STUDY PROTOCOL

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1. Aims/Objectives

The great majority of individuals with Parkinson's disease (PD) develop speech impairments (Ho et al., 1999; Miller et al., 2007; Schalling et al., 2017), most of which are grouped together and called hypokinetic dysarthria. Hypokinetic dysarthria is typically characterized by altered prosody (e.g., reduced loudness and pitch variation), phonation (e.g., breathy or harsh voice), and articulation (e.g., imprecise consonants, centralized vowels) (Fox & Ramig, 1997; Ho et al., 1999; Hillenbrand & Houde, 1996). Changes in speech may appear early in PD (Miller et al., 2008; Rusz et al., 2011; Skodda et al., 2013) and progress in severity over time (Skodda et al., 2013; Skodda et al., 2009; Skodda, Flasskamp, et al., 2011). Further, such changes in speech lead to significant declines in functional communication and quality of life (Miller et al., 2006 & 2007). Pharmacological and surgical interventions that alleviate motor symptoms in PD are largely ineffective or sometimes even detrimental for speech (Ho et al., 2008; Schulz & Grant, 2000). We propose a pilot randomized, controlled trial (RCT) in patients with hypokinetic dysarthria in PD to assess the potential effectiveness of a home-based exercise intervention with interactive automated speech response features that encourage a higher level of speech performance. The overall goal of this project is to determine if this intervention leads to improved global speech function. The results of this project will provide important information that can be used to design a definitive future trial. Our Specific Aims are:

Primary Aim

Specific Aim 1: To determine whether there is a difference in change in speech intelligibility (how well an individual is understood by others) between patients randomized to the intervention program vs. patients randomized to the health education control program.

Hypothesis: Patients in the intervention program will improve in speech intelligibility at 6 months, as compared with patients in the health education control program.

Secondary Aim

Specific Aim 2: To determine whether there is a difference in change in self-perceived communication ability (measured via the Communication Effectiveness Index) between patients randomized to the intervention program vs. patients randomized to a health education control program.

Hypothesis: Patients in the intervention program will improve in the Communication Effectiveness Index at 6 months, as compared with patients in the health education control program.

2. Background Information

2.1 Parkinson's Disease in the VA Healthcare System

The Veterans Health Administration (VHA) treats an estimated 80,000 veterans with Parkinson's disease (PD) each year (VA Office of Research and Development, 2018). With the aging of the population, this number is expected to increase significantly in the next decade (Dorsey et al., 2007). The VA has demonstrated its strong commitment to providing the best possible care to all US veterans with PD by establishing six Parkinson's Disease Research, Education and Clinical Centers (PADRECCs) around the country (Parkinson's Disease Research, Education and Clinical Centers, 2018). These centers subsequently facilitated development of a collective to improve delivery of care across the VA healthcare system (the National VA Parkinson's Disease Consortium). Even with this extensive network of neurologic specialists, many veterans still are unable to access care from this network due to disability or distance.

The magnitude of the disability of PD and related burden is well known to the VA system. Indeed, a comprehensive study of VHA databases found that compared to other chronic conditions, PD imposes a particularly heavy burden on veterans in the VHA healthcare system and their family (Gage et al., 2003). Relative to veterans with other chronic conditions, those with PD were more likely to report recent deteriorations in physical health, rely exclusively on the VHA for health care services, and ultimately to be

disabled. Of particular interest for the current proposal, veterans with PD were also much less likely to engage in regular exercise than veterans with other chronic conditions.

2.2 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 to 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). While levodopa is quite effective at treating cardinal manifestations of PD, its effects on speech and voice are limited and variable (Ho et al., 2008; Schulz & Grant, 2000).

2.3 Hypokinetic Dysarthria in Parkinson's Disease

Nearly 90% of individuals with PD develop speech impairments (Ho et al., 1999; Miller et al., 2007; Schalling et al., 2017), most of which are grouped together and called hypokinetic dysarthria. Hypokinetic dysarthria is typically characterized by altered prosody (e.g., reduced loudness and pitch variation), phonation (e.g., breathy or harsh voice), and articulation (e.g., imprecise consonants, centralized vowels) (Fox & Ramig, 1997; Ho et al., 1999; Hillenbrand & Houde, 1996). Changes in speech may appear early in PD (Miller et al., 2008; Rusz et al., 2011; Skodda et al., 2013) and progress in severity over time (Skodda et al., 2013; Skodda et al., 2009; Skodda, Flasskamp, et al., 2011). For example, imprecise vowel articulation has been shown to be present even in mild stages of PD (Skodda, Visser, et al., 2011) and is a determinant of reduced speech intelligibility (Neel, 2008; Bradlow et al., 1996). Research indicates that such changes in speech lead to significant declines in functional communication (Miller et al., 2006 & 2007).

2.4 Speech Treatment in Parkinson's Disease

Pharmacological and surgical interventions that alleviate motor symptoms in PD are largely ineffective or sometimes even detrimental for speech function (Pinto et al., 2004; Ho et al., 2008; Schulz & Grant, 2000; Tripoliti et al., 2014). Given the lack of benefit of these medical interventions, behavioral interventions have become the core methods for speech rehabilitation, especially those that facilitate attention to effort, self-monitoring of vocal output, and generalization of treatment effects into improved ability to communicate effectively in daily life (Donovan et al., 2008; Dykstra et al., 2015; Atkinson-Clement et al., 2015).

Behavioral treatments for speech have demonstrated increases in several overall loudness and other voice characteristics (Atkinson-Clement et al., 2015; Broadfoot et al., 2019; Ramig et al., 2018). However, studies of speech intelligibility, an important determinant of communication effectiveness, have some limitations. Observational studies reporting ratings of intelligibility before and after Lee Silverman Voice Treatment (LSVT) by patients and their families with the use of visual analog or ordinal scales have produced equivocal results (Ramig et al., 1994; Ramig et al., 1995; El Sharkawi et al., 2002; Ramig et al., 2004). Further, the subjective ratings used in these uncontrolled studies suffer from measurement bias because the patients and their families were invested in the treatment and were not blinded to pre- and post-treatment conditions (Rosenthal, 1966; Cannito et al., 2012). Two additional stimulus-based, objective scaling studies have been reported but one focused on intelligibility in terms of sounds or isolated words rather than sentences (sentence intelligibility) (Sapir et al., 2007) and the other was limited to the study of a comfortable loudness condition (Ramig et al., 1994) rather than a more natural condition where ambient noise is typically present.

LSVT has become well established as a behavioral treatment modality for voice and speech in PD, requiring intense daily therapy for 4 weeks (Trail et al., 2005; Ramig et al., 2018). The high intensity and required consistency that makes this program successful is also associated with a tendency for patients to decline starting therapy or to miss therapy appointments (Sackley et al., 2018; Covert et al., 2018), likely mediated by distance from a center providing specialized speech training or the limited functional mobility that characterizes PD (Fox et al., 2012; Theodoros et al., 2016). The opportunity for a person with PD to receive speech treatment within his or her own home may alleviate issues with patient access.

To optimize behavioral interventions such as LSVT, it would seem important to ascertain PD patients' experiences with these interventions. Yorkston and colleagues conducted face-to-face, semistructured interviews with patients who reported that PD interfered with everyday communication (Yorkston et al., 2017a; Yorkston, et al., 2017b). Although many patients reported positive experiences with speech treatment, some reported dissatisfaction with speech drills, describing them as repetitive, irrelevant, and even boring. Based on these negative impressions as well as the motor and mobility impairments that characterize PD, the authors suggest one strategy for enhancing engagement and relevance is to integrate speech activities into a physical exercise program (Yorkston et al., 2017a). In this context, exercise training has the added benefit of improving parkinsonian motor signs (Corcos et al., 2013; Kelly et al., 2014).

2.5 Limitations of Speech Treatment in Parkinson's Disease

Behavioral treatments to improve speech tend to require intense efforts (LSVT [Ramig et al., 2018], SPEAK OUT! [Behrman et al., 2020], respiratory effort treatment [Ramig et al., 1995]). For example, LSVT involves intensive respiratory/phonatory training during 16 sessions per month. Despite the evidence for the effectiveness of LSVT, the intensive nature of therapy can be a concern for both clinicians and patients (Sackley et al., 2018; Theodoros et al., 2016; Covert et al., 2018; Miller et al., 2011), particularly within the context of increasingly stretched clinical resources (Theodoros et al., 2016; Miller et al., 2011). Therefore, it's not surprising that clinicians may not always follow the LSVT prescribed form or intensity (Miller et al., 2011; Covert et al., 2018). Clearly, the level of clinic attendance required for speech treatment can be demanding for the patient (Sackley et al, 2018); furthermore, the physical symptoms of PD and related mobility challenges can sometimes make participation extremely difficult (Theodoros et al., 2016; Fox et al., 2012). In addition, access to treatment can be limited for patients in rural areas. In the VA, approximately 34 to 36% of its enrollees live in rural areas (National Center for Veterans Analysis and Statistics, 2016; West et al., 2010). Veterans geographically removed from medical centers can only access limited VA service networks that could address their speech impairment and improve their ability to maintain independent functioning (Doyle & Streeter, 2017; Covert et al., 2018).

2.6 Speech Treatment in the Home

The availability of speech treatment such as LSVT remains limited because of distance to a treatment facility and availability of certified clinicians (Theodoros et al., 2016; Miller et al., 2011). Moreover, sustained delivery of speech treatment can be difficult, often resulting in short treatment periods without follow-up episodes of care (Miller et al., 2011). A potential solution to these challenges is to capitalize on advances in technology-supported treatment delivery to the home (Theodoros et al., 2016). One such phone-based platform being used to deliver health behavior interventions is interactive voice response (IVR) (Tsoli et al., 2018). IVR is very appealing given that patients simply use a telephone to participate in a given intervention, avoiding the need for patients to have previous computer experience or home internet access. Further, an IVR-supported program requires fewer personnel and financial resources and gives patients the opportunity to participate in training over the long term in the home environment.

3. Rationale and Purpose

We propose to conduct an RCT in patients with hypokinetic dysarthria in PD to assess the potential effectiveness of a novel home-based intervention with interactive automated speech response features that encourage a higher level of speech performance. Pharmacological and surgical interventions have been shown to be largely ineffective or sometimes even detrimental with regard to speech outcomes (Pinto et al., 2004; Ho et al., 2008; Schulz & Grant, 2000; Tripoliti et al., 2014). Behavioral therapy remains the primary treatment but tends to require intense and frequent face-to-face sessions at a health care facility making participation very difficult for patients who have mobility challenges or who live far from these facilities (Sackley et al., 2018; Theodoros et al., 2016; Covert et al., 2018; Miller et al., 2011). Moreover, facility-based training programs may not lead to sustained speech practice beyond the period of supervised training. The proposed

intervention is home-based and combines speech and exercise training. The intervention involves a system programmed to continually challenge patients to improve their speech performance within a progressive framework where speech adjustments facilitate movement through the exercise regimen.

The current proposal is consistent with the VA's national priority of employing telehealth approaches to help increase access to needed health care (Darkins, 2014; Wilkinson et al., 2016). In addition, this proposal addresses an overall area of RR&D interest related to one of the most complex medical conditions increasing in prevalence in veterans, i.e., PD, which is characterized by multiple impairments including hypokinetic dysarthria.

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. The great majority of these veterans have speech impairments that negatively impact their ability to communicate effectively in daily life. This study will test the hypothesis that a combined speech and exercise intervention will improve speech intelligibility in people with PD and speech impairment. Remotely-delivered intervention programs have 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 and speech impairment.

5. Study Design

We will conduct a pilot RCT to evaluate the combined speech and exercise intervention program in patients with hypokinetic dysarthria in PD. One hundred four patients with PD will be randomly assigned (1:1) to the 6-month intervention program or the 6-month health education control program. All evaluations will take place at the Jamaica Plain campus of the VA Boston Healthcare System.

5.1 Intervention Program

The program is designated the Telephone-Linked Computer-based Long-term Interactive Fitness Trainer (TLC-LIFT) (Sparrow et al., 2011). TLC-LIFT uses IVR technology, including speech-recognition software, to communicate with a participant during each session. Over the course of each TLC-LIFT session, the system provides verbal prompts to which the participant must respond by speaking.

To reduce the risk of an injury from exercising, participants are instructed in every session to stop exercising immediately if they experience 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.).

All exercise equipment will be shipped to participants' homes at enrollment and will be picked up by carrier service after the 6-month follow-up evaluation.

Adherence to this intervention will be encouraged by intermittent newsletters, birthday cards, holiday greeting cards, and certificates of study participation. Participants will earn certificates of achievement, which will be mailed after completion of blocks of 12 sessions (approximately monthly if fully adherent).

5.2 Health Education Control

The group randomized to receive health education will serve as an attention control. The health education control system is designed to deliver general information 3 times per week via auditory content about a variety of health topics including content on exercise and speech enhancement. Participants are provided with illustrations (e.g., types of exercises important for persons with PD) with written instructions to accompany the auditory content. In addition, participants select a topic from 4 content areas: common symptoms, medical conditions, preventive medicine topics, and tips for healthy living with PD. These PD-

specific tips include recommendations to promote effective communication, mobility strategies, such as strategies for moving from lying down to a sitting position, and from sitting to standing position, and tips to help with performance of daily activities including organization of the physical environment and reducing time pressure. Control participants also receive an illustrated booklet demonstrating these strategies and tips.

6. Study Subject Selection

a. Sample Description

We will recruit 104 patients using a protocol similar to what we are using in our ongoing project to reduce falls in veterans with PD (VA RR&D Merit Review; PI: Sparrow). Specifically, this approach will involve searching the VA's Corporate Data Warehouse (CDW) to identify patients with PD who potentially meet the eligibility criteria (see 6b & 6c). For patients identified this way, data from the medical records will be abstracted. 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; absence of secondary causes of Parkinsonism; Hoehn and Yahr stage 2-3 disease; stable antiparkinsonian medication for at least 2 weeks; hypokinetic dysarthria; and an age of 40 years or older.

c. Subject Exclusion Criteria

Specific exclusion criteria will include a Mini-Mental State examination score lower than 24; a Beck Depression Inventory-II > 24; previous laryngeal surgery; a diagnosis of angina pectoris (unless symptomatically resolved post-revascularization); a history of myocardial infarction (MI) within 6 months, or remote (>6 months) MI with current ischemia on exercise stress test; a history of ventricular dysrhythmia requiring current therapy, or current atrial fibrillation without adequate rate control (resting HR <90); participation in a regular exercise program (2 or more times weekly for 30 minutes or longer per session) during the previous 2 months; and presence of other conditions limiting the ability to participate or associated with poor short-term prognosis, for example, severe degenerative joint disease, stroke with severe residual deficits, severe peripheral neuropathy, severe psychiatric illness, advanced cancer, or renal failure on renal dialysis.

7. Data Collection

7.1 Speech Intelligibility

Speech intelligibility has been described as the primary goal of dysarthria treatment (Miller, 2013; Cannito et al., 2012). In the proposed study, speech intelligibility will be measured as the percentage of words

understood from the acoustic recordings of participants. Participants will be recorded while reading a random set of 11 sentences from the Assessment of Intelligibility in Dysarthric Speech Sentence Intelligibility Test (SIT) stimulus bank (Yorkston & Beukelman, 1980). All recordings will be obtained with the use of a head-mounted condenser microphone.

A group of native speakers of American English with no history of speech, language, or hearing disorders or experience rating speech will participate as listeners in an assessment of speech intelligibility. Listeners will be asked to transcribe a single sentence from each study participant's recording. Amplitude-normalized speech stimuli will be played over headphones. Listeners will be asked to orthographically transcribe each sentence to the best of their ability. Their transcriptions will be compared with the actual stimuli to calculate a percentage of intelligibility.

7.2 Communication Effectiveness Index

Research indicates that the impact of hypokinetic dysarthria in PD goes beyond severity of speech impairment; it reduces the patient's ability to effectively communicate in daily life (Miller et al., 2008; Miller et al., 2006; McNamara & Durso, 2003). In the proposed study, we will measure the Modified Communication Effectiveness Index (CETI-M), a comprehensive patient-reported outcome. Specifically, participants will rate their communicative effectiveness in 10 different speaking situations (e.g., in noisy environments, over the phone) on a 10-point Likert scale, where 1 = not effective and 10 = extremely effective.

8. Statistical Analysis Plan

Primary Aim

Specific Aim 1**:** Our primary outcome will be the change in speech intelligibility at 6 months. Because each individual contributes up to two values, at baseline and at 6 months, PROC MIXED (SAS) will be used to estimate regression parameters based on a mixed-effects longitudinal model (Diggle et al., 1994) with the use of the REPEATED statement with an unstructured covariance matrix.

Secondary Aim

Specific Aim 2: We will perform univariate analyses based on the Mann-Whitney U test to compare the distribution of change in CETI-M scores from baseline to 6 months in the intervention vs. control group.

8.1 Power

With the use of a randomized pre-post LSVT design in patients with hypokinetic dysarthria in PD, Cannito et al. (2012) observed an effect size of 0.75 for the outcome speech intelligibility treated as a continuous variable (our primary outcome). With a sample size of 39 participants per group, we will have 90% power (α=0.05) to detect this effect size.

9. References

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