STUDY PROTOCOL

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1. Aims/Objectives

A meta-analysis indicates that falls are very common in Parkinson's disease (PD), even within a brief period of 3 months, when about half of patients will sustain at least 1 fall (Pickering et al., 2007). Randomized, controlled trials (RCT) have examined the effects of exercise interventions on reducing falls in this population; however, with mixed results. The goal of the proposed research is to evaluate two approaches to implementing an exercise program: 1) an in-person exercise program that demonstrated a significant decline in fall rates over time in a small sample of patients (Sparrow et al., 2016) and 2) a home-based program centered around remote, exercise instruction.

In the proposed RCT, 162 VA patients with PD will be randomly assigned to one of three 3-month interventions: in-person exercise, remotely-delivered exercise, or health education. Fall rates will be compared between each exercise intervention group and the health education group.

2. Background Information

2.1 Clinical Manifestations of Parkinson's Disease

PD is a progressive neurodegenerative disorder, characterized by insidious onset. The first signs become clinically manifested when about 70-80% of the dopamine producing cells of the substantia nigra have degenerated (Booij et al., 2001). The cardinal clinical manifestations of PD include resting tremor, rigidity, bradykinesia, and postural instability/gait disturbance (Olanow et al., 2009). Falls are one of the most serious complications of gait disturbances and postural instability in people with PD. People living in the community with PD fall frequently, with 60% falling annually and two-thirds of these falling recurrently (Latt et al., 2009; Allen et al., 2013; Bloem et al., 2001).These fall rates are double those in the general older population (Bloem et al., 2001), and contribute to inactivity, restrictions in mobility, fear of falling, and greater disability (Allen et al., 2010; Wielinski et al., 2005).

2.2 Medical Management of Parkinson's Disease

The treatment of PD primarily focuses on symptom management (Olanow et al., 2009). While dopaminergic drugs have positive effects on symptoms such as bradykinesia and tremor, these drugs have negligible effects in ameliorating balance deficits and reducing falls in patients with PD (Hall et al., 2013; Curtze et al., 2015). The suboptimal pharmacological management of PD led the Movement Disorder Society Evidence-Based Medicine Panel to recommend exercise as an efficacious adjunct to levodopa and other drugs (Fox et al., 2011).

2.3 The Benefits of Exercise in the Management of Parkinson's Disease

Exercise is a key part of the management of PD because it has been shown to retard the deterioration of motor functions and to prolong functional independence (Mak et al., 2017). A recent RCT in PD showed significant improvements in Unified Parkinson's Disease Rating Scale, motor subscale (UPDRS-III) scores following a progressive resistance training program, as compared to a non-progressive stretching, balance, and strengthening program suggesting the importance of progressively more challenging exercises (Corcos et al., 2013). Also, prior work in the area of exercise in both animal models and humans with PD suggests the importance of goal-based motor skill training to enhance motor learning and motor control (Petzinger et al., 2013; Fisher et al., 2008).

Recent clinical trials have specifically examined the effects of exercise interventions on reducing falls in patients with PD. A tai chi program and a strength training program both resulted in a lower incidence of falls, as compared to a stretching program (Li et al., 2012). A group strengthening and balance training program vs. usual care in PD showed no statistically significant reduction in fall rate (Goodwin et al., 2011). A strength training program and a movement strategy training program both resulted in significantly fewer falls, as compared to a life-skills education program (Morris et al., 2015). A minimally supervised, home-based balance

and strengthening program vs. usual care did not significantly reduce fall rate (Canning et al., 2015). Although these recent studies provide some evidence suggesting that falls are modifiable in PD, results are mixed.

There is limited availability of effective treatment options to reduce falls in PD. In this context, evidence from two meta-analyses (Sherrington et al., 2017; Allen et al., 2011) indicates that highly challenging exercise approaches may lead to better outcomes. We investigated the effects of a theoretically driven, highly challenging balance program on fall rate in a randomized, controlled cross-over trial (Sparrow et al., 2016). Twenty-three patients with PD were randomly assigned to 3 months of active exercises (strengthening, range-of-motion, balance activities) or usual care followed by the reverse. The results showed that the balance program was effective in reducing falls.

3. Rationale and Purpose

Identifying interventions that successfully reduce fall rate is critical to reduce disability, improve quality of life, and potentially increase survival in patients with PD. RCTs have examined the effects of exercise interventions on reducing falls in patients with PD; however, with mixed results. Evidence from two meta-analyses (Sherrington et al., 2017; Allen et al., 2011) indicates that progressive and challenging exercise programs may lead to better outcomes.

Patients with PD often have limited access to exercise programs because of distance from a center providing specialized exercise training or their inherent limited functional mobility. An evidence-based exercise program remotely delivered to the home in these patients has the potential to keep patients exercising over the long term and to reach the majority of patients regardless of geographic location or functional limitations to participating in in-person programs. In this context, approximately 34 to 36% of its enrollees live in rural areas (National Center for Veterans Analysis and Statistics, 2016; West et al., 2010). To the best of our knowledge, this will be the first RCT to compare a remotely-delivered program with an in-person program on reducing fall rate in patients with PD. Both programs incorporate the most salient features from prior work (e.g., theoretically driven, progressive, goal oriented).

4. Relevance to Veterans Health

Parkinson's disease is the second most common neurodegenerative disorder, affecting over 80,000 veterans treated within the VA Healthcare System. Falls are a major problem for many patients. A remotely-delivered home-based exercise program has the potential to be accessed easily and conveniently by large numbers of people with PD. The findings of this study may help VA clinicians provide optimal care for the many veterans with PD at risk of falls.

5. Study Design

We will conduct a three-group RCT with a 3-month intervention period and three assessment points (baseline, 3 months, and 6 months). Patients with PD will be randomly assigned to one of three interventions: in-person exercise, remotely-delivered exercise, and health education. All patients will be asked to complete 3 training sessions per week over the 3-month intervention period.

5.1 In-person Exercise Program

The in-person exercise program is guided by Horak's theoretical balance framework for PD (Horak et al., 2009), which describes several interacting systems contributing to balance control (Sparrow et al., 2016). A range of exercises (i.e., strengthening, range of motion, anticipatory and reactive balance activities, altering sensory input, and gait training) address one or more of the systems of balance control and consist of a progression ranging from less challenging to more challenging.

To reduce the risk of an injury from exercising, exercise sessions are stopped immediately if a

participant has symptoms suggestive of a musculoskeletal injury, significant respiratory symptoms, or any suspected cardiac issues. In addition, participants are instructed to contact research staff if they are hospitalized for any reason. VA electronic medical records are reviewed at least once per month for potential adverse events. Participants are called when they miss sessions for 1 week to determine the reason for missing sessions (e.g., adverse event, vacation, etc.). There is an immediate suspension of participation in the exercise program when specific cardiovascular events (myocardial infarction, angina pectoris, symptomatic arrhythmia either supraventricular or ventricular tachycardia, syncope, stroke/TIA) or new concerning symptoms (significant shortness of breath or chest pain, significant lightheadedness, significant muscle discomfort in either arm during or after exercise) occur.

5.2 Remotely-delivered Exercise Program

We have experience successfully implementing remote home-based exercise programs in 3 separate VA clinical trials in PD. The remotely-delivered home-based program includes a variety of exercises (strengthening, range of motion, anticipatory and reactive balance activities, altering sensory input, and gait training) that have been modified in such a way to ensure safe execution in the home environment. The specific exercises are aimed at addressing one or more of the systems of balance control described by Horak et al. (2009).

At the conclusion of the baseline exam, each exercise will be shown to the participant and then the participant will be asked to perform each exercise. Subsequently, exercise sessions are performed at home over a 3-month period and progressed from less challenging to more challenging over time. In order to conduct this in-home training, we have designed and programmed a system taking advantage of smartphone technology to provide remote instruction.

To reduce the risk of an injury from exercising, participants are instructed in every session to stop exercising if they experience symptoms suggestive of a musculoskeletal injury, significant respiratory symptoms, or any suspected cardiac issues and to call their physician as well as study staff. At enrollment, participants are instructed to contact research staff if they are hospitalized for any reason. VA electronic medical records are reviewed at least once per month for potential adverse events. Participants are called when they miss sessions for 1 week to determine the reason for missing sessions (e.g., adverse event, vacation, etc.). There is an immediate suspension of participation in the exercise program when specific cardiovascular events (myocardial infarction, angina pectoris, symptomatic arrhythmia either supraventricular or ventricular tachycardia, syncope, stroke/TIA) or new concerning symptoms (significant shortness of breath or chest pain, significant lightheadedness, significant muscle discomfort in either arm during or after exercise) occur.

5.3 Health Education Control

The group receiving health education will serve as an attention control. The health education control system provides general information via a smartphone about a variety of health topics, including topics on exercise. Participants will be prompted to complete health education sessions three times weekly. The delivery of the system's content makes use of both the audio and video capabilities (still and video images) of the smartphone technology to enhance the educational value of the presentation. There are opportunities for participant interaction, for example, the ability to request additional information within the content area.

During the first four weeks of the intervention, content on exercise based on the Fitness Counts program developed by the National Parkinson Foundation (Chapters 3 & 4) (Cianci, 2006) will be sequentially presented focusing on the benefits of exercise for people with PD (1 session), the types of exercises important for people with PD (1 session), principles of stretching and strengthening exercises (2 sessions), descriptions of safe stretching and strengthening exercises for people with PD (6 sessions), and strategies to overcome barriers to exercise (2 sessions). Participants will be provided with illustrations of the exercise program with written instructions (from the Fitness Counts booklet) to accompany the auditory content. Subsequently, during each session, participants will select a topic from four content areas: common symptoms, medical

conditions, preventive medicine topics, and tips for healthy living with PD.

6. Study Subject Selection

a. Sample Description

Patients with PD will be identified from the VA Boston Healthcare System (Boston, West Roxbury, and Brockton VA medical centers and their five satellite clinics) and the Bedford VA Medical Center and its four satellite clinics with the use of the Corporate Data Warehouse (CDW). Specifically, this approach will involve searching the CDW to identify patients who are 40 years of age or older with an ICD code for PD and a prescription for a dopaminergic medication. To assess electronic medical records we will use the CAPRI system, which provides one interface into the VISTA systems within VISN 1. Patients with PD typically have an initial Neurology consultation and then are seen in Neurology Clinic every 6 months. A standardized VA note format is utilized which includes HPI, medications, and detailed neurologic examination at each visit. The initial VA Neurology consultation will be reviewed with as many subsequent clinic notes as needed to establish the diagnosis of PD and responsiveness to dopaminergic therapy. The two most recent Neurology Clinic notes will also be reviewed to determine current medication use and functional status. Pharmacy records will also be reviewed to confirm stability of medication dosage. Also, Primary Care provider notes and any hospital discharge summaries from the previous year will be reviewed for evidence of exclusionary conditions.

b. Subject Inclusion Criteria

Patients with PD who meet eligibility criteria will be recruited into this study. Specific inclusion criteria will include a physician diagnosis of idiopathic PD; at least 2 of the 3 cardinal signs of PD (resting tremor, rigidity, bradykinesia); response to dopaminergic medication; and an age of 40 years or older.

c. Subject Exclusion Criteria

Specific exclusion criteria will include a diagnosis of angina pectoris (unless symptomatically resolved post-revascularization); a history of myocardial infarction (MI) within 6 months; and a history of ventricular dysrhythmia requiring current therapy.

7. Data Collection and Management

7.1 Falls Assessment

The rate of falls will be assessed prospectively. The collection of detailed and prospective information about falls follows the recommendations of the Prevention of Falls Network Europe consensus statement (Lamb et al., 2005) and a Cochrane Collaborative review (Gillespie et al., 2012). A fall is defined as an unexpected event in which a participant comes to rest on the ground, floor, or lower level. A near fall is defined as an occasion in which a participant felt that he was going to fall but did not actually do so. Participants will be asked to record falls as they occur on monthly calendars supplied by the investigators. Also, they will be asked to record the circumstances surrounding a fall or near fall (i.e., location, time of day, direction of fall, activity being performed, presence of an environmental trigger, injuries sustained, and medical attention received).

7.2 Data Management and Security

For the purposes of this study, each patient will be assigned a unique randomly generated ID number, which will be used on all electronic data stored locally. A walk across file will be maintained to link the patient

with the random ID number and will be encrypted and stored in a separate location from all other data extracted. Only the study coordinator and PI will have access permissions to this file.

All electronic databases related to this protocol will be stored locally on a VA server in an entry controlled, locked room at the Jamaica Plain campus of the VA Boston Healthcare System. There are multiple levels of security to ensure the integrity and confidentiality of all data. The computer system operates entirely within the VA network, which is protected by a firewall maintained by the VA Office of Information Technology. Part of the maintenance of the VA server is that it is backed up regularly; therefore, all data related to this protocol will be routinely backed up and stored behind the VA firewall. Only authorized users can log on to the server. An additional layer of restrictions is at the file and directory level. Users can only access portions of the data to which they are entitled. Access to all data on the server is password protected.

All paper forms will be secured in a locked fireproof study cabinet. Only the PI will have keys to the study cabinet. All data will be kept indefinitely or until the law allows their destruction in accordance with the VA Record Control Schedule.

To minimize data entry errors, all data collected on paper forms will be entered twice by a trained staff member using software that allows specification of valid responses for each entry field. Upon second entry of each record, the software will analyze each field to check for discrepancies in the two entries. Entry errors will be corrected on the spot and any errors requiring more extensive review will be deleted and re-keyed after the errors are resolved.

8. Statistical Analysis Plan

The rate of falls over 3 months will be compared between each intervention group and the control group and between the two intervention groups, with the use of negative binomial regression models. We will base our analyses on the following model

$$\log\left[\frac{E(FALLS_i)}{t_i}\right] = a + b1.IN\_PERSON + b2.REMOTE + c.CONFOUNDER \quad (1)$$

where $FALLS_i$ is the number of falls for the i^{th} participant over 3 months, t_i is the person-months of follow-up between the baseline exam and the 3-month exam for the i^{th} participant, IN_PERSON and REMOTE are two dummy variables indicating that the patient was randomized to receive the in-person intervention (IN_PERSON=1, REMOTE=0), to receive the remotely-delivered intervention (IN_PERSON=0, REMOTE=1), or to the control group (IN_PERSON=0, REMOTE=0), and CONFOUNDER is a mean-centered hypothetical confounding variable. In the above model we will include an offset for the time between baseline and follow-up, which may vary slightly around the 3-month target date. **Coefficient a** estimates the log(rate of falls per month) for a control participant. The incidence rate ratio (IRR) in falls per month for a participant in the in-person exercise group vs. a participant in the control group with the same level of confounders is estimated by exp(b1). The IRR in falls per month for a participant in the remotely-delivered exercise group vs. a participant in the control group is estimated by exp(b2).

To compare the fall rates between groups, the coefficients of interest are b1 and b2. **Coefficient b1** will be tested to compare the in-person intervention vs. the control group and **coefficient b2** will be tested to compare the remotely-delivered intervention vs. the control group. Furthermore, the linear contrast b1-b2 will be tested to compare the fall rates between the in-person intervention and the remotely-delivered intervention. Specifically, exp(b1-b2) is the estimated IRR in falls per month between the in-person and remote groups.

8.1 Power

We have estimated a loss to follow-up rate of approximately 25%, i.e., ~120 of the 162 participants will finish the entire protocol. Fall rates will be compared between each exercise intervention group and the control group with the use of negative binomial regression models. Despite mixed results with exercise interventions, two RCTs have shown that in-person exercise programs reduced fall rates (61% reduction in fall rate, Morris et al., 2015; 67% reduction in fall rate, Li et al., 2012) in patients with PD. We conducted an analysis of statistical

power using the PASS program to determine the sample size needed to detect a reduction in fall rate as low as 45%. A total of 40 participants per group will be required to provide 95% power to detect a between-group difference in fall rate of 45% for a specific exercise group vs. the control group (the group receiving the in-person program vs. the control group and the group receiving the remotely-delivered program vs. the control group), each at a two-sided significance level of 0.05. We assumed the control group rate of falls would be 1.3 falls per person month (Morris et al., 2015).

9. References

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