recently been used in testing coenzyme Q10 in ALS⁴⁰ and brain oxygen monitoring for the treatment of brain injury.⁴¹ Subjects assigned to the no-exercise arm will be randomized to an exercise arm after completing the 6-month control period. This approach will be taken because: 1) it is expected to enhance compliance in the control arm; 2) it addresses the ethical concern of asking subjects to join an exercise study and then asking them not to exercise; and 3) the exercise data can be included in a secondary analysis of attrition.
- * *Justification for 3.5 as futility threshold:* The futility threshold for this trial is based on: (1) previous futility trial designs,³⁴ (2) 6-month changes of motor scores in drug trials,^{42,43} and (3) minimal clinically important changes.³⁴ First, futility trials in PD have primarily been single-armed studies

powered around $\theta=30\%$ lessening of decline based on the UPDRS Total score at 12 months³⁴ compared to historical controls. The Elm study stated: “the choice of θ , the maximum allowable worsening, was relatively arbitrary”,³⁴ and that other rates could be used if well justified. We are not using a *percentage* lessening of decline in motor symptoms at 6 months. Studies show minimal change in motor symptoms at 6 months ranging from 0 (no worsening) to 3.5.³⁸ Power analyses based on percentage lessening decline would result in unattainable sample sizes for null hypotheses that are not clinically meaningful.³⁴ Second, studies of ropinirole versus bromocriptine and ropinirole versus levodopa in de novo patients⁴³ showed 30%-35% improvement in motor scores at 6 months relative to baseline in the ropinirole arms, translating to ≈ 7 points absolute change. As we demonstrate in our third point, it is reasonable to postulate a 6-point change with exercise. Third, the minimal clinically important change (MCIC) in the UPDRS motor score at six months is a 5 unit improvement (-5).⁴⁴ This MCIC applies to *within*-patient change, not difference in change between two intervention arms. We used an absolute difference of $\theta = 3.5$ in the 6-month UPDRS change between control and intervention as the *lower boundary* for what would be considered clinically important and worth further investigation. Our null hypothesis is that exercise *improves* change in motor scores by at least 3.5 points more than controls and the alternative is that exercise yields less than this improvement compared to controls. We used this conservative threshold, which is supported by preliminary data, to ensure that the sample size will be adequate. We anticipate that we will actually observe a 5-point difference in change in UPDRS between exercise and control arms because: 1) the intervention is 2 months longer than in our previous work (Schenkman, unpublished data), (2) we expect the high-intensity (80-85% HRmax) to enhance efficacy, and (3) we have evidence that improvement in UPDRS score measured on medication (Schenkman, unpublished data) is less than when measured off medication.

- * **Randomization:** Subjects will be randomized to three groups (1) usual care (2) exercise 4x per week at 60-65% HRmax (3) exercise 4x per week at 80-85% HRmax. Dr. Moore (biostatistician) will generate the randomization list in SAS version 9.2 using permuted block randomization stratified by site. The University of Pittsburgh Center for Research on Health Care Data Center systems analyst will load the randomization list into the web-based data management system such that allocation concealment will be preserved for consecutively enrolled patients.
- * Subjects will be followed for 52 weeks after randomization. Six months (26 weeks) is the primary and secondary end point for two reasons: First, it is likely that most subjects will remain off of dopaminergic therapies for six months than 12 months. Second, we have greater assurance of compliance of the protocol as prescribed for six as compared to 12 months. Additional feasibility outcomes are at 12 months (52 weeks); this is important for two reasons. First, we will use the time to initiation of dopaminergic therapy to compare interventions for sample size estimates for the Phase III trial. Second, because PD is progressive, it is necessary for subjects to remain on exercise to generate lasting benefits. Therefore it will be important to establish feasibility of subjects remaining on the exercise regimen for 12 months.

9.2. Outcomes

9.2.1. Primary Outcome

- * The primary outcome measure for achieving levels of exercise intensity is derived from the average heart rate during an exercise session (HR_{ex}) and expressed as a percentage of the maximal heart rate for the individual: $\%HR_{max} = (HR_{ex}/HR_{max}) * 100$. Because exercise intensity will be gradually increased over weeks 1 to 8 to the target intensity, we will use the daily session data from weeks 9 to 26 to calculate an average $\%HR_{ex}$ for each week and for the entire period. For adherence, we will determine the average number of days/wk exercised and duration (min.) of the exercise at the target HR.

9.2.2. Secondary Outcomes

- * (Aim 2) The change in the Unified Parkinson’s Disease Rating Scale (Motor Score) from baseline to either 6 months or last off-medication study visit⁴⁵ will be the measure used for the futility component of the analysis. The UPDRS Motor score measures the severity of the symptoms of the disease, and is most appropriate for our study given that the overarching goal is to modify the

symptoms of the disease. The change in the UPDRS Motor has been recognized as an outcome for futility studies along with onset of need for L-DOPA.

- * It is important to emphasize that the non-futility threshold (i.e., beneficial changes in UPDRS) can still be met, even if subjects do not attain the prescribed intensity of exercise (i.e., do not reach the prescribed average HR Max and/or days of exercise). The UPDRS will be assessed at baseline, 3, 6, and 12 months. Some participants will initiate dopaminergic therapy during the course of the study. At 6 and 12 months, participants in “off” medication state for dopaminergic therapies will show improvement over their true trajectory if no therapy had been initiated. The amount of improvement is positively correlated with the duration of treatment. This could significantly impact the intervention effect estimates if one group has a higher rate of drug initiation. For the primary outcome of 6 month change, the UPDRS from the last off-medication study visit will be used for participants who initiate dopaminergic therapy prior to 6 months.
 - * NOTE - should a participant require PD related medication before the 3-mo or 6-mo time points, an additional visit will be scheduled prior to initiation of the drug therapy during which the UPDRS and MDS-UPDRS will be administered.
- * (Aim 3) Adverse Events (AEs) are defined as exercise-related discomforts (e.g., muscle and joint soreness/pain), minor injuries (e.g., strains, sprains), and non-injurious falls; and attrition is defined as the number of patients dropping out of the study. Serious Adverse Events (SAEs) are defined as hospitalization, surgery, death, or permanent disability. We will compare AEs, SAEs, and attrition by both treatment intervention and site.

9.3. Sample Size and Accrual

- * *Sample size justification for Aim 1:* Aim 1 will determine if subjects can achieve the target intensity of endurance exercise. The primary outcome is the average %HR max during exercise in weeks 9-26. The sample size analysis was based on within-group precision and comparisons to the targeted exercise intensity. Preliminary data were taken from a study of the effects of gender, age, and fitness level on response to training in 60-71 year olds.⁶ The within-group standard deviations (SD) of %HRmax ranged from 5 to 6 at 6 months of training for men and women. We determined the number of subjects needed per exercise arm to provide good precision ($\pm 2.5\%$) for the average %HRmax. A sample size of 36 per arm produces a 95% confidence interval with half width of 2.4% (conservative $\sigma=7.0$, 80% upper bound for the SD) and 83% power to detect a difference of 3.5% from the specified intensity in each group ($\sigma=7$, effect size=0.5, $\alpha=0.05$, two-sided test). For Aim 1, we also want to establish that subjects assigned to 80-85% HRmax actually exercise at the expected higher intensity than the subjects assigned to 60-65% HRmax. Very few subjects would be needed to establish a 20% point difference between two groups given the standard deviations (effect size >2.0). We decided *a priori* that we want to be able to detect differences in relative exercise intensity as small as 5% between the two groups. With $n=36$ subjects per group and $\sigma=7$, we will have 85% power to detect a difference of 5% or greater between the two groups. A sample size of $n=42$ is required per exercise group if we assume an attrition rate of 15% at 6 months. With respect to adherence (average days exercised), with $n=36$ per group we will be able to estimate the average days exercised per week with ± 0.24 precision (95% CI, standard deviation=0.7)⁶.
- * *Sample size justification for Aim 2:* For Aim 2, published and preliminary data for the UPDRS motor score in *placebo groups* show average decline ranging from 0.88³⁶ to ~ 3.47 ³⁸ points at 6 months and standard deviations of change ranging from 4.43³⁴ to 6.37 (Schenkman, unpublished data) to 6.68.³⁴ Another study suggested the natural progression of motor impairment measured by the UPDRS to be a 2-3 unit decline per year.⁴⁶ Concurrent placebo controls in a recent *de novo* PD study for creatine and minocycline³⁷ did not show as much decline as DATATOP controls for UPDRS Total scores.³⁸ Given these studies and the preliminary data from Schenkman (unpublished data) we assumed a 6 month change = 1 on the UPDRS motor for our usual care controls. We used a range of standard deviations from 5.5 to 6.5 and a one-sided $\alpha = 0.1$ for the power analyses. The null hypothesis (non-futility) is that the difference in the rates of change is greater than $\theta=3.5$ points (6 month change control group = 1, worsening; 6 month change exercise group = -2.5, improvement; $\theta=\Delta\text{UPDRS}_{\text{control}} - \Delta\text{UPDRS}_{\text{exercise}}$). The alternative

hypothesis (futility) is that the difference in the rates is less than $\theta=3.5$. An $n=36$ per group completing the study provides over 84% power to reject the null hypothesis of further testing if there is truly no difference in the rates of change in the UPDRS motor score between the control and exercise group.

9.4. **Data Monitoring**

- * The Study Monitoring Committee will review data for safety and adherence and will compare these data across sites. There are no planned interim analyses for efficacy or futility.

9.5. **Data Analyses**

Statistical Analyses

- * **Aim 1: Ave %HRmax:** The analyses for Aim 1 are two-fold: (1) within-exercise group comparisons to test for differences from the specified exercise intensity of either 60-65% HRmax or 80-85% HRmax and (2) between-group comparisons to test for differences in achieved levels. We will estimate the overall average %HRmax and its corresponding 95% confidence interval for each exercise group at 6 months. We will then compare the average to the intended target intensity (62.5% or 82.5%) using a one-sample t-test ($\alpha=0.05$). In addition, it will be important to look at changes in the average %HR max over time to determine if there was a pattern of increase or decrease. We will use a repeated measures analysis of weekly %HRmax stratified by group and employ linear mixed models to tests for any trends over time from weeks 9 to 26. For the second part of the analysis, we wish to test if the groups actually exercised at different levels of intensity even if they did not reach the intensity specified. We will use a two-sample t-test to compare the overall average %HRmax between the two groups over weeks 9 to 26 and combine the repeated measures analyses from both arms to test for any differential changes in performance over time. The primary variables of interest in the repeated measures analysis would be the exercise group, time in weeks, and group*time.
- * **Aim 1 Adherence:** All adherence analysis for Aim 1 will be specific to the treadmill exercise specified in the protocol. Descriptive statistics by exercise group will be calculated for average number of days per week exercised (primary adherence measure) and duration of time (mins) they exercise at the specified intensity. We will determine if the 95% confidence interval for average number of exercise days per week falls above 3 days to test the hypothesis that subjects in each exercise group demonstrate adherence levels of more than 3 days per week.
- * **Aim 2: Futility threshold of $\theta=3.5$ points:** In futility trials, the null hypothesis is that the intervention should be studied further (non-futility) and the alternative hypothesis is that no more investigation is warranted (futility). We are using this strategy to guide our decisions about larger trials involving intensive exercise in PD. The outcome is defined as the 6-month change in the UPDRS Motor Scores (6 months measurement – baseline). An increase in the UPDRS motor scores infers worsening of symptoms and a decrease infers improvement of symptoms. We will use the intention to treat ‘as randomized’ treatment assignment for each subject regardless of adherence. For the primary outcome of 6 month change, the UPDRS from the last off-medication study visit will be used for participants who initiate dopaminergic therapy prior to 6 months.
- * We will compare the rate of change in each exercise group to the concurrent controls: control group rate of change - exercise group rate of change, such that a positive difference implies the exercise group is doing better than the control group. We will use a two-sample t-test with one-sided $\alpha=0.10$ for the efficacy analysis and a futility threshold of $\theta=3.5$ points on the UPDRS motor scale. We will also calculate the null-adjusted ($\square-3.5$) difference in the rates and a 90% confidence interval (upper bound for the null-adjusted difference in the rates). In secondary analyses, we will adjust for any baseline variable that either statistically or clinically differs between groups.
- * **Aim 3: Adverse events and levels of attrition:** The analyses for Aim 3 are two-fold: between-exercise group comparisons and across-site comparisons. The 6-month incidence of individual AEs (including SAEs) and exact confidence intervals will be calculated for each group. We will use Fisher’s exact or Poisson exact tests to compare exercise groups for AEs that are definitely,

probably, or possibly related to the exercise interventions. We define attrition as incomplete 6-month data for primary disease outcomes and incomplete monthly data for secondary outcomes. We will estimate the 6-month attrition using proportions and 95% confidence intervals. We will also monitor the percent of targeted recruitment numbers, and protocol deviations. In secondary analysis, we will combine attrition data from the original exercise groups with data from the control group after exercise participation (see section C.5.1 and Figure 2).

- * **Additional Analyses:** We will conduct three sets of analyses that expand and illuminate the specific analyses proposed in the specific aims. The first set of analyses is designed to gain greater insight into whether additional variables may account for our findings in Aims 1 and 2 and may inform a Phase III clinical trial. Three such analyses are proposed based on: 1) the average physical activity level measured by via physical activity monitors, 2) the initial cardiovascular fitness of the subjects as determined by VO₂ max from the stress test, and 3) PD subgroup. The second set of analyses is designed to determine if dose of exercise affects quality of life as a secondary outcome. In the third set of analyses, we will explore the impact if participants initiating dopaminergic treatment on intervention affects using “off” medication state at 6 months and using “just prior to treatment initiation” UPDRS assessments. These analyses are informative for not only planning the larger confirmatory study but they will contribute methodological information for future studies in de novo patients.
- * Physical activity data are measured monthly for 6 months on all subjects and will be treated as continuous data in total number of activity counts. We are particularly interested in the impact high intensity exercise has on other physical activity. We will use linear mixed models to compare all three groups with respect to physical activity outside of the pre-specified protocol treadmill walking. Models will include fixed effects for group, time, and group*time and random effect for subject and time (if pattern is linear) to account for repeated measures. We will use ANCOVA to adjust for initial baseline fitness as measured by VO₂ max and to explore potential attenuating effects of high baseline fitness on exercise for PD symptoms. We will use regression analysis to explore if PD subgroup modifies the response of patients to exercise. We will use ANCOVA to compare the PDQ at six months among the three intervention groups controlling for baseline PDQ.
- * **Other statistical considerations (missing data, initiation of drug therapy):** We do not expect substantial item response missing data due to the electronic nature of data collection that is used by the Center for Research on Health Care Data Center (CRHC-DC). We anticipate <15% attrition at the 6-month assessment based on our pilot work and have accounted for this in sample size analyses. We will compare baseline characteristics between subjects with the 6-month assessment to those without to assess potential biases. We will try to obtain reasons for study drop out so that we can assess the missing data mechanism. We will use linear mixed models for analysis of weekly %HRmax that are more robust to missing data than traditional multivariate models.
- * **Lost to follow-up:** for subjects missing 6-month follow-up data on the primary futility measure (UPDRS), we will conduct several sensitivity analyses. First, we will assign the worst change score observed within each intervention arm to evaluate the impact on our study results.^{36, 37} Secondly, we will also use a “nearest neighbor” approach where best- and worst case scenarios are created by imputing values of the best and worst decline in the UPDRS motor scores from 5 subjects that had similar baseline UPDRS scores.⁴⁷ Third, we will use multiple imputation in exploratory analyses. These three approaches should result in consistent results if our findings are robust to missing data. We will declare futility if at least two of these analyses with different missing data methods show futility. If only one of these analyses shows futility, we will thoroughly assess the assumptions for the missing data approach and determine if the assumptions are reasonable based on the data available for missing visits and baseline variables associated with attrition. In all scenarios, the final futility or non-futility decision will be discussed with the Study Monitoring Committee and final decision will be made with the SMC’s approval.

10. DATA COLLECTION, SITE MONITORING AND ADVERSE EXPERIENCE REPORTING

10.1. Records to Be Kept

- * The following records will be kept in locked file cabinets in the office or laboratory of the site P.I., and /or his or her collaborators. Only study personnel will have access to these files.
 1. Informed consent
 2. Medical Screening data including physician notes, Graded Exercise Test results
 3. MoCA
 4. Exercise logs
 5. Data related to physical activity levels (raw data)
- * Most records will be stored in the database and will not be in paper form. Included are the following:
 1. Demographics
 2. Screening data
 3. PDQ-39
 4. RAND
 5. Health Status Update
 6. ESS
 7. PDSS-2
 8. MFIS
 9. BECK
 10. Scored physical activity levels (acquired monthly)
 11. HR data (acquired during each exercise session)
 12. AE and SAE reports
 13. UPDRS and MDS UPDRS data
 14. 6 and 12 month Feedback Surveys
 15. 24 month Exercise Habit Feedback Survey
- * The data management system will be developed by the University of Pittsburgh Center for Research on Health Care Data Center. The system will be web-based for direct data entry with a fully-featured relational database. (eSYSMDM). Subjects will be identified by a unique identification number and no personal identifying information will be stored in the study database or used in any of the analyses files.

10.2. Role of Data Management

10.2.1. *Clinical Site Responsibilities in Data Collection and Management.*

- * At the initial phone screen, the site-specific study coordinator will enter eligibility information into eSYSMDM using their desktop computers. Once a subject is deemed eligible, an appointment will be made for their neurological screening exam that will be performed in neurology outpatient clinics or research centers (Chicago, Denver, Pittsburgh). Data will be directly entered into eSYSMDM using laptop computers or recorded on paper by the neurologists to be double data entered into eSYSMDM by the study RA at each site. At the same visit, eligible subjects will undergo blood tests and a maximal graded exercise test (GXT) with data double-entered by the study RA into eSYSMDM. Exercise data (data of visit, exercise duration, average % HR Max, adherence) collected at study visits will be entered into eSYSMDM using tablet, laptop, or desktop computers with web access. Site coordinators will be responsible for gathering electronic data from physical activity monitors and HR monitors to be merged with the study database. Twice monthly, subjects will be asked about adverse events by the blinded study RA using a standard form and data will be entered directly into eSYSMDM. These visits will occur when subjects receive their physical activity monitors and a week later when the activity data are downloaded. Mild side effects of the exercise intervention will be assessed at each study visit.

10.2.2. *Statistical Center Responsibilities in Data Management.*

- * The data management system will be developed by the University of Pittsburgh Center for Research on Health Care Data Center. The system will be web-based for direct data entry with a fully-featured relational database. All data management will use an electronic System for Data

Management (eSYSMDM), using both the Internet and tablet PCs with backup paper data collection. The Steering Committee will work with the Data Center to develop effective data collection forms and a study Manual of Procedures to ensure the highest data quality. Extensive pre-testing of the database will be conducted prior to study start up. All study coordinators will attend a project initiation meeting (possibly via web conference) and undergo a competency based training program and certification process prior to enrolling subjects. All neurologists will participate in a training session for use of the UPDRS and MDS UPDRS prior to testing subjects.

10.3 Quality Assurance

10.3.1. Prior to data collection, the following will take place:

1. The Study Monitoring Committee will review and approve all protocols.
2. All study personnel will be trained in all study procedures for which they are responsible.
3. Personnel who implement the UPDRS and MDS UPDRS will document training and proficiency on both measures.

10.3.2. We will monitor protocol compliance as follows:

1. Each site P.I. will monitor exercise records on a monthly basis to determine whether subjects are adhering to the exercise protocol as prescribed.
2. The Steering Committee will review the summary of exercise records on a monthly basis to determine any site specific deviation from the protocol.
3. Schenkman (P.I.) and Moore (statistician) will visit each site annually to review all protocols for compliance.

10.3.3. Protocol Compliance:

1. A checklist of potential protocol violations will be created and maintained for tracking by the Steering Committee. Each protocol violation report will include the violation, whether the subject is continued on exercise, the impact on the site procedures, and next steps for subject continuation. The number and type of violations will be monitored by site relevant to the total number of subjects recruited. Examples of protocol violations include enrollment of an ineligible subject, randomization of an ineligible subject, failure to collect all screening tests, serious adverse events not reported in a timely fashion, breach of confidentiality, subject lost to follow-up, and visits outside of time window
2. A tracking report will be developed as part of the database to allow each site coordinator to assess recruitment, consent, subject status, upcoming visits, and outstanding assessments. Reports will be created to monitor site compliance with data entry and data errors. Data errors should be limited since fields will be set to exclude implausible entries. We will monitor adherence to study visits and exercise interventions by site.

10.4. Adverse Experience Reporting

- * A case report form (CRF) will be created and housed in the electronic data base for anticipated mild side effects of the exercise interventions and these will be monitored at each study visit to be entered by the exercise training RAs. In addition, all AEs and SAEs will be documented as soon as they are reported.
- * We will also develop automated reports for data and safety monitoring.

10.5 Study Monitoring Committee

- * A Study Monitoring Committee (SMC) will be established and will be comprised of three individuals. One will be appointed chair of the SMC and will be responsible for generating minutes from each meeting. These individuals may be from one or more of the three sites, but may have no other involvement in the study. The committee will be comprised of a movement disorders neurologist, a statistician, and an individual with expertise in exercise interventions. The SMC will review and approve the study protocol prior to initiation of enrollment, will review SAEs and AEs at least twice annually and will be alerted to any interim concerns. The Chair of the Study Monitoring Committee will review data collectively from all three sites and will communicate immediately with the PI and NINDS regarding any interim concerns. Should any SAEs occur, they will be reported within 24 hours to the site PI, the Grant PI (Schenkman), the Chair of the SMC and the Research Subject Advocate. At least twice annually, the SMC will review enroll-

ment to assure that targets are met. The Chair will write a report after each meeting, summarizing the study status and outlining any concerns. A copy of this report will be given to Barb Ham-mack, Research Subject Advocate.

11. HUMAN SUBJECTS

11.1. Institutional Review Board (IRB) Review and Informed Consent

- * This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study at each site. A signed consent form will be obtained from the subject. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject and this fact will be documented in the subject's record.

11.2. Subject Confidentiality

- * All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, or the sponsor's designee.

11.3. Study Modification/Discontinuation

- * The study may be modified or discontinued at any time by the IRB, the NINDS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12. PUBLICATION OF RESEARCH FINDINGS

- * Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the NINDS prior to submission.

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