CLINICAL TRIAL PROTOCOL

Split-belt treadmill training to rehabilitate freezing of gait and balance in Parkinson's Disease

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List of Abbreviations/ Terminology *(in alphabetical order)*

- ABC scale: Activities-specific Balance Confidence scale
- FOG: Freezing of gait
- HRQoL: Health-related quality of life
- MOCA: Montreal cognitive assessment
- MMSE: Mini Mental State Exam
- NFOGQ: New Freezing of Gait questionnaire
- PD: Parkinson's Disease
- PDQ: Parkinson's Disease Questionnaire
- SBTM: Split-belt treadmill
- TM: Treadmill with belts tied to the same velocity

Protocol Summary

Title:
Split-belt treadmill training to rehabilitate freezing of gait and balance in Parkinson's Disease

Sample Size
N= *28*

Study Population
Individuals with Parkinson's Disease without severe balance problems and with treatment-resistant freezing of gait

Accrual Period
6 months

Study Design
This is a prospective, single-blinded, parallel-group randomized control trial to assess the benefit of split-belt treadmill training in preventing falls and improving gait and balance. The intervention group will receive 18 sessions of SBTM training, and the control group will receive 18 sessions of TM training.

Study Duration
1. *Enrolment*
2. *3 month falls monitoring*
3. *Pre-training analysis*
4. *Training (30 minutes to 1 hour, 3 times/week for 6 weeks)*
5. *3- month post-training follow-up*

Total time= 7.5 months

Study Intervention
Subjects will walk on a split-belt treadmill (Grail systems®, by Motek, Netherlands), with the two belts either moving at the same speed ('tied' configuration) or different speeds ('split' configuration). The 'tied' configuration is adjusted to the individual's over ground speed. The Grail system also generates a virtual reality-based environment by generating a visual scenery. A motion capture system with 6 infrared cameras (Vicon Motion Systems Ltd, V5, UK; 420 Hz sampling frequency) will be used. This captures various variables of gait based on markers that are placed on the subject.

The over-ground walking speed before and after each training session will be determined by calculating the time it takes the subject to walk 10m.

At the pre-training assessment and post-training follow-up, subjects will walk on a 6-metre walkway and dedicated movement analysis software (Zeno walkway® by

Protokinetics, USA) to measure individual gait speed, assess additional gait parameters of over-ground walking and capture turns, which is otherwise not possible using the treadmill.

Video assessment of gait will be captured during both 6m walkway and treadmill analyses.

Primary Objective
Cumulative incidence of falls 3 months after treadmill training.

Secondary Objectives
To determine:
-Balance and postural stability, measured by the ABC scale
-Freezing of gait, measured by the NFOGQ
-Gait parameters between the TM and SBTM groups
-Factors that determine strong after-effect after SBTM training
-Health-related quality of life (PDQ39)
-UPDRS I-IV

Exploratory Objectives
-Gait parameters on treadmill versus over-ground walking

1.0 General Information

1.1 Protocol Title

Split-belt treadmill training to rehabilitate freezing of gait and balance in Parkinson's Disease

1.2 Lead Investigator

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2.0 Background and Study Justification

2.1 Introduction

Gait disorders in Parkinson's Disease (PD) are characterized by bradykinesia, gait asymmetry and an increased risk of falls during gait transition.[1] Patients with freezing of gait (FOG) are particularly disabled, because they experience progressive decrease in step length[2] and increase in gait asymmetry,[3] thus increasing their risk of falls during tasks like gait initiation,[4] turning[5] and avoiding obstacles.[6]

Treadmill training is an existing rehabilitation strategy for physiotherapy in PD, as it increases stride length, lowers cadence and improves foot clearance; long-term treadmill training results in clinically improved gait velocity and postural stability.[7, 8] The advent of SBTM training can further optimize the gait instability that arises from asymmetric pathology in this population.[9] The SBTM has 2 belts, which can either move in unison (tied) or at different speeds (split), and it has been effective in restoring symmetrical gait in the stroke population, with gait adaptations retained for up to 3 months.[10] The motor symptoms in PD develop asymmetrically, with the burden of symptoms often lateralizing to one side,[11] so the SBTM offers a unique opportunity to modulate spatial and temporal gait parameters to study gait adaptation in the PD population.

Split-belt treadmill training uses the concept of adaptive learning, which is error-driven motor leaning in response to changes in the external environment.[12-17] It can be used to target specific gait deviations, and preliminary research has indicated that it can improve gait disorders in PD by decreasing limb asymmetry.[18] Adaptive learning occurs when there is an adjustment of leg-speed perception during locomotor movement. When using a split-belt treadmill (SBTM) to adjust the speed of each leg, the step length and double support time during gait can be manipulated.[18, 19] Individuals can therefore be prompted to 'adapt' to the asymmetric gait (e.g., the leg walking on a slow belt will take longer steps to accommodate to the leg walking on the faster belt) and 're-adapt' with return to symmetrical gait.[18, 20]

2.2. Rationale for the study

Parkinson's disease-related gait and balance disorders are challenging to treat, and the motor symptoms of PD cannot be optimized with pharmacological intervention alone. This treatment gap is important to address because gait asymmetry and impairments in bilateral coordination of gait having been associated with falls and can be functionally debilitating for individuals with PD.[3, 21-24] Research on individuals with deep brain stimulation (DBS) has shown that decreasing the subthalamic nucleus voltage stimulation by 50% on the least affected limb decreases the asymmetry in FOG, and can therefore reduce the duration and frequency of FOG.[22] However, DBS is an invasive procedure and not all patients qualify for it, so it's important to determine alternate strategies to improve freezing of gait in PD.

There is also currently no standard of care for the physiotherapy that individuals with PD receive, and there are a wide range of approaches that therapists employ that extend beyond treadmill training. Even those who undergo treadmill training do not follow a fixed protocol, pre-determined treadmill speed or duration spent on the treadmill. Moreover, although physicians encourage patients to have physiotherapy, not everyone ca afford it they have to pay out of pocket to cover the cost of the services they receive. There is a lacking consensus on the rehabilitation that this population needs.

Our aim is to assess the benefit of SBTM training to rehabilitate gait imbalance and freezing of gait in PD. In doing so, we can contribute towards a protocol to identify and treat certain gait discrepancies in PD. A study by Fasano et al demonstrated that velocity reduction by 25% on the least affected side results in a more symmetric and coordinated gait with reduced sequence effect, after 10 minutes of SBTM training.[2, 25]

The study will assess the:

- Feasibility of using SBTM training (3 days/week for 6 weeks) to improve gait parameters in PD, specifically FOG and balance
- Identify factors that prolong the benefit of the after-effect

Innovative aspects of our proposal include:

- Whereas preliminary reports have suggested the benefit of SBTM walking in PD, there has not previously been a trial to assess the impact of prolonged training on adaptation and aftereffects.
- Previous studies have used fixed velocities on the SBTM, but we will adjust velocities to the subject's over-ground walking speed
- We will employ virtual reality technology with treadmill training to mimic natural gait as closely as possible in a simulated setting.

2.3 A summary of the known and potential risks and benefits, if any, to human subjects.

2.3.1 Potential Risks

Split belt treadmill training carries little to no risk. The potential risk of falls on a treadmill are addressed by a harness that subjects will be strapped into during the training period. The duration of the training can last up to 1 hour, which could cause patients to feel fatigued, and further increase the risk of falls. However, we have implemented a progressive increase of training duration, included rest breaks in to the training protocol, and the inclusion criteria selects subjects based on their stamina to tolerate this intervention (e.g. patients with shortness of breath, obesity, cardiac conditions, severe dysautonomia, etc. will be excluded).

2.3.2 Potential Benefits

This trial offers a means to rehabilitate gait in a non-invasive and cost-effective manner. Additionally, based on reports from pilot studies, SBTM reduces the sequence effect which is hallmark feature of FOG that is not otherwise treatable with levodopa. The overall benefit of reducing the risk of falls alleviates the anxiety that these individuals have around walking.

2.4 Description of the population to be studied.

The study population includes individuals with idiopathic PD who experience FOG without severe imbalance (defined as Hoehn & Yahr stage of 3 or more). These patients will be selected from the Movement Disorders Clinic at Toronto Western Hospital, and will have to be stabilized on their treatment (drugs and/or stimulation settings in case of DBS) management for at least 3 months. Based on the inclusion criteria, these subjects will be selected recognizing that they will need to ambulate on a motor-driven treadmill.

The study will be conducted in compliance with the protocol, ICH, GCP and the applicable regulatory requirements.

3.0 <u>Study Objectives and Hypothesis</u>

3.1 Objectives

Our aim is to study the feasibility and safety of SBTM training on the rehabilitation of FOG and gait imbalance in PD, as well as its efficacy compared to TM training. Individuals with PD and FOG will be randomized to 2 groups, where they will receive 18 sessions of TM training or 18 sessions of SBTM training. The primary outcome measure will be the incidence of falls for 3 months after completing treadmill training. Falls will be assessed at multiple stages during the 7.5-month study period (using a falls calendar; refer to Appendix I, Figure 1), to understand the duration and benefit of the SBTM intervention. Additional objectives include:

- Balance and postural stability, measured by the Activities-specific Balance Confidence (ABC) scale (Appendix I, Figure 4)
- Freezing of gait, measured by the New Freezing of Gait Questionnaire (NFOGQ) (Appendix I, Figure 3)
- Gait parameters as a means of gait analysis between the TM and SBTM groups

- Factors that determine strong after-effect after SBTM training
- Health-related quality of life (PDQ39)
- Unified PD Rating Scale I-IV
- Gait parameters on treadmill versus over-ground walking

3.2 Study hypotheses.

- SBTM is superior to conventional TM training in improving response time and ability to adapt to gait asymmetry, and therefore improves FOG and reduces risk of falls in patients with PD.
- The after-effect from SBTM training is reproducible to over-ground walking
- Younger PD patients, with shorter disease duration and no cognitive impairment are more likely to adapt to gait manipulations from the SBTM, and demonstrate prolonged after-effects
- SBTM results in HRQoL improvement in PD with FOG

4 Study Design and Methodology

4. 1 Design overview

This is a prospective, single-blind, parallel-group randomized control trial to assess the feasibility and safety of SBTM in preventing falls and improving gait and balance, as well as its efficacy compared to TM training. The assessor will be blinded to their randomization. Patients will not be blinded to the intervention, and will be informed about the rationale of the study. The subject population will include 28 people with PD and FOG, who will be randomized into one of 2 groups. The intervention group will receive 18 sessions of SBTM training, whereas the control will receive 18 sessions of TM training (refer to Figure 1). After to being recruited to the trial, subjects and/or their caregivers will document the frequency and details of falls 3 months leading up to the training period using a Falls calendar (refer to Appendix I, Figure I). During this time, they will continue their routine activities without restriction, including any physiotherapy they might be receiving. The study is divided into 3 phases:

1. **Pre-training analysis:**

Prior to randomization, subjects will undergo a 6-meter walk test to determine their baseline gait parameters. We will use the Zeno walkway® gait mat (® *by Protokinetics, USA*) to obtain quantitative gait and posturographic analysis. The analysis is standardized to a 5-step protocol: 1) stand for 25 seconds at the starting edge of the walkway, 2) walk at regular pace towards the other end, 3) turn around towards the right, 4) walk back towards the starting point and 5) stand for 10 seconds. These 5 steps will be repeated twice (to assess the left turn and posturography with closed eyes) and data of straight walk will be averaged. Subjects will have a clinical assessment of gait and UPDRS (I-IV) scoring, and will fill out the HRQoL (PDQ39) and standardized falls questionnaire (refer to Appendix I, Figure II).

2. Training:

The training sessions (intervention and control) will take place 3 times a week for 6 weeks (refer to Figure 2). The first training session will take place in the same week as the pre-training analysis. The duration of training will vary each week, as described below, but will be no longer than 1 hour. The sessions will take place as follows:

i) The patient's over-ground walking speed will be determined based on Zeno walkway® *(by Protokinetics, USA*) gait mat analysis. The 5-step protocol, to obtain more sophisticated gait parameters will be performed after the last training session. Gait parameters will not be repeated for the first training session because they will be obtained at the pre-training analysis which takes place in the same week (refer to Table 1).

ii) Acclimatization on treadmill (2 minutes). The belts of the treadmill are tied to the same velocity, and will be increased to the subject's over-ground walking velocity at their comfort.

iii) a) Intervention group: The velocity of the belt will be adjusted to the over-ground speed of the subject, and ***will be reduced on the least affected side by 25%.*** While the speed of the treadmill will not change throughout the study, the duration of the training will increase each week. In the first week, the SBTM training will take place for 10 minutes. There will be a 5-minute rest period, and the split-belt conditions will continue for another 10 minutes of training (total training time= 20 minutes).

b) Control group: The subject will continue to walk under tied-belt conditions adjusted to the over-ground walking speed. In the first week, the treadmill training will be for 10 minutes. They will get a 5-minute break, similar to the intervention group, and continue for another 10 minutes under tied-belt conditions.

The duration of each session will increase by 8 minutes every week. For example, in week 1, the treadmill training will be for a total of 20 minutes; in week 2, for 28 minutes; in week 3, for 36 minutes, and so forth, until it gets to 60 minutes by week 6. The rest period will remain at 5 minutes each session, and will always take place at the halfway mark. All 3 sessions in the week will have the same duration of training.

If the subject cannot tolerate the velocity or duration of the session, the protocol will be adjusted to most recently tolerated session (and will be recorded for further interpretation and analysis).

iv) Tied adaptation: The treadmill belts will be tied to the over-ground velocity in the intervention group (5 minutes). The control group will continue to ambulate for an additional 5 minutes.

Gait analysis: In the intervention group, the treadmill gait analysis will be captured (*Vicon Motion Systems Lts, V5, UK; 420 Hz sampling frequency*) twice a week, at the

beginning and end of the training session (40 sec for each recording). Prior to the first and last training sessions, gait analysis will be carried out towards the end of the acclimatization period ('baseline'), at the beginning of the SBTM ('early adaptation'), after 10 minutes of SBTM ('late adaptation', to capture the modifications induced by this condition), and at the beginning of the tied adaption ('after effect'), in keeping with Fasano et al , 2016.[26] Each recording will be captured for 30 seconds.

In the control group, the TM gait analysis will be captured once a week, at the beginning the training session (40 sec for each recording). Additionally, gait analysis will be carried out towards the end of the first training session ('baseline') and at the beginning of the last epoch of training (beginning of last 5 minutes).

3. **Post-training follow-up:**

This will take place 3 months after treadmill training. The subject will ambulate on the Zeno walkway® gait mat (® *by Protokinetics, USA*) as per the standard 5-step protocol, have a clinical assessment and UPDRS (I-IV) scoring, and complete the HRQoL (PDQ39) and a standardized falls questionnaire (refer to Appendix I, Figure 2). They will also provide their falls calendar (provided to the patient at recruitment; refer to Appendix I, Figure 1) that documents their adverse events.

Duration of the trial and other considerations:

The duration of the study is 7.5 months. During this time, the subject's PD medications will not be adjusted by the study team, and they will be advised to take their medications per their usual schedule and as recommended by their neurologist. However, in case of decline of motor conditions or occurrence of other bothersome symptoms, medications changes will be allowed and the change will be recorded along with the reason that prompted it

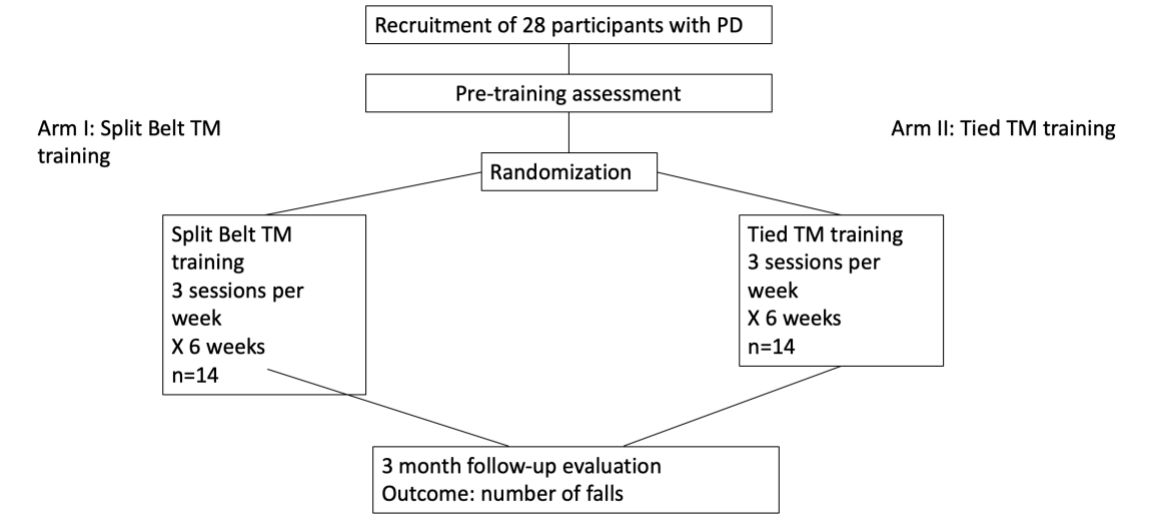

Figure 1: *Schedule of assessments*

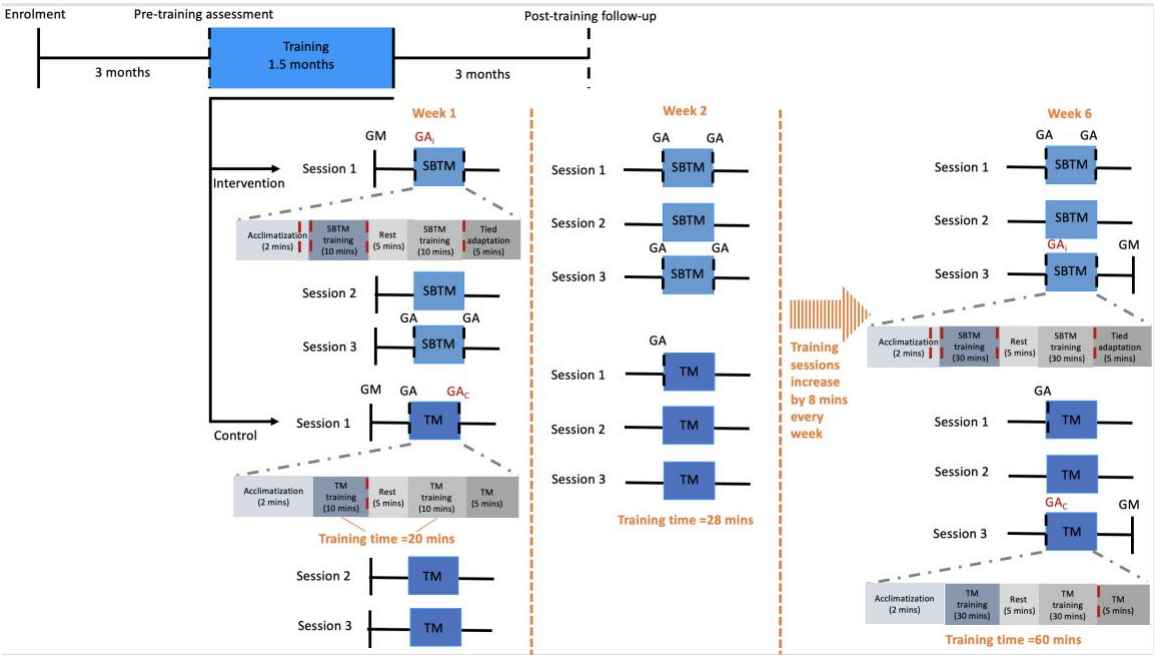

Figure 2: Overview of training schedule. The velocity of the treadmill is matched to the patient's over-ground walking speed, captured at the gait mat analysis before the first training session. The velocity on the least affected side is reduced by 25% on the SBTM. The velocity otherwise remains the same throughout the training period. However, the duration of training increases by 8 minutes every week. The timing of the gait analyses from Weeks 2-5 are identical. GM=gait mat analysis using Zeno walkway® *(by Protokinetics, USA);GA=40 second gait analysis on treadmill; GA$_i$=detailed gait analysis of the interventional group at beginning and end of training period; this includes a 30 second analysis of the end of the acclimatization period ('baseline'), beginning of the SBTM ('early adaptation'), after 10 minutes of SBTM ('late adaptation' and at the beginning of the tied adaption ('after effect'); GA$_C$= detailed gait analysis of the control group at the beginning and end of the training period; this takes place at the end of the training period of the first session, and before the last 5 minutes of the last session for 40 seconds each; SBTM=split-belt treadmill; TM=Treadmill with belts tied to same velocity*

4.2 Expected Outcomes

4.2.1 Primary outcome measure:

The incidence of falls for 3months after completing treadmill training. This will be assessed at multiple stages during the 7.5-month study period (as detailed in the Study Design), to understand the duration of benefit of this intervention. This data will be obtained from the falls calendar (Appendix I, Figure I) that will be provided to subjects upon their recruitment to the study.

4.2.2 Secondary outcome measures:

- Gait analysis between intervention and control groups will be measured using the following parameters:

  - Cadence
  - Stride time
  - Duration of stance
  - Swing
  - Double limb support phase
  - Step length, calculated by multiplying the 'step time' and 'belt speed'
  - Step width height
  - Kinemetics of joint excursion (expression as degree of range of motion)
  - Foot angle
  - Ratio of single support time/ double support time, which reflects dynamic stability
  - Symmetry ratio (best leg step length/worst step)
  - Coefficients of variation (which measures the variability of the temporal parameters of the swing phase duration and gait cycle time, and is represented by the (SD/mean) x100
  - Sequence effect (progressive reduction in step length), measured by a linear regression slope determined by plotting consecutive stride time intervals against stride number
- Health-related quality of life (PDQ39)
- Balance and postural stability, measured by the ABC scale (Appendix I, Figure 4)
- Freezing of gait, measured by the NFOGQ (Appendix I, Figure 3)
- PD signs and symptoms assessed by the MDS-UPDRS scale

All secondary outcome measures will be obtained at baseline evaluation, at the end of the training of period, and 3-months post intervention (refer to Table 1).

Adverse events will be collected with a standardized list of problems plus patient's interview for unsolicited issues.

To minimize bias, all outcome measures will be collected in a single-blinded fashion. Statistical analysis will be conducted by a researcher blinded to group allocation.

	Screening	Enrolment	Falls documentation	Pre-training Assessment	Training Week 1	Training Week 2	Training Week 3	Training Week 4	Training Week 5	Training Week 6	Falls documentation	Post-training Follow-up
Timeline (T)		T=0		T=3 months						T=4.5 months		T=7.5 months
Review inclusion criteria	X	X										
Consent		X										
Clinical assessment of gait				X								X
UPDRS (I-IV)				X								X
ABC Scale				X								X
NFOGQ				X								X
HRQoL questionnaire (PDQ39)				X								X
Falls questionnaire				X								X
Falls calendar			X	X	X	X	X	X	X	X	X	X
Zeno walkway® gait mat for over-ground walking speed only					X							
Zeno walkway® gait mat for detailed gait analysis				X						X		X
Treadmill training and gait analysis					X	X	X	X	X	X		

Table 1: *Timeline of assessments.*

5.0 Selection of Subjects

Twenty-eight PD patients with FOG will be recruited at the Movement Disorders Clinic by the primary investigator. If interested, the potential study participant will be screened, informed and consented according to the following criteria. Participants will be recruited regardless of whether they are receiving concurrent physiotherapy.

Inclusion criteria include:

1. Idiopathic PD
2. Hoehn & Yahr Stage 2-3, on levodopa
3. FOG, resistant to dopaminergic therapy
4. Disease duration: 5-15 years
5. Stable clinical response to medications or stimulation parameters (in case of DBS) for at least 3 months
6. MMSE >24/30
7. Able to walk on a motor-driven treadmill

Exclusion criteria:

1. Severe imbalance that limits ambulation (Hoehn &Yahr score above 3)
2. Orthopedic conditions and other systemic disease affecting locomotion
3. Cardiac conditions limiting the ability to walk uninterrupted for 1 hour
4. Presence of other neurological disorder
5. Inability to be fluent in English

6.0 Study Intervention

Subjects will walk on a split-belt treadmill (Grail systems, by Motek, Netherlands), with the two belts either moving at the same speed ('tied' configuration) or different speeds

('split' configuration). The 'tied' configuration is adjusted to the individual's over ground speed, which alters on a weekly basis (refer to 'Study Design' for details).

The Grail system also generates a virtual reality-based environment by generating a visual scenery. The scenery will be standardized to South Manhattan and the belts will be synchronized to the visual input. A motion capture system with 6 infrared cameras (*Vicon Motion Systems Ltd, V5, UK; 420 Hz sampling frequency*) will be used (refer to Figure 3). This system captures and calculates various temporal variables of gait, based on vertical coordinates and foot markers that are placed on the subject. Video assessment of gait will be captured with 3 video cameras synchronized to the motion system.

The over-ground walking speed will be analyzed using a 6-metre walkway and dedicated movement analysis software (Zeno walkway® by Protokinetics, USA). Video assessment of gait will be captured with 2 video cameras.

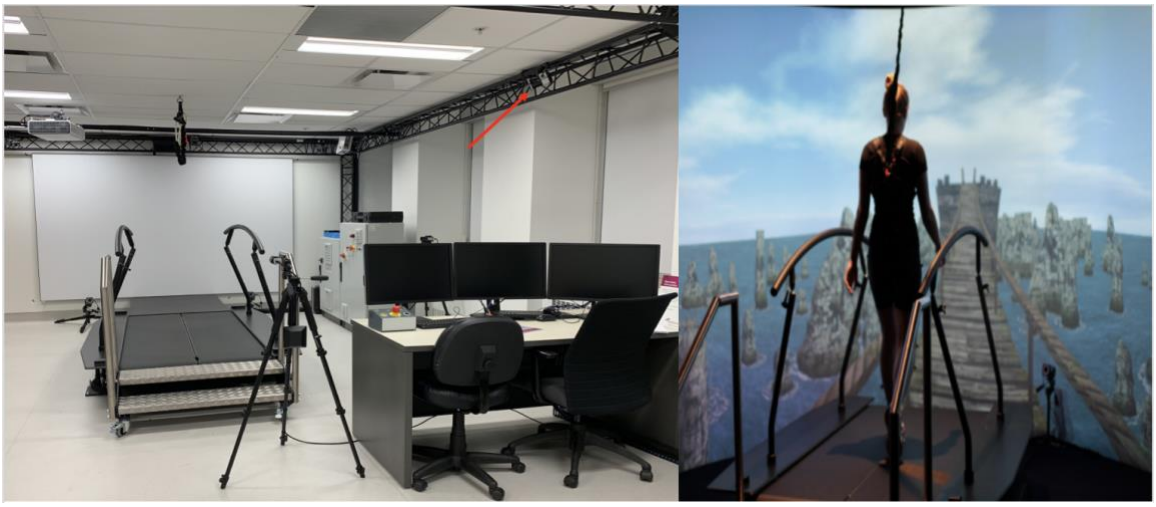

Figure 3: Treadmill training with the virtual reality system. **A)** The gait lab, featuring the SBTM (Grail systems®, by Motek, Netherlands), virtual reality screen, and desk where the study coordinator will monitor the experiment. The arrow points to one 6 infrared cameras (Vicon Motion Systems Ltd, V5, UK; 420 Hz sampling frequency) which constitute the motion capture system **B)** Simulation of a subject walking on the SBTM, while attached to a harness to prevent falls, adapted from the MOTEK website.

7.0 Statistics

This will be conducted on an intention-to-treat principle using all participants who complete randomization. Demographic characteristics and baseline data will be summarized by 'conventional' descriptive statistics (i.e., means, standard deviations and 95% confidence intervals for continuous variables, median and inter-quartile ranges for non-normal continuous ordinal data and percentages for categorical data), and will be evaluated for normalcy and homogeneity. Fall rate will be analyzed by calculating relative risk using negative binomial regression models that adjust for any potential confounders. The secondary outcome measures will be analyzed using repeated measures

analysis of variance (ANOVA) to assess differences between the intervention and the active control groups, and across the endpoints of the assessments. All analyses will be adjusted for multiple comparisons.

Statistical analysis will be conducted by a researcher blinded to group allocation.

Power analysis was performed for this trial. The primary outcome measure is falls rate during the 3-month follow-up period after treadmill training. To demonstrate superiority of the SBTM to conventional TM training, we set an a priori threshold of 20% reduction in falls rate. The sample size was calculated based on a trial by Mirelman and colleagues,[20] who studied the impact of conventional treadmill training with non-immersive virtual reality on falls rate. As this reflects the control group in this trial, we used their reported incidence of falls post-training, and estimated the standard deviation using the range rule (s=range/4). Because the duration of follow-up in our study is 3 months, we halved the mean and standard deviation. To obtain a power of 80% and alpha of 0.05, we need to recruit 14 subjects per group.

8.0 Data Handling and Record Keeping

Case report forms (CRFs) will be used to collect study data. The CRFs will be electronically viewed and signed by the principal investigator. All CRFs will be completed within two weeks of the visit date. Only the clinical investigators will have access to the participants' data. The information that is collected for the study will be kept in a locked and secure area at Toronto Western Hospital by the study team for 10 years.

9.0 Consent and Ethics

Voluntary written informed consent will be required for participation in this study and will be obtained from participants with PD and FOG.

No study procedures will be undertaken until such consent is obtained. Even after a patient has provided initial consent to participate, baseline and subsequent visits and the implementation of study procedures will be used as opportunities to again explain what is being done, why it is being done, to assure continuing informed consent on the part of the proxy, to maintain assent by the patients, and to assess capacity.

Capacity to give consent will be assessed in clinical interviews of participants by clinicians experienced in clinical research who will also be trained in this for the study. During these interviews, these clinicians will assess the ability of participants to:

- Comprehend the study and its consent form, by asking them to repeat the key elements of the research
- Understand the study and its consent form, by answering questions about the key elements of the research
- Appreciate of the personal nature and consequences of what will or could happen to them if they participate.

If in this process a potential participant is found not capable of fully providing consent for participation, then they will not be recruited to the study. The process of obtaining consent will be documented in every case. Should the patient be illiterate, an impartial witness (i.e. individual who is not part of the study team or family) will sign as a surrogate.

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