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Statistical Analysis Plan

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Walking and mHealth to Increase Participation in Parkinson Disease (WHIP-PD)

STATISTICAL ANALYSIS PLAN

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INTRODUCTION

Design

This is a two-arm, single-blinded, 1-year randomized controlled trial (RCT). Persons with mild to moderate Parkinson disease (PD) are randomly assigned to one of two treatment arms (mHealth or active exercise control). Two sites are participating in this RCT: Boston University (BU) and Washington University (WU) School of Medicine.

Intervention overview

Participants in the ***mHealth*** condition participate in a cognitive-behavioral community-based walking program plus home-based walking enhancing progressive resistance exercises delivered using a mobile health platform. Specifically, the program will employ a "Connected Behavioral Approach" to target self-efficacy by identifying maladaptive thoughts, providing feedback to reinforce desired behavior, promoting goal setting and action planning, and offering tailored instruction via a mobile health technology that connects participants to a physical therapist.

In this treatment arm, participants will attend a total of eight, 1-1.5 hour, in-person visits with a trained physical therapist in the clinic at BU or WU. Six of the eight visits will be spread out over the first three months (one visit the 2nd and 3rd week after baseline assessment; then bi-weekly) of the 12-month intervention period to optimize uptake of the walking program and walking enhancing exercises. Remote interaction using the mHealth platform will also occur during this 3-month period. Early visits will also ensure that each participant is able to successfully use the technology. The remaining two physical therapist sessions will be "booster" visits occurring at 3-month and 6-month to review goals, address barriers to exercise, and discuss strategies for relapse prevention. During the final 6 months (months 7-12), no interactions (in person or remote) will occur between the physical therapist and participants; however, participants will continue to use the mHealth application to support continued successful engagement in the exercise program. Participants will be able to contact the physical therapist through the app during months 7-12 if needed; however, planned interactions will not be scheduled.

Participants in the ***active exercise control condition*** receive the same components and dose of walking and exercise but without a cognitive-behavioral approach or the use of mobile health technology. Participants in the control group have eight in-person visits with the intervention physical therapist over 12-months. Six visits occur in the first three months with follow-up booster visits at 3 and 6 months – equivalent to the dose provided to the mHealth condition. Participants are instructed by the physical therapist to engage in walking and perform the same progressive resistance exercises (tailored to their needs and provided in written format) at the same frequency (5x/week) as participants in the mHealth condition. Participants in the active control condition will also be instructed to gradually progress their exercise program and to increase the amount of walking over a 1-year period. No cognitive-behavioral approaches or mHealth technology will be provided.

1 ANALYSIS OBJECTIVES

Hypotheses/Aims

Aim 1: Determine if "Connected Behavioral Approach" is more effective than an active exercise control in increasing real-world walking activity in persons with PD.

Hypothesis 1: Participants in the mHealth arm will have greater change in (1a) daily steps (Step Activity Monitor (SAM) worn in the free-living environment) and (1b) moderate intensity minutes (number of minutes in which participants walk greater than 100 steps per minute per day) between baseline and 12-months compared to the active exercise control condition.

Aim 2: Determine if our "Connected Behavioral Approach" is more effective than an active exercise control condition in improving walking capacity in persons with PD.

Hypothesis 2: Participants in the mHealth arm will have greater change in walking capacity (6-min walk test, 10-meter walk test) between baseline and 12 months compared to the active exercise control arm.

2 ANALYSIS SETS/POPULATIONS/SUBGROUPS

Sample size

Steps per day via SAM: In our pilot study, low activity participants in the mHealth group had 6028 (SD 1046) steps per day at baseline and 6918 (1900) at 12 months. Participants in the active control group had 6330 (SD 560) steps per day at baseline and 6788 (SD 1636) at 12 months.[1] Using the Two-Sample T-Test Allowing Unequal Variance Procedure in PASS Power Analysis and Sample Size software, group sample sizes of 61 participants per group will be needed to achieve 80% power, α = .05. To account for 20% drop out rate, 74 participants will need to be recruited per group for a total of 148 participants.

Two-Sample T-Tests Allowing Unequal Variance

Numeric Results for an Unequal-Variance T-Test
$\delta = \mu1 - \mu2$
Hypotheses: H0: $\delta \neq 0$ vs. H1: $\delta \neq 0$

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.80	0.80342	61	61	122	890.0	458.0	432.0	1046.0	560.0	0.050

Moderate Intensity Minutes (# of minutes in which >100 steps were accumulated): We will have sufficient power to detect differences in number of minutes of moderate intensity steps collected over 7 days via the SAM. With 74 participants per group we will have 86%

power to detect an effect size of 0.5 in number of minutes of moderate intensity steps collected over 7 days via the SAM.

Two-Sample T-Tests using Effect Size

Numeric Results for Two-Sample T-Test
Alternative Hypothesis: H1: d ≠ 0

Power	N1	N2	N	Effect Size d	Alpha
0.2270	74	74	148	0.20	0.050
0.8557	74	74	148	0.50	0.050
0.9980	74	74	148	0.80	0.050

Randomization and relevant demographics

Block randomization (to keep randomization equal throughout the study) of participants to the two treatment arms by site using Data Access Groups will be completed using the REDCap Randomization Model. Participants will also be randomized by gender and Hoehn & Yahr. The study coordinator will click a randomize button in the REDCap database for their site after confirming eligibility and obtaining consent.

3 DATA SOURCE

Motor assessments:

Step Activity Monitor (SAM): These small activity monitors measure an individual's number of steps during real world activities. The ankle strap of the SAM will be attached to the least affected limb and should be positioned on the inside (medial) aspect just above the anklebone. It should be worn over a sock, so as not to be rubbing on skin, and the arrow on the front of the monitor should be pointing up. The number of steps and number of minutes in which participants walk greater than 100 steps per minute per day (moderate intensity minutes) over the 7-day period at each time point will be used in analyses.

Six-Minute Walk Test (6MWT): This is a measure of the distance a participant walks in a six-minute time period. The six-minute walk test is a safe, simple, and useful measure of walking ability in patients with Parkinson's disease. The test will be carried out on level, obstacle-free enclosed corridors. Each participant will be instructed to cover as much ground as possible on foot in six minutes. A tester will accompany the participant, acting as a timekeeper and guarding the participant as needed. This test takes about 10 minutes to administer. Greater distances indicate increased ability for community ambulation.

Ten-Meter Walk Test (10MWT): This is a measure of gait speed. The test includes an initial two meter acceleration phase, followed by six meters of ambulation, and finished

with a two meter deceleration phase. Each of the distances mentioned will be marked for accuracy, and only the middle six meters will be timed. Each participant will be instructed to walk at a comfortable walking pace (2 trials). A tester will accompany the participant, acting as a timekeeper and guarding the participant as needed.

4 ENDPOINTS AND COVARIATES

Endpoints

The primary outcomes are the change from baseline to one year in mean number of steps per day over a seven-day period (via SAM) and the number of moderate intensity minutes (number of minutes with greater than 100 steps) for the mHealth compared to active exercise control participants.

Secondary outcome is the change from baseline to one year in walking capacity. Walking capacity will be the number of meters walked during the 6MWT and meters per second for the 10MWT.

5 HANDLING OF MISSING VALUES OR OTHER DATA CONVENTIONS

Missing data

Vigorous attempts will be made to obtain follow-up assessments on all participants, regardless of compliance with treatment protocols. If a participant cannot complete any of the follow-up assessments, the reason will be clearly documented.

Non-normal data

Distributions will be examined to determine the need for data transformation, winsorizing, or nonparametric analyses.

6 STATISTICAL PROCEDURES

Primary Outcome Analyses

Our primary aim is to determine effectiveness of the intervention to improve walking behavior at one year. We will conduct the main analyses on the full sample and compare SAM data for change from baseline to one year in (1a) mean number of steps per day and (1b) number of minutes in which participants walk greater than 100 steps per minute per day (moderate intensity minutes) over a seven-day period for the mHealth versus active exercise control participants.

The unadjusted treatment comparison will be determined using a Satterthwaite unpooled t-test to allow for unequal variance in treatment groups.

The two-sided 0.05 level will be used for significance in all analyses.

Secondary Outcome Analyses

We will use a similar approach to the analysis described above to analyze the effect of the intervention on secondary outcomes of walking capacity (6MWT and 10MWT).

Each hypothesis will be tested two-sided (level of significance of 0.05).

7 QUALITY CONTROL PLANS

Data quality will be assessed on an ongoing basis, as data will be processed immediately after each evaluation session. Our study team will conduct quarterly reviews of data to ensure that the study is progressing in a timely manner and prepare reports for the DSMB twice a year.

8 STATISTICAL SOFTWARE AND DATA MANAGEMENT

SAM data will be downloaded to a personal password protected computer for data reduction and analysis using the manufacturer's software. Other data will be collected on paper versions of the outcome measures and entered into REDCap® - a cross-platform, secure and accessible data collection application that allows for multiple concurrent users to enter data directly into pre-specified fields. Data will be stored at BU on a secure encrypted database and will only be accessed by the research team for data safety monitoring and quality control and assurance purposes.

SAS, SPSS, and R will be used for data analyses.

References

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