NCT02598973
Effect of Exercise on recovery in drug-induced parkinsonism and Parkinson's Disease
1/19/2019

CMCVAMC SPECIFIC PROTOCOL SUMMARY
Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center (CMCVAMC)
Institutional Review Board (IRB)

Instructions: Click in box and start typing or click 'choose an item' and choose the applicable entry.
NOTE: If you are using a MAC, you may have difficulty with checkboxes and "choose an item" boxes.

Section 1. General Information

Protocol Title: *Effect of exercise on recovery in drug-induced parkinsonism and Parkinson disease*

CMCVAMC Protocol Version Number and Date: *V # 7 1/11/2019*

Principal Investigator (PI) Name: *James Morley*

PI's Academic Degree(s): MD, PhD

Is the study funded? YES If "yes", specify funding agency: *VA RR&D CDA-2 Award*

Is a grant application requesting funds for the study currently being reviewed? NO

CMCVAMC is the only institution involved: NO

CMCVAMC is the coordinating center in which the PI is the lead investigator: YES If this answer is yes, complete the next two sections:

- **List the name(s) of the other site(s) involved.** *University of Pennsylvania Exercise Medicine Unit at PennPresbyterian Medical Center*
- **Provide the FederalWide Assurance (FWA) numbers for each site.**

State name of coordinating center if this is not CMCVAMC.

Describe PI's qualifications to conduct this project, and attach a copy of PI's VA or NIH biosketch. Be specific in regard to PI's research experience. *NOTE: If PI does not have any prior research experience, indicate what provisions are being made to provide oversight or mentoring.* *Dr. Morley is a board-certified neurologist and fellowship-trained movement disorder specialist with extensive experience in PD. He has a PhD in cell biology and genetics and has engaged in clinical research since residency training at Penn. He will be mentored in this career development award by Drs. Duda, Weintraub and Robinson.*

Does any research staff member have an actual and/or perceived conflict of interest with this study? NO If yes, explain.

Is this study a clinical trial? YES If yes, specify the type. Phase II

State the estimated length of time to complete enrollment of subjects. *5 years*

State the expected duration of participation by individual subjects (including any follow-up, e.g., need to re-contact subject for follow-up questions prior to closure of the study). *1 year*

Specify the projected date of completion of the study. *6/2022*

Section 2: Participating Site Specifications

2.1. **Where will the research project be conducted? (Check all that apply)**

- ☐ **VA Inpatient Setting**
- ☑ **VA Outpatient Clinic/Office**
- ☑ **VA Laboratories**
- ☑ **Participant Homes**
- ☑ **University of Pennsylvania**
- ☐ **Community Based Outpatient Clinics (CBOCs)**
- ☐ **Other *(Specify)*:**

2.2. **If research is conducted at a non-VA site, please specify where and how much of the project will be conducted at that location**.

Three study visits including treadmill exercise testing, education and set-up of remote monitoring devices (heart rate monitors and accelerometers) will take place at the Exercise Medicine Unit of the University of Pennsylvania. These visits will comprise approximately 15% of the subjects face-to-face time with study staff.

Section 3: Introduction

3.1. **Provide scientific background and rationale for study. Including summary of gaps in current knowledge, relevant data, and how the study will add to existing knowledge.**

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting approximately 1 million US adults and as many as 80,000 Veterans, representing a priority area for VA research. PD causes significant morbidity across a prolonged progressive disease course with an annual economic burden of $14 billion in the US alone(1). While dopaminergic replacement with levodopa or dopamine agonists improves symptoms, "disease-modifying" or "neuroprotective" therapies affecting disease onset or progression are lacking(2). Medical and surgical therapies are ultimately associated with motor and non-motor complications, and non-pharmacologic therapies, including exercise, are of interest as symptomatic and disease-modifying interventions. This proposal will focus on exercise as a symptomatic and potentially disease-modifying therapy in PD and related disorders.

Benefits and opportunities for exercise and rehabilitation therapies in PD

Exercise improves motor symptoms in PD

Exercise and physiotherapy have long been cornerstones of symptomatic management in PD, but convincing clinical trial evidence was limited by small sample sizes and unstandardized methodologies(3). More recently, a number of controlled trials have examined this approach. Shulman *et al.* reported a prospective, randomized single-blinded trial comparing three types of exercise (low-intensity treadmill walking, higher-intensity treadmill walking, combined resistance and stretching) in PD(4) finding improvements in gait speed in addition to cardiovascular fitness. Another study of a mixed-stage PD cohort compared tai-chi to resistance training or stretching in biweekly sessions over 6 months(5). Tai-chi and resistance training were both associated with improvements in motor scores, gait and balance, though the greatest gains in postural stability and balance were observed in the tai-chi group. A structured Cochrane Database review recently analyzed 39 exercise trials in more than 1800 PD patients and concluded that short-term (weeks to a few months) exercise interventions were associated with improvements in motor function, particularly gait and balance(6). These authors also found that there was insufficient evidence to support one exercise program as superior compared with others (7). However, aerobic walking is a particularly attractive intervention, as it requires no special equipment and can be self-administered in the home environment. A recent phase I/II trial demonstrated

the safety and feasibility of aerobic walking (8 weeks, 3 times/week) in a community setting among 45 PD patients (8). Although motor and gait measures improved, this was not a controlled trial.

Could exercise benefit other forms of Parkinsonism?

While many questions remain regarding the optimal type, timing, duration and populations to maximize benefit from exercise interventions, the balance of evidence suggests that many different exercises undertaken in a variety of settings are broadly beneficial in PD. However, little attention has been focused on the potential benefits of exercise in secondary or atypical Parkinsonian disorders that share elements of basal ganglia pathophysiology but respond poorly to dopamine replacement therapy. For example, symptoms of PD may be mimicked in drug-induced Parkinsonism (DIP), most commonly associated with dopamine receptor blocking antipsychotic (AP) drugs and antiemetics including metoclopramide(9). The overall reported incidence of DIP has varied depending on the drugs or populations studied (10) but is at least 10-20% in routine practice(11)and DIP has been described as the second most common cause of Parkinsonism in population-based studies (12, 13). Disability from DIP can be comparable to that of PD and is associated with falls and nursing home placement(14, 15).

The definitive treatment of DIP is to remove, reduce or replace the offending agent, though this is often challenging due to the severity of psychiatric symptoms that necessitated treatment with APs (16). When changing the offending agent is not possible, there is little evidence to guide therapy. A small placebo controlled crossover trial suggested that amantadine and trihexypehnidyl were equally effective in reducing parkinsonism and superior to placebo in a chronic schizophrenic population with DIP (17). Other anticholinergics, like benztropine, are used empirically but adverse effects can be limiting (particularly worsening of balance and cognition), especially in the elderly (18). Dopamine replacement therapy is the mainstay of treatment in most forms of parkinsonism, but the response to levodopa is mixed in DIP (especially when dopamine receptors remain blocked with continued AP administration) and is often withheld over concerns of worsening psychiatric symptoms including mania and psychosis(19). The impact of DIP on the care of Veterans continues to grow as AP drugs are increasingly prescribed for secondary indications including bipolar disorder and depression as well as off-label uses such as anxiety and post-traumatic stress disorder (PTSD)(20). Investigation of alternative treatments, including exercise, that do not require discontinuation of beneficial AP drugs, offers opportunities to improve care for Veterans with DIP.

Exercise as a potential disease-modifying therapy in PD

In addition to its symptomatic benefits, exercise has more recently been proposed as potentially neuroprotective(21). The capacity for exercise to modify disease progression in PD was first suggested by observations in animal models. For example, forced exercise has been shown to both ameliorate motor deficits and preserve dopaminergic terminals in rodent models of PD induced by neurotoxins (MPTP or 6-hydroxydopamine) (22-24). This effect may depend on growth factors including brain-derived neurotrophic factor (BDNF) (24), and elevation of serum BDNF is a well-described marker of exercise in humans(25). Intriguingly, BDNF is downregulated in the substantia nigra of PD brains(26), lower in the serum of PD patients(27) and was recently shown to be upregulated after 4 weeks of intensive rehabilitation in a small early PD cohort(28). Though they have not been examined directly, other biomarkers of PD risk such as apoliporoteinA1 (the major protein component of HDL cholesterol) and uric acid may be exercise sensitive and related to the effect of these interventions in PD (29). Despite these observations, concerns about whether animal models using dopaminergic neurotoxins faithfully replicate PD pathophysiology and the translation of animal activity paradigms to human exercise regimens have led to skepticism about the relevance of these findings to human disease. A recent small positron emission tomography study, however, demonstrated increased striatal dopamine receptor density in 4 early PD patients individual after 8 weeks of regular treadmill walking suggesting that exercise may be linked with dopaminergic neuroplasticity in humans(30). This hypothesis is further supported by a small randomized controlled trial demonstrating increased corticomotor excitability (measured by repetitive transcranial magnetic stimulation thresholds) after a high-intensity (body-weight supported treadmill walking) exercise intervention in 30 mixed-stage PD patients (31).

The plausibility of a disease-modifying effect of exercise in PD is further supported by epidemiologic observations that prior physical activity may influence future risk of PD. Analysis of

prospectively acquired data from over 100,000 subjects in the Health Professionals Follow-up Study and the Nurses Health Study (32) demonstrated an inverse association between both baseline physical activity at study entry and strenuous activity in early adulthood and future PD risk. However, these effects were significant only in men (p=0.06 in women). In a study of more than 200,000 subjects in the NIH-AARP Diet and Health Study, self-reported participation in moderate or vigorous activity (swimming, biking, heavy housework) was associated with significantly decreased risk of PD whether the activity was in the prior 10 years or as early as ages 35-39 (average age of study participants at PD ascertainment was approximately 62) (33). However, low-intensity physical activities were not associated with PD risk, perhaps suggesting that vigorous exercise is necessary to affect PD risk. These same authors performed a meta-analysis of 4 studies (including their own) and described an odds ratio of 0.67 (95% CI 0.56-0.80) of PD risk for individuals in the intense activity group. While these results could be consistent with disease-modification by exercise in PD, an equally plausible hypothesis is that subtle motor or mood dysfunction in the years before PD diagnosis leads to a more sedentary lifestyle explaining the inverse association between activity and disease. Prospective trials with prolonged exercise interventions and outcome measures appropriate to define disease-modification are needed to characterize this relationship.

Innovation

Prodromal cohorts to study disease modification in PD

The already heavy burden of pathology at the time of motor symptom development in PD (50-75% dopaminergic neuron loss in the substantia nigra) is frequently invoked to explain failed clinical trials of promising disease-modifying agents, suggesting the therapies were employed too late in the disease progression. This problem has led to intense interest in strategies for earlier diagnosis of PD before the emergence of motor symptoms, and evidence for such a "pre-motor" phase has accumulated in recent years (34). Detailed neuropathological analyses (35, 36) suggest that the olfactory bulb, lower brainstem, and even the peripheral autonomic nervous system, may be induction sites from which Lewy pathology spreads slowly through the midbrain and ultimately to cortical areas. In association with the progression of pre-motor pathology, a variety of non-motor symptoms including olfactory impairment (hyposmia), REM-sleep behavior disorder (RBD) and dysautonomia (constipation, urinary) often appear years or even decades before motor findings (37-40). Thus, what has been historically considered *de novo* PD actually represents a pathological process already years or decades in the making. Pre-motor features are promising biomarkers to facilitate early diagnosis but are limited because none of the prodromal features alone is specific for PD and may be seen in other neurodegenerative disorders or in the general population during aging.

An alternative biomarker for early PD is functional dopamine imaging using measures including Ioflupane I^{123} SPECT (DaTscan™, GE Healthcare) which binds avidly to striatal presynaptic dopamine transporters, and has been recently FDA-approved to distinguish PD from essential tremor with 95% sensitivity and 94% specificity (41-43). Dopamine transporter imaging (DaTI) abnormalities have also been detected in asymptomatic subjects at-risk for PD by virtue of genetic mutations in LRRK2 (44), or the combination of family history of PD with hyposmia (45), demonstrating that these methods are sufficiently sensitive to detect subclinical dopaminergic dysfunction. However, the associated cost and relative invasiveness (injection of a radiopharmaceutical) of these methods limit their feasibility as population-based screening tools. One solution is a combined “tiered” approach using simple, sensitive initial screens to identify an “at-risk” population with a higher pre-test probability of disease where more expensive or invasive specific testing might be warranted. One such example is the Department of Defense funded “Parkinson’s Associated Risk Study” (PARS) in which olfactory tests and symptom questionnaires were completed by almost 5000 asymptomatic individuals (most of whom were “at-risk” by virtue of having a first-degree relative with PD). Subjects with olfactory dysfunction (along with a subset of normal controls) were evaluated longitudinally with rigorous clinical exams and DaT SPECT (46, 47). Individuals with olfactory dysfunction were 11 times more likely to have DaT SPECT deficits and also more likely to exhibit additional non-motor features of PD including constipation and RBD, supporting tiered screening approaches to identify prodromal PD patients. However, the success of these strategies on a large scale is likely to be dramatically improved by identifying at-risk populations for screening.

*Could patients with drug-induced Parkinsonism help define an at-risk prodromal cohort for PD?*An epidemiologic study from Olmstead County Minnesota indicated a 24-fold higher risk of future PD in patients with a history of DIP(48)and a small autopsy study has shown the presence of PD-related Lewy pathology in patients who were thought to have drug-induced symptoms(49), suggesting that DIP can represent "unmasking" of underlying prodromal PD. A few recent studies have examined DaTI in patients with DIP and found abnormalities in 30-50%(50-52), suggesting the presence of an underlying degenerative disorder. Few studies have investigated a role for olfaction as a biomarker in DIP and provided somewhat conflicting evidence. In one study of 59 AP-treated patients, 15 developed extrapyramidal symptoms (EPS) and, as a group, olfaction was worse in patients with EPS(53). However, in another small study, 14 of 15 subjects with DIP had normal olfaction but the one subject with anosmia had evidence of cardiac sympathetic denervation, another early non-motor feature of PD(54). Additionally, we have recently reported an association of prodromal features including hyposmia (odds ratio 30, 95%CI 1.5-500, p=0.03) with persistent parkinsonism in DIP after AP withdrawal, suggestive of prodromal PD (55).

Taken together, these findings suggest that DIP represents a cohort of patients at high-risk of prodromal PD that may be further refined using biomarkers such as olfactory testing and DaTI. Whereas the risk of PD in a cohort of first-degree relatives is increased 2-fold (approximately 2% absolute risk in one study of 233 families) (56), the prevalence of underlying PD or a related disorder in DIP, based on epidemiologic data and DaTI abnormalities, may be an order of magnitude higher. Thus, the predictive power of screening tools including olfactory testing is likely to be even better in such an enriched population.

A trial of exercise in a prodromal PD cohort using a symptom-independent biomarker of progression

A major limitation for disease-modification trials in PD is difficulty in separating symptomatic improvement from disease-modifying effects when using outcomes based exclusively on motor measures such as the UPDRS. "Delayed-start" trial designs(57), wherein a therapy is started in two parallel groups at separate time points and disease-modification is thought to be reflected in durable separation between the groups because the delayed start subjects cannot "catch up" have been proposed as a potential solution. This design has been used in several disease-modification trials in PD using dopamine agonists or MAO-B inhibitors but remains controversial (58, 59). The effect of exercise in early PD was recently studied using a delayed start design where thirty-one subjects were randomized to 48 weeks of a supervised combination of aerobic walking and strength training or to begin the same intervention after a 24 week delay (delayed start group) (60). While both groups tended to improve with respect to UPDRS motor scores and gait assessments, there was no durable separation between the groups at the end of the study. The negative result could be due to the lack of an underlying disease-modifying effect, or, more likely, that a relatively subtle difference would require many more subjects or longer duration using the delayed start design to detect disease-modification.

An ideal biomarker to monitor disease-modification should track with disease progression but be insensitive to symptomatic effects or to direct pharmacologic effects of the therapies being tested. DaT SPECT has been demonstrated to track with PD duration (61) and other methods of dopamine functional imaging have been used as endpoints in several disease-modification trials in PD (62, 63). Despite reasonable concerns that these techniques have not been validated by direct comparison with human pathology and that sensitivity to progression has not been reported in large longitudinal cohorts(64), DaTI remains a promising biomarker for disease-modification trials in PD. We propose to test whether exercise has a disease-modifying effect in PD by employing a prodromal cohort (derived from patients with DIP) and measuring striatal dopamine transporter SPECT as a symptom-independent biomarker of progression.

Significance

AP drugs are increasingly prescribed for newly-approved indications including mood disorders and a variety of off-label uses including anxiety, mood stabilization and PTSD (20, 65, 66). For example, in a study of prescribing patterns within the VA, 168,442 of 279,778 individuals (60.2%) who received an AP had no record of a diagnosis for which the drugs were approved(20). In addition to the immediate morbidity attributable to motor symptoms in DIP, APs may act as a "stress test" for the brain revealing subclinical dopaminergic dysfunction such as prodromal PD offering the opportunity for study and

intervention at the earliest stages of disease. The study of disease-modifying therapies in general (and exercise in particular) has been limited by significant dopaminergic denervation already present at motor diagnosis of PD and lack of biomarkers to reliably measure changes in progression. The identification of a prodromal PD cohort will offer the opportunity to study exercise as a symptomatic treatment for DIP and disease-modifying therapy in PD using DaT SPECT as a symptom-independent marker of disease progression.

Section 4: Objectives Section

4.1. **Describe the study's purpose, specific aims, or objectives.**

AIM 1: To test the effect of regular aerobic exercise on motor function in DIP.
AIM 2: To test whether regular aerobic exercise influences disease progression in prodromal PD
AIM 3: To characterize the mechanism and biochemical correlates of exercise-induced changes in subjects with preclinical PD.

4.2. **State the hypotheses to be tested.**

Hypothesis 1: Short-term home exercise will improve motor function and could be an effective rehabilitation intervention in DIP.
Hypothesis 2: Exercise subjects will exhibit slower decline in quantitative DaTI, suggesting a disease-modifying effect of exercise in PD.
Hypothesis 3: The relationship of serum markers with clinical and imaging variables will suggest pathways involved in functional changes or disease modification.

Section 5: Study Procedures

5.1. **Study Design**

5.1.1. **Describe in detail the experimental design, i.e. from recruitment procedures to study closure.**

Subjects: Patients aged 40-89 with a clinical diagnosis of DIP or PD will be recruited from the PVAMC PADRECC and Behavioral Health Service (BHS) clinics.

Inclusion criteria: We will recruit subjects with parkinsonian signs (rest tremor, rigidity, bradykinesia) occurring after the institution of therapy with a medication having a known association with DIP (examples include haloperidol, chlorpromazine, fluphenazine, perphenazine, risperidone, thioridazine, thiothixene, lithium, valproic acid, ziprasidone, olanzapine and aripiprazole). Potential subjects with DIP will be pre-screened using a brief (12 item) scratch and sniff smell test with hyposmic subjects invited to learn more about the study (see script). Brief olfactory testing should be completed in 5-10 minutes. We will also invite subjects from Dr. Morley's CPPF pilot study "Degenerative nigrostriatal dysfunction in drug-induced parkinsonism" PROM#01481 who have abnormal DaT-SPECT to enroll in the present protocol. These subjects will have explicitly agreed to future contact for related studies in the ICF for PROM#01481. We may also invite subjects identified by their PADRECC provider who had DaT-SPECT (with an abnormal result) performed clinically outside of a research protocol within the prior 3 months and agree to be contacted. We will also recruit subjects with a clinical diagnosis of PD (Hoehn & Yahr (H/Y) stage ≤ 2 made by a PADRECC provider.

Exclusion criteria: 1) Subjects with a known diagnosis of, atypical parkinsonian syndromes (i.e. dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy) or other neurodegenerative condition, with the exception of PD, will be excluded; 2) Subjects with a history of sinus trauma or surgery, encephalitis, current nasal congestion or other known reason for olfactory impairment will not be screened 3) Subjects with a contraindication to DaTI (sensitivity or allergy to iodine, treatment with a drug with a significant effect on DaTscan that cannot be temporarily weaned)

will be excluded; 4) Subjects with known unstable cardiac, pulmonary, orthopedic or other conditions that would preclude safe participation in exercise training will be excluded (see below for further fitness screening prior to exercise); 5) Subjects currently engaging in exercise more than 45 minutes per day, 3 days per week will not be enrolled.

Assessments/Procedures:

Demographic/disease characteristics: Clinical variables will be recorded into a standardized template (via the computerized medical record) and will include age, gender, suspected offending agent and dose (converted to chlorpromazine equivalents(77)), psychiatric indication for which the agent was prescribed, presenting symptom duration of therapy before symptoms and duration of symptoms before enrollment. Additionally, cerebrovascular risk factors including a history of hypertension, coronary artery disease, cigarette smoking, diabetes, and obesity will be recorded.

Motor assessments: Severity of motor symptoms will be measured using the MDS-UPDRS motor score (Part 3) and assessment for the presence of tardive dyskinesia, administered by a movement disorders neurologist or trained research personnel blinded to the results of non-motor symptoms and intervention group. An additional measure of motor function will be the instrumented Timed Up and Go (iTUG) administered by trained research personnel. The iTUG is a modification of the traditional Timed Up and Go using small (watch-sized) monitors worn by subjects housing an accelerometer, gyroscope and magnetometer to allow measurements of gait parameters including arm swing and stride length, increasing its sensitivity as measure of motor function(76). The iTUG and necessary equipment are already being used in the PADRECC for an IRB-approved pilot study of quantitative motor assessment in PD. Subjects on dopamine replacement therapy will be asked to report for visits without taking their morning dose so that motor assessments will be performed in the "OFF" state.Subjects will take their medicines immediately following motor assessments so that treadmill exercise testing will be performed in the "ON" state.

Non-motor assessments: The University of Pennsylvania Smell Identification test (UPSIT) is a 40-item, forced choice, scratch and sniff test used to evaluate odor identification that has been well-validated for use in patients with parkinsonism and an associated brief smell test (12 items) is also widely used(78). The brief Montreal Cognitive Assessment, 10-item REM sleep disorder symptom questionnaire and non-motor symptom scale for PD will also be administered at baseline. The Ohio State University Traumatic Brain Injury (TBI) Identification Method (OSU TBI-ID), is a brief screening tool to elicit lifetime history of TBI that has been validated and previously used in Veterans.

Biochemical analysis: Serum uric acid and ApoA1 will be collected and reported per usual protocol by the CMC VAMC laboratory. Blood draws for BDNF will be performed at the University of Pennsylvania Exercise Medicine Unit (PENN EMU).Serum from these specimens will be analyzed for BDNF in Dr. Duda's laboratory using a human BDNF ELISA assay system (RAB0026, Sigma-Aldrich, St. Louis, MO). Mean values of triplicate determinations will be reported for each sample.

Dopamine transporter imaging: *Ioflupane I^{123} SPECT Image Acquisition:* Women of childbreaing age will undergo serum hCG the morning of the test. If the test is positive, the subject will not undergo the scan. Prior to radiopharmaceutical administration, patients will be given orally either 0.5 ml of SSKI or 1 ml of Lugol's mixed with fruit juice to protect the thyroid gland from unnecessary radioiodine absorption. Approximately one hour later, 3-5 mCi of I-123 Ioflupane will be intravenously administered as a bolus. Then, there will be at least a 3 hour radiopharmaceutical biodistribution time period, but not more than 6 hours, in order to achieve steady state within the central nervous system. image acquisition will then commence on a Siemens SPECT camera and include the following imaging parameters: low resolution/high energy collimators, 159 KeV photopeak with +/-10% energy window, 128 x 128 matrix, 180 degree circular orbit per camera head; 360 degrees total, step &shoot mode, 64 views per camera head; 128 total, camera radius 11-15 cm, dedicated head holder and acquisition of 1.5 million counts (approximately 30 minutes). Subjects will be advised to hydrate before and after being scanned and to void frequently for 48 hours to decrease bladder dose

If subjects become claustrophobic during camera placement or at any time during image acquisition, they may discontinue the study. If the subject wishes to re-attempt image acquisition, they may be offered a

single dose of a sedative medication. A study neurologist will review the subject's CPRS record for contraindications. If deemed appropriate, a single clinically appropriate dose (as judged by the study neurologist) of a sedative medication (typically lorazepam 0.5-1mg) will be ordered through CPRS and administered by the study neurologist. Subjects will be monitored by study staff for any adverse effects or sedation and will not be allowed to depart until cleared by a study clinician. If a patient drove or took public transportation to the study visit, they will be observed to make sure any effects of the sedative medication that could affect driving or taking public transportation have worn off. We feel the risk/benefit ratio of offering a sedative is reasonable because the subject would have already been injected with the radioactive tracer. In more than 65 of these scans performed to date, only one subject has become claustrophobic. Certain medications, primarily antidepressants and amphetamine derivatives, can interefere with DAT-SPECT. If an otherwise willing and eligibile subject is taking one of these drugs, we will ask permission to contact the prescribing provider. If the prescribing provider thinks it is safe, we will provide the subject with instructions to wean off and on (if indicated) and hold the medication for the number of days (ranging from 2 to 8) indicated in the table below (adapted from Kagi (2010) *J Neurol Neurosurg Psych*; 81:5-12). Communication with providers will be documented and maintained with study regulatory documents.

Drug	Days to be stopped prior to DAT-SPECT
Venlafaxine	3
Paroxetine	5
Citalopram	8
Escitalopram	8
Duloxetine	3
Fluvoxamine	5
Sertraline	6
Imipramine	5
Ziprasidone	2
Memantine	5
Amantadine	6
Cocaine	2
Amphetamine	7
Methylamphetamine	3
Methylphenidate	2
Dexamphetamine	7
Mazindol	3
Modafanil	3
Bupropion	8
Benztropine	5

DVR Determination: Quantification of SPECT dopamine transporter is determined using distribution volume ratios, DVR's. Essentially, a DVR can be thought of as a punch biopsy of neuroanatomical location. In keeping with previously published TRODAT imaging analysis, average counts per millimeter cubed will be obtained for seven volumes of interest (VOIs), the same obtained from each data set in prior publications: [1] Right Caudate Nucleus (RC), [2] Left Caudate Nucleus (LC), [3] Right Anterior Putamen (RAP), [4] Left Anterior Putamen (LAP), [5] Right Posterior Putamen (RPP), [6] Left Posterior Putamen (LPP) and a cortical background value (Right Superior Parietal Lobule, RSPL). Cerebellar VOIs may also be used in keeping with prior studies. Both cortex superior to the level of the basal ganglia and cerebellum are appropriate as reference regions as they have very low concentrations of DAT. VOIs will be determined using in-house developed software based on the Siemens platform. VOIs will be defined using the corresponding low dose CT images for anatomical localization. Mean distribution volume ratios (DVR's) will be calculated of each striatum VOI relative to cortical background using the following formula : DVR= (VOI−Reference Region)/Reference Region. For

comparison, Similar ROIs will be quantified using DaT-quant automated analysis (GE Healthcare) and MIMNeuro (MIM Software).

All subjects receiving I-123 Datscan will be older than 18, as our inclusion criteria specify recruiting only subjects 40 years and older. Each dose administered to subjects will be recorded as part of the CRF and any doses previously received by subjects recruited from Dr. Morley's CPPF pilot protocol will also be documented. For subjects recruited from the CPPF protocol, we anticipate that their scan from the pilot protocol will also serve as their baseline scan for the present study. If more than 3 months have elapsed since the pilot study scan, subjects will be asked to complete a new baseline scan for the present study as well as the post-intervention phase scan 12 months later (3 scans over 15 or more months).

The effective radiation dose from I-123 Datscan is 0.021-0.024 mSv/MBq, or 0.078-0.09 Rem/mCi. The effective dose resulting from our typical dose of 185 MBq (5 mCi) 123I-ioflupane administration is 0.39-0.45 Rem in adults (JOURNAL OF NUCLEAR MEDICINE • Vol. 53 • No. 1 • January 2012. SNM Practice Guideline for Dopamine Transporter Imaging with 123I-Ioflupane SPECT 1.0).

The lungs and the liver are the organs that receive the highest radiation dose from I-123 Datscan, with effective dose equivalent of 0.031-0.035 mSv/MBq, or 0.115-0.131 Rem/mCi. Our typical dose is 5 mCi, which is 0.575-0.655 Rem for lungs and liver. (Eur J Nucl Med Mol Imaging, 2009, EANM procedure guidelines for brain neurotransmission SPECT using 123I-labelled dopamine transporter ligands, version 2).These are well below the limits of 3 Rem for whole body and 5 Rem for a specific organ even for subjects who receive a total of 3 scans over 15 months or more, though we anticipate nearly all subjects will have only 2 scans over approximately 12 months.

Exercise Intervention:

As described in detail below, the exercise intervention will be coordinated through the Exercise Medicine Unit (EMU) at the University of Pennsylvania School of Medicine. The EMU is headed by Dr. Kathryn Schmitz, a PhD trained exercise physiologist with two decades of experience in clinical exercise testing and intervention. Dr. Schmitz and her staff provide consultation on all aspects of the design, implementation, troubleshooting and analysis of exercise intervention protocols. Additionally, the EMU houses specialized equipment not currently available at PVAMC.

Safety screening and assessment: Subjects will be prescreened to determine safety of exercise testing using the American Heart Association/American College of Sports Medicine (AHA/ACSM) pre-participation screening survey, as well as a primary care provider review of the study eligibility criteria and written clearance to participate in maximal exercise. On the day of baseline testing, participants will arrive at the EMU testing room in clothing and footwear appropriate for exercise. Standard 12 lead ECG prep and a resting 12 lead ECG will be performed to ensure the participant is in normal sinus rhythm prior to test initiation. Resting blood pressure will also be taken to ensure no participant engages in testing with uncontrolled hypertension (e.g. systolic over 150, diastolic over 100). During the exercise intervention, subjects will receive weekly phone calls from study staff to monitor for injury including falls. Any subject reporting an injury associated with pain for more than 2 hours after exercise will be instructed to limit exercise until pain resolves and will be evaluated over the phone (or a clinical visit if necessary) by one of the physician investigators. In a systematic review and meta-analysis of exercise trials in PD, Allen and colleagues found no differences in falls or other exercise-related injuries among ambulatory PD patients(79, 80). As our recruited cohort will be comprised of preclinical or very early PD subjects, we expect that they will all be ambulatory at baseline and should be at minimal increased risk. However, vigilant safety monitoring will be performed as described above.

Fitness testing (VO2max): Exercise will be performed in on a motorized treadmill. Participants will be exercised to maximal volition using a standardized graded exercise protocol. The increment of work

rate rise will be chosen to result in subjects reaching their normal predicted maximal work rate values based on age, sex, and weight, with a goal of a maximum of 12-15 minutes of total exercise time.

Prior to exercise, participants will be fitted with a mouthpiece and noseclip to allow analysis of expired respiratory gases using a pre-calibrated Parvomedics True One metabolic measurement cart. Heart rate will be monitored continuously and a 12-lead ECG will be recorded every minute. Oxygen consumption (V02), carbon dioxide production (VC02), and minute ventilation (VE) will be monitored on a breath-by-breath basis. Respiratory exchange ratio and ventilatory equivalents of oxygen (VE/V02) and carbon dioxide (VErVC02) recorded graphically every 15 seconds. Every 30 seconds during exercise, subjects may be asked to rate their effort on the Borg scale of physical exertion (range 6-20, higher values representing increased effort) which has been shown to correlate well with heart rate and VO2 in most subjects and is a useful assessment in subjects with variation in predicted heart rate responses due to age, sex or pharmacologic therapy(81, 82).

Tests will be considered maximal if the participant reaches a respiratory exchange ratio of 1.15, maximal age predicted heart rate is achieved (220-age), reported effort on the Borg scale ≥18, or VO2 fails to increase with increasing workload. Tests may also be terminated using ACSM guidelines for exercise testing and prescription guidelines for safe testing procedures. Subjects may also choose to end tests due to intolerable symptoms. Measurement of VO2max has been validated as a reliable and repeatable measure of cardiovascular fitness in patients with mild to moderate PD (83), suggesting it may be appropriately used in patients with DIP.

Screening and safety measures for exercise testing and enrollment are summarized in the figures below:

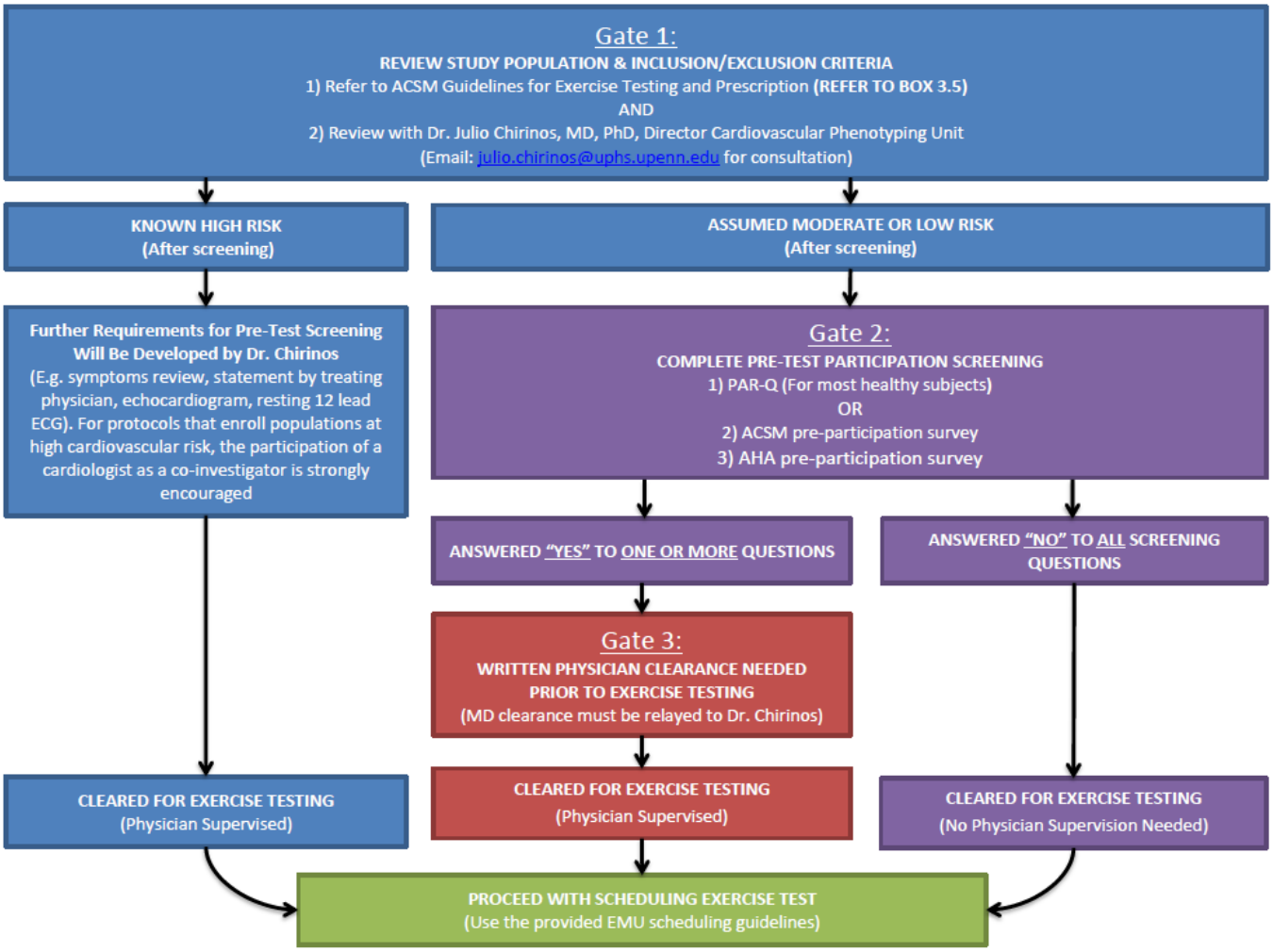

Figure 1: EMU screening and safety guidelines for exercise test scheduling

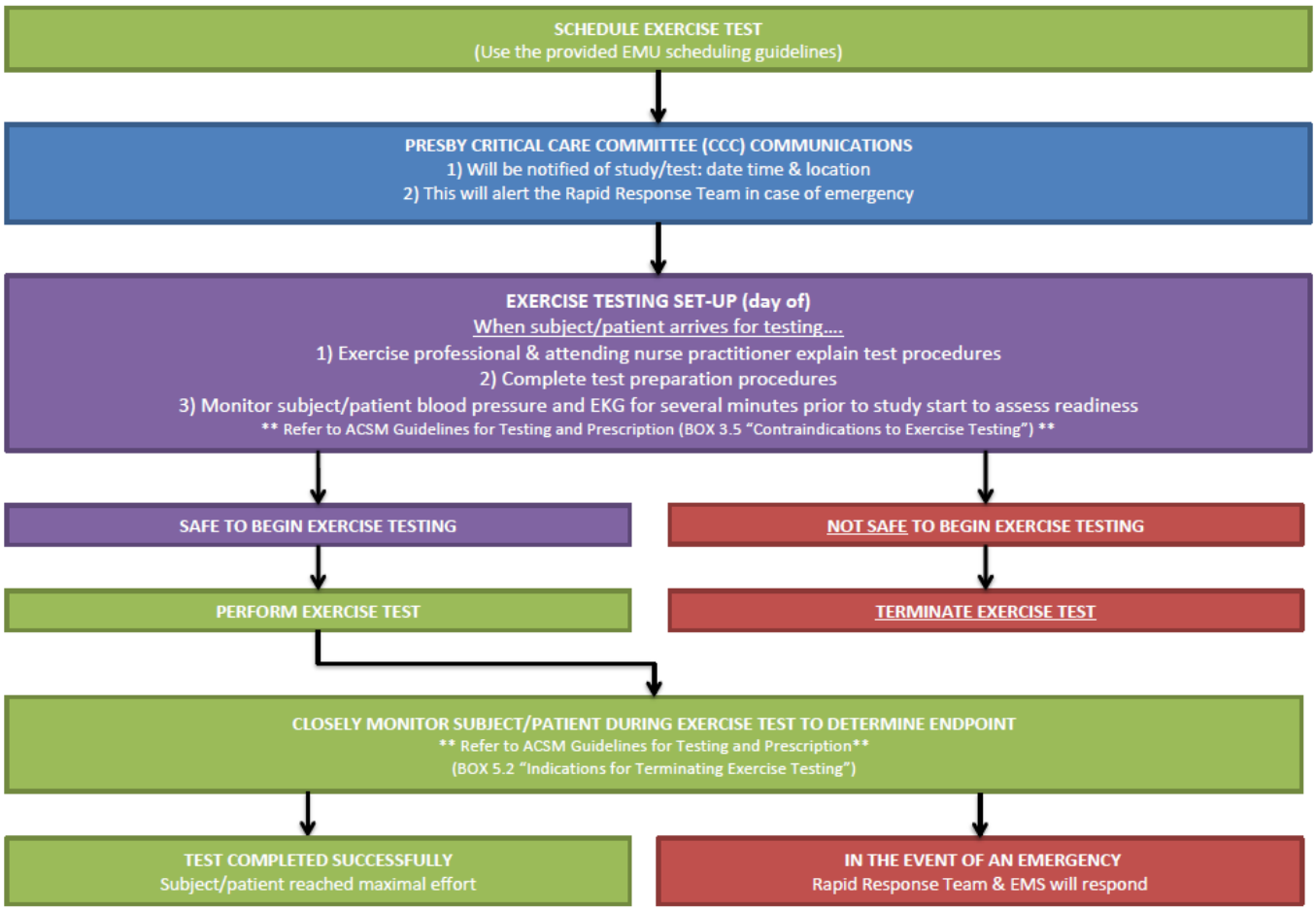

Figure 2: EMU screening and safety guidelines on the day of exercise testing

Home exercise, monitoring and promotion of adherence:

The primary exercise to be performed will be moderate-intensity aerobic walking (60-80% of age adjusted maximum heart rate) for 45 minutes (including 5 minutes each of warm up and cool down), 5 times per week. In individuals for whom heart rate response to exercise is not an accurate indication of intensity, the Borg rated perceived exertion (RPE) will be taught as above and used to monitor intensity. Participants using RPE will be asked to exercise at an intensity level of 12-15 on a scale of 6-20. Overall, this level of exercise exceeds ACSM/ACRM guidelines and has been associated with increases in serum BDNF, a likely marker and/or mediator of the benefits of aerobic exercise. Exercise subjects will also receive a Pedlar® Light Workout Exerciser (Patterson Medical Item #5252). This lightweight pedal exerciser will allow subjects to exercise using their arms or legs in the home when outdoor walking is not feasible (e.g., inclement weather). This model is currently provided to Veterans through our prosthetics department for home exercise. In the event that this model was no longer available through VA, a comparable model available through the prosthetics department would be substituted and an updated IRB amendment would be submitted. The targets for time and heart rate will be the same as those for walking. The Pedlar® will arrive at the subjects' homes fully assembled and at no cost to them. It will be theirs to keep at the end of the study. Subjects will receive training on use of the Pedlar® at their baseline EMU visit. Exercise adherence and intensity will be monitored by subject report and supported by heart rate response from the Polar heart rate monitor. Each participant in the intervention arm will be provided with a Polar heart rate monitor and ongoing support from study staff. Participants will receive instruction in how to use the Polar Heart Rate monitors from the fitness professionals and instructions not to exceed 85% of maximal heart rate during exercise sessions. An exercise professional will instruct participants in the use of the exercise logs and injury prevention (warm-up, cool down, stretching, proper

footwear). Polar Heart Rate Monitor watches will be swapped via mail or in person (subjects may drop off at CMC VAMC with study staff who will swap and mail new monitors to subjects) monthly based on subject preference. The trainer will view the heart rate files and discuss any need for revising workout schedule or intensity with subjects based on this objective data. Study staff will contact the participants weekly for brief phone counseling and to discuss recent exercise sessions and any need for support. Telephone support has been shown to be an effective method of supporting exercise adherence (86). It is anticipated that these calls will take less than 10 minutes each. During these calls, participants will be asked to report any symptoms or soreness so that the stretching, footwear, and exercise sessions can be modified to ensure injuries are minimized. A phone script template detailing the topics that will be discussed in each call and will be used as a data recording instrument is provided as an appendix.

Exercise setting: The exercise training sessions will take place in the home neighborhoods of the participants. Study staff will help subjects find appropriate local facilities or outdoor routes for the walking intervention. The choice to do the exercise training in the community is based on evidence from the literature that adherence to a home based program is higher than for a facility based program and data from multiple long term weight loss maintenance interventions that indicate that this approach is feasible and sustainable for research subjects (87, 88). The most commonly reported barrier to participation in regular exercise is lack of time (89), and home-based exercise will remove the time that would be spent traveling to and from a facility. The participants recruited into this study may be relatively sedentary. However, we anticipate that they will be able to complete three 30 minute sessions at 40-60% of age predicted maximal heart rate from the first week of training, increasing to the target as advised by study staff based on tolerance.

Assessment of compliance: Compliance with the prescribed exercise regimen will be measured using data from Polar heart rate monitors and subject-completed exercise logs. A reported exercise session in subjects' logs will be judged as completed if the heart rate monitor data supports that the subject achieved 75% or more of the prescribed time in the heart rate range suggested for each individual. The overall percentage of sessions completed will be treated as continuous variable, or, for dichotomous analyses, subjects will be judged as compliant if they completed at least 75% of the prescribed exercise sessions. For subjects taking beta-blockers, heart rate requirements will be decreased by 20% and effort will be prescribed according to Borg RPE as described above. This standard exceeds the ACRM/ACSM recommendations of 150 minutes/week of moderate activity. Subjects will receive weekly phone calls from study personnel to review heart rate records and exercise logs to provide feedback and encouragement to increase or maintain exercise levels.

Assessment of energy expenditure (EE): Energy expenditure throughout the intervention will be estimated using the Flex-HR method with individual calibration from exercise testing data to adjust for the non-linear relationship between HR, VO2 and energy expenditure at high and low levels of activity(90, 91). The Flex-HR will be considered as the average between the highest resting HR and the lowest recorded exercise HR during exercise testing and combined with estimates of basal metabolic rates to determine total EE according to the method of Spurr(92). Additionally, EE will be estimated at baseline, 8 weeks and 52 weeks in all subjects using accelerometry in the "free-living" condition. Participants will be asked to wear an accelerometer (Actigraph GT3X, FI; Actigraph, Pensacola, FL) that records movement on the vertical and horizontal axis, during waking hours for 7 consecutive days. This instrument is the most widely used objective monitor of physical activity used in research, including use in NHANES (93), which provides population based norms for a broad cross-section of U.S. residents. Participants will be given the accelerometer in person at study visits as described and provided with standardized instructions for use. Accelerometers will be returned by prepaid mailer provided by the study. The accelerometers will be initialized and downloaded using the ActiLife software provided by the manufacturer (ActiGraph LLC). The data will be collected in 10-s epochs. Actilife software will be used to implement quality control procedures, derive wear time, and summarize minute-by-minute data. Non-wear time will be defined as intervals of at least 60 consecutive minutes of 0 cpm, with allowance for up to 2 min of observations of some limited movement (>50 cpm) within these periods. Days with at least 10 h of wear time that did not contain excessively high counts (>20 000 cpm) will be considered valid.

Monitoring of control subjects**:** All subjects (control and intervention) with abnormal DaT SPECT will be referred to the PADRECC for clinical followup including usual care for monitoring of symptom progression and institution of any necessary symptomatic therapies. Study participation will not limit any aspect of routine clinical care. Importantly, levodopa and other common dopaminergic therapies do not interfere with Ioflupane binding to dopamine transporters and do not significantly influence DaT SPECT. Enrolled non-intervention subjects will receive similar weekly phone calls from study staff as will intervention subjects. During the weekly phone calls, staff will administer the Parkinson's Disease Questionnaire-8 (96), a short well-validated assessment of parkinsonian symptoms and quality of life that can be completed in only a few minutes. During the baseline visit, at 8 weeks and at the 52 week assessment, study staff will administer the International Physical Activity Questionnaire, a well-characterized self-report instrument that has also been used to measure physical activity in subjects with PD(97, 98), allowing monitoring of any changes in activity over the course of the intervention using paired t-tests.

Study Design:

AIM 1: To test the effect of regular aerobic exercise on motor function in DIP. In this aim, we will test the hypothesis that a short term home exercise regimen will improve motor function in DIP subjects and could be an effective rehabilitation intervention.

Subjects/Procedures: A cohort of DIP subjects with presumed prodromal PD will be defined by a two-tiered screening procedure. First, DIP subjects will undergo olfactory testing administered by trained study personnel. Subjects with hyposmia (defined as scores below the 25th percentile for age and gender using well-established normative data for the UPSIT) on initial olfactory testing will undergo DaT imaging. We will also recruit subjects with a clinical diagnosis of PD by a PADRECC provider. SPECT scans will initially be read as normal, mildly abnormal or clearly abnormal, in accord with current clinical practice, by a nuclear medicine physician blinded to clinical status. High inter-rater agreement (kappa 0.89-0.93) has been reported for clinical reading of DaTI(99). All patients with abnormal (mildly or clearly) DaT SPECT will be referred for clinical follow-up in the PADRECC. The combination of DIP, hyposmia and abnormal striatal DaT imaging will be operationally defined as prodromal PD. All subjects with abnormal olfaction and DaT deficit will undergo baseline motor testing (UPDRS motor and instrumented Timed Up and Go) together with safety screening for exercise. If eligible based on safety screening, baseline cardiovascular fitness testing (VO2max measurement) will be obtained as described above. Subjects will be then be randomized in a 1:1 ratio to a home-based exercise intervention (5 days/week aerobic walking with confirmation by remote activity monitoring) or no intervention. Subjects will receive weekly phone calls from staff to monitor safety and compliance. After 8 weeks, subjects will undergo repeat clinical (UPDRS motor), quantitative (iTUG) and fitness testing (VO2max) to examine short-term symptomatic effects of exercise. Eight weeks is a common duration for short-term rehabilitation interventions and was recently reported in a Phase I/II trial of aerobic walking in PD(8).

AIM 2: To test whether regular aerobic exercise influences disease progression in prodromal PD. In this aim, we will test the hypothesis that exercise subjects will exhibit slower decline in semi-quantitative striatal DaT SPECT, suggesting a disease-modifying effect of exercise in prodromal PD.

Subjects/Procedures: Subjects will be the same prodromal PD cohort described above in Aim 1. Subjects will continue the exercise intervention (or no intervention) for a total of 52 weeks to examine a potential disease-modifying effect. Subjects will continue to receive weekly phone calls from staff to monitor safety and compliance. At the end of the intervention period, control and exercise subjects will undergo repeat DaT SPECT with quantitation of signal in 6 different striatal regions (right and left caudate, right and left anterior putamen, right and left posterior putamen) and repeat exercise testing. If subjects choose to drop out, we will attempt to obtain the final DaT imaging study as soon as possible after notification of the subject's intent to withdraw if they have completed at least 24 weeks of the intervention.

AIM 3: To characterize the mechanism and biochemical correlates of exercise-induced changes in subjects with prodromal PD. In this aim, we will test the hypothesis that serum biomarkers of exercise effects and PD risk will change in the intervention group compared to no intervention.

Subjects/Procedures: Serum biomarkers associated with PD risk or exercise-induced changes (i.e. BDNF, uric acid and apolipoproteinA1) will be measured at baseline, 8 and 52 weeks as described above. The primary outcome of this aim will be differences in the rate of change between intervention groups as assessed using independent samples t-tests. A secondary outcome will examine the rate of change using linear mixed-effects models controlling for age, gender and other potential confounders. Additionally, relationships of biomarkers to VO2max, UPDRS, quantitative motor and quantitative DaTI will be examined using partial correlations controlling for age and gender. An intention-to-treat analysis will be applied primarily but pre-planned secondary analyses will compare only exercise subjects deemed compliant with controls.

A schematic demonstrating the flow of recruitment, assessments and analysis is provided below:

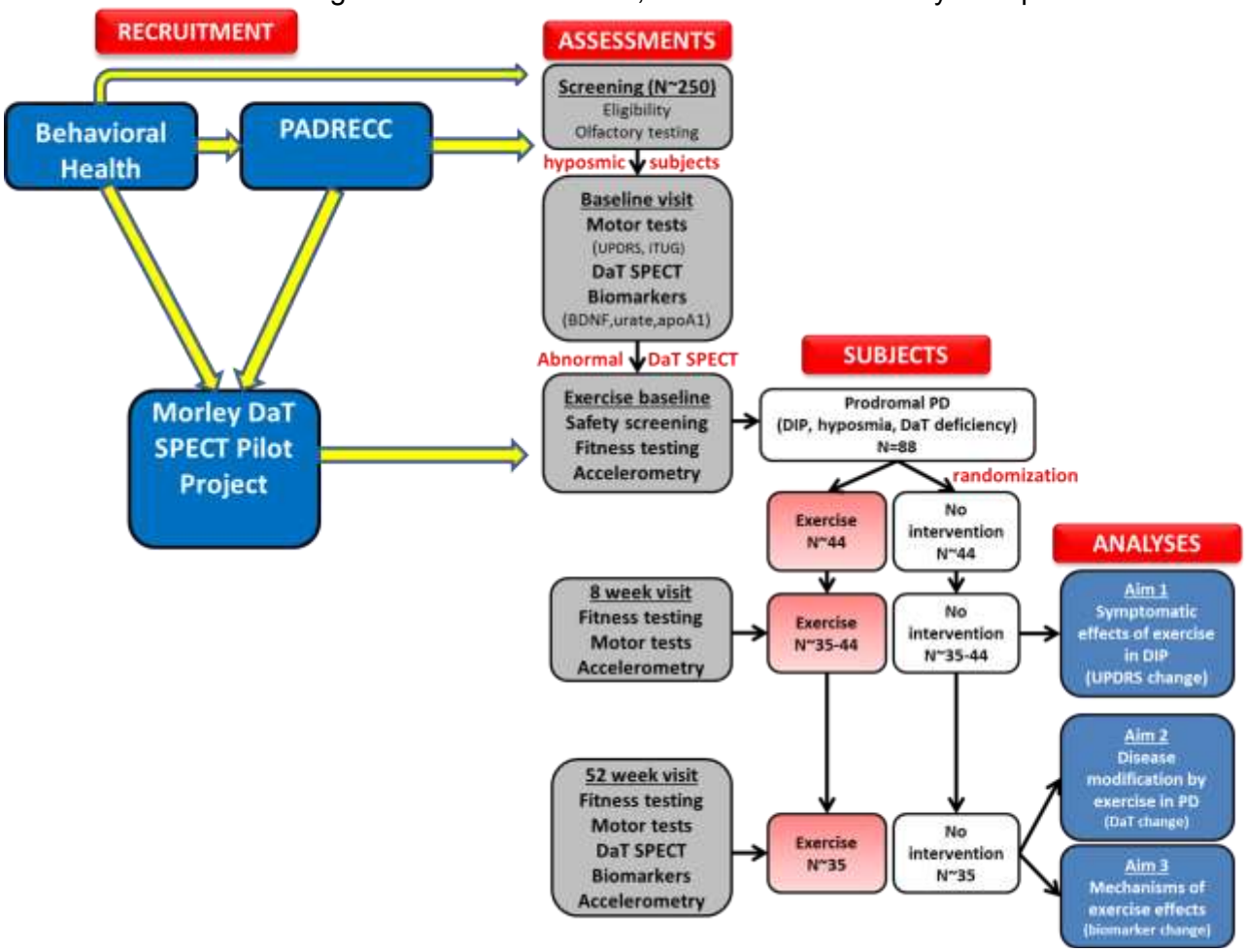

Figure 3: Overview of study design

5.1.2. **What research methods will be used in the project*? Check all that apply.***

☑ **Surveys/Questionnaires**	☐ **Interviews**	☐ **Audio Taping**
☐ **Behavioral Observations**	☑ **Chart Reviews**	☐ **Video Taping**
☐ **Focus Groups**	☑ **Randomization**	☐ **Double-Blind**

☑ **Control Group** ☐ **Placebo** ☐ **Withhold/Delay Treatment**

☑ **Specimen Collection** ☐ **Deception** ☑ **Telephone Survey**

☐ **Other (Describe)**

5.1.3. **Provide description of the study population (delineate all categories of subjects – male, female, inpatients, outpatients, providers, family members, employees, etc.). Include anticipated initial enrollment numbers (and number of subjects anticipated to complete all aspects of the protocol).**

Patients aged 40-89 with a clinical diagnosis of DIP will be recruited from the CMC VAMC PADRECC and Behavioral Health Service (BHS) clinics. We will recruit subjects with parkinsonian signs (rest tremor, rigidity, bradykinesia) occurring after the institution of therapy with a antipsychotic medication having known dopamine receptor blocking activity (examples include haloperidol, chlorpromazine, fluphenazine, perphenazine, risperidone, thioridazine, thiothixene, ziprasidone, olanzapine and aripiprazole). Potential subjects with DIP will be pre-screened using a brief (12 item) scratch and sniff smell test with hyposmic subjects invited to learn more about the study (see script). Brief olfactory testing should be completed in 5-10 minutes. We anticipate screening 250 subjects with olfactory testing. Approximately 120 subjects will undergo baseline assessment including DAT-SPECT as described above. Subjects with abnormal DaT-SPECT will be invited to be randomized into the exercise study. In addition to the screening described above, we will invite subjects from Dr. Morley's CPPF pilot study "Degenerative nigrostriatal dysfunction in drug-induced parkinsonism" PROM#01481 who have abnormal DaT-SPECT to enroll in the present protocol. These subjects will have explicitly agreed to future contact for related studies in the ICF for PROM#01481. We may also invite subjects identified by their PADRECC provider who had DaT-SPECT (with an abnormal result) performed clinically outside of a research protocol within the prior 3 months and agree to be contacted. We will randomize 88 subjects to either exercise intervention or no intervention and anticipate that 70 subjects will complete all aspects of the study. Additionally, letters will be sent to potential participants letting them know that they may be eligible for a study with a brief description of the study and give them a number of they would like to learn more or to request no further contact. 2018 Amendment: We anticipate enrolling 56 additional subjects under the modified inclusion criteria with 48 (24 per group) expected to complete all study activities. This will still allow for meaningful analysis of our primary outcomes according to the sensitivity analysis of sample size from the original protocol (20 per group adequate).

5.1.4. **As applicable, provide rationale and information on any added protections and safeguards for vulnerable populations (children, prisoners, pregnant women, physically or mentally-disabled persons, and economically or educationally disadvantaged persons).**

NA

5.1.5. Does this project target a specific race or ethnic group as participants? **NOT APPLICABLE** **If yes, check all that apply.**

Race **Ethnicity**

☐ **American Indian or Alaska Native**

☐ **Asian**

☐ **Black or African American**

☐ **Native Hawaiian or other Pacific Islander**

☐ **White**

☐ **Other** ☐

☐ **Hispanic or Latino**

☐ **Not Hispanic or Latino**

5.1.6. Will this study bank data and/or specimens? **YES**

5.1.6.1. **If yes, include information on data and specimen banking.**
Coded plasma samples not exhausted in measuring BDNF will be stored in

5.1.6.2. ***IF BANKING SPECIMENS, IT MUST BE AT A VA APPROVED FACILITY*****.**
(For additional information, go to the following website http://www.research.va.gov/programs/tissue_banking/, or contact the IRB office.)

5.1.6.3. **If specimens will be banked, specify banking location**.
Coded Specimens will be stored in alarmed freezers within a locked laboratory in Building 21 Lab A405. Only appropriate personal have access to the specimens. The freezers have alarm settings to monitor temperature (high alarm at -70C, low alarm at -90C). Freezers are equipped with an alarm that will sound if the freezers' temperature is compromised.

5.1.6.4. **If the location is a non-VA site, has the mandatory approval from VA Central Office been obtained through submission of a tissue banking application? Choose an item.**

5.1.6.4.1. **If yes, provide a copy of the response from VA Central Office.**

5.1.6.5. **If applicable, explain how destruction of banked samples will be substantiated.**
N/A

5.1.6.6. **Do you anticipate using the banked specimens for other studies beyond the defined study period and defined study parameters? YES**

5.1.6.6.1. **If yes, will you need to re-contact subjects? How will this be done?**
Banking and potential future use of specimens will be detailed during the informed consent process. Subjects will not be re-contacted.

5.2. **Participant Recruitment Methods**

5.2.1. **State how many subjects will be needed**.
We will screen approximately 250 subjects with brief olfactory testing. We anticipate about 120 subjects with abnormal olfactory testing will undergo baseline assessment including DAT-SPECT as described above. We will randomize 88 subjects to either exercise intervention or no intervention and anticipate that 70 subjects will complete all aspects of the study. 2018 Amendment: We anticipate enrolling 56 additional subjects under the modified inclusion criteria with 48 (24 per group) expected to complete all study activities.

5.2.2. **Who will be responsible for recruiting potential participants**? **Provide titles of individuals.**

After referral from providers (see below), recruitment will be coordinated by the study coordinator or one of the study PI or co-Is

5.2.3. **How will initial contact with potential participants be made? (*e.g., local clinics, physician referrals, letters to prospective participants)*** *NOTE: VA policy prohibits "cold calls" to potential VA research participants. Provide an introductory letter and telephone script.* Additionally, letters will be sent to potential participants letting them know that they may be eligible for a study with a brief description of the study and give them a number of they would like to learn more or to request no further contact.

The potential subjects will be identified by their treating psychiatrist or neurologist. Subjects will be initially told about the study by their primary psychiatrist or neurologist emphasizing that participation is entirely voluntary and will not affect their clinical care. Those subjects that express interest will meet with the study PI, co-PI or research staff to receive detailed information about the study. Potential subjects with DIP will be pre-screened using a brief (12 item) scratch and sniff smell test with hyposmic subjects invited to learn more about the study (see script). Brief olfactory testing should be completed in 5-10 minutes. Hyposmic subjects will be asked if they wish to they proceed with informed consent. In addition to the screening described above, we will invite subjects from Dr. Morley's CPPF pilot study "Degenerative nigrostriatal dysfunction in drug-induced parkinsonism" PROM#01481 who have abnormal DaT-SPECT to enroll in the present protocol. These subjects will have explicitly agreed to future contact for related studies in the ICF for PROM#01481. We may also invite subjects identified by their PADRECC provider who had DaT-SPECT (with an abnormal result) performed clinically outside of a research protocol within the prior 3 months and agree to be contacted. In addition to recruiting directly from clinics as above, we will obtain a list of patients prescribed medications associated with DIP in the last 12 months using the CACs or Clinical Pharmacy Database (with the ability to re-query every 4 months for new drug starts). This list will contain only names,last 4 SSN digits and medication prescribed without other clinical information and will be transmitted through encrypted email using a password protected spreadsheet. The list will be used to identify CPRS charts for screening under the conditions of our HIPAA waiver (rather than blindly screening all charts with a Behavioral Health appointment). We will contact providers of potentially eligible active or control subjects such that initial contact about the study will come through their clinical providers. Additionally, letters will be sent to potential participants letting them know that they may be eligible for a study with a brief description of the study and give them a number of they would like to learn more or to request no further contact. Subjects with a clinical diagnosis of PD will be directly referred by their PADRECC provider.

5.2.4. **Will you be using any of the following methods to recruit participants? (Check all that apply.)**

- ☐ **N/A**
- ☑ **Local database for which participants have NOT given prior permission to be contacted for Research.** *NOTE: If this option is checked, please submit a Waiver of Individual Authorization for Disclosure of Protected Health Information.*
- ☑ **Personal contact with patients over whom you have direct/indirect oversight**
- ☑ **Provider (Clinician) Referrals of potential participants**

5.2.5. **Indicate the types of recruitment/advertisement materials that will be used: Check all that apply. Submit copies of recruitment materials, for IRB review**.

☐ **Not applicable; none to be used**

☑ **Fliers** ☐ **Newspapers** ☐ **Letters** ☐ **Websites** ☐ **Television**

☐ **Radio** ☐ **Audio** ☐ **Video** ☐ **Surveys**

☐ **Other (Specify, e.g. employee newsletters**)

5.2.6. **Participants will be given a copy of the Notice of Privacy Practice. YES**

5.3. **Compensation for Participation - YES If yes, complete the following**.

5.3.1. **Summarize any financial compensation that will be offered to subjects**.

- *Subjects will paid $50 for completion of each of the study visits (baseline assessment including DAT-SPECT and each of three assessments including fitness and motor testing. Results of the brain scan will not be known before conclusion of the baseline visit, thus all patients (regardless of normal/abnormal scan results) will be asked to provide a blood sample and all will be paid.*

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5.3.2. **Provide the schedule for compensation**.

5.3.2.1. **Per study visit or session.**

$50 for each baseline visit (VA and exercise), $20 for the 8-week visit and $50 for each completion visit (VA and exercise)

5.3.2.2. **Total amount for entire participation.**

$220

5.3.3. **State how compensation will be provided: : Check**

Compensation will be provided in check form after the visit. The check will be mailed to the patient's home address.

5.4. **Informed Consent Procedures**

5.4.1. **Indicate if informed consent will be obtained and/or if you are requesting a waiver of informed consent or waiver of documentation of informed consent. Consent to be obtained**

5.4.2. **If the research involves multiple phases, specify for which phases of the research the waiver(s) is/are being requested.**

5.4.3. **Describe circumstances, if any, that may need to be addressed in seeking informed consent (e.g., subjects with impaired decision making ability and the use of a legally authorized representative, etc.)**

Subjects who cannot provide their own consent will not be recruited.

5.4.4. **If applicable, indicate how study personnel will be trained regarding human subjects protections requirements and how to obtain and document informed consent.**

All study personnel received CMCVAMC-mandated training and obtained requisite Certificates of Completion.

5.4.5. **Inclusion/Exclusion Criteria: Describe the criteria that determine who will be included in or excluded from the study.**

5.4.5.1. **Inclusion Criteria**

We will recruit subjects with parkinsonian signs (rest tremor, rigidity, bradykinesia) occurring after the institution of therapy with a medication having a known association with DIP (examples include haloperidol, chlorpromazine, fluphenazine, perphenazine, risperidone, thioridazine, thiothixene, lithium, valproic acid, ziprasidone, olanzapine and aripiprazole). Potential subjects with DIP will be pre-screened using a brief (12 item) scratch and sniff smell test with hyposmic subjects invited to learn more about the study (see script).). Brief olfactory testing should be completed in 5-10 minutes. We will also invite subjects from Dr. Morley's CPPF pilot study "Degenerative nigrostriatal dysfunction in drug-induced parkinsonism" PROM#01481 who have abnormal DaT-SPECT to enroll in the present protocol. These subjects will have explicitly agreed to future contact for related studies in the ICF for PROM#01481. We may also invite subjects identified by their PADRECC provider who had DaT-SPECT (with an abnormal result) performed clinically outside of a research protocol within the prior 3 months and agree to be contacted. We will also recruit subjects with a clinical diagnosis of PD (Hoehn & Yahr (H/Y) stage ≤ 2 made by a PADRECC provider.

5.4.5.2. **Exclusion Criteria**

1) Subjects with a known diagnosis of atypical parkinsonian syndrome (i.e. dementia with Lewy bodies, progressive supranuclear palsy, corticobasal degeneration, multiple system atrophy) or other neurodegenerative condition other than PD will be excluded; 2) Subjects with a history of sinus trauma or surgery, encephalitis, current nasal congestion or other known reason for olfactory impairment will not be screened or enrolled 3) Subjects with a contraindication to DaTI (sensitivity or allergy to iodine, treatment with a drug with a major effect on DaTscan that cannot be temporarily weaned) will be excluded; 4) Subjects with known unstable cardiac, pulmonary, orthopedic or other conditions that would preclude safe participation in exercise training will be excluded (see below for further fitness screening prior to exercise); 5) Subjects currently engaging in exercise more than 30 minutes per day, 3 days per week will not be enrolled.

5.5. Withdrawal of Subjects

5.5.1. **Describe how a subject can withdraw from the study**.

Subjects may withdraw from the study at any time by notifying study staff.

5.5.2. **Describe any anticipated circumstances under which subjects will be withdrawn from the research without their consent**.

Any subject who, in the opinion of the PI or co-investigators, has suffered significant injury or has demonstrated high risk for such may be withdrawn involuntarily

5.5.3. **Describe the consequences of a subject's decision to withdraw from the research and the procedures for orderly termination of participation by the subject (e.g., the subject contacting the investigator for an end-of-study visit)**.

Early withdrawal from the study will not result in any consequences for the study subject. The subjects may inform the PI, co-PI, or research coordinator/assistant of their intention to withdraw in person or over the phone at any time. Subjects who wish to withdraw after completing at least 3 months of the study will be asked if they would be willing to complete a final study visit including DAT-SPECT but will be assured that this strictly voluntary as described in the Informed Consent Form.

5.6. Potential Risk/Benefit Analysis

5.6.1. **Potential Study Risks**

5.6.1.1. **Describe and assess all of the following risks that may be associated with the research**:

5.6.1.2. **Physical**

Screening: Some odors in the sniff test (eg, turpentine) may create momentary discomfort, upon which time the subject will stop sniffing the odor immediately. Dopamine transporter imaging with Ioflupane I123 SPECT is an FDA-approved test that is well-tolerated and will be administered by trained nuclear medicine clinicians and staff. In clinical trials, no serious adverse reactions were reported. Other adverse reactions consisted of headache, nausea, vertigo, dry mouth or dizziness and were considered mild. Holding a medication before DAT-SPECT could lead to worsening symptoms but will only be done when the prescribing provider believes it is safe, and this is routinely done for scans obtained clinically without incident. Obtaining a blood sample can result in mild discomfort at the time of needle insertion or a small bruise, which will usually disappear in 1-2 weeks. If subjects choose to take a sedative to facilitate DaTscan, this could result in adverse effects including sedation, dizziness, nausea or an allergic reaction. Subjects will be monitored by study staff for any adverse effects or sedation and will not be allowed to depart until cleared by a study clinician. Patients who are given a sedative and also drove to the study visit or took public transportation will be observed to make sure any effects of the sedative medication that could affect driving or taking public transportation have worn off.

Exercise: *Testing:* Preparing the skin on the chest for ECG during exercise testing requires removing the top layer of skin in order to get good readings. It is possible that the abrasive tape and alcohol used for this process will sting and that skin might become red for a few hours. There is always risk of a cardiovascular event during exercise testing. Among individuals with known cardiovascular disease, less than 1 in 10000 individuals experience a cardiac event during exercise testing. In the exceedingly unlikely event of a medical emergency during exercise testing, appropriate medical personnel and equipment and supplies are in place to ensure safety. A multi-gated pre-screening procedure and adequate medical monitoring during testing will be undertaken to ensure safety of participants. See above and below. *Intervention:* Muscle or joint soreness or injury from the exercise training. These are usually mild, last a week or less, and require little medical attention, if any. The types of injuries that are most common from aerobic exercise are hip, knee, ankle, or foot joint pain, or muscle aches. Sometimes these injuries are mild enough that they will not need medical attention and daily activities will not be altered. It is estimated that over any given month, 4% of adults who walk for exercise on a regular basis will incur an injury severe enough to cause a change in activities of daily living for a week or more and that require medical attention. These injuries are rarely serious in nature and generally resolve with reduced activity and greater attention to appropriate footwear and adequate stretching (as proposed).

5.6.1.3. **Psychological.** Subjects may potentially become frustrated, embarrassed or otherwise uncomfortable while completing these assessments. Care will be taken to minimize this at the time of the assessments. Subjects will be

advised that they may refuse to answer any question or stop a test at any time and for any reason. Some subjects will be distressed when hearing again that one of the medications they are on has led to or can lead to symptoms of parkinsonism or that they are at high risk for PD. DAT-SPECT results will be communicated to subjects by a study neurologist. If subjects become distressed, they will be appropriately counseled by the study neurologist. If subjects remain distressed or express suicidal ideation, an attempt will be made to have the subject see their behavioral health provider (or a substitute) on the same day. If this is not possible and the subject remains distressed or expressing suicidal ideation, they will be referred for urgent evaluation in the CMC VAMC Emergency Department. All subjects with abnormal DAT-SPECT will be referred for appropriate clinical follow-up and counseling in the PADRECC.

5.6.1.4. **Social/Economic**

Not applicable

5.6.1.5. **Legal**

Not applicable

5.6.1.6. **Loss of Confidentiality**

This risk is associated with all research involving human subjects, but is minimized by training all study personnel and rigorous enforcement for properly protecting PHI.

5.6.1.7. **Other, e.g. radiation, placebo, washout of medications**

DAT-SPECT involves the use of a FDA-approved radiopharmaceutical as described above.

5.6.1.8. **Assess the likelihood and seriousness of such risks**.

Physical discomfort associated with odors has not been observed during years of routine clinical use in the PADRECC. This theoretical risk is presumably low and should be short-lived. Subjects will be appropriately reassured and reminded that they may stop their participation in the study at any time. In clinical trials of I—123 Ioflupane SPECT, no serious adverse reactions were reported. Other adverse reactions consisted of headache, nausea, vertigo, dry mouth or dizziness and were considered mild. Risk of cardiac events or physical injury during exercise testing and intervention are potentially serious but low overall and minimized further by the gated screening procedures described above and weekly monitoring by study personnel. The risk of loss of confidentiality, while serious, is minimal due to rigorous training of all study personnel on PHI protection.

5.6.2. **Include a description of how anticipated risk will be minimized and include an analysis of risk vs. potential benefit.**

Multiple strategies will be used to mitigate risk as described above including: gated staged screening and clearance for exercise, monitoring during exercise testing, weekly contact with study staff, rigorous privacy practices and clinical follow-up in the PADRECC. Cumulative radiation dose will be monitored and kept below recommended whole body and target organ limits as described in Section 5.1.1.

5.6.3. **Potential Study Benefits**

5.6.3.1. **Indicate potential benefits to be gained by the individual subjects, as well as benefit(s) that may accrue to society in general as a result of the**

planned work. If the subject will not receive any direct benefit, this fact must be stated here and in the consent form.

While this study is designed to test the benefits of exercise in DIP and PD, these are not guaranteed. However, exercise is widely recognized for its general health benefits which may accrue to those in the intervention group. Subjects in the non-intervention group may not directly benefit from the study.

5.6.4. **Alternative Treatments Outside the Study**

5.6.4.1. **Describe alternatives available to the subject outside the research context. If there are no such alternatives, state that the alternative is not to participate in the research study**.

There are no demonstrated disease modifying therapies for PD. Subjects may choose not to participate in the study

5.7. **Data Monitoring (***Monitoring plans describe how a monitor, independent of the study team, regularly inspects study records to ensure the study is adhering to the study protocol and applicable research regulations and CMCVAMC requirements. Monitoring plans do not necessarily require the use of an independent Data and Safety Monitoring Board (DSMB). Such independent boards are usually reserved for high-risk phase I studies, or large, multi-center phase III trials. Federally funded studies may require the use of an independent DSMB.)*

5.7.1. **Will a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) oversee the project? NO**

5.7.1.1. **If yes, provide contact information for the DSMB or DMC representative**.

5.7.1.2. **If the project will not be overseen by a DSMB or DMC, describe the data and safety monitoring plan to be followed.**

The PI will monitor the study to ensure that the study team adheres to the study protocol and applicable research regulations and CMC VAMC requirements. The research procedures will be fully explained to all participants and written informed consent will be obtained either by the PI, co-Is, or research coordinator or research assistant. Informed consent will also be documented in CPRS. The study team will be trained on the proper way to monitor and handle protocol deviations. The PI will, personally, monitor and address any deviation that may occur. Weekly monitoring calls to exercise subjects will include safety screening. Additionally, the PI will meet regularly with EMU personnel to review safety data from weekly monitoring calls.

5.8. **Reporting of Protocol Deviations, Adverse Events (AEs), Serious Adverse Events (SAEs), Breaches of Confidentiality, Unanticipated Adverse Device Effects (UADEs), and Unanticipated/Unexpected Problems**

5.8.1. **Include procedures for reporting these events to the CMCVAMC IRB and sponsor**. (*Note: Except for AEs, all other events must be reported to the CMCVAMC IRB within 5 business days of discovery. Use the CMCVAMC Serious-Adverse Event form for reporting SAEs, UADEs, and unanticipated/unexpected problems. Use the CMCVAMC Protocol Deviation form for reporting protocol deviations. On-site AEs should be reported at the time of continuing review.)*

In the event that there is a protocol deviation, serious adverse event, or a breach of confidentiality, the PI will notify the CMC VAMC IRB within 5 business days of discovery and the appropriate measures will be taken to rectify the situation. All serious adverse events will be reported to the IRB by submitting a form of "Report of Adverse Event or Safety Concern involving Human Research Subjects". All adverse events will be reported to the IRB at the time of Continuing Review. Any protocol deviations will be reported in accordance with CMC VAMC regulations.

5.9. **Privacy and Confidentiality**

5.9.1. **Describe whether the study will use or disclose subjects' Protected Health Information (PHI).**

This study will use PHI as outlined below

5.9.2. **Check the PHI to be collected on all subjects for this research protocol.**

- [x] **Name**
- [x] **All geographic subdivisions smaller than a State, including street address, city, county, precinct, ZIP code, and their equivalent geographical codes, except for the initial three digits of a ZIP code if, according to the current publicly available data from the Bureau of the Census:**
  - **a. The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people; and**
  - **b. The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.**
- [x] **All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.**
- [x] **Telephone numbers**
- [ ] **Fax numbers**
- [ ] **Electronic mail addresses**
- [x] **Social Security/Medical Record Number**
- [ ] **Health plan beneficiary numbers**
- [ ] **Account Numbers**
- [ ] **Certificate/license numbers**
- [ ] **Vehicle identifiers and serial numbers, including license plate numbers**
- [ ] **Device identifiers and serial numbers**
- [ ] **Web universal resource locators (URLS)**
- [ ] **Internet protocol (IP) address numbers**
- [ ] **Biometric identifiers, including fingerprints and voiceprints**
- [ ] **Full-face photographic images and any comparable images**
- [ ] **Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.**

☐ **HIV (testing or infectious disease) records** ☐ **Sickle cell anemia**

☐ **Drug Abuse Information** ☐ **Alcoholism or Alcohol Use**

5.10. **Information Security** (*Contact the Information Security Officer for additional assistance regarding confidentiality (storage/security) of research data.)*

5.10.1. **List the data/information that will be stored (including signed, original informed consent and HIPAA authorization forms, if applicable, case report forms, etc.)** Demographic information, study questionnaires, smell test results, imaging data, lab values, fitness testing results, heart rate recordings, accelerometer data, phone monitoring call logs, original signed informed consent and HIPAA authorization forms.

5.10.2. **Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, Certificates of Confidentiality, and separation of identifiers and data)**.

- All information collected in this study will be kept strictly confidential. All study personnel received CMCVAMC-mandated training and obtained requisite Certificates of Completion. Data are all collected at PADRECC clinic and will be stored in a filing cabinet in the PADRECC research coordinator's office, PVAMC Building 1 PADRECC 4th floor Room A447 which is locked and only assessable by PI, co-Is and other staff members involved in this study at PADRECC. Subjects' clinical information is stored on the PADRECC's Z drive which is only accessible by staff with appropriate login credentials and server permissions at CMCVAMC desktop computers or through secure remote VPN access with password protection. Data will not be downloaded to non-VA computers. Analyzed DaT-SPECT data will be stored on the PADRECC Z drive. Original fitness testing data, heart rate recordings and accelerometer data will be stored in locked file cabinets (paper data) or on a password protected server located at the Penn EMU. Penn Presbyterian Medical Center, 1st floor Mutch Building Room 109. This server is accessible only to appropriate staff of the Penn Clinical and Translational Research Center/EMU staff with login credentials. Patient identifiable data will be accessible only to PI, co-PIs or research staff who have appropriate PVAMC training for accessing medical records. Data will be stored only on the secured PVAMC server and coded using a coding system to assign each patient with an unique research subject number. Numbers will be assigned sequentially on the day patient consents to participate in the study. The participant/identifier key (that will link the unique subject code to the subject) will also be kept on the PADRECC server, separate from the research data. Location of PADRECC Server: \\VHAPHIFPC19\shares\Current Studies\ZZ_DIP_EX. All other research materials will be stored and locked in the office of the Research Coordinator (PADRECC 4th Floor Room A447.) Per discussions with privacy officer, UPENN results will be transported by study staff on secure VA thumb drive or paper copies will be hand carried.

5.10.3. **Indicate how and where data/information will be stored, and specify pertinent security systems**.

Data are all collected at PADRECC clinic and will be stored in a filing cabinet in the PADRECC research coordinator's office, PVAMC Building 1 PADRECC 4th floor Room A447 which is locked and only assessable by PI, co-Is and other staff members involved in this study at PADRECC. Subjects' clinical information is stored on the PADRECC's Z drive which is only accessible by staff with appropriate login credentials and server permissions at CMCVAMC desktop computers or through secure remote VPN access with password protection. Data will not be downloaded to non-VA computers. Analyzed DaT-SPECT data will be stored on the PADRECC Z drive. Original fitness testing data, heart rate recordings and accelerometer data will be stored in locked file cabinets (paper data) or on a password protected server located at the Penn EMU. Penn Presbyterian Medical Center, 1st floor Mutch Building Room 109. This server is accessible only to appropriate

staff of the Penn Clinical and Translational Research Center/EMU staff with login credentials. Patient identifiable data will be accessible only to PI, co-PIs or research staff who have appropriate PVAMC training for accessing medical records. Data will be stored only on the secured PVAMC server and coded using a coding system to assign each patient with a research subject number. All research data will be coded by assigning each patient a unique research subject number. Numbers will be assigned sequentially on the day patient consents to participate in the study. All research data will be stored on the password-protected secure PADRECC server. The participant/identifier key (that will link the unique subject code to the subject) will also be kept on the PADRECC server, separate from the research data. Location of PADRECC Server: \\VHAPHIFPC19\shares\Current Studies\ZZ_DIP_EX. All other research materials will be stored and locked in the office of the Research Coordinator (PADRECC 4th Floor Room A447.)

5.10.4. **Will PHI be transmitted or transported outside of CMCVAMC? YES**
If yes, complete sections 5.10.4.1 through 5.10.4.4. <u>If no, go directly to section 5.11.</u>

5.10.4.1. **Does the informed consent document and Authorization for Use & Release of Individually Identifiable Health Information for Veterans Health Administration (VHA) Research form disclose entities/individuals to which/whom PHI will be transported or transmitted? YES**

5.10.4.2. **Specify entities/individuals outside CMCVAMC to which/whom data will be disclosed, the justification for such disclosure and the authority, and how they will access it**.
Subject names and phone numbers will be transmitted to Penn EMU staff via password protected documents and secure email to facilitate scheduling. ZIX secure email will be used to send the files within the UPenn environment.

5.10.4.3. **List the data/information that will be transmitted or transported, and specify how data will be transported or transmitted from one location to another and how it will be protected during transmission or transportation outside of CMCVAMC.**
Subject names and phone numbers will be transmitted to Penn EMU staff via password protected documents and secure email to facilitate scheduling.

5.11. **<u>Communication Plan</u>**

5.11.1. **Include plan for ensuring that the study is conducted according to the IRB-approved protocol.**
The PI will monitor the study to ensure that the study team adheres to the study protocol and applicable research regulations and CMC VAMC requirements. The research procedures will be fully explained to all participants and written informed consent will be obtained either by the PI, co-PI, or research coordinator or research assistant. Informed consent will also be documented in CPRS. The study team will be trained on the proper way to monitor and handle protocol deviations. The PI will, personally, monitor and address any deviation that may occur. Additionally, the PI will meet regularly with all study staff, co-Investigators and collaborators to ensure adherence.

5.11.2. **If a multi-site study, include information on**
- **ensuring that all required local site approvals are obtained and notifying the Director of any facility where the research is being conducted but the facility is not engaged, and**

- **keeping all engaged sites informed of changes to the protocol, informed consent, and HIPAA authorization**, and
- **informing local sites of any Serious Adverse Events, Unanticipated Problems, or interim results that may impact conduct of the study**, and
- **notifying all local facility directors and local site investigators (LSI) when a multi-site study reaches the point that it no longer requires engagement of the local facility (e.g., all subsequent follow-up of subjects will be performed by the PI from another facility).**

N/A

5.12. **Investigational Drug NO If yes, complete the rest of this section. If no, go directly to section 6.** *NOTE: If this study involves an investigational drug, investigator must contact the Pharmacy and Therapeutics (P&T) Committee and provide its approval to IRB.*

5.12.1. **Specify if the drug or biological agent is:**

5.12.1.1. **FDA approved: Choose an item.**

5.12.1.2. **Used for off-label purposes: Choose an item.**

5.12.2. **Include the FDA Investigational New Drug (IND) number for all non-FDA approved and off-label drugs, biological agents or nutritional supplements. If not applicable state, "Not Applicable."**

5.12.3. **Provide all relevant information about the drug, including pre-clinical data.**

5.12.4. **Explain any wash-out periods, rescue medications permitted and any type of medications not permitted while enrolled in the study.**

5.12.5. **Describe blinding and un-blinding procedures.**

5.12.6. **Include the dosage, route of administration, previous use, and the safety and efficacy information on any drug used for research purposes.**

5.12.7. **Describe rationale for the dosage in this study.**

5.12.8. **Justify why the risks are reasonable in relation to anticipated benefits and/or knowledge.**

5.12.9. **Describe where drug preparation will be done.**

5.12.10. **All drugs for CMCVAMC subjects must be dispensed through the VA investigational pharmacy.**

5.12.11. **Describe where the study treatment will be administered.**

5.12.12. **Describe plan for tracking a non-compliant treatment study subject.**

5.12.13. **Describe the process for the storage, security, dispensing and return of an investigational drug.**

5.13. **Investigational Device - NOT APPLICABLE If yes, complete the rest of this section.**

5.13.1. **The Investigational Device Exemption (IDE) number must be submitted for all significant risk devices and if an IDE exists for a non-significant risk device.**

5.13.2. **Significant Risk or Non-significant Risk - If a device is not approved by the FDA, specify whether or not the sponsor has determined this device to be a "significant risk" or "non-significant risk" as defined by the FDA.**

5.13.3. **Provide all relevant information about the device.**

5.13.4. **Describe blinding and un-blinding procedures.**

5.13.5. **Specify if device is:**
5.13.5.1. **FDA approved: Choose an item.**
5.13.5.2. **Used for off-label purposes: Choose an item.**

5.13.6. **Explain if the investigational device will be delivered and/or stored by the Principal Investigator or Pharmacy Service.**

5.13.7. **Describe the process for the storage, security, dispensing and return of an investigational device.**

5.13.8. **For research involving an investigational device, describe the SOP or plan for device control.**

5.13.9. **Address how the device will be stored in such a way that only research staff associated with the protocol will have access to the device.**

5.13.10. **Describe measures that will be put into place to ensure that the device will only be used in subjects of this research protocol.**

Section 6: Resources and Personnel

6.1. **Include where and by whom the research will be conducted**.

Study recruitment, consent, assessments, monitoring and data analysis will be conducted in the CMC VAMC PADRECC and Nuclear Medicine departments by study staff as indicated above and below. Exercise testing and monitoring will occur at the Penn EMU as indicated above and below.

6.2. **Provide a brief description of each individual's role in the study. Indicate who will have access to protected health information and who will be involved in recruiting subjects; obtaining informed consent; administering survey/interview procedures; and performing data analysis**.

Morley: access to PHI, recruiting, consent, assessments, data analysis, oversight. Wood: access to PHI, recruiting, consent, assessments, data analysis. Duda: access to PHI, recruiting, consent, assessments. Weintraub: recruitment, data analysis. Cheng: access to PHI, assessments, data analysis. Dubroff: access to PHI, assessments, data analysis. Salvatore: access to PHI, assessments, data analysis. Schmitz: access to PHI, data analysis. Xie: data analysis.

6.3. **If applicable, provide information on any services that will be performed by contractors, including what is being contracted out and with whom**.

Exercise testing and monitoring will be performed by staff of the Penn EMU as described throughout the protocol.

6.4. **If applicable, provide information on any Memoranda of Understanding (MOUs) or Data Use Agreements (DUAs) that are being entered into, including with whom and for what reason**.

NA

Section 7: Genetic Testing

7.1. **Does the project involve genetic testing? Not Applicable, SKIP TO SECTION 8**

7.2. **Will specimens be kept for future, unspecified use? Choose an item.**

7.3. **Will samples be made anonymous to maintain confidentiality? Choose an item.** (*If there is a link, it is not anonymous. Coding is not anonymous.)*

7.4. **Will specimens be destroyed after the project-specific use is completed? Choose an item.**

7.5. **Will specimens be sold in the future? Choose an item.**

7.6. **Will subjects be paid for their specimens now or in the future? Choose an item.**

7.7. **Will subjects be informed of the results of the specimen testing? Choose an item.**

7.8. **Are there any implications for family members based on specimen testing results? Choose an item.**

7.8.1. **If answer to section 7.8 is yes, they may be participants**.

7.9. **Will subjects be informed of results obtained from their DNA? Choose an item.**

7.10. **Explain if the study is looking for an association between a genetic marker and a specific disease or condition, but at this point it is not clear if the genetic marker has predictive value**.

7.11. **Describe if the study is based on the premise that a link between a genetic marker and a specific disease or condition is such that the marker is clinically useful in predicting the development of that specific disease or condition.**

7.12. **Will the subject be notified of the results and the provision for genetic counseling? Choose an item.**

Section 8: International Research

8.1. **Does this study involve international research? NOT APPLICABLE If no, go directly to section 9.**

8.1.1. ***For further instructions, refer to VHA Directive 2005-050, Requirements for Conducting VA-Approved International Research Involving Human Subjects, Human Biological Specimens, or Human Data***

8.1.2. ***VHA Handbook 1200.05 definition of international research - VA international research is any VA-approved research conducted at international sites (not within the United States (U.S.), its territories, or Commonwealths); any VA-approved research using either human biological specimens (identified, de-identified, or coded) or human data (identified, de-identified, or coded) originating from international sites; or any VA-approved research sending such specimens or data out of the U.S. NOTE: For the purposes of the VHA Handbook 1200.05, research conducted at U.S. military bases, ships, or embassies is not considered international research.***

Section 9: Statistical Analysis

9.1. Include statistical power calculations and the assumptions made in making these

calculations.

Aim 1: A meta-analysis of 39 physiotherapy and exercise intervention trials in PD estimated an effect size (mean(SD)) of a 5.0(7.3) point improvement in UPDRS motor score comparing intervention to control groups (6). This change in UPDRS motor score corresponds to a "moderate clinically meaningful difference" as described by Shulman and colleagues(100). Using a two-sample t-test with 80% power, we need 35 subjects per group to detect this difference between the control and intervention groups. Accounting for 20% drop-out, we would need 44 subjects per group. Recent studies completed by Dr. Schmitz and EMU staff include 2 community-based weightlifting interventions lasting 52-weeks with drop-out rates of 8% (N=141 randomized) and 14% (N=154 randomized)(101, 102). A two-year trial with a similar intervention had a drop-out rate of 13% (N=164 randomized) (103). EMU staff and protocols have been very successful in promoting retention in long-term exercise trials. The drop-out rate assumed for this aim may be an over-estimate for the short-term intervention but allows recruitment to adequately power the long-term intervention in Aim 2, as well. Based on our preliminary data that approximately 50% of DIP subjects have olfactory deficits and that hyposmia is strongly predictive of abnormal DaTI (we will assume 75% of subjects with hyposmia will have DaT SPECT abnormalities), we anticipate screening approximately 250 DIP subjects with olfactory tests to achieve the required cohort size. Olfactory screening with the UPSIT is straightforward and can be completed in 15-20 minutes.

Aim 2: Because DaT SPECT signal loss is be most sensitively detected in the putamen (particularly posterior putamen) in early PD, we will use this region to power our analysis. In our analysis of longitudinal DaT SPECT data from the PPMI study, average putamen signal was 0.83 (0.30) at baseline and 0.68 (0.23) at year 1 (absolute change 0.15 (0.13)), representing the expected change in the non-intervention group. With 35 subjects per group expected to complete the study (accounting for 20% drop-out), we are able to detect at least 0.06 points difference of change in average putamen signal between intervention and control groups (i.e., control group changes by 0.15 and intervention group changes by 0.09) with 80% power using two-sample t-test (alpha=0.05). As described in our preliminary data, the rate of rate of striatal degeneration during the prodromal period that we will capture may be greater than what been reported for the clinically manifest period of PD. Thus, the above estimates of the required sample size are conservative and it is likely that we could detect a significant effect of the intervention even if fewer than projected subjects complete the intervention (owing to greater attrition or decreased recruitment). For example if the non-intervention change in DaT uptake is 10% higher than we assumed (0.165 vs. 0.15), we could detect a similar effect size of the intervention with 29 (rather than 35) subjects per group. If the rate were 20% higher, we could detect a similar effect with 24 subjects. If the baseline rate of decline were 0.2 rather than 0.15 (33% higher), we could detect the effect with only 20 subjects per group.

Aim 3: One study has measured BDNF levels in PD patients before and after an 8 week exercise intervention(28). Baseline levels were mean (SD) 21 (3.4) and average post-intervention levels were 25(6.4) in the intervention group with no significant change in the non-intervention group. With 35 subjects per group expected to complete the study (accounting for 20% drop-out), we are able to detect a 4 point difference of change in BDNF between intervention and control groups using two-sample t-test with 80% power (alpha=0.05). This calculation assumes a conservative estimate of SD of change in the above calculation (SD=6.4, the largest SD of outcome in the above study).

9.2. Define plans for data and statistical analysis, including key elements of the statistical plan, stopping rules and endpoints.

Aim 1: The primary outcome of this aim is comparison of the change in average UPDRS motor scores between the exercise and no intervention groups after 8 weeks. Between groups changes will be assessed with a two (independent) sample t-test. Secondarily, within group changes from baseline for UPDRS scores and quantitative assessments will be assessed using paired t-tests. Additionally, the relationship between change in fitness (Vo2max) and change in UPDRS scores will be assessed using partial correlations controlling for age, gender and baseline fitness levels. An intention-to-treat analysis will be applied primarily but pre-planned secondary analyses will compare only exercise subjects deemed compliant with controls.

Aim 2: The primary outcome of this aim is comparison of the change in semi-quantitative DaT uptake from scans at baseline and 52 weeks (post-intervention). Because DaT SPECT signal loss is most sensitively detected in the putamen (particularly posterior putamen) in early PD(69)., we will focus the primary analysis on this region, though we will also examine signal changes in the caudate, anterior putamen and an index of right/left asymmetry. Differences in the rate of DaT signal change between groups will also be assessed using linear mixed-effects models which will allow us control for the influence of age, gender or other confounders. Linear mixed-effects modelling also accommodates the inclusion of data points with different follow-up times, allowing the analysis to include all subjects even if they do not complete the full intervention period. In this analysis, we will determine whether there is a significant effect of the "treatment group x time" interaction (rate of change) on the predictive value of models with DaT uptake as the dependent variable. An intention-to-treat analysis will be applied primarily but pre-planned secondary analyses will compare only exercise subjects deemed compliant with controls.

Aim 3: The primary outcome of this aim will be differences in the rate of change between intervention groups as assessed using independent samples t-tests. A secondary outcome will examine the rate of change using linear mixed-effects models controlling for age, gender and other potential confounders. Additionally, relationships of biomarkers to VO2max, UPDRS, quantitative motor and quantitative DaTI will be examined using partial correlations controlling for age and gender.

9.3. Provide sample size determination and analysis (include anticipated rate of screen failures, study discontinuations, lost to follow-up, etc.)

Based on power calculations, we anticipate screening 250 DIP subjects with olfactory testing, with the expectation that approximately 125 (50% of those screened) will be included in the imaging cohort, 88 (75% of those with abnormal olfactory testing) will be enrolled in exercise cohort and approximately 70 (assuming a 20% drop-out rate) will complete the study. 2018 Amendment: We anticipate enrolling 56 additional subjects under the modified inclusion criteria with 48 (24 per group) expected to complete all study activities. This will still allow for meaningful analysis of our primary outcomes according to the sensitivity analysis of sample size from the original protocol (20 per group adequate).

9.4. Describe how, where and by whom the data will be analyzed.

Preliminary statistical analyses will be conducted by the PI in the CMC PADRECC. Coded data will also be analyzed by Sharon Xie, PhD, Associate Professor of Biostatistics at Penn and statistical advisor on Dr. Morley's CDA award. Dr. Xie will have no access to the code that relates subjects' PHI to their study data

Section 10: References - Bibliography of cited literature

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