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Mobility in Daily Life and Falls in Parkinson's Disease: Potential for Rehabilitation
Informed Consent Form

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Minimal Risk Protocol

1. Title

Mobility in Daily Life and Falls in Parkinson's Disease: Potential for Rehabilitation

2. Objectives

The long-term goal is to develop effective physical rehabilitation approaches to improve balance and gait to prevent falls in people with Parkinson's disease and other elderly people at high fall risk. To reach this goal, we will identify objective measures of turning, gait and mobility activity during daily life that best reflect fall risk and to explore the use of home monitoring of mobility as outcome measures for rehabilitation to improve turning quality. We will also test the effectiveness of a Turning Boot Camp rehabilitation intervention to improve quality of turning and mobility in people with Parkinson's disease.

Specific Aims

Parkinson's disease (PD) is responsible for more mobility disability and falls than any other chronic disease. Turning is an especially challenging walking task for people with PD, requiring control of dynamic balance that is an essential part of mobility in daily life. In fact, the majority of activities in the home require turning steps. Studies show that the majority of people with PD, even early in the disease, have difficulty turning. Falls while turning are eight times more likely to result in hip fracture compared to straight walking and falls and fractures are five times more common in people with PD than age-matched people without PD. However, effective rehabilitation protocols for improving turning have not been established, largely due to a poor understanding of: 1) the relationship between turning characteristics in daily life and falls and 2) the potential for rehabilitation to improve quality of turning.

Recently, we demonstrated the feasibility of quantifying turning characteristics, as well as other measures of mobility, during daily life with body-worn inertial sensors. Our pilot studies show that people turn 800-1000 times per day and that quality and variability of turning, but not quantity of turning, are altered in people with PD and in elderly people without PD who fall*. We now hypothesize that objective measures of turning during daily life will be sensitive to fall risk and that turning during daily life can be improved with turning rehabilitation*. We will identify objective measures of turning, gait and mobility activity during daily life that best reflect fall risk and will explore the use of mobility during daily life as outcome measures for rehabilitation to improve quality of turning.

Aim I. Retrospective falls: To compare mobility during daily life over 7 days with body-worn, inertial sensors in fallers and nonfallers with PD. *This aim will test the hypothesis that turning quality and variability over 7 days will differentiate between PD with and without a history of falls better than gait quality or activity.* We will also determine the shortest number of daily life monitoring days needed to separate fallers from nonfallers. In addition, we will relate mobility in the home to clinical function, activity and participation characteristics, and objective measures of balance/gait fall risk in the On medication state prior to daily life monitoring. To compare PD with and without a history of falls, we will characterize turning, gait and activity throughout the day (about 10 hours/day) for 7 days using body-worn, inertial sensors on the feet and belt in 120 people with PD. Half the subjects with PD will have a history of falling (≥1 fall) and half of the subjects will have 0 falls in the previous 12 months, matched for disease severity. We will compare differences in daily and weekly turning, gait and activity between fallers and nonfallers to determine which, specific measures of continuous monitoring of mobility best separate fallers from nonfallers.

Aim II. Prospective falls: to identify the best measures of mobility during daily life associated with fall risk. *This aim will test the hypothesis that turning quality will be the most sensitive measure of mobility to estimate the time to first fall among subjects who report no history of falls.* Prospectively, it has been reported that 25% of people with PD with no fall history will experience a fall in the following year. We will use the data collected in Aim I during daily life to determine which

measures of mobility during daily life can predict which nonfallers will transition to having a fall over the next 12 months. We will recruit an additional 40 nonfallers with PD to add to the nonfallers recruited for Aim I to ensure we are adequately powered to prospectively predict falls for one year in all 100 nonfallers.

Aim III. Rehabilitation: To explore the effectiveness of Turning Boot Camp rehabilitation intervention to improve quality of turning in people with PD. *We hypothesize that rehabilitation focused on improving turning will improve quality of turning sufficiently to justify a clinical trial.* We have developed an unique exercise program – Turning Boot Camp – that involves practicing turning while dual-tasking in a body-support harness with 5 stations; Flexibility, Anticipatory Weight Shifting, Tai Chi, Boxing, and Agility. The 60 fallers with PD from Aim I will be randomized into a 6-week, 3x/week, one-on-one Turning Boot Camp group or No Intervention Control group. This pilot intervention study will determine the number of subjects needed for a future clinical trial and will determine the sensitivity to change with rehabilitation of our daily life turning quality measures (mean and variability of number of steps to turn, turn amplitude, turn velocity). We predict that the Turning Boot Camp rehabilitation intervention will improve turning in daily life enough to justify a larger clinical trial.

3. Background

SIGNIFICANCE

Balance disorders and falls are common in people with Parkinson's disease (PD) and lack effective treatment. PD is responsible for more falls than any other chronic disease and imposes a heavy burden on over 3% of people over 65 years [1]. Functional mobility depends on neural control of gait, balance and attention. Levodopa does not improve, and may worsen, balance and attention. In general, as the disease progresses, levodopa is less efficacious for balance and cognitive function, likely because non-dopaminergic systems are impaired later in the disease course [2,3]. In addition, deep brain stimulation is not effective for improving balance, cognitive function or reducing falls.

Falls often occur while turning. The majority of tasks in the home require 3-4 turns and over 40% of daily steps are turning steps[4]. In addition, when a fall occurs during a turn, it is 8 times more likely to result in a hip fracture[5]. In fact, falls that occur while attempting a turn result in sideways falling to the ground, often onto the greater trochanter of the hip[5]. A recent video analysis of the most common circumstances of falls in daily life in 130 elderly people residing in long-term care revealed that that 41% of 223 recorded falls occured during turning[6]. The majority of people with PD have difficulty turning, even early in the disease, because of the complex interaction of gait with balance during turning[7-9]. PD is associated with stiff, 'en bloc' turning due to impaired multisegmental control and impaired neural control of balance. As a result, people with PD fall 5 times more than age-matched elderly people and often fall while turning [10].

Turning may be a sensitive marker for fall risk because it reflects complex neural control of dynamic balance. 'Dynamic balance' is the ability to control the body center of mass (COM) with respect to the moving base of support (Fig. 1) [11]. Turning safely requires the complex interaction of many neural processes. Effective turning requires control of axial flexibility, adequate size and speed of steps, top-down coordination of eyes-head-trunk rotation, multisensory integration, motor planning, anticipatory postural adjustments, attention and set-switching, all of which are affected by both aging and PD [12,13]. Since turning is such a complex and common functional mobility task, we expect quality of turning to differ for those with a high versus a low risk of falls. *Aim I will compare mobility during daily life over 7 days using body-worn inertial sensors in people with PD who have a history of falling from those who do not have a fall history. Aim II will follow nonfallers for a year to determine if mobility during daily life, and specifically turning quality, predicts first falls*.

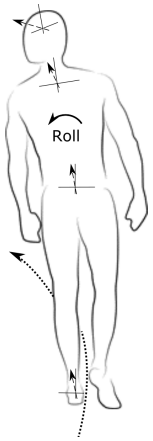


Figure 1. Turning involves complex neural control of balance and gait.

Turning quality may reflect freezing of gait (FoG). We previously demonstrated that FoG can best be elicited during turning, especially large turn angles in small areas[14]. Because FoG is usually associated with "trembling of the knees" related to repeated, lateral postural weight shifts, we predict that freezers will show larger lateral trunk motion, increased jerkiness as well as slower and smaller turns than nonfreezers. These impaired turns during daily life may lead to falls. However, no studies have yet compared turning quality in freezers versus nonfreezers during daily life in the home and community and how these measures of turning may relate to falls. *Aim I will also determine if mobility during daily life differ in people with PD with and without FoG.*

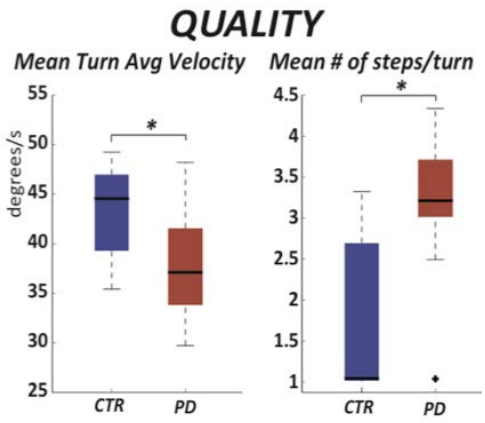


Figure 2. Quality of turning in PD and control subjects [24].

Quality, but not quantity, of turning during daily life is different for patients with PD and age-matched control subjects [15]. Our pilot study showed that daily activity, *e.g.,* percent of the day subjects were walking or turning and the mean number of turns per day were not different between 13 subjects with PD and 13 control subjects. However, the quality of turning, such as turn velocity and number of steps to turn were significantly different between the PD and age-matched controls groups (Fig. 2). Since quality of turning is affected by PD and people with PD fall more than age-matched elderly people, we predict that turning performance in daily life will also be related to fall risk. *Aim I will investigate the extent to which turning measures and measure variability (compared with gait and activity) across 7 days differentiate PD fallers versus nonfallers.*

We recently showed that measures of mobility during daily life are more sensitive than clinical tests to detect impairments leading to fall risk in the elderly[16]. Although we found no differences in objective measures of turning and walking during a single test observed in the clinic, measures of mobility during daily life, and specifically mean turn velocity during 7 days of monitoring, significantly separated performance of 19 retrospective fallers and 16 nonfallers (Fig. 3). More sensitive and specific fall risk measures will identify appropriate patients in need of a change in treatment or referral to rehabilitation to prevent falls. In addition, ongoing studies will be collecting daily life mobility data in 100 elderly people for 7 days. *Aim I will build on this pilot study in elderly subjects to determine whether mobility during daily life will separate retrospective fallers from nonfallers with PD.*

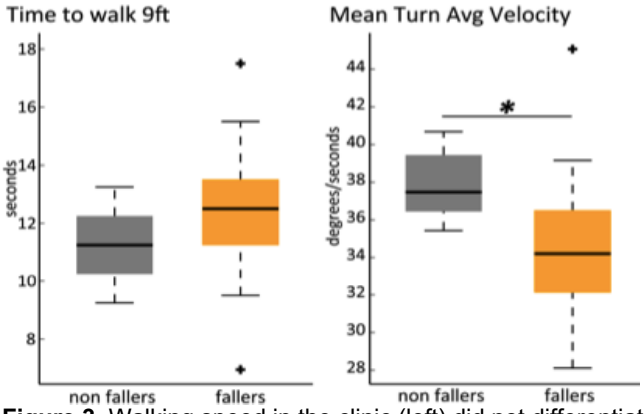
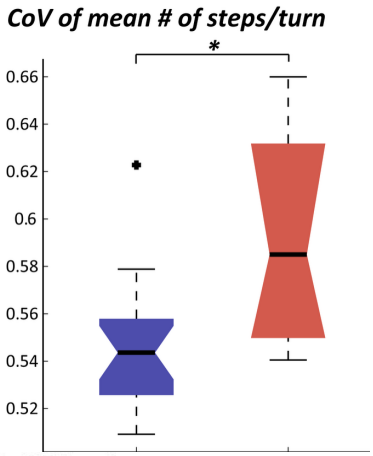


Figure 3. Walking speed in the clinic (left) did not differentiate elderly fallers versus nonfallers like mean turn velocity during daily life (right) [36].

We showed that variability of turning during daily life is larger in older fallers than nonfallers[16]. Recently, we published a pilot study in 35 older adults to determine whether continuous monitoring of turns during daily life was feasible and sensitive to those with falls (both retrospectively and prospectively). Results showed that whereas quantity of turns and speed of turns per day or week did not differentiate prospective fallers versus nonfallers, variability of number of steps per turn across 7 days was significantly larger in the retrospective and prospective faller groups (Fig. 4). We currently are examining turning quality over 7 days in a larger sample of elderly people. *Aim II will also determine if turning can help estimate time to first fall.*

The potential for rehabilitation to improve mobility during daily life is unknown, partly because objective measures of mobility during daily life are unavailable. Motion analysis laboratories have used complex equipment and analysis to understand the biomechanics and neural control of turning and walking. A few, small laboratory trials have demonstrated improved turning speed with rehabilitation focused on turning in people with PD but none have examined effects on turning during daily life[31-34]. In addition, laboratory kinematic equipment is impractical for clinical trials or clinical practice, whereas body-worn inertial sensor measures of turning are accessible for clinical environments[17]. A recent Cochrane review of rehabilitation for PD has demonstrated improvements in gait speed but turning ability has not been studied [18,19]. *Aim III will evaluate responsiveness of turning during daily life to a new Turning Boot Camp rehabilitation program.*



The lack of successful rehabilitation for impaired turning may be because current approaches seldom address underlying impairments that constrain turning. Physical therapists aiming to improve mobility generally focus on straight-ahead gait training for walking and quiet stance practice for balance[18]. This separate gait-static balance approach does not attempt to train dynamic balance during turning. Training dynamic balance during turning requires practicing very challenging turning tasks that require a fall-protection system and a focus on underlying impairments, such as lack of axial flexibility. *Aim III will test a novel turning rehabilitation that focuses on the neurophysiological impairments due to PD that limit quality of turning.*

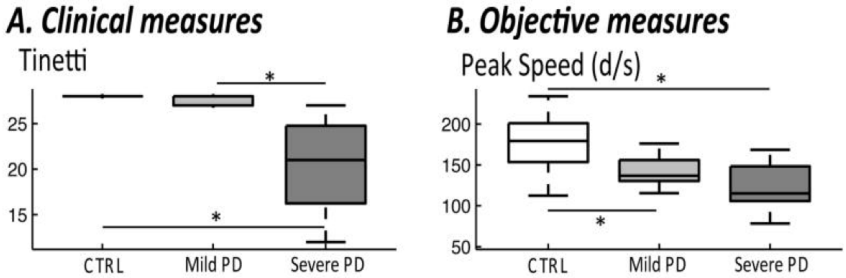


Figure 5. Clinical rating scales like the Tinetti are less sensitive to mild PD than objective turning measures, such as peak speed [8].

INNOVATION

Lack of valid, instrumented measures of turning thwarts testing of efficacy of rehabilitation for dynamic balance impairments. It has not yet been possible to test effectiveness of novel rehabilitation approaches for dynamic balance impairments because of lack of accessible, objective measures of turning for clinical environments and during normal daily activities. We showed that current clinical tests of balance and patient-reported outcomes do not reflect turning deficits in mild PD[7]. For example, Fig. 5 shows the poor sensitivity of the Tinnetti Balance and Gait Scale to mild PD, compared to the good sensitivity of inertial measures of turning in the laboratory [7]. We have demonstrated that new, wearable technology, involving small, wireless, inertial sensors, can provide automatic measures of angular velocities and linear accelerations that quantify the duration, velocity and number of steps used to turn [15,17,20].

We were the first to demonstrate the feasibility of measuring quality and quantity of turning during daily life [20]. Fig. 6 shows how we can identify turning periods (gray bars) from the pelvis gyroscope during continuous activities. When turns occur very close in time, as the first two examples, they can be merged as one turning activity. Our inertial sensor algorithms identified an average of 866 turns per day (min: 300; max: 1511). Despite the large number of turns, walking bouts (periods > 10 seconds) were often limited to a few per day (6-26% of the day) showing that people turn more often than they walk straight during daily activities. *Aim I will relate quality of turning during community living to fall history in PD (retrospective) and Aim II will determine*

the measures during daily life that can predict the first fall (prospective).

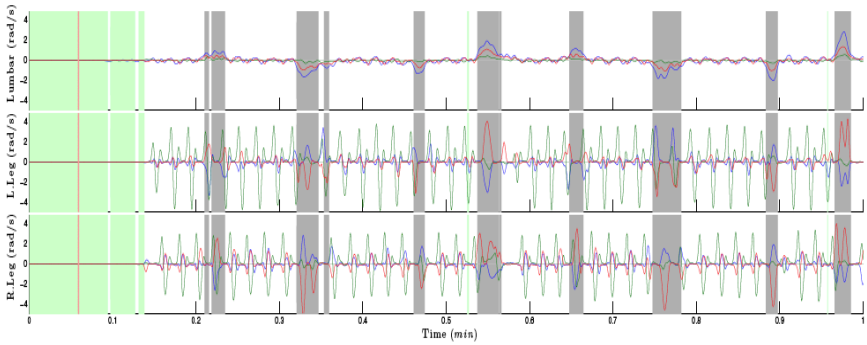


Figure 6. 3D Gyroscope activity over 1 minute in a subject wearing sensors on the lumbar segment and each leg during standing, walking and turning (gray areas).

Effective training protocols for improving turning performance in people with PD have not been established. Very few studies have focused on improving turning. A recent study showed that external auditory, visual, or vibrotactile cues could increase the speed of turning in people with PD in the clinic, but this approach is not practical in daily life[21]. A one-session trial of practicing walking on a rotating treadmill was shown to improve 360-degree turning for a few minutes, but only toward the side that was practiced, and the improvement did not transfer to walking turns[22]. We also published a pilot study showing that an *Agility Boot Camp* exercise program improved the speed of 180-degree turns better than treadmill training but our intervention was not focused on improving turning, did not measure dynamic balance, and did not measure turning during daily activity[23]. No other studies have investigated the effects of rehabilitation on turning, particularly on turns during daily living tasks. *Aim II will test the usefulness of measuring community living turning as a rehabilitation outcome measure for an innovative turning retraining intervention.*

The potential impact of effective turning rehabilitation in aging populations may be profound. Turning is an example of a task requiring control of dynamic balance that is impaired in many elderly, neurological, and orthopedic patients. Turning is affected by many conditions of aging because coordination of walking with balance control required of turning involves the interplay of so many biomechanical, sensory and motor systems. For example, hip and/or spine osteoarthritis may limit axial rotation; gaze instability or vestibular or somatosensory loss may impair sensory integration; and impaired bilateral coordination after a head-injury may limit asymmetrical stepping, all required for effective turning. Because turning behavior is a complex, dynamic balance skill that is critical for most functional activities, rehabilitation that can improve turning will improve independence in functional activities and reduce falls and fall-injuries for the majority of elderly people with mobility disability seeing physical therapists.

4. Study Design

This project consists of three aims. We will compare mobility in 60 people with PD with a fall history (1 or more fall in the past 12 months) with 60 nonfallers (0 falls in the past 12 months) of similar PD severity (Aim I). Forty more subjects who are nonfallers with PD will be added to the nonfaller group of Aim I to determine if we can predict the time to first future fall (Aim II). All subjects will be tested in the laboratory in the ON levodopa medication state. Immediately after testing, the nonfallers will undergo 7 days of continuous-monitoring of their mobility with wearable sensors on their belt and imbedded in SmartSocks, followed by 12 months of fall diary tracking. The 60 PD with a history of falls from Aim I, will be randomized to a 6-week *Turning Boot Camp* intervention or into a No Intervention Control group (30 subjects in each group) for Aim III. They will also use wearable sensors on their belt and imbedded in SmartSocks for 7 days of monitoring immediately before and after the 6-week intervention period. The technological approach is cutting edge and will allow us to develop sensitive, functional objective biomarkers for mobility disorders for use in future clinical trials and practice.

All subjects will complete several cognitive tests on an iPad. We hypothesize, based on our pilot data and the literature, that visuospatial cognitive function, specifically, Benton Judgement of Line Orientation (JLO)[1,2], will be related to turning mobility. This specific test of visuospatial function is one of 3 tests we will use to assess visuospatial and executive function. Cognitive testing will use the free, UCSF Memory and Aging Center, *Tablet-based Cognitive Assessment Tool*[3] *(*TabCAT) tests on an IPAD, Figure 1. The collected data is uploaded to the UCSF administrative hub that allows users to assemble TabCAT batteries, set up login credentials for examiners, and download data. The total battery of 3 memory tasks, 6 executive tasks, 3 visuospatial tasks, 1 language task, and 2 spatial memory tasks, takes approximately 90 minutes to complete. However, for our purpose we will only perform 3 tasks for a total of about 20 minutes to complete.

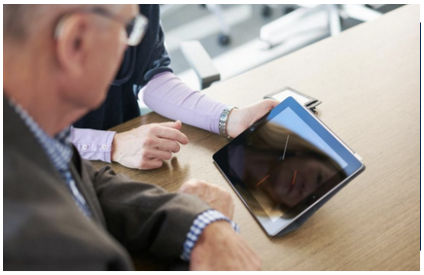


Figure 1: The Tablet-based Cognitive Assessment Tool (TabCAT) is a software platform developed at UCSF for the administration of clinical and research tools and for the secure storage of, and access to, the data collected https://memory.ucsf.edu/research-trials/professional/tabcat

1 Benton, A. L., Varney, N. R. & Hamsher, K. D. Visuospatial judgment. A clinical test. *Archives of neurology* **35**, 364-367 (1978).

2 Specketer, K. *et al.* Visuospatial functioning is associated with sleep disturbance and hallucinations in nondemented patients with Parkinson's disease. *Journal of clinical and experimental neuropsychology*, 1-11, doi:10.1080/13803395.2019.1623180 (2019).

3 Possin, K. L. *et al.* The Brain Health Assessment for Detecting and Diagnosing Neurocognitive Disorders. *Journal of the American Geriatrics Society* **66**, 150-156, doi:10.1111/jgs.15208 (2018).

Since FoG is thought to increase fall risk in people with PD, we will also determine whether daily life monitoring of turning quality is also related to freezing of gait. Based on our previous studies recruiting people with PD taking levodopa and with moderate to severe disease severity (Hoehn and Yahr II-IV), we expect approximately 30% of our subjects will report FoG in the New Freezing of Gait Questionnaire (NFOGQ)[15]. We will also investigate the association between turning quality (as well as straight walking and activity) with PD severity, balance confidence, clinical and objective balance performance, quality of life, age and other demographics (see above).

One-hundred subjects with PD who report no falls in the previous 12 months will wear sensors for 7 days and be followed for 12 months with a bimonthly fall questionnaires (see Falls Tracking below). We expect 25%- 30% of the 60 PD without a history of falls to convert to falling[48]. Therefore for Aim II we will recruit 40 additional subjects with no falls in the previous 12 months to have enough subjects for Aim II analysis. Aim II will determine if turning measures over a week of daily life can predict time to first fall over the next 12 months in 100 nonfallers. *We hypothesize that daily life measures of turning (a challenging, frequent dynamic balance task) will best predict first falls.*

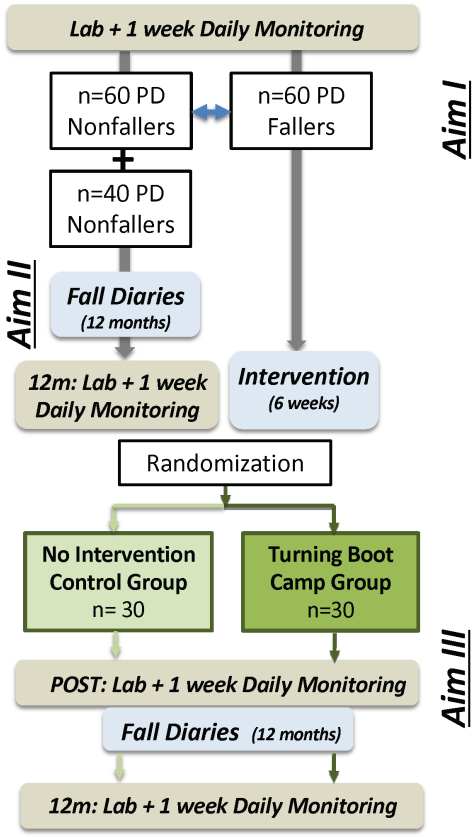


Figure 7. Schematic of subject testing and randomization for all Aims.

Falls Tracking: To record falls prospectively after for 12 months, subjects will receive automated messages (via the Research Electronic Data Capture database system, REDCap; email or phone message) every other week. If subjects respond YES to the question: "Did you experience a fall in the last two weeks?" then a research assistant will call the subject for more details about cause of fall, if injured, location of fall, etc.

Immediately after the study visit, subjects will wear the body-worn sensors during seven consecutive days (8-10 hrs/day), when sensors are taken off and placed in a charger. At the end of the week, subjects will mail the sensors in a self-addressed, prepaid *US Post* box to the laboratory.

This is a single-blinded, randomized, pilot study to determine how many subjects would be needed for a future clinical trial to improve mobility during daily life with rehabilitation. The researchers collecting and analyzing the data will not know the group in which subjects were randomized. After baseline testing in the laboratory and one week of home monitoring with body-worn inertial sensors, the 60 fallers from Aim I will begin either the Turning Boot Camp Intervention or No Intervention Control. (Fig. 7). One week of daily life monitoring and laboratory testing will occur again 6-weeks later (corresponding to the intervention duration).

Study Interventions. Participants in the treatment group will attend supervised, 1-hour classes, 3 times per week for 6 weeks, one-on-one with the same exercise trainer, overseen by a physical therapist investigator. Each intervention minimizes reliance on expensive equipment and uses simple, easily-performed exercises based on functional movements. We will use a ceiling-fixed harness system that does not provide support but would prevent falls during challenging turning exercise practice. Both interventions will be matched as closely as possible in progression from the low- to high-end of the range for moderate intensity. The instructor will indicate exercise

progression and compliance for each subject on a weekly basis in the REDCap database to define individual participant efforts, based on tolerance.

5. Study Population

a) Number of Subjects

We will compare mobility in 60 people with PD with a fall history (1 or more fall in the past 12 months) with 60 nonfallers (0 falls in the past 12 months) of similar PD severity for Aim I. Data from 100 subjects with PD and 0 falls in past 12 months (60 from Aim I + 40 more) will be analyzed for Aim II to determine if we can predict the time to first future fall. 60 people with PD and a fall history (subjects from Aim I) will be included for intervention (Aim III).

b) Inclusion and Exclusion Criteria

PD Inclusion Criteria: 1) Diagnosis of idiopathic PD from movement disorders neurologist with the United Kingdom Brain Bank criteria of bradykinesia with 3 or more of the following - rest tremor, rigidity, bradykinesia and balance problems not from visual, vestibular, cerebellar or proprioceptive conditions; 2) excellent response to levodopa; b) Hoehn & Yahr [24] stages II-IV; and 3) ages 55-85 years old.

PD Fallers Inclusion Criteria: Same as above plus: 1) self-report of at least one fall in the last 12 months, 2) able to maintain current exercise activities while participating in the intervention, 3) cognitive ability sufficient to participate in testing procedures and exercise classes, 4) free of any medical conditions or medication that contraindicates participation in moderate intensity exercise and 5) willing and able to participate in exercise intervention 3x/week for 6 weeks.

Exclusion criteria (all subjects): 1) Major musculoskeletal or neurological disorders, structural brain disease, epilepsy, acute illness or health history, other than PD, significantly affecting gait and turning (*i.e.,* musculo-skeletal disorder, vestibular problem, head injury, stroke, cardiac disease, etc.); 2) no medical condition that precludes exercise; 3) ≤ MoCA 21 or inability to follow directions; 4) excessive use of alcohol or recreational drugs; 5) recent change in medication; 6) inability to stand and walk for 2 minutes without an assistive device.

c) Vulnerable Populations

None.

d) Setting

Study visits will be in the OHSU Balance Disorders Laboratory in Richard Jones Hall (RJH).

Both at home and in the laboratory, subjects will wear three inertial sensors – one on each foot (embedded in neoprene SmartSocks; Fig. 8) and one at the lumbar spine level to quantify mobility. To determine the added value of daily life monitoring of mobility for identifying fall risk over laboratory/clinic mobility measures, we will collect the following balance and gait tests: postural sway in standing with eyes open and eyes closed on a firm and compliant foam surface for 30 seconds x 4 conditions [35], postural responses with the Push and Release test [36], anticipatory postural adjustments prior to step initiation [37] and a 2-minute walk with 180-degree turns, both with and without a cognitive dual task, in addition to clinical measures. In one walking trial, subjects will be instructed to walk at their natural, comfortable pace with natural turns and in the other trial, while reciting serial subtractions. A portion of the gait and balance assessments will be performed while wearing a headband which measures change in blood flow in the prefrontal cortex. Functional near infrared spectroscopy



Figure 8. SmartSocks with inerial sensors on top of foot (A) and battery to outside of leg (B).

(fNIRS) provides a measurement of cortical blood flow as a proxy for brain activity and can be used during mobile balance tasks. It is a non-invasive wireless portable monitoring system that includes functional channels embedded in a headband (OctaMon, Artinis Medical system, Figure 8.5). The fNIRS system is flexible to lay flat against the subjects' head, allowing the sensors to maintain an orthogonal orientation to the skin surface. The fNIRS system will be used at the baseline visit for both fallers and non-fallers, and at the 6-week follow-up visit for the fallers.



Figure 8.5. Artinis Octamon fNIRS headband.

e) Recruitment Methods

Subjects will be recruited on a convenience basis from the OHSU Balance Disorders Laboratory Database and Movement Disorders Clinic. Co-Investigators Dr. Dale and Dr. Quinn (Movement Disorders) will guide the clinic recruitment efforts to identify potential subjects and refer them to the Balance Disorders Laboratory, via handing out/send electronically advertisements, obtaining permission to give their contact information to us, and by having one of our study staff in the clinic to directly recruit when they identify an eligible patient. We will also expand recruitment to include posting study advertisements/sending electronically at physical and virtual locations such as health clubs, social media sites such as Facebook, community centers, retirement communities, support group meetings, Parkinson Center newsletters, and at outreach events. We will use a screening survey hosted by Qualtrics to determine initial eligibility. This survey may be linked to study advertisements or administered in person (e.g., at outreach events). Survey data from respondents who did not meet inclusion criteria or were not interested in the study will be discarded. Such respondents will be provided with the lab's contact information and invited to contact the lab if they would like to be considered for future studies.

Members of the Balance Disorders Laboratory will screen potential subjects in person, via email, over the phone or video conference, using the uploaded screening form and telephone script (see also HIPAA Waiver form). Screening is done before the first study visit because it would be a burden for subjects to come all the way to the OHSU laboratory for screening that could be completed over the phone or in the clinic.

Nonfaller participants will be compensated $15 for both virtual visits and $70 for the week wearing the sensors at home (or $10/day, if less than one week) – at baseline for a total of $100. Intervention participants will be paid $100 for each study visit + wearing Smart Sox for one week ($200 for the baseline and 6 weeks later post visit). Subjects who are randomized into the No Intervention Control group will receive an additional $150 after completing post-test sessions, as an incentive to stay in the study (total for Control group will be $350). We propose the $150 incentive, because there would likely be a high drop-out rate for subjects who do not get assigned to the rehabilitation intervention group. Control subjects could use the additional money for 6 weeks of community exercise classes, if they wanted to.

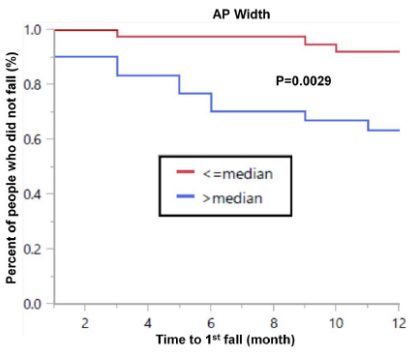


Figure 9. Survival curves showing time to first fall among 67 subjects who reported no falls in the year prior to the study. Gait width variability was larger (blue) in those who experienced a fall [25].

Nonfallers: One-hundred PD subjects who have no history of falls will each have one study visit to the laboratory, followed by one week of continuous monitoring and tracking falls for one year.

Fallers: The 60 subjects with PD who have a history of falls will have two study visits, six weeks apart (before/after intervention, for those randomized to it and same duration for those randomized to Control group), each followed-up by one week of continuous monitoring and also track falls for one year. Subjects will not be reimbursed for the intervention sessions

For ease of payment to the subjects after completing the week of wearing the sensors, we will give each subject a ClinCard, debit card, during the study visit. We will load the appropriate amount of money on the card after the study visit and following wearing the sensors at home. This will be a quicker way to pay the subjects, rather than having a check sent to them.
**Adaptations during COVID-19 restrictions: Screening and recruitment by research coordinators will occur over the phone or via video conference.*

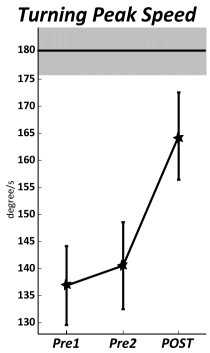


Figure 10. Mean and SEM of peak speed turning180 degrees, before (PRE1 and PRE2) and after (POST) a 4-week agility training pilot study[50].

f) Consent Process
For subjects who wish to participate, an informed consent will be presented and explained to the subjects. The informed consent explains the nature of the study and the possible risks and benefit of the experiment, as well as HIPAA privacy information. This form also informs the subjects that they may withdraw from testing at any time without penalty. Subjects will be given ample opportunity to read, ask questions, and when satisfied, document their consent to participate by signing the informed consent form.

Modifications to the Consent Process
**Adaptations during COVID-19 restrictions: We will email consent forms to potential participants who qualify for the study, so they can read through it. Then we will call/video conference to discuss consent form and answer any questions. At this time the person can choose to sign the consent form and email/mail it back to us.*
**Re-Consent for COVID-19 Modified Operations: Subjects will be notified of modified operations due to COVID-19 and the discussion will be documented in the subject chart.*

We may telephone screen subjects to determine eligibility for the study before consenting. We will have a HIPAA waiver to allow collecting health information prior to consenting.

Non-English Speaking Subjects
We plan to recruit non-English speaking subjects. We will include a short form in the person's native language and have an interpreter present during recruitment and the test session translate and ensure the person fully understand the study and their role in the study. We have included the Spanish short-consent form in our study documents, as this is the most likely foreign language. However, we can add other languages if there is the potential of recruiting someone with a different primary language.

6. Procedures
The 60 subjects with a history of falls from Aim I will be randomized in 2 groups: 1) Turning Boot Camp or 2) No Intervention Control group. Both groups will have a baseline test session and 7-days of continuous monitoring (Aim I). Post-testing and 7-days of continuous monitoring will occur immediately after the 6-week intervention time period (Fig. 7). Thus the timeline will be: Week 1 Baseline Study Visit, Week 2 Continuous monitoring, Weeks 3-8 Intervention, Week 9 Post-Study Visit, Week 10 Continuous monitoring. Week 52 – Falls Tracking completed.

**Adaptations during COVID-19 restrictions: No in-person test sessions for the non-fallers. We will only collect assessments that can be given to the participant to complete (paper/electronic forms) or we can complete during a phone or video conference. A member of the study team will deliver in a*

box to the participant's home: 1) an iPad that will be used for cognitive tests and also for video conference call, if person does not have a computer with a camera, and 2) the body-worn sensors that are a worn at home for 7 days. There will be no direct interaction with the participants and we will thoroughly wipe-down/disinfect the sensors and iPad after each use. At the end of the week there will be a second video conference session in which one of the study team members will remotely conduct the MDS-UPDRS and perform a simple prescribed gait task with the participant. If the participants has agreed, this session will be recorded so that the videos can be reviewed for consistency of scoring. After the participants is finished with assessments and wearing the sensors, we will pick up the box of equipment from their home.

Randomization for Rigor. After recruitment, each participant will learn their group assignment by opening a sealed, sequentially numbered envelope that contains the randomly determined group assignment. To maintain rigor of study design, subjects will be randomized into either the *Turning Boot Camp* or *No Intervention* Control groups via a blocked random allocation strategy. The same therapist will lead both groups to minimize effects of expert clinicians. Randomization will use an adaptive design to balance the distribution of 'PD severity' (Hoehn and Yahr II or III-IV) covariate between arms. An adaptive approach was selected over stratification since there is no *a priori* assumption about the relationship between study outcomes and PD severity. The blocking will help ensure equal numbers in the two arms, and we will vary block sizes (2, 4, 6 or 8) to help avoid selection bias. All subjects will agree not to change their exercise activities or antiparkinson medication during the pre-intervention week of baseline testing, 6-week intervention/delay or post-intervention week of testing. Further details in the *Statistical Design document (Clinical Trials)*.

Study Interventions. Participants in the Turning Boot Camp group will attend supervised, 1-hour classes, 3 times per week for 6 weeks, one-on-one with the same exercise trainer, overseen by a physical therapist investigator. Each intervention minimizes reliance on expensive equipment and uses simple, easily-performed exercises based on functional movements. For safety, we will use a ceiling-fixed harness system (ZeroG by Aretech) that does not provide support but would prevent falls during challenging turning exercise practice. Both interventions will be matched as closely as possible in progression from the low- to high-end of the range for moderate intensity. The instructor will indicate exercise progression and compliance for each subject on a weekly basis in a Research Electronic Data Capture (REDCap) database to define individual participant efforts, based on tolerance.

No Intervention Control Group. Subjects will not receive any intervention between the two study visits.

Turning Boot Camp. The Turning Boot Camp rehabilitation program will consist of a progressive program of training turning strategies tailored to each subject's impairments (Fig. 11. Because turning is quite challenging to dynamic balance, subjects will wear a body-weight support harness (ZeroG) to safely practice turning. The *Turning Boot Camp* reflects our experience with the *Agility Boot Camp* we developed previously, based on the PD-impaired neural control systems, but has been adapted to focus on turning ability[51]. Figure 10 summarizes the impairments from

physiological systems due to PD that affect turning, their impact turning function and the exercise principles aimed at each physiological constraint. Based on the exercise motor learning principles, participants spend 10-15 minutes at each of 5 Exercise Stations that focus on particular constraints of turning ability with prescribed Exercise Actions and Progressions (Table 2). The *Aerobic Turning station* is based on our laboratory study of fast, continuous turning[8]; the Rotation *Flexibility Station* is a subset of movements from Pilates and Shenkman exercises that focus on whole body rotation[52]; the *Boxing Station* is adapted from 'Rock Steady' [53], Adapted Tai Chi was from Dr. Fuzhong Li [54] and a *Functional Turning Station* is task-specific, with dual-task training of turning strategies practicing many size turns while walking[55].

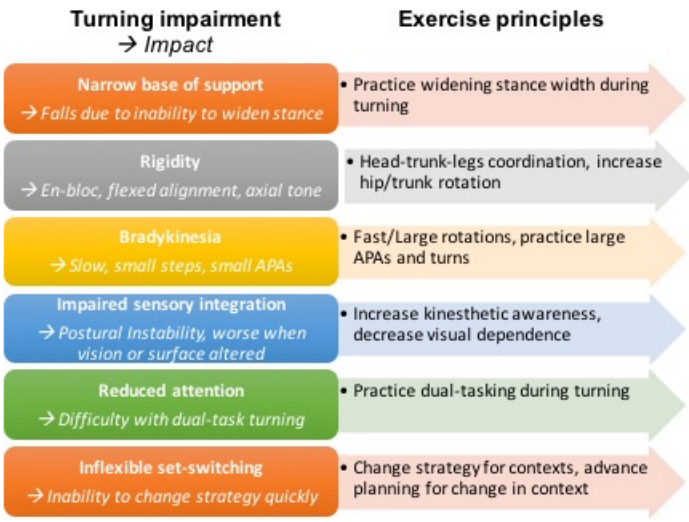


Figure 11. Summary of the main physiological impirments affecting turning mobility in people with PD, how each impairment affects turning skills, and the exercise principles targeting each impairment in the Turning Boot Camp.

Blinding for Rigor. Clinical pre- and post-testing will be carried out by a researcher who is blinded to group assignment. Scientists analyzing daily life monitoring data will be blinded to pre-post status. *Safety issues.* All adverse events, either during therapy or during the week of data collection will be recorded and reported. Falls and musculoskeletal strains are the greatest risk for exercise in patients with PD who have balance and gait impairments. Wearing sensors at home should not increase risk of injury or falling (See *Human Subjects*).

Table 2. *Turning Boot Camp* exercise stations with each exercise focus, action and progression

Exercise Station	Exercise Focus	Exercise Actions	Exercise Progressions
Aerobic Turning	Agility with fast rotations and quick switching, warm-up aerobic, looking first	Fast walking/turning on preplanned, sequential turning course	I. Comfortable speed, varied angles II. Fast switching angles and change step width III. Dual task
Rotation Flexibility	Axial mobility, flexibility, large and fast segmental rotations	Cervical, trunk, and hip rotations	I. Segmental twisting chair II. Standing rotations III. Floor rolling
Boxing Circles	Quickly changing rotation strategy, weight shifting, postural responses, agility footwork	Cross-punches of punching bag	I. Standing focus weight shift and axial rotation II. Increase speed and force and sequence III. Walking around bag
Tai Chi Rotation	Kinesthesia, sequential coordination, APAs, postural, head leads turn	Brush knees, cloud hands and repulsing monkey	I. Follow leader II. Glasses block view of the body, eyes closed III. Lead the sequence
Functional Turning	Attention, functional context, cognitive challenge	Turning course: moving objects, navigation around obstacles, narrow spaces.	I. Follow direction II. Sudden turns to external cues III. Complex turning sequence from memory

Outcomes. To test our hypothesis that rehabilitation can improve turning performance, the *primary outcome measure* for this pilot study will be *the variability the number of steps to turn averaged over the 7 days of daily monitoring.* We anticipate that this measure will be the one to best separate fallers and nonfallers[17] in Aim 1. Secondary outcome measures will be: 1) other weekly objective

gait and turning measures (Table 1), 2) activity (Table 1), 3) clinical measures (PDQ-39, UPDRS, w-FCI, LLDI, Life Space, Neuro QOL, IPAQ short form, MiniBESTest and ABC), 4) fear of falling (FES-I), 5) Patient and Clinician Global Impression of Change Scales (PGIC/CGIC), and 6) fall rate during 12 months after intervention. As noted in Aim I, we will explore combinations of activity, gait and turning measures that best separate fallers and nonfallers and respond to therapy. This process will inform potential outcome measures for future clinical trial(s).

Falls. To determine whether intense turning rehabilitation has the potential to reduce falls (at least to power a future study) participants will complete a 12-month, fall-monitoring diary after the 6-week interventions. Participants will be called or emailed every 2 weeks via REDCap (each subject's discretion) about whether they experienced a fall in that period. If a fall has occurred, participants will answer additional survey questions to determine the severity and circumstances of the fall and whether it resulted in an injury or required medical intervention. A fall will be defined as "an event that results in coming to rest unintentionally on the ground or other lower level" [57].

Table 1. Summary of Daily Life Monitoring Measures

Turning Quality (and CoV)	**Activity - Mobility**	**Gait Quality (and CoV)**
# Steps to complete a turn*	% of day active	Stride velocity (cm/sec)
Turn peak velocity (degree/s)	# turns per hour	Stride length (m)
Turn angle amplitude (degree)	# walking steps/day	Cadence (steps/minute
Turn duration (sec)	# walking bouts/day	Double support time (ms)
Turn trunk jerk (m^2/sec^2)	Duration of longest bout/day (sec)	Angle of foot at heel strike (degree)
		Lateral trunk range (cm)

*Primary outcome to be different in fallers versus nonfallers. Power computations are based on this measure.

7. Data and Specimens

a) Handling of Data and Specimens

Upon enrollment, subjects will be assigned a subject ID code that will be used instead of their name, medical record number or other personally identifying information. Electronic and paper files for data analysis will contain only the subject code. The code will be held separately from the data and accessible only to IRB approved study staff, who need to know it. Subject information and study data will be stored in study binders in offices with electronic badge access (if paper), or behind a secure firewall on OHSU network drives requiring password authentication (if electronic).

b) Sharing of Results with Subjects

There is no plan to share results with the subjects, aside from availability of final published manuscripts.

c) Data and Specimen Banking

If subjects also sign our Balance Disorders Laboratory Data Repository consent form (eIRB# 7997), then their data will be stored indefinitely in the repository (located on secure OHSU server).

8. Statistical Analysis

Compare Fallers and Nonfallers: To address the hypothesis that the objective turning measures in Table 1 will discriminate differences in daily life measures between 60 fallers and 60 nonfallers (matched for age) with PD. As discussed and shown in Table 1, we are primarily focused on Turning Quality measures, and have designated the variability of # steps in a turn as the primary measure of interest. We will test differences between the groups for each Turning Quality measure using nonparametric tests for independent samples that compare distributional ordering (rather than simply comparing mean levels) between groups. This is a purposeful strategy, not only because some of the measures may have non-normal distributions, but because the nonparametric Mann-Whitney U test statistic is mathematically equivalent to the area under the ROC curve (AUC) [38,39].

ROC curves will be produced for each turning quality measure and AUCs compared via methods outlined in Pepe et al[40]. To account for multiple comparisons within the Turning Quality domain, we will carefully allocate alpha levels to each statistical test so that the familywise error rate does not exceed 0.05. That is, we will test the primary measure at alpha = 0.01 and will use the Hochberg's sequential procedure [41] assess significance of remaining Turning Quality measures ensuring alpha does not exceed 0.04. Note that we have incorporated a more conservative adjustment (standard Bonferroni) for multiple testing in our power computations (see above), so are confident that our study will be amply powered to detect hypothesized differences in the primary measure.

Compare Value of Turning with Straight walking and Activity Measures: To address the hypothesis that turning measures will outperform straight walking and activity measures to differentiate fallers and nonfallers with PD, we will first statistically compare AUCs for turning measures versus straight walking and activity measure. We will then fit logistic regression models, compute model fit and c-statistics (multivariable AUCs) to ascertain whether combinations of turning, plus other straight walking/activity, measures classify better than single measures. In particular, we will assess the incremental value of straight walking and activity measures in models that also contain top performing turning measures via the category-free net reclassification index (NRI) and decision-analytic statistics [42]. To corroborate and add robustness to findings from multivariable regression models, we will also investigate ensemble learning approaches, such as random forests [43], to suggest candidate classifiers based on decision trees and prioritize importance of measures.

Determine how many days are needed to observe differences in turning among fallers and nonfallers. To determine the shortest number of home monitoring days needed to separate fallers from nonfallers, we will compare measures over 3 days, 5 days, and 7 days. Mean and variability of turning measures will be compared between fallers and nonfallers by comparing standardized differences between groups, as well as AUCs after 3, 5 and 7 days. Statistical comparisons of the total and partial AUCs from paired ROC curves will be made between data summarized from 3 vs 5 days and 5 vs 7 days [40].

Compare Laboratory with Daily Life Turning/Straight walking for fallers versus nonfallers: To assess whether turning (and/or straight walking) measures extracted from daily life mobility are better at distinguishing fallers from nonfallers versus those extracted from a clinic-based 2-minute walk, postural sway, or push and release postural response, we will fit mixed effects linear regression models to data from 60 fallers and 60 nonfallers measured both ways. The mixed models will account for repeated measures from individual participants via a random effect, and will include fixed effects for clinic vs. home and faller versus nonfaller, as well as their interaction. Statistical tests of contrasts will assess the difference in differences of faller and nonfaller turning.

Turning Related to Freezing of Gait (FoG): Analyses will also be conducted to determine whether measures of turning quality that are related to history of falls are also related to FoG. Freezers will be identified as subjects (from all 120 PD participants, both fallers and nonfallers) who rate their freezing as >1 in the New Freezing of Gait Questionnaire (NFOGQ). If a subject scores 0 in the NFOGQ but displays clinically apparent FoG in the laboratory testing, we will also consider them in the FoG category. Logistic regression modeling will proceed as outlined for fall history, above, substituting FoG (yes/no) as the outcome variable in the models, and assessing the association with each turning measure individually and in combination. Furthermore, we can ascertain whether FoG mediates the association(s) between turning quality and falls by adding FoG to the fall history logistic regression models, and quantifying the attenuation in the turning – fall associations.

Interpretation. *Comparison of Fallers and Nonfallers*. If turning characteristics distinguish between fallers and nonfallers, this will support our contention that objective measures of daily turning may be used as fall-risk markers. We also expect weekly variability of turning measures will be associated with the occurrence of the first fall (in the non-faller group). This analysis will be helpful for preliminary data for the next step for future, large clinical trials focused on fall risk to include continuous monitoring of turning during natural ambulatory activity. If turning measures are also

significantly correlated with severity of disease, these measures could be used by clinicians to monitor progression of PD.

Compare Value of Turning and Straight walking and Activity Measures: If turning proves to be superior to straight walking and activity measures for determining fall risk in PD, future studies could use only one sensor on the low back, without the sensors on the feet. The accelerometers on the low back can be used to detect (but not characterize) walking bouts before and after turns and number of steps during turning, and turning speed, duration, and angle is measured with the transverse gyroscope. A single sensor solution would be most feasible for large clinical trials and longer-duration monitoring. If we find that 3 or 5 days are just as useful as 7 days of monitoring to separate fallers from nonfallers and to predict transitions from nonfaller to faller status, this will also reduce the cost and effort for future clinical trials and clinical practice. If objective measures of balance, straight walking or turning with a single prescribed task in the clinical predict fall risk as well as home monitoring, patients can be tested in the clinic, rather than wearing sensors during daily life.

FoG: If differences in turning quality between freezers and nonfreezers are similar as between fallers and nonfallers, this supports the notion that FoG is contributing to falls. We expect to see changes in activity, such as avoiding large and fast turns, to also characterize compensatory patterns to avoid falls in freezers.

9. Privacy, Confidentiality and Data Security

During this study, demographic, clinical, cognitive, and motor assessments will be obtained. All of the information is for research purposes only, and data will be kept in strict confidence. No information will be given to anyone without permission from the subject. The consent form will include the informed consent statement required by the Oregon Health & Science University IRB for studies involving a clinical trial. A separate informed consent form will be used to request permission to maintain subject data in a laboratory data repository for future use. Confidentiality will be ensured by the use of unidentifiable subject ID codes. Data will be obtained by using questionnaires stored in a binder or on an encrypted computer, in lab offices with electronic badge access. All study data, whether electronically saved in the computer or in the subject's binder will be identified by a subject ID code only. Any identifiable subject information (name, phone number, address) will be maintained separately from study data, in a OHSU secure database to which only specific study staff have access.

Also, *since an iPad will be used during virtual visits to complete some cognitive tests, some risk, however slight, may exist that the subjects' IP address (i.e., a computer's general physical location) could be revealed when using a home network to send data through that device. This risk exists because the IP address attaches to the data – even de-identified data - being sent to another computer or network. In using a study device capable of sending data, the subject understands and agree to assume the risk, however slight, that the IP address could be disclosed to an unauthorized third party. This risk is outlined in the consent form.*

All meetings about Adverse Events (AE) and study monitoring will be closed meetings.

10. Risks and Benefits

a) Risks to Subjects

The most common adverse events that could happen are: skin irritation from the straps used to secure the wearable sensors and safety straps of overhead harness system (ZeroG) and - falls during rehabilitation intervention: balance will be challenged and so they could be at a slightly higher risk for falls. To minimize the risk of skin irritation – we will carefully put on the sensors during study visits and instruct the subjects on how to best wear the sensors during the 7 days of

daily life monitoring and to make adjustments as needed to overhead harness system during intervention training, to minimize irritation. To minimize falls, participants will be in an overhead safety harness system (ZeroG) when undergoing the rehabilitation intervention. The ZeroG system works during a loss of balance by slowing the person's trunk motion to come to a stop and fully support the person's body weight, before contact with the floor could occur, thus avoiding injury risks. Overall, these risks are considered minimal and will be addressed in the protocol and consent form. Dr. Dale will be notified directly if an AE occurs and will make recommendations. Drs. Dale and Carlson-Kuhta will report to the IRB about advisability of continuation of the trial, changing the protocol or other safety concerns. We don't foresee stopping rules needing to be employed for this intervention, as likelihood of AEs is low due to subjects being tested/trained in the ON medication state and with the use of a sophisticated support harness.

Loss of Confidentiality. There is a minimal risk of the loss of confidentiality, however this risk will be minimized by the measures mentioned in section 9, above, to restrict access to data and keep it stored safely.

b) Potential Benefits to Subjects

Subjects may benefit from the progressive program of training turning strategies tailored to each subject's impairments. Subjects randomized to the Control group will benefit from the extra $150 they will receive, that could be used for a community exercise program.