## Section 1:Full Study Title

**Effects of combined arm and leg high-intensity interval training on motor and non-motor symptoms in people with mild to moderate Parkinson's disease:**

**A randomised controlled feasibility trial**

**Short Study Title**

**PD\_HIIT**

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# STATEMENT OF COMPLIANCE FOR NON-DRUG OR DEVICE CLINICAL TRIALS

This document is a protocol for a clinical research study. The study will be conducted in compliance with all stipulations of this protocol, the conditions of ethics committee approval, the [NHMRC National Statement on Ethical Conduct in Human Research](https://www.nhmrc.gov.au/guidelines-publications/e72) (as updated) and the [Handbook for Good Clinical Research Practice (GCP)](https://extranet.who.int/prequal/sites/default/files/documents/GCP_handbook_1.pdf). The Therapeutic Goods Act has adopted [ICH Guideline for Good Clinical Practice](https://www.tga.gov.au/publication/note-guidance-good-clinical-practice).

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| Section 2: Protocol Signature Page  |  |  | | --- | --- | | **Protocol title:** | Effects of combined arm and leg high-intensity interval training on motor and non-motor symptoms in people with mild to moderate Parkinson's disease:  A randomised controlled feasibility trial | | **Protocol number:** | (not known) | | **Protocol version and date:** | Version 1, 24/10/2023 | | **Sponsor name** | The University of Sydney |   **Principal Investigator Declaration** | |
| I will conduct the clinical trial in accordance with Good Clinical Practice, Declaration of Helsinki, National Statement on Ethical Conduct in Human Research 2007 (as updated), Australian Code for the Responsible Conduct of Research 2018 and the moral, ethical, and scientific principles that justify clinical research. The clinical trial will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of participants.  I agree to adhere to the protocol as approved by the Human Research Ethics Committee/s in all circumstances other than where necessary to protect the well-being of the participant. | |
| **(Coordinating) Principal Investigator name:** | Daniel Hackett |
| **(Coordinating) Principal Investigator signature:** |  |
| **Date of signature:** | 9/11/2023 |

## Section 3:1. GENERAL INFORMATION

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**Sponsor:** The University of Sydney, Camperdown, NSW, Australia

**Primary Faculty/Department:** Discipline of Exercise and Sport Science; Sydney School of Health Sciences, Faculty of Medicine and Health

**Trial identifier and registry name:** Nil currently

## Section 4: SYNOPSIS

|  |  |
| --- | --- |
| **Title** | **Effects of combined arm and leg high-intensity interval training on motor and non-motor symptoms in people with mild to moderate Parkinson's disease.** |
| **Objectives** | An 8-week randomised feasibility trial will be conducted to investigate motor and non-motor responses to high-intensity interval training utilising a combined arm and leg ergometer in individuals with mild to moderate Parkinson's disease (PD). |
| **Primary Hypothesis** | High-intensity combined arm and leg ergometry added to usual care will lead to increases in habitual gait speed in people with PD compared to usual care. |
| **Design** | All participants will be randomly allocated to a control (no exercise) or intervention (high-interval combined arm and leg ergometry) added to usual care of PD. |
| **Blinding / Masking** | Assessors blinded to primary outcome and statistical analyses conducted blinded to study group assignment. |
| **Outcomes** | Outcomes: Habitual gait speed, muscular strength and power, aerobic capacity, severity of PD symptoms, performance/functional measures, brain-derived neurotrophic factor (BDNF), and cognitive function. |
| **Study Duration** | 11 weeks. 2 weeks baseline assessments; 8 weeks intervention with 3 visits a week x 8 weeks for intervention group, 1 week post-testing = 11 weeks total, 28 visits total for intervention group and 4 visits total for control group. |
| **Intervention/s** | High-intensity interval training (HIIT) on a combined arm and leg ergometer (Rogue Echo) (Rogue Fitness, Columbus, Ohio, U.S.A) |
| **Number Of Participants** | 30 participants randomised to 2 groups, 15 to no exercise intervention (usual care) and 15 to intervention group (HIIT). |
| **Population** | Males and females 18+ years with a confirmed diagnosis of idiopathic PD with a severity of 3 or less on the Modified Hoehn and Yahr scale. |
| **Selection And Enrolment** | Inclusionary criteria: Diagnosis of idiopathic PD with a severity of 3 or less on the Modified Hoehn and Yahr scale.  Exclusionary criteria: A rating greater than 3 on the Modified Hoehn and Yahr scale or no physician diagnosis of PD. Non-community dwelling residential status. Currently participating in greater than 150 minutes of moderate- to high-intensity exercise training (defined as aerobic, resistance or high-intensity interval training) per week. Individuals with secondary PD or other progressive neurological disease. Unstable medical conditions that would preclude individuals from exercising. Known diagnosis of current or past coronary or cerebral artery disease, symptomatic peripheral vascular or other medical conditions precluding exercise: e.g., congestive heart failure, untreated aneurysms, cardiac arrythmias including atrial fibrillation, moderate-to-severe pulmonary disease, advanced renal disease or permanent non-ambulatory status, retinopathy or history of retinal detachment, a diagnosis of dementia or significant cognitive impairment as defined by a score less than 19 on the Montreal Cognitive Assessment (MoCA) indicating difficulties in aspects such as memory, communication, and ability to focus, medications that could indicate treatment of dementia, medications that could affect neurological function and safety including but not limited to anti-psychotics, sedatives-hypnotics or narcotic analgesics, as determined by the study physician assessment. Current musculoskeletal injuries, conditions, or limitations (e.g., muscle strain/pain and joint instability) of the lower body (i.e., ankle, knee, or hip joints), or current lower back pain. Symptoms consistent with current major depressive episode, suicidality, psychosis, or active substance use disorders, as defined by the Diagnostic and Statistical Manual, version 5R (DSM-5R). Recurrent falls. Non-ambulatory status (use of walker or stick allowed). Recurrent falls. Terminal or rapidly progressive illness. |

## Section 5.1: BACKGROUND

Parkinson’s disease (PD) is a complex progressive neurodegenerative disorder affecting approximately 6.1 million people globally and one in every 100 older adults over 60 years old (Dorsey et al.,2018). It is the second most common neurodegenerative disease and is characterised by a loss of the neurotransmitter dopamine with associated motor symptoms (O’Callaghan et al., 2020) including bradykinesia, rigidity, tremor, and loss of postural control (Kouli et al.,2018). Additionally, PD is often linked with non-motor symptoms such as cognitive impairment, hallucinations, sleep problems and difficulties swallowing, leading to diminished quality of life (Chaudhuri et al.,2006).

Whilst medications offer symptomatic relief, they may also cause side effects such as motor fluctuations and dyskinesias (Rezak.,2007), highlighting the need for exploration of complementary therapies. Exercise has been demonstrated to have promising outcomes in both improving functional capacity in people with PD (PwP) (Schenkman et al.,2018) and ameliorating some of the negative side effects of Parkinsonian medications (Xu et al.,2019). Although there have been recent advances in exercise prescription in PwP and demonstrations of reductions in rate of loss of function (Oliveira de et al., 2018), most exercise interventions have focused on utilising exercise with lower limbs such as walking/jogging (Lamotte et al.,2015) and cycling (Rosenfeldt et al.,2015). In the context of PD management, exercise interventions have primarily focused on low to moderate intensity regimes. However, the SPARX trial (Schenkman et al.,2018) not only indicated the potential superiority of high intensity aerobic exercise (80-85% maximal heart rate) over moderate intensity aerobic exercise (60-65% maximal heart rate) on motor outcomes, but also had a central focus on evaluating feasibility measures such as adherence to protocol volume of three days per week and prescribed intensities of exercise protocols. This novel trial showed for the first time a significant attenuation of disease progression via the MDS-UPDRS motor score with high intensity exercise vs. the moderate intensity or usual care groups, both of which worsened over 6 months of follow-up.

An even higher intensity paradigm known as high-intensity interval training (HIIT; approximately 90% maximal heart rate) has also been investigated recently with promising results (Harpham et al.,2023). These emerging data suggest that high-intensity exercise (both continuous and interval training) may be a potentially innovative new pathway in PD treatment. Although conclusive evidence is still pending, initial research suggests that higher intensities can be safe (Harpham et al., 2023) (Schenkman et al.,2018) and effective for improving functional capacity and motor symptoms (Chen et al.,2020). Despite this, substantial gaps remain in the existing literature, including mechanism of benefit or disease modification, long-term efficacy and sustainability, precise workloads/intensities for optimal adaptation and safety, and utility and feasibility of various types of equipment across the spectrum of patients with PD.

The potential for exercise to act as a disease-modifying intervention is suggested by the SPARX trial (Schenkman et al.,2018), and is the focus of intense animal and human investigation. The mechanism of exercise benefit is not precisely known but is thought to be related in part to exercise effects on stimulation of the motor cortex (Fisher et al.,2008). The relationship between dopamine levels and performance outcomes in PwP is complex and interconnected (Latif et al., 2021). Loss of dopamine producing neurons in the substantia nigra pars compacta in the brain of PwP leads to diminished excitatory stimulation of the motor cortex (Lang and Lozano, 1998), an ensuing reduction in recruitment of motor units (David et al.,2012), and associated hallmark motor symptoms such as rigidity, tremor, and bradykinesia (Segura‐Aguilar et al.,2014). These symptoms often manifest as reduction in muscular strength and power, subsequent reduced mobility, and loss of functional capacity (Dibble et al.,2006). Such reductions in capacity may lead to inactivity and disuse atrophy, further impairing exercise performance and mobility.

One pivotal motor impairment in PwP is a reduction in gait speed (Linder et al.,2022), often considered a future predictor of global health and functional capacity (Hass et al.,2014). Gait impairments are often a defining feature of motor dysfunction in PwP. These reductions are manifested as a reduction in walking speed, step length and irregular step frequency and cadence (O’Sullivan et al.,1998). Mean gait speed in PwP is 0.94 m/s (0.27-1.67m/s) (Paker et al.,2015) compared to healthy older adult controls (>60-year-old) of 1.2-1.4 m/s (Kasovic et al.,2021). This marked reduction in gait speed leads directly to reduced mobility and loss of independence (Kim et al.,2018), a subsequent reduction in aerobic capacity (Canning et al.,1997) and higher risk of falls (Creaby et al.,2018). Impaired gait speed and mechanics restrict duration and intensity of aerobic exercise which in turn reduces the subsequent maximal oxygen consumption (Thrue et al.,2023), thereby elevating the risk of chronic cardiometabolic disease (van Nimwegen et al.,2011). Therefore, due to this vicious cycle, gait speed is often a key target area in exercise interventions aiming to reduce the global burden associated with ageing populations as well as in specific cohorts with PD.

Other physiological deficits linked to lower aerobic capacity are the well-described reduced muscle strength and power in PwP. Inefficient oxygen utilisation in weakened muscles limits the duration of sustained aerobic activity, leading to increased levels of fatigue (Ross et al.,2016), increased sedentary behaviour (Ellingson et al.,2019), reduced functional capacity and increased reliance on care givers (Macleod et al.,2016) and decreased quality of life (Chapuis et al.,2005).

Addressing all the above deficits in PD requires a targeted and evidence-based exercise prescription. One potential approach is the use of HIIT, which has been popularised by its use in healthy populations and has recently gained recognition in global clinical exercise guidelines as a viable alternative to traditional forms of exercise treatments in clinical cohorts as well (Keating et al.,2020; Taylor et al., 2019; ACSM.,2019). It typically incorporates higher intense bursts of exercise with durations generally ranging from 30 seconds to 4 minutes interspersed with intervals of passive rest or active rest (i.e., lighter activity). Whilst HIIT has shown considerable cardiometabolic advantages including optimised oxygen utilisation (Wen et al.,2019) and improved insulin sensitivity (Jelleyman et al.,2015), it is essential to note that the current body of evidence specifically focusing on the application of HIIT in PD is still emerging.

The sole existing meta-analysis about HIIT’s application in PD conducted by Harpham et al. (2023) is notably limited, encompassing 11 articles with diverse study designs. These comprised one randomised control trial featuring a usual care group (Marusiak et al.,2019), three randomised exercise comparative trials (Uc et al.,2014), (Duplea et al.,2020), (Fernandez et al.,2020), and one randomised controlled pilot study (O’Callaghan, 2020). Additionally, one pseudo-randomised control trial (Demonceau et al.,2017), three single group studies with a pre/post design (Zoladz et al.,2014) (Hass et al.,2016), (Uygur et al.,2017) and lastly two grey area theses’ (Osbourne, 2018 and Duplea, 2020). Program duration ranged from three weeks to 24 months, with a frequency of thrice weekly commonly used. Most studies used cycle ergometry (Hass et al., 2016; Demonceau et al., 2017; Uygur et al., 2017; Osbourne, 2018; Marusiak et al., 2019; Duplea, 2020), while other modalities included high intensity walking (Uc et al., 2014), running (Fernandez et al., 2020), and circuit-type resistance training (O’Callaghan et al., 2020). “High” intensity was variably prescribed via incremental exercise testing, maximal heart rate, peak power outputs, and rates of perceived exertion. In five distinct studies, VO2 peak tests were utilised to establish individualised exercise workloads using various diverse metrics of intensity derived from the maximal oxygen consumption measurements. Specifically, Duplea (2020) set a target 80% of peak power, O’Callaghan (2020) aimed for 85% of maximum heart rate and Demonceau et al. (2017) also set training intensity at peak power workloads of 80 %@ V02 peak. Meanwhile both Hass et al., (2016) and Osbourne (2018) prescribed workloads based on up to 100% peak heart rate. Work to rest ratio was also variable, ranging from 3 minutes work:3 minutes rest to 15 seconds work:45 seconds rest. Most protocols were supervised by exercise professionals in various environments including exercise centres and laboratories.

Amongst the studies that utilised various HIIT protocols, only seven studies reported on adverse outcomes. Four studies employing cycle type ergometers reported no adverse events, (Hass et al., 2016; Uygur et al., 2017; Osborn et al., 2018; Duplea et al., 2020). Uc et al. (2014) used a community walking HIIT protocol and reported three incidents of knee pain in their HIIT group which led to one drop out from the 24-month programme. O’Callaghan (2020) reported one single adverse event with an episode of hypotension. Demonceau et al. (2017) reported five adverse events in their protocol that combined high-intensity resistance training with cycle ergometry. These events included knee strain and pain, headache and hypotension that led to one participant dropping out of the study.

Despite the limited data specific to HIIT on PD, available studies indicate that that this type of exercise offers meaningful clinical benefits. Notable improvements in maximal oxygen capacity have been reported by Demonceau et al. (2017) and Duplea et al. (2020), findings that are of clinical significance given the cardiometabolic comorbidities often present in people with PD. Furthermore, significant within group improvements in the United PD rating scale part III (motor symptoms) were noted in three studies, (Uygur et al., 2017), Marusiak et al. (2019), Duplea et al. (2020), a finding that underscores the potential clinical importance of HIIT in managing the often-debilitating disease progression commonly experienced in PD.

Although the existing body of literature points to favourable correlations between HIIT and various clinical outcomes in PD, it appears likely that the optimum methodology for inducing robust clinical and functional changes in this cohort remains undefined, underscoring the need for innovative paradigms to optimise adaptations in people with PD. In the prevailing scientific literature, treadmill walking is often cited as eliciting the highest oxygen consumption rates, but also having advantage due to its task-specificity for walking-related outcomes so crucial to independence in PD. However, it is imperative to consider specific medical conditions that may impose limitations on the suitability of certain exercise modalities. For example, Parkinson's Disease (PD) symptoms, such as diminished muscular strength (Inkster et al., 2003) and reduced muscle activation affecting postural stability (Dimitrova et al., 2004), contribute to early exercise termination and balance issues (Schoneburg et al., 2013). Moreover, gait abnormalities, rigidity, and bradykinesia (Bartels et al., 2003) can limit the ability of those with PD to safely perform treadmill exercises at effective speeds for aerobic improvement. In such cases, alternative exercise modes that can elicit a comparable cardiometabolic stimulus may be more appropriate. Consequently, the efficacy of a structured exercise intervention is not exclusively determined by the type of exercise but also by the extent of muscle mass involved (Zeni et al.,1996), variance in additional elements such as amount of support of body mass (Hill el., 2018), the characteristics of muscle contractions and feasibility of movement patterns, having potential neurophysiological, clinical, and functional outcomes.

Building on this notion of optimising exercise modalities for specific outcomes in neurological disease, previous research indicates that combined arm and leg exercise elicits distinct physiological responses, notably heightened cardiovascular output when compared to leg exercise alone (Secher et al., 1973), (Reybrouck et al.,1975). This is likely due to increased metabolic demand stemming from larger working muscle mass when both upper and lower limbs are engaged. Therefore, it is important to consider the distinct physiological responses generated when combining arm and leg exercise which may be relevant to outcomes in PD. Specifically, adding to this preliminary evidence for HIIT’s effectiveness as an intervention targeting PwP, the incorporation of increased working muscle mass, achieved through the addition of arm to leg movements could potentially amplify the efficacy of this form of exercise. Furthermore, the higher activation of working muscle mass with greater velocity of movement patterns with combined arm and leg ergometer high intensity exercise, prompts considerations about its impact on functional performance and clinical outcomes as well. This presents as a promising avenue for therapeutic strategies in managing the progression of PD.

Despite the strong rationale outlined above, comparatively little is known about physiological responses and clinical and functional outcomes of combined arm and leg ergometry compared to more traditional exercise such as treadmill walking or cycling ergometry, particularly in clinical cohorts. Most of the acute investigations have focused on energy expenditure in healthy, younger cohorts, with increases in VO2 peak ranging from 6-14% (Gleser et al.,1974), (Nagle et al.,1974), (Reybrouck et al.,1975), (Secher et al., 1974) compared to traditional cycle ergometers. These investigations employed non-coupled separate arm and leg ergometers integrated into a single unit for the purpose of the study. Zeni et al. (1996) and Jensen et al. (2019), found that the use of combined arm and leg ergometers resulted in significantly lower heart rates when intensity was prescribed at specific rating of perceived exertion (RPE) levels of 11, 13, and 15 (Borg 6-20), compared to exercising on treadmills and cycling on traditional cycle type ergometers. Hoffman et al (1996), observed that the combined arm and leg exercise led to lower RPE but was also associated with higher oxygen uptake and heart rate when training intensity was gauged by RPE or blood lactate levels. Collectively, these studies indicate that utilising a larger muscle mass in combined arm and leg exercise not only modulates heart rate and RPE, but also holds the potential for enhanced cardiorespiratory outcomes.

The mechanically coupled air braked ergometer, known commercially as the air bike or Rogue Echo (Rogue fitness, Columbus, Ohio, U.S.A), represents a distinct class of exercise equipment that has gained prominence in HIIT among healthy populations when aiming to elicit higher rates of work intensities and subsequent downstream effects on improvements in functional performance (Schlegel et al.,2022). Distinct from conventional stationary bicycles that engage the legs only, air bikes are designed to integrate both arm and leg motion against air resistance. The design is such that power output increases directly with incremental increases in rotational speed of the pedals, a feature that is not typically representative of other traditional modalities of ergometers. This unique feature of air bikes, which differentiates them from traditional ergometers, has led to their application in a diverse range of clinical studies, demonstrating their versatility across different populations.

In the existing literature, air bikes have been utilised in various protocols in clinical populations including older adults (Kim et al.,2015), and individuals with type 2 diabetes (Hwang et al.,2019), myocardial infarction (Nyquist-Byttie et al.,2007) and developmental disability (Fernandez and Pitetti,1993). Interventions commonly spanned 8 to 16 weeks, with exercise frequencies ranging from two-to-four times per week and intensities between 70 to 90% of maximal heart rate. The predominant clinical focus has been cardiovascular outcomes in older adults, with key findings including improvements in arterial stiffness (Kim et al., 2015), cardiac ejection fraction and insulin resistance (Hwang et al.,2016), VO2 peak (Hwang et al.,2019), and work capacity in time trials (Nyquist-Byttie et al.,2007). These studies demonstrate the potential utility of incorporating air bikes across various clinical populations as an effective intervention. However, there are no published studies to our knowledge investigating the effect of exercise interventions with the Air bike on neurodegenerative conditions like PD. The only trial investigating high intensity combined arm and leg exercise in PD that we are aware of, is the trial of O'Callaghan et al (2020). Participants underwent a 12 week, three times a week, high intensity circuit type training programme utilising specialised resistance training equipment. This modality enabled dynamic multi limbed functional motor patterns that when performed at high intensity, produced heart rates greater than 85% max heart rate. The authors found statistical differences in brain derived neurotrophic factor, a hormone that may contribute to the survival of dopaminergic neurons which are progressively lost in PD, compared to the control of moderate intensity continuous exercise. Therefore, building on these findings, our proposed protocol draws logically from the existing literature while offering a completely novel approach.

## Section 5.2: RATIONALE

PD presents as a complex neurodegenerative disorder, including a complex array of both motor and nonmotor symptomology, significantly decreasing functional capacity, and undermining quality of life. A substantial portion of these challenges arise from reduction of muscular strength and power, which notably manifests as reduced gait speed, amplifying the risk factors for chronic disease and falls, and restricting mobility. Furthermore, the observable declining power output underscores the significance of targeted exercise interventions. HIIT emerges as a potential modality believed to amplify power generation more effectively than other training protocols due to the higher rate of motor patterns induced in HIIT protocols. This could potentially lead to improved gait speed and alleviation of the overall severity of clinical manifestations of low muscle power. However, there is only one investigation to our knowledge evaluating the efficacy of a high intensity combined arm and leg exercise (O'Callaghan et al., 2020), highlighting a significant gap in existing literature. Given these extensive gaps in our current understanding, it is crucial to investigate how combined arm and leg exercise affects neurological biochemistry, pathology and progression in PD, strength and power, mobility, and other clinical outcomes. Studying all these outcomes will ultimately require several investigations and large cohorts followed over time. As this is the first such investigation, we will focus on the feasibility and adherence to the prescribed modality and exercise intensity and investigate whether the intervention leads to clinically relevant changes in motor and non-motor symptoms in PwP.

## Section 6.1 AIM:

To evaluate the efficacy of an 8-week high intensity interval training (HIIT) intervention utilising a combined arm and leg ergometer in people with idiopathic mild-to moderate PD (as measured by a Modified Hoehn and Yahr score of 3 or less) on motor and non-motor symptoms.

## Section 6.2: HYPOTHESIS:

1. HIIT performed on a combined arm and leg ergometer added to usual care, will lead to a significant improvement in habitual gait speed in individuals with mild-to-moderate PD compared to a control group receiving usual care.

2. HIIT performed on a combined arm and leg ergometer added to usual care will lead to significant improvements in aerobic capacity as measured by a maximal oxygen consumption test (VO2peak) compared to a usual care control group.

3. HIIT performed on a combined arm and leg ergometer added to usual care will lead to significant improvements in peak muscular power as measured by Keiser pneumatic resistance machines (chest press and leg press) compared to the usual care control group.

4. HIIT performed on a combined arm and leg ergometer added to usual care will lead to significant reductions in PD motor symptomology as measured by the Movement Disorder Society Unified PD Rating Scale (MDS UPDRS) Part 3: Motor examination, compared to the usual care control group.

5. HIIIT performed on a combined arm and leg ergometer added to usual care, will lead to significant improvements in functional performance measures including the six-minute walk test and the Short Physical Performance Battery (SPPB) (Guralnik et al.,1994) compared to the usual care control group.

## Section 7: PARTICIPATING SITES

This single site training study will be conducted, inclusive of screening, assessments and intervention delivery, in-person at The University of Sydney, Susan Wakil health building, clinical research space.

## Section 8: RESEARCH PLAN / STUDY DESIGN

## Section 8.1: Study design

A randomised controlled feasibility trial will be conducted to investigate the effects of HIIT in a novel mode of combined arm and leg ergometry, on physiological and functional outcomes in individuals with mild to moderate PD. The trial will run for 8 weeks with 24 sessions in total for the intervention group, excluding 3 baseline assessment sessions and one reassessment session at conclusion of the intervention in both groups. Secondary outcomes will also include adherence to both exercise intensity and modality. The study will adhere to the CONSORT (Consolidated Standards of Reporting Trials) guidelines for RCTs.

## Section 8.2: POPULATION / SAMPLE SIZE INCLUDING POWER CALCULATION

***Sample size:***

In the realm of feasibility and pilot studies, valuable insights have been provided by Lancaster et al., 2004). Their comprehensive work delves into various aspects of research methodologies, offering significant guidance to researchers. One key aspect they address pertains to estimating essential parameters, such as standard deviations, crucial for conducting precise sample size calculations. According to their recommendations, an optimal approach involves an overall sample size of 30. This guidance plays a pivotal role in ensuring the adequacy of sample sizes, thereby enhancing the robustness and reliability of research findings. Researchers often rely on such methodological recommendations to design studies effectively and draw meaningful conclusions.

## Section 8.3: STATISTICAL ANALYSES

Descriptive statistics will be calculated for habitual gait speed, aerobic capacity, muscle strength/power, MDS-UPDRS score**,** functional performance (six-minute walk test and the SPPB) and cognitive impairment before and after the intervention. The normality of the absolute data will be investigated using the Shapiro–Wilk test, and the Levene’s test will be used to assess the homogeneity of variance. For normally distributed data, means ± standard deviation (SD) and confidence interval (95% CI) will be reported. For non-normally distributed data median and interquartile ranges will be reported. Conditions will be analysed using repeated measures mixed models for normally distributed data and an appropriate non-parametric test for non-normally distributed data if necessary. The primary analysis of interest is the group x time interaction from the mixed model. Covariates which will be added to the unadjusted model include age, sex, and baseline Modified Hoehn and Yahr rating. The primary analytic strategy will be intention-to-treat (ITT), with all randomised participants included in the models, regardless of adherence or availability of follow-up data. Secondary exploratory analyses will consider those with complete follow-up data (completers analyses) and those with high adherence (per protocol analyses). Statistical significance will be considered at the p<0.05 level. Mean differences, 95% CIs, and Hedges’ bias corrected Effect Sizes will be calculated for all outcomes.

## Section 8.4: RECRUITMENT AND SELECTION OF PARTICIPANTS

***Recruitment:***

Recruitment will be conducted via outreach to local PD associations and support groups in N.S.W. and older adult exercise facilities. Participants must be residents of the Sydney area or be willing to travel to the University of Sydney campus for the study duration where free parking is provided at the clinic.

## 8.5: INCLUSIONARY AND EXCLUSIONARY CRITERIA

***Inclusionary criteria:***

This study aims to recruit males and females age 18+ years with a confirmed diagnosis of idiopathic PD of a severity of 3 or less by the Modified Hoehn and Yahr scale, assessed by a trained researcher and on a stable medication regime for greater than 3 months.

**Modified Hoehn and Yahr scale (1-3)**

Stage 1 Unilateral symptoms with minimal or no functional disability.

Stage 1.5 Unilateral and axial involvement.

Stage 2 Bilateral symptoms without impairment of balance

Stage 2.5 Mild bilateral disease with recovery on pull test

Stage 3 Bilateral symptoms with mild to moderate balance dysfunction but physically independent.

***Exclusionary criteria:***

A rating greater than 3 on the Modified Hoehn and Yahr scale or no physician diagnosis of PD. Non-community dwelling residential status. Currently participating in greater than 150 minutes of moderate to high intensity exercise training (defined as aerobic, resistance or HIIT). Individuals with secondary PD or other progressive neurological disease. Unstable medical conditions that would preclude individuals from exercising. Known diagnosis of current or past coronary or cerebral artery disease, symptomatic peripheral vascular or other medical conditions precluding exercise: e.g., congestive heart failure, untreated aneurysms, cardiac arrythmias including atrial fibrillation, moderate-to-severe pulmonary disease, advanced renal disease or permanent non-ambulatory status, retinopathy or history of retinal detachment, a diagnosis of dementia or significant cognitive impairment as defined by a score less than 19 on the Montreal Cognitive Assessment (MoCA) indicating difficulties in aspects such as memory, communication and ability to focus, medications that could indicate treatment of dementia, medications that could affect neurological function and safety including but not limited to anti-psychotics, sedatives-hypnotics or narcotic analgesics, as determined by the study physician assessment. Current musculoskeletal injuries, conditions, or limitations (e.g., muscle strain/pain and joint instability) of the lower body (i.e., ankle, knee, or hip joints), or current lower back pain. Symptoms consistent with current major depressive episode, suicidality, psychosis, or active substance use disorders, as defined by the Diagnostic and Statistical Manual, version 5R (DSM-5R). Recurrent falls. Non-ambulatory status (use of walker or stick allowed). Terminal or rapidly progressive illness.

## Section 8.6: SCREENING.

Potential participants who express interest in the study after seeing promotional materials through PD support groups, older adult exercise facilities or through social media will be given a phone number and email to contact a research team staff member to learn more about the study. Research staff will first email people who are interested in this study a Participant Information Statement (PIS) and then arrange a phone call to perform an initial telephone screen. A series of brief questions are included, which is considered the initial screening (Stage 1). After completion of this initial assessment and review by research staff to decide if the person is potentially eligible and they are interested, the participant will then be invited to the baseline assessment process and be scheduled to present at the Susan Wakil health building at the University of Sydney, Camperdown campus.

The Stage 1 Screening Form will include:

1. A further description of the study
2. Confirmation that the person understands and is willing to answer a few questions about their health status/eligibility
3. Questions related to the diagnosis of PD and their current Hoehn and Yahr score
4. Demographic information, marital status, educational level, occupation history
5. Place of residence
6. Known diagnosis of current or past coronary or cerebral artery disease, symptomatic peripheral vascular or other medical conditions precluding exercise: e.g., congestive heart failure, untreated aneurysms, cardiac arrythmias including atrial fibrillation
7. All chronic diseases including a diagnosis of dementia or current medications that would indicate treatment of cognitive impairment
8. Current medications, including alcohol or drug use, Parkinsonian medications or other neurological symptoms
9. Current or previous musculoskeletal injuries that would limit exercise, recent surgeries and fractures, and their current stability
10. Current exercise history
11. Terminal or rapidly progressive health condition
12. Ambulatory status and fall history over past 12 months
13. Level of functional independence and activities of daily living
14. Intention to reside in the greater Sydney area for the next 3 months
15. Willingness to participate in the study assessments and intervention protocols
16. Participant signs participant consent form
17. Contact details of current GP or medical specialist(s) so that research staff can prepare a permission form allowing us to contact them for medical information if needed, as well as to send the results of any pertinent medical tests or information we elicit during assessment and intervention protocols. This permission form will be signed by the potential participant at the time of their first presentation to the Susan Wakil health building, and then faxed or emailed/mailed to the relevant practitioner to keep in their medical records
18. Reason for ineligibility, on-hold status, or disinterest in the study
19. Potential participants who are interested but currently unable to participate due to unstable disease or symptoms, or recent surgery will be placed on hold, and contacted again to determine interest and confirm eligibility

After review of this form by the research team, and the team agrees to allow the participant to move to the next stage, they will be contacted and be asked to proceed to the initial assessment. The participants will attend the Susan Wakil health building for their in-person medical screening with the study physician Prof. Maria Fiatarone Singh (Stage 2 screening). Following this, participants deemed eligible by the study physician will be formally invited to join the study and will immediately begin the first day of assessments with two more subsequent assessment days scheduled over the next two weeks.

Participants deemed eligible and who consent to join the study are required to complete a release of information form. This form will request their permission to share relevant information with their GP or specialist/s. Following this consent, a letter will be dispatched to the GP/specialist notifying them of the participants involvement in the study and requesting any pertinent medical information deemed necessary, based on the outcomes of stage one or two screening assessments.

## Section 9: INTERVENTIONS

***Baseline assessments, familiarisation, and* *Initial Testing Sessions (3 visits over two weeks).***

***Assessors will be blinded to outcomes and data analysis.***

## Section 9.1: Initial assessment visits

**(Stage 2 screening day and a further 2 separate days).**

During the Initial assessment phase, research staff will discuss with participants the history and progression of their Parkinsonian symptoms with a focus on freezing, rigidity, balance issues, falls, current medication regime and peak time of medication on/off effect on symptoms and exercise interactions with Parkinsonian symptoms. All measurements will be performed at a time of optimal medication effect as defined by the participant, and the time of day and time of last PD medication dose will be recorded on the assessment form.

***Assessment day 1***

***Cognitive impairment***:

Cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA). The MoCA evaluates multiple cognitive domains including attention, executive function, memory, language, visual constructional skills, conceptual thinking, calculations, and orientation. The tool consists of 13 subsets and yields a total score ranging from 0 to 30, with a high score indicative of better cognitive function. A score below 26 is generally considered to signal cognitive impairment and the assessment is utilised to identify mild cognitive dysfunction and track cognitive changes over time.

***Brain derived neurotrophic factor and other PD biomarkers***:

Blood samples will be collected from participants for future analysis of specific biomarkers, Brain Derived Neurotrophic Factor (BDNF), alpha synuclein, and other cytokines and inflammatory markers, key indicators in understanding PD progression/response to the exercise intervention. Participants will fast for 12 hours prior to collection. For serum samples SST tubes will be utilised, whilst EDTA tubes will be utilised for plasma samples. These samples will be aliquoted into separate samples and frozen at -80 degrees Celsius storage, pending the acquisition of adequate funding to facilitate bioanalytic examination of potential correlations with PD pathology. These samples will be collected by the SWHB clinical registered Nurse attached to the level 5 clinic space.

***Orthostatic blood pressure:***

Participants will initially be in a supine position for 5 minutes after which their baseline blood pressure and heart rate will be measured. Subsequently, the participant will stand, and measurements will be repeated at 1- and 3-minutes post standing. Orthostatic blood pressure will be evaluated using a standard sphygmomanometer and stethoscope and any symptoms recorded. A significant drop in systolic pressure (>20mmHg) and diastolic pressure (>10mmHg) upon standing is indicative of orthostatic hypotension. This assessment serves to evaluate cardiovascular responses to postural change.

***Gait Speed Test:***

Habitual gait speed will be measured over a straight path of 4 meters and a 2-meter deceleration lane following the 4-meter path. Participants can use any habitual assistive device if relevant. For the test of habitual gait speed, participants will be asked to walk at their normal and comfortable speed. For the maximal gait speed test, the participants will walk for four meters as fast as possible without breaking into a run, with a 2 metre acceleration/deceleration stage. The instructions will be “One-two-three-GO!” to prompt maximal effort. The same footwear will be required across all assessment timepoints.

***Functional Performance (Short Physical Performance Battery):***

Functional performance will be measured by the Short Physical Performance Battery (SPPB). The SPPB measures lower limb function across three domains: static balance, gait speed (inclusive of acceleration phase) and strength. Each subset scores 0-4, with a total of 12 points, a higher score indicating better function.

***The Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS UPDRS):***

The (MDS UPDRS) is a comprehensive tool employed by trained clinicians to evaluate the severity of PD symptoms measuring both motor and non-motor symptoms and is divided into four parts. Researchers will utilise both Part II & Part III only in the assessment process.

1. Non-Motor Experiences of Daily Living: Assesses mental functioning, mood, and social interactions through patient and caregiver questionnaires
2. Motor Experiences of Daily Living: Covers motor aspects during daily activities, based on patient reports and caregiver observations
3. Motor Examination: Performed by a trained clinician, this section measures motor function, such as bradykinesia, rigidity, and tremors
4. Motor Complications: Evaluates medication-related motor fluctuations and dyskinesia

A high score is an indication of greater impairment or more severe symptoms. Each of the four parts of the scale has its own scoring system, and these scores are generally summed to provide a total score that represents the overall severity and impact of the disease on the individual's life. A lower score is generally considered to be better, signifying fewer or less severe symptoms.

***Maximal oxygen consumption test: (VO2 peak)***

An incremental ramp protocol will be conducted on a cycle ergometer with 12-lead electrocardiogram (MGC Diagnostics Corporation, USA), and automated blood pressure cuff measurements (Suntech medical, Morrisville, N.C, USA). Participants will be instructed to aim for an RPM of 50 revolutions/minute. After a 5-minute warm up they will begin the protocol at a predetermined load (Watt/kg body weight). The resistance of the flywheel will be increased so that the workload increases in increments of 10-25 Watts every 60 seconds until the participant reaches a state of volitional fatigue or until other established criteria for maximal effort are met. These may include a plateau in oxygen consumption despite an increasing workload, achieving a heart rate within 10 beats of the predicted maximum for their age, respiratory exchange ratio of >1.1, or a RPE greater than 18/20 (Borg scale). Prior to the onset of the assessment, participants will be familiarised with the Borg (6-20) RPE scale, which is a self-reported measure of intensity ranging from 6 (no exertion) to 20 (maximal effort). Integrating heart rate data with RPE enables researchers to precisely customise exercise interventions to facilitate potential intervention outcomes whilst ensuring participant safety. Heart rate, ventilatory and metabolic data will be collected and measured by Medgraphics Ultima CPX breath by breath metabolic cart (MGC Diagnostics Corporation, USA).

***Assessment day 2,***

***One-repetition maximum (1RM) testing:***

Muscular strength assessment will be performed by a 1RM for the lower body using the leg press and upper body using the chest press, in that sequence. Keiser A420 pneumatic resistance training equipment (Keiser Sports Health Equipment, Inc., Fresno, CA 93706, USA) will be used. Prior to attempting heavier loads, a warm-up of 2-4 repetitions with a light load will be performed followed by approximately 2 minutes rest. When lifts beyond an RPE of 15 are attempted, if successful, another lift will be attempted with a heavier load with approximately 1-minute rest between attempts. This will be continued until the participants are unable to complete a lift in good form to full unweighted range of motion twice (i.e., they must fail twice at the highest attempted load), with the 1RM being the heaviest load that was successfully lifted once with good form. The 1RM test will be repeated twice 1 week apart, with the higher of the two values recorded as the baseline 1RM.

***6-Minute Walk Test:***

Functional capacity will be evaluated using the six-minute walk test. To reduce instances of freezing of gait that is associated in PwP, participants will perform the walking test in an open outdoor space designed to minimise turning and associated freezing episodes. The goal is to cover as much ground as possible, by walking as fast as possible without running. Participants will be allowed to stop to rest, if necessary, but they will be asked to resume walking as soon as possible*.* Periods of stopping and freezing episodes will be recorded, as well as any other symptoms. Heart rate will also be collected at the beginning and the end of the test. Standard protocol includes verbal prompting to encourage maximal effort every 30 seconds as well as time checks every 2 minutes. The distance is recorded to the nearest cm using a rolling trundle wheel.

***Assessment Day 3***

***One-repetition maximum (1RM) testing, (retest):***

The maximal strength assessment will be repeated one week later after the initial testing. A subsequent repeat strength assessment may provide a more accurate assessment of the individual's true maximum strength due to various factors such as participant unfamiliarity with the equipment or the specific movement, psychological factors, or sub-optimal physical conditions on the day of the initial test. The assessment process, equipment, data collection and protocols will replicate the initial strength assessment.

***Muscular power testing:***

Muscular power will be evaluated on the day of the second 1RM test, after a rest period of at least 1 hour during which non-exercise assessments are carried out, using the same resistance equipment as the initial maximal muscular Strength Assessment (1RM). Muscular power will be measured for the upper body using the chest press and lower body using the leg press, in that sequence. Prior to the power tests, participants will engage in a warm-up phase involving two light loads (lowest resistance on the machine) at maximal velocity to prepare the neuromuscular system for the assessment as well as to assess maximum velocity. During the test participants will perform explosive movements with strong verbal cueing to push as fast as possible against resistances ranging from 20% to 100% of the previously determined 1RM, at 10% increments, with rest intervals of at least one minute between trials. The average power output and average velocity across the concentric phase at each load will be recorded using the chip system of the A420 electronics. The peak velocity, peak power achieved and the percent of the 1RM at which this was achieved will be recorded.

**End of baseline assessments.**

On the completion of all the above assessments, participants will be randomised into one of two groups. Should the participant be allocated to the control usual care group, the participant will have completed the initial baseline testing as above and then is free to leave. Should the participant be allocated to the exercise experimental protocol, they will engage in the following final stage of assessment process.

***Familiarisation:***

The group randomised to the exercise intervention during the final portion of the last testing day will acquaint themselves with the array of assessment tools and equipment including the combined arm and leg ergometer (Rogue Echo).

***Anaerobic capacity testing:***

Participants randomised to the intervention will undertake a 60-second anerobic capacity test on a combined arm and leg ergometer (Rogue Echo). Power output will be continuously recorded for each 10-second time point during this effort. The individualised workloads for the subsequent HIIT experimental protocol will be calculated based on 85% of the overall mean power output across the entire 60-second test. This approach enables the customisation of the HIIT protocol to suit each participant 's exercise capacities while ensuring optimal safety.

**Regardless of which group the participant is randomised to, they will participate in the following.**

***Weekly status check:***

A structured weekly status check will be implemented at the end of each week of the exercise intervention component, capturing details on any recent medical or allied health consultations, medication changes, changes in physical activity levels, acute illnesses or new symptoms of any kind, any hospitalisations, any falls, and variations to current Parkinsonian symptoms.

***Medication changes throughout study period:***

During the study duration, a detailed record of all medications and dosages, and subsequent alterations in medication regime will be tracked for each participant, facilitating a clearer interpretation of study results, factoring pharmaceutical influences on physiological measurements taken during the study period.

## Section 10: Exercise intervention protocol:

## Section 10.1:Randomisation

Participants will find out if they are allocated to the intervention or control group following the conclusion of all screening, and initial assessment and testing sessions (assessment day 3). The allocation will be determined by a block randomisation method utilising various randomly permuted block sizes of < 4, to ensure balanced representation and prevent predictability of the allocations. ([www.random.org](http://www.random.org)). Allocation to randomised groups will be implemented by a person not involved with the project who will prepare sequentially numbered opaque envelopes with the sequence allocation sealed inside which will be handed to each participant to open at the completion of all baseline testing.

## Section 10.2: Intervention protocol:

***Control Group and Exercise Intervention (24 visits)***

The intervention will consist of three days a week of training (Monday, Wednesday, and Friday) spread over 8 weeks at the University of Sydney campus Susan Wakil health building research spaces. All sessions will be supervised by accredited exercise physiologists. Participants will be randomly allocated to one of two groups:

1. Control group or usual care.
2. HIIT group.

**Usual care** will be defined as no participation in any form of moderate or high-intensity exercise (aerobic or progressive resistance training) or HIIT. Standard or routine medical or pharmacological management of PD symptoms, medical appointments with health care providers (this may include physiotherapy, occupational therapy and other allied health practitioners excluding new regular structured physical activity), general advisory support (this may include nutritional and hydrational support, mobility support), observational/symptomatic support (Parkinsonian symptom support without addition of new treatment of physical/pharmacological intervention, no change in medication for 3 months).

Usual care physical activity will be defined as any standard exercise regimen (at community exercise facilities or via home-based online platforms), designed to maintain current functional status and capacity. This can include community PD specific classes, generally taught by trained exercise physiologists, physiotherapists, or personal trainers. Other modalities might include balance training, PD warrior classes, yoga, tai chi, Pilates, stretching and flexibility training. These structured exercise sessions must be present before the start of the study, and not newly initiated during the study. Any engagement in these activities will be recorded on the weekly status checks.

**HIIT protocol.**

Participants enrolled in the HIIT group will undertake an eight week/thrice-weekly exercise program (Monday, Wednesday and Friday) with a total of 24 sessions. The target intensity of the sessions will be individually prescribed at 85% of mean power output as calculated from the participants individual initial 60-second anerobic capacity assessment. A RPE of 15-18 (hard to very hard), Borg (6-20) scale will also be utilised to assist in prescribing adequate doses of HITT. The Borg (6-20) RPE scale serves as a subjective yet robust and reliable measure for gauging exercise intensity in HIIT. Aligning well with the high-intensity bout characteristics of typical HIIT protocols, this approach enables individual tailoring of exercise participant intensity, thereby accommodating variations in clinical disease and subsequent fitness levels and, day-to-day physiological fluctuations. Moreover, concurrent use and coupling of RPE in conjunction with objective measures like power output and heart rate can offer a more comprehensive understanding of exercise intensity, enhancing both interventional effectiveness whilst maintaining optimum safety of participants. Training will be conducted on a mechanically coupled combined arm and leg air braked ergometer (Rogue Echo).

Each training day will be separated by a rest period of at least 24 hours between sessions.

1. **Warm up phase**: 5 minutes of gentle warm-up at an RPE of 9 Borg scale (6-20).

2. **HIIT Phases**. (two sets). Each set consists of four intervals, followed by an active/passive rest period as follows.

**Session structure:**2 sets of 4 x 60-second intervals.

**Intensity:**RPE ranging between 15-18 Borg (6-20), classified as hard to very hard, the beginning of the interval starts as hard, 15 Borg (6-20) and at the completion of the interval the aim for workloads will be very hard, 18 Borg (6-20).

**Power output:**Work rates (watts) during each interval will be at approx. 85% of mean power obtained during a 60-second anerobic capacity test. Work intensity is solely determined by the speed of the fan, thus, participants who are observed to be exerting either too much or too little effort will be advised to adjust the revolutions per minute (RPM) either by accelerating or decelerating the pedal/handle speed.

**Intra-set recovery:** Each high-intensity bout will be followed by a 3-minute recovery phase, comprising both active and passive elements. The initial minute will involve cycling on the Rogue Echo at an effort of 9 (6-20) Borg scale, serving as active recovery. For the subsequent 2 minutes, participants will be seated on the ergometer whilst being closely monitored for cardiovascular and perceptual response parameters to ensure adequate physiological preparation for the next upcoming interval.

**Inter-set recovery:** Post completion of the first set of 4 x 60-second intervals, participants will engage in a prolonged recovery period of passive resting lasting 10 minutes, consisting of quiet resting sitting in a chair. Physiological metrics consisting of heart rate, blood pressure and RPE will be monitored and recorded throughout this period. After this recovery period, the participant will complete another 4 x 60-second intervals, with all testing and data collection replicating the initial first rounds of intervals.

The entire session will have a duration of ~40 minutes and is organised as follows; an initial 5-minute warm-up will proceed the first set of 4 intervals. This round contains 4 x 60-second acute high-intensity intervals. These intervals are interspersed with three minutes of active/passive recovery phases, amounting to 13 minutes per set. Between the two sets a 10-minute passive recovery phase will be implemented. Subsequently another set of 4 x 60-second high-intensity intervals, interspersed with three minutes of active/passive recovery phases will be repeated amounting to 13 minutes per round. This will be followed by an active/passive cool down of 5 minutes.

## Section 10.3: Measurements during experimental sessions:

***Both intervention and control group will have the following assessment during the 8-week study period.***

***Weekly status check:***

A structured weekly status check will be implemented at the beginning of each week of the exercise intervention component, capturing details on any recent medical consultations, medication changes, changes in physical activity levels, any hospitalisations, and variations to current Parkinsonian symptoms. Throughout the study duration, researchers will track specific details of when participants take their Dopamine agonist medications and doses. Additionally, PD motor symptoms, particularly “on/off” stages denoting medication peak effectiveness will be monitored to facilitate periods of improved motor control and function, aimed at augmenting the efficacy of the intervention and participant safety.

***Intervention only group.***

Any symptoms will be recorded, as well as whether they used both arms and legs during the exercise intervention, and whether any freezing episodes occurred.

***Rating of Perceived Exertion (RPE)***

Relative physiological and psychological responses to work demands induced, will be measured using the Borg RPE scale. Participants will be familiarised with the Borg scale prior to the experimental sessions (Borg, 1985) during the VO2peak test.

***Blood pressure/peripheral haemodynamic response to exercise:***

Blood pressure will be monitored utilising a standard sphygmomanometer before the start of each exercise session, and during the passive rest period prior to commencing the next imminent interval, during the 10-minute recovery inter cycle rest period at minute 1, 5, and 9 prior to recommencing the 2nd set. This series of haemodynamic monitoring will be repeated during the 2nd set of intervals also during the cooldown period.

***Heart rate***

Participants will have their heart rate recorded continuously throughout the entire protocol including pre exercise, during exercise, during intra round recovery and cool-down phases recovery via a heart rate monitor (Polar Electro Oy, Kempele, Finland) (i.e., watch and chest strap). Heart rate response will be recorded throughout the exercise bouts continuously, with data downloaded for later analysis, and data reported as both the average over each minute of the protocol, as well as at the end of each minute of exercise or rest, and recovery.

## Section 11: ETHICAL CONSIDERATIONS

## Section 11.1: Ethics approval

Ethics approval will be sought from the University of Sydney Human Research Ethics Committee in November 2023.

This study will be conducted in full conformance with principles of the “Declaration of Helsinki”, Good Clinical Practice (GCP) and within the laws and regulations of the country in which the research is conducted. This study will also meet the recommended requirement for an ethical clinical study suggested by Emmanuel and colleagues (2000).

## Section 11.2: Scientific validity

This study has been designed with thorough rationales, scientific objectives, and methods. Testing protocols have been prepared, and the research staff responsible for the testing sessions will have adequate time to practice before performing the tests.

## Section 11.3: Social and scientific value

The information gathered from this interventional experimental study has the potential to further our understanding of the relationships between higher doses of physical activity performed on this novel modality of combined arm and legs exercise and its ensuing effects on motor and non-motor symptoms. This information is vital for future precise and accurate dosage of prescriptions of physiological stressors in clinical exercise physiology, particularly the neurodegenerative disease process.

## Section 11.4: Favorable risk benefit ratio

In accordance with Declaration of Helsinki and Good Clinical Practice (GCP), the well-being of the individual research participant will be the priority. Before participating in this study, interested adults will meet with researchers to complete a demographic, health, and basic exercise history questionnaire. If they meet inclusion/exclusion criteria, are deemed medically fit and agree to participate in this study, then they will be invited to attend an initial medical screening with the study physician Prof. Maria Fiatarone Singh to assess eligibility and safety for the study. The “Adverse Event Management Plan” has been developed for any researcher involved in this project to follow. It is believed that the risks undertaken in this research are minimal and are far outweighed by the information gained by developing a better understanding of the physiological adaptations to this novel modality of physical work and its ensuing effects on Parkinsonian symptoms and subsequent quality of life in PwP. Furthermore, the outcomes of this interventional study could have implications for serving as an adjunctive treatment strategy aimed at addressing the burden associated with neurodegenerative disease.

## Section 11.5 Informed consent process

During each stage of the screening and assessment process, participants will be informed of the purpose of the screening, and what will happen to their data. Participants will be provided with a Participant Information Statement (PIS), outlining all the procedures of the study, and what their participation will involve. The PIS will outline any potential risks, and benefits of the study. Participants will be made aware that participation is voluntary, and that they are free to withdraw at any time, without any effect on their relationship with the University of Sydney. Participants will consent to the study by signing the Participant Consent Form.

## Section 11.6 Participant reimbursement

There will be no participant reimbursements. Parking is provided without charge.

## Section 11.7 Monitoring of clinical trial

We will have weekly in-person case-conferences with the research team to discuss all participants and their progress and health status.

## Section 11.8 Respect for potential and actual participants

Participants will be allowed to withdraw from the study at any point in time without any explanation and without prejudice. It is the duty of research staff who participate in this project to protect the integrity, privacy, and confidentiality of personal information of research subjects. An identification code will be used to identify participants. The identification code will be created by the study chief investigator and these details will not be shared with the rest of the research team. This will be done to help explain potential outliers of results pertaining to the study. Data gathered will be entered by the research staff into REDCap Digital which is a secure web application hosted by The University of Sydney for building and managing databases.

To protect gathered information from the participants, the researchers will not store any hard copy material generated during this study. Any paper material will be scanned to and entered in REDCap and destroyed securely. Electronic copies of information will be stored in two places:

1. Study materials will be stored on the University’s Research Data Store (RDS) during the project. The RDS is a secure, enterprise-grade Network Attached Storage device located within NSW. Researcher Dashboard (DashR) will be used to store contact information, progress databases, digital copies of consent forms, medical letters, and correspondence and manuals of procedures and a complete copy of the data from the study. This is a password protected server only accessible to researchers involved in the project. All documentation will be password protected.
2. Study materials will be stored on the University’s licensed version of REDCap during the project. The REDCap project is named “HIIT in PD” REDCap is an online data capture tool that stores data on secure servers within NSW. All data entered into the database will be stored on a secure server of the University of Sydney. As such, no project data is ever transmitted at any time by REDCap to another institution. Access to the database will be provided only to research staff working on the study. User privileges will be used to limit the viewing and/or editing access that research members have within the database. This also minimises the number of people that can view each section of the database. All these access rights will be managed by the Chief Investigator.

The researchers will not store any hard copy material generated during this study. Any paper material will be scanned to and entered in REDCap or the chief investigator’s RDS site and destroyed securely. Study materials will be stored on the University’s Research Data Store (RDS) at the completion of this project. All study materials will be retained for 20 years. Data will be deleted from RedCap Digital upon the completion of the storage period. Published results will be summarised as average data for all participants and no individual data will be published or presented.

Participants have a right to receive feedback about the overall results of this study. If they want to receive feedback or discuss their performance, research staff will provide a brief 1-page lay summary.

## Section 11.9 WITHDRAWAL/TERMINATION

Participants will be allowed to withdraw from the study at any point in time without any explanation and without prejudice. The following content have been presented in the Participant Information Statement:

*“Participation in this study is completely voluntary. You are under no obligation to participate. Your decision will not affect your current or future relationship with the researchers or anyone at The University of Sydney.*

*If you decide to take part in the study and then change your mind you can withdraw by contacting Dr Daniel Hackett via email (daniel.hackett@sydney.edu.au).*

*If choose to withdraw, we will not collect any more information from you. Please let us know at the time you withdraw what you would like us to do with the information we have collected about you up to that point.”*

The date and reason for withdrawal from the study will be recorded in REDCap.

## Section 12: SAFETY CONSIDERATIONS

## Section 12.1 ADVERSE EVENTS

Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

AE: Any untoward or unfavourable medical occurrence in a participant, including any abnormal sign or symptom that is temporally associated with the participants’ involvement in the research, whether considered related to participation in the research.

SAE: Any adverse event that:

* Results in death
* Is life threatening, or places the participant at immediate risk of death from the event as it occurred
* Requires or prolongs hospitalisation
* Causes persistent or significant disability or incapacity
* Is another condition which investigators judge to represent significant hazards

At the start of the study, all participants will be screened with the exercise and sport science screening form. This will screen out people with unstable conditions, and they will be told that they are unsuitable for the trial and referred to their general practitioner if warranted.

All staff working with participants have current first aid and CPR. There are first aid kits and an automatic defibrillator in the research space being used (level 5) where all assessments and study interventions will be implemented. All research staff are accredited exercise physiologists.

All SAE will be reported to the approving HREC as per their usual procedures.

The following procedure (table below) is designed for research staff involved in this project to be followed in the case of chest pain, acute injury, non-specific symptoms or pain, or an AE that may be associated with any activity involved in the study.

|  |  |
| --- | --- |
| **Event** | **Procedure** |
| **Chest Pain** | During exercise, a participant may report pain in their chest. This may be due to angina, or other non-serious issues such as rib pain or pain in the chest muscles.  1.If they are having chest pain or other cardiac symptoms, the emergency management plan will be followed, which involves calling 000.  2.The the study coordinator Dr Daniel Hackett will be notified of the event for reporting purposes (HREC and Riskware) immediately by email or telephone. |
| **Fall** | If a participant has a fall, all exercise will be stopped. The Study Coordinator Dr Daniel Hackett will be notified on 0424 133 724 for reporting purposes. If they report pain, or any symptoms, they will not continue with the session and the emergency management plan will be followed (i.e., calling 000).  Any fall with (i.e., head strike, unconscious) or without an injury will be reported in Riskware within 48 hours. Any injury may need to be reported to the HREC. |
| **Acute Injury** | If a participant reports a sudden or immediate pain or injury, exercise will be stopped immediately. The acute care guidelines for an injury below will be followed:   1. Rest 2. Ice 3. Compression 4. Elevation   The Study Coordinator Dr Daniel Hackett will be notified of the event immediately by email or telephone for reporting purposes (HREC and Riskware). |
| **Pain or other symptoms** | If the participant reports any new-onset symptom such as pain in their muscles or joints, dizziness, abnormal fatigue etc. the exercise will be stopped. It will be determined if it is OK for the participant to continue.  The participant will be asked to describe the pain.   1. Is it sharp, dull, ache, burning etc. 2. Is it constant/persistent or intermittent? 3. Does it come on during the exercise or after? 4. They will be asked to rate the pain out of 10   If pain persists or worsens, even after steps are taken to mitigate the pain, the exercise session will be stopped. Emergency services will be called if pain persists.  Dr Daniel Hackett will be notified of these symptoms, to determine if these exercises can continue in the future. |
| **Cardiopulmonary Resuscitation (CPR)** | All staff working with participants will have current first aid and CPR qualifications. There is a first aid kit and an automatic external defibrillator (AED) in the research space where the HIIT exercise session will be delivered. The SWHB emergency management plan for medical emergencies will be followed.  CPR is most successful when administered as quickly as possible. The DRSABCD table will be followed. Briefly, CPR will only be performed when a person shows no signs of life or when they are:   1. unconscious 2. unresponsive 3. not breathing or not breathing normally   If unsure whether a person is in cardiac arrest or not, CPR should commence. If a person does not require CPR, they will probably respond to attempts when researchers commence. By performing CPR, it is unlikely to cause any harm to the person if they are not actually in cardiac arrest.  The Study Coordinator Dr Daniel Hackett will be notified of the event immediately by email or telephone for reporting purposes (HREC and Riskware). |
| **Health check before each session.** | All participants will be asked to report their health status since their last visit. The status check asks for any new symptoms that the participant has experienced or changes in their overall health. If they report a new injury, a fall or emotional or physical symptoms, these may require reporting as adverse events, even if they are unrelated to the intervention.  Any report of a new injury, hospitalisation, or other serious event will be reported to the study coordinator Dr Daniel Hackett immediately and recorded in Riskware. |

## Section 12.2: RISKS OF THE STUDY

Outlined below are possible risks associated with the assessment and acute interventions.

The exercise familiarisation, testing and acute study may cause some muscle soreness and fatigue. There is also a small risk of musculoskeletal soreness or injury during physical function tests. Mental fatigue and psychological distress may also accompany testing. Participants will be closely supervised by trained and experienced exercise physiologists during all testing procedures. To minimise these risks, we will carefully monitor participants throughout the testing to maximise their safety. Exercise intensity will be monitored throughout all training sessions via continuous monitoring of RPE, heart rate, blood pressure and close monitoring of signs and symptoms. The acute session will be terminated prematurely if a participant shows signs of any discomfort. Adverse events during testing and exercise will be immediately reported to HREC.

## Section 13: DATA MANAGEMENT

**Section 13.1 Data Collection**

An identification code will be used to identify participants. The identification code will be created by the study chief investigator and these details will not be shared with the rest of the research team. This will be done to help explain potential outliers of results pertaining to the study. Data gathered will be entered by the research staff into REDCap Digital which is a secure web application hosted by The University of Sydney for building and managing databases.

The researchers will not store any hard copy material generated during this study. Any paper material will be scanned to and entered in REDCap or the chief investigator’s RDS site and destroyed securely. Study materials will be stored on the University’s Research Data Store (RDS) at the completion of this project.

**Section 13.2 Data Usage**

Published results will be summarised as average data for all participants and no individual data will be published or presented. If requested, a lay summary of the results will be provided to the participants following their involvement in the study. Also, a copy of published results can be obtained from the investigator upon request.

## Section 14: TIMELINES / MILESTONES

The table below illustrates the expected project timeline.

|  |  |
| --- | --- |
| **November 2023** | Final study protocol will be drafted, and ethics application submitted. |
| **November 2023** | Clinical Trial Risk and Governance documentation will be completed and submitted. |
| **March 2024** | Ethics and Clinical Trial Risk and Governance approval. |
| **April 2024** | Recruitment will begin |
| **Study duration: 12 months.**  **May 2024 –May 2025** | It is expected that the study will be carried out over a 12-month period. |
| **June 2025** | Publications in appropriate scientific journals and dissemination of results will be prepared in late-2024. |

## Section 15:FINANCIAL

This study will be completed by HDR postgraduate research student Philippe Jacquot. The intervention will require the purchase of another Rogue Echo ergometer.

## Section 16: PUBLICATION POLICY / DISSEMINATION OF RESULTS

Primary and secondary outcomes from the study will be published in appropriate scientific journals. All scientific papers, including authorship will be agreed upon by consensus of the study investigators.

Dissemination of results will also occur by presenting results at scientific conferences, and in presentations to the public. In addition, participants may elect to receive a one-page summary of the study findings.

## Section 17:REFERENCES

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