Title: Pragmatic Cyclical Lower Extremity Exercise Trial for Parkinson's disease

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SPECIFIC AIMS

An unmet need in the treatment of Parkinson's Disease (PD) is identification of an effective disease-modifying intervention (e.g. pharmaceutical, surgical or behavioral).[1,2] Increasing evidence, from our laboratory[3-7] and others,[8-10] coupled with our recently completed NIH-sponsored randomized controlled trial (RCT), *CYClical Lower Extremity exercise for Parkinson's trial (CYCLE)*, indicates high intensity aerobic exercise is a candidate to alter PD progression. CYCLE trial data demonstrate that exercise delivered in a controlled, supervised laboratory setting results in global improvements in motor and non-motor function. Global improvements were preserved following exercise cessation, suggesting exercise is likely enhancing CNS function.[3,4,7] The precise mechanism underlying improved post-exercise motor function in PD is unknown. Our imaging data[5,6,11] and others[12,13] suggest a plausible mechanism is improved thalamo-cortical connectivity, facilitated through elevation of neurotrophic factors.[14,15] A multi-site pragmatic RCT is proposed, in which PD patients complete the CYCLE protocol at home, to address the following questions: 1) What are the disease-altering capabilities of a PD-specific long-term, high intensity aerobic exercise intervention? 2) What are the relationships of patients' phenotype and exercise performance variables to PD progression within such an exercise program? Based on preliminary data, we hypothesize that long-term high-intensity aerobic exercise slows PD progression relative to Usual and Customary Care (UCC). In sum, approximately 250 mild to moderate PD patients from Cleveland Clinic and University of Utah will be randomized to a high-intensity home exercise or a UCC group. The CYCLE protocol, involving aerobic intensity between 60-80% of heart rate reserve with a target cadence between 80-90 RPMs, will be delivered to the patients' home via the commercially available *Peloton Cycle.* The exercise group will be asked to cycle 3x/week for 12 months. The UCC group will be instructed to engage in their normal activities. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) will be used to evaluate disease progression or rate of physical decline. Blinded MDS-UPDRS III evaluations will be completed at: enrollment, 6 and 12 months. Biomechanical iPad assessments of motor and non-motor function[16-19] will be completed at each time point; thus augmenting clinical outcomes to provide a comprehensive understanding of the effects extended exercise on specific aspects of PD motor control and executive function. Overall activity levels will be monitored for both groups via a wearable sensor.

Aim 1: To determine the disease-altering effects of a home-based high-intensity aerobic exercise program. 12-month MDS-UPDRS III rate of decline while off medication will serve as the primary outcome.
Hypothesis: Those in the high intensity exercise group will have a significantly smaller one-year rate of decline in MDS-UPDRS III scores compared to the UCC group.

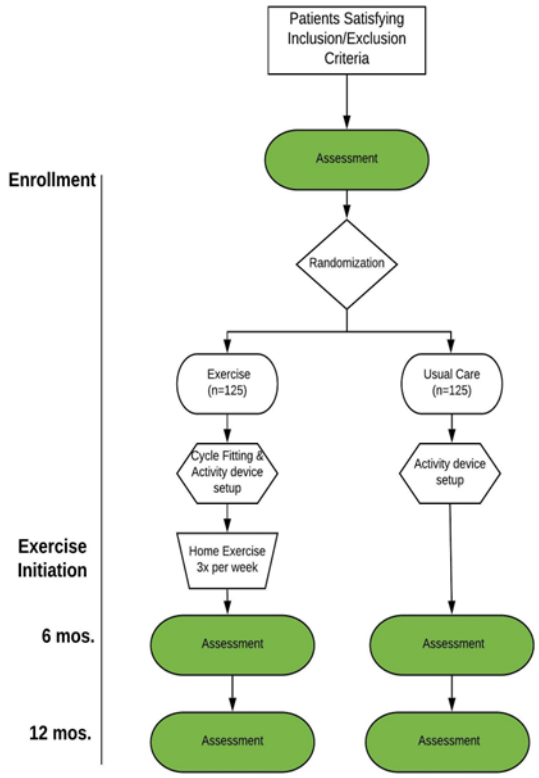
Aim 2: To determine the effects of a home-based aerobic exercise program on upper and lower extremity function using biomechanical outcomes. Our Nine Hole Peg Test (9HPT),[19] gait speed[19] and Timed Up and Go (iTUG)[20,21] iPad modules will be used to quantify upper and lower extremity function.
Hypothesis: Performance on 9HPT, gait speed and iTUG will show significantly slower rates of decay over 12 months for those in the exercise group compared to the UCC group.

Aim 3: To determine the effects of a home-based aerobic exercise program on non-motor function. Non-motor assessments will be evaluated using our iPad-based tests of processing speed (Processing Speed Test[19,22]), working memory and set switching (Trail Making Test A & B).
Hypothesis: Rates of decline in executive functions from enrollment to 12 months will be significantly less in the exercise group compared to the UCC group.

Aim 4: To develop a prognostic model to predict 12-month MDS-UPDRS III decline for patients participating in a home-based high-intensity aerobic exercise program.
PD demographics (age, gender, disease duration, primary symptoms, age of onset, etc.) coupled with exercise performance variables (compliance, duration, cadence, heart rate, power, heart rate variability) will be used to predict 12-month change in MDS-UPDRS III scores among the exercise cohort.
Hypothesis: Demographics, baseline PD status and comorbidities, and exercise performance will predict 12-month PD progression. Time in target heart rate zone and cadence, particularly, will notably improve predictions over those from baseline measures only.

APPROACH

To test the hypothesis that high intensity exercise completed by PD patients in their the home can alter disease progression, we will consent and randomize approximately 250 CC and UU PD patients to home-based high-intensity aerobic exercise or UCC within 3 years, and monitor group exercise parameters, activity levels, and PD progression in both groups. The trial will be conducted under Data Safety Monitoring Board (DSMB) oversight.



Participant Recruitment, Screening and Randomization: CC's Center for Neurological Restoration (CNR) manages 6,000+ PD patients; each patient typically has semi-annual neurology visits which include a complete MDS-UPDRS III evaluation. UU's Movement Disorders Program manages 2,000+ PD patients. Their respective Directors, Drs. Fernandez (Cleveland) and Moretti (Utah), will lead their medical teams to screen in recruiting for this project and will complete MDS-UPDRS III clinical evaluations, blinded to group assignment. The pragmatic clinical trial design, with exercise at home and relatively few visits to the study site, will minimize travel burden, easing recruitment and facilitating recruitment of a racially and socio-economically diverse patient group.[23] It is anticipated that study sites will enroll an equal number of participants. Adults with idiopathic PD who meet inclusion criteria and cleared for exercise will be randomized to either the home exercise or UCC group, using a permuted block randomization stratified by site, with random block sizes of 8, 10, or 12 for the first 8 blocks at each site, and 4, 6, or 8 subsequently, preloaded into a secure and shared RedCap electronic data management system developed at CC. Both sites have effectively utilized RedCap across in previous multi-site clinical trials,[24-31] and clinical programs. Figure 1 depicts study flow. Total study participation time is projected to be 12.5 months, including ~2.5 weeks for cycle delivery and completion of initial Comprehensive Assessments (On-/Off- meds).

As shown in Figure 1, three Comprehensive assessments of motor and non-motor function will be conducted for all participants. Comprehensive (90 mins) assessments (Table 1) will be overseen by Drs. Fernandez and Moretti, and will be completed at project enrollment (On- and Off-medication), 6 months (Off-medication), and 12 months (Off-medication). Visit windows will be within ± 10 days of their nominal dates. Participants will be reimbursed for time and travel expenses of $50 for each assessment. All clinical and self-report data will be entered into the RedCap database (see Data and Safety Monitoring). Each site's biomechanical data from the iPad will be uploaded securely, with encryption, to the CC HIPAA-compliant cloud instance (ClearData), processed in the cloud, and integrated into the Alberts lab's on-premises, firewall protected, server.

Asking participants to withhold medication for Off-state examinations imposes a burden, but the Off-state (12 hours off meds) will increase insight into the direct effect of exercise on PD itself. Since medication changes are frequent with PD and often result in symptomatic fluctuations, the Off-state provides a more reliable, less confounded time comparisons. Medication reconciliation will be completed at each examination, and levodopa equivalent daily doses (LEDDs) will be determined and utilized in the prediction model (Aim 4). To determine the potential impact of overall physical activity in disease progression, all patients will be provided a Garmin activity monitor to measure overall daily activity (e.g., active minutes and steps per day). Currently, the Garmin activity monitor is utilized by 30,000+ participants in the CC Health System employee health plan, and accurately counts steps and activity levels of individuals with PD.[32] Patients will wear the device on their belt/waistband or shoe during waking hours and upload the data every 30 days via the supplied application. Device batteries typically last ~6-months. To ensure no loss of data the battery will be replaced at the 6 month assessment. Activity monitor data will be synchronized with the secure CC Health system portal and downloaded to the Alberts research server behind the CC firewall. The number of steps and minutes of activity, binned by day, week, month and year, will be considered for inclusion in the predictive model in Aim 4.

Leveraging a Widespread Consumer-based Home Exercise Platform: Our previous model of deploying a consumer-based interactive and connected exercise cycle to the home will be leveraged for this trial.[27] The Peloton Indoor Cycle (New York, NY) will serve as the platform to deliver the CYCLE exercise protocol and actively measure exercise performance variables. To ensure safety in exercising and understanding of the Peloton, exercise participants will be properly fit to the Peloton. Dr. Alberts and Dr. Dibble will be responsible for conducting this fitting session as both have extensive experience in fitting PD patients on exercise cycles. During this session seat height, reach, clipless or platform pedals, etc. will be optimized for comfort and safety in mounting and dismounting the cycle. Patients will complete a tutorial related to using the cycle, heart rate monitor and data transmission. Patients will be informed of their target HRR (Karvonen method: [(220-age)-resting HR] x 60-80% + resting HR) and complete a brief exercise session to ensure they fully understand the exercise requirements and Peloton interface. They will be provided a Garmin activity monitoring device and instructed on its use. Within 10 days of the clinical fitting session, a Peloton cycle will be delivered to the

Outcome Measure	Domain	Comprehensive
Aim 1		
MDS-UPDRS III	Rater-observed PD global motor symptoms	✓
Aim 2		
Nine Hole Peg Test	Upper extremity dexterity	✓
Timed Up & Go & 10M walk	Transfers, turning, gait speed	✓
Postural sway	Postural stability and Balance	✓
Self-reported falls	Prospectively recorded via fall diary	✓
Six Minute Walk Test	Cardiovascular fitness	✓
Aim 3		
Processing Speed	Info processing speed, implicit learning	✓
Visual Memory Test	Episodic Memory	✓
Trail Making Test A & B	Set-switching, attention, working memory	✓
Neuro-QoL	Quality of life questionnaire	✓
MDS-UPDRS I, II, IV	Part I: non-motor symptoms; Part II: self-reported motor symptoms; Part IV: motor complications	✓

patient's home by a certified technician. They will assemble and setup the cycle according to patient-specific fitting specifications. The certified technician will ensure all aspects of the cycle are working properly. The study coordinator will contact the patient within 48 hours of delivery to ensure the system is functioning as intended.

Standardized High-Intensity Home Exercise Program: The Peloton platform contains thousands of pre-recorded cycling classes with varying levels of intensities and recommendations. Study staff will select cycling protocols from this pre-recorded list for cyclists entering the study at different levels of fitness (beginners, intermediate, or advanced). Participants will be safely increased in RPMs, heart rate, and overall levels of perceived exertion over subsequent weeks of the study to reach study recommendations. Participants will be will be asked to exercise on the Peloton 3 times per week for 50-60 minutes (40 minutes at their target HRR + 5-10 minute warm-up and cool-down) for 12 months and encouraged to exercise using a relatively high cadence (80-90 rpms). To increase engagement, modules containing different professional Peloton instructors will be utilized. All instances of the modules will be similar in terms of aerobic intensity; however they will vary in type of background music and general personality of the instructor. In addition to the selected CYCLE modules, the patient will have the option to join more than 20 daily "live" sessions or select one of 300+ scenic courses on the Peloton platform. These additional options empower each patient to exercise in a manner best suited for them and will facilitate compliance. Considering the Peloton records, stores, and transmits heart rate, power, speed, estimated distance, time and cadence for every exercise session, regardless of whether the patient is completing a CYCLE module, live class or scenic ride, the specific module they complete is not critical as data are recorded, transmitted and downloaded to the study database regardless. Secure data transmission procedures are detailed in Protection of Human Subjects.

Study staff at each site will make bi-monthly calls to patients to address technology issues or compliance obstacles for those patients not meeting exercise recommendations. During these calls, exercise may be

progressed as deemed appropriate based on physiological signs monitored by the Peloton and patient subjective report (see Protection of Human Subjects for details).

Usual and Customary Care Group: Participants randomized to the UCC group will be asked to maintain their current exercise habits for 12 months. UCC can entail referrals to physical or occupational therapy or voluntary exercise. Due to the overwhelming evidence that those services are beneficial to individuals with PD, we will not restrict individuals from those programs. Similar to the home exercise group, a member of the study team will call these patients twice per month to inquire about activity levels, medication changes and technology assistance with the activity monitoring device and data.

Alternate Data Capture:

Due to the Covid-19 situation, the Cleveland Clinic and the University of Utah are requesting the ability to conduct virtual visits with participants. The Cleveland Clinic will utilize either FaceTime or Zoom, and the University of Utah will utilize the preferred platforms of their institution.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

a) Adult with a diagnosis of idiopathic PD by a physician or physician extender
b) Hoehn and Yahr stage I-III
c) Demonstrate the ability to safely mount and dismount the Peloton stationary cycle
d) In-home WiFi (Peloton system requires WiFi to transmit exercise data)*

*2017 report indicates WiFi rates of 76% and 83% in Ohio and Utah households respectively

Exclusion Criteria:

a) Participation in pharmaceutical or behavioral disease modifying PD-related clinical trial or study
b) Diagnosis of dementia or any neurocognitive impairment that compromises one's ability to provide informed consent.
c) Implanted deep brain stimulation electrodes
d) Recommendation for medical clearance using the American College of Sports Medicine (ACSM) Preparticipation Health Screen (Figure 2)[33]
    a. If the ACSM screen recommends medical clearance, the subject must obtain medical clearance by their health care provider prior to participation.
    b. Those who choose not to obtain physician clearance will not be eligible for participation. Those who do not receive physician clearance for high intensity exercise will not be eligible.
e) A musculoskeletal issue (arthritis, osteoporosis, back problem) that would limit one's ability to engage in exercise
f) Neurological disease other than Parkinson's disease (i.e. multiple sclerosis, Huntington's disease)
g) Current or active cardiac arrhythmia
h) DeNovo patients (have not begun Parkinson's disease medications).
i) Previous or planned treatment of focused ultrasound for Parkinson's disease management

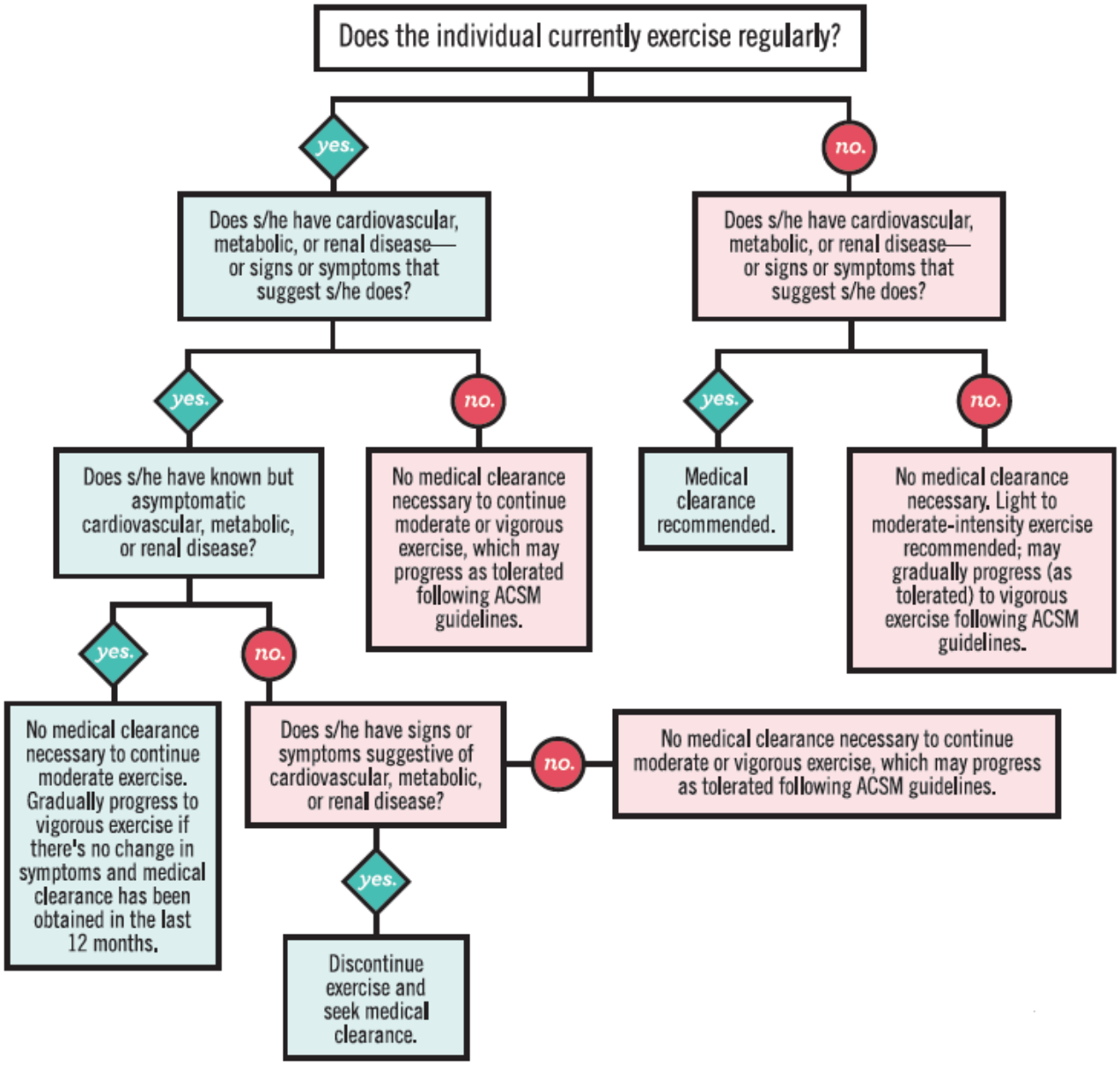


Figure 2: *Schematic of ACSM exercise readiness questionnaire. Detailed questions will be part of the pre-screening process.*

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