A Telemedicine Intervention to Improve Cognitive Function in Patients With PD

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PROTOCOL

1. SPECIFIC AIMS

Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by insidious onset. Characteristic features of PD include resting tremor, rigidity, bradykinesia, and postural instability/gait disturbance. PD also includes a spectrum of nonmotor symptoms. One of the most important and disabling of these symptoms is progressive cognitive impairment leading to dementia. The effects of nonpharmacological interventions on cognitive impairment in older adults at risk for Alzheimer's disease (AD) have been studied systematically, but additional data are needed to evaluate the effects of such interventions on cognitive impairment in PD (Hindle et al., 2013). Controlled trials in older individuals with cognitive impairment and in small samples of patients with PD have indicated a significant positive effect of physical activity on cognitive measures.

We propose to build on our experience with objective, physiologically-based measurements of physical activity in randomized, controlled trials (RCTs), to conduct an RCT of a home-based physical activity intervention program among patients with mild cognitive impairment (MCI) in PD (PD-MCI) – a group at high risk of experiencing further cognitive decline and most likely to benefit from physical exercise. We will test the effects of the intervention over 6 months on the Alzheimer Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). We hypothesize that patients with PD-MCI in the intervention arm will have less decline in this outcome over 6 months compared with those in the control arm. Furthermore, we will test for the durability of the effect with a tapered physical activity dosage through 18 months of follow-up.

2. BACKGROUND AND SIGNIFICANCE

2.1 Parkinson's Disease in the VA Healthcare System

The Veterans Health Administration (VHA) treats an estimated 80,000 veterans with PD each year (www.parkinsons.va.gov/New_Front_Page.asp). 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 (www.parkinsons.va.gov/New_Front_Page.asp). 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 distance or disability. In this context, the use of a novel telemedicine approach as described in this proposal would permit this group of veterans to access needed assistance.

2.2 Cognitive Impairment in Parkinson's Disease

Cognitive impairment is one of the most common and important nonmotor impairments of PD contributing to profound levels of disability. Variable degrees of cognitive impairment are common in the first 3 to 5 years following diagnosis of PD, most frequently revealing impairment in areas of attention-executive function, visuospatial ability, working memory, and verbal memory recall tasks (Copeland et al., 2013).The underlying mechanisms of cognitive impairment and dementia associated with PD are incompletely understood and no mechanism-based treatments are currently available. The present theoretical consensus postulates that both dysmetabolism of α-synudein and amyloid-protein and cholinergic deficits contribute to cognitive impairment in PD.

The average prevalence of dementia in PD is approximately 30% based on cross-sectional studies (Aarsland et al., 2005; Riedel et al., 2010). The 8-year cumulative prevalence, however, approaches a staggering 80 percent (Aarsland et al., 2003). Mean time to diagnosis of dementia was approximately 6 years.

MCI is also common in PD and frequently progresses to dementia. In a population-based study of an incident PD cohort, Pedersen and colleagues (Pedersen et al., 2013) reported that among patients with MCI almost half progressed to dementia. Uniform criteria of PD-MCI have recently been proposed to improve comparability between studies (Litvan et al., 2012).

Given the profound negative health and social consequences associated with the development of dementia, it is critical to identify interventions that effectively slow the decline of cognitive function to prolong

the time to onset of dementia. Rehabilitation programs for individuals with PD have been primarily aimed at improving motor function. Nonmotor complications, such as cognitive impairment, are less commonly treated using nonpharmacological approaches. In a recent review of cognitive impairment in PD, the authors conclude that urgent treatment of cognitive impairments is necessary to improve function, enhance quality of life (QOL), and reduce caregiver burden, health care costs and risk for nursing home admissions (Svenningsson et al., 2012).

2.3 Societal Burden/Economic Impact

A study investigating the economic burden of PD on society estimated the direct health care cost of PD in the United States to be $10,349 per patient per year (Huse et al., 2005). The economic impact of PD is substantially increased in persons with PD who have cognitive impairments. In a study investigating the extent to which cognitive impairment and dementia contributed to direct medical and nonmedical costs in PD, results revealed that costs in those with dementia were more than 3 times greater than in those without dementia per year of survival (Vossius et al., 2011). Importantly, cognitive decline was associated with increased costs, even in nondemented persons with PD, suggesting that delaying cognitive decline may decrease the economic burden of PD.

2.3.1 Burden to the VA

The burden of PD is also well understood by the VA. 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 (Gage et al., 2003). Compared to veterans with other chronic conditions, those with PD were more likely to be disabled and rely exclusively on the VHA for health care services. Of particular interest for the current proposal, veterans with PD were much less likely to engage in regular exercise than veterans with other chronic conditions. This sedentary lifestyle likely contributes to further decline in both physical and cognitive function in PD (Speelman et al., 2011).

2.3.2 Burden to Persons with Parkinson's Disease and Caregivers

Persons with PD who develop cognitive dysfunction experience poorer QOL and greater disability than those with PD without cognitive impairment. In a recent multivariate analysis, cognitive dysfunction and a higher Lewy Body score were the most important independent predictors of increased progression of disability (Velseboer et al., 2013). Dementia and depression have been identified as independent determinants of QOL in PD. The presence of dementia decreased QOL by 47% in an Italian cohort study (Winter et al., 2011). In a veteran sample with PD, cognitive function predicted activities of daily living (ADL) score (UPDRS-ADL) revealing the negative impact of cognitive dysfunction on disability related to daily function and self-care (Weintraub et al., 2011). Another study compared 3 groups of patients with PD: 1) those with MCI (PD-MCI), 2) those with dementia (PDD), and 3) those with no cognitive impairment (PD-NC). QOL (PDQ-8) was significantly reduced in those with PDD compared to both PD-MCI and PD-NC – even after adjusting for age and motor severity (Leroi et al., 2012). ADLs were progressively worse across the 3 groups. Furthermore, caregiver burden was found to be the greatest for the PDD group. The magnitude of caregiver burden has important implications regarding the ultimate institutional placement of patients with PD.

2.4 Cholinesterase Inhibitors to Improve Cognitive Function

A recent Cochrane review assessed the efficacy, safety, and tolerability of cholinesterase inhibitors (donepezil, rivastigmine) in PDD (Rolinski et al., 2012) based on randomized placebo-controlled trials. Cholinesterase inhibitors lead to an improvement in cognitive function as measured by the ADAS-Cog (Dubois et al., 2007; Dubois et al., 2012; Emre et al., 2004; Ravina et al., 2005) (weighted mean difference, -2.72, 95% confidence interval [CI], -3.61 to -1.83, $p < 0.001$). Those taking a cholinesterase inhibitor were more likely to experience an adverse event (odds ratio 1.64, 95% CI, 1.26 to 2.15, $p < 0.001$) and to drop out (odds ratio 1.94, 95% CI, 1.33 to 2.84, $p < 0.001$).

In the Express trial (Emre et al., 2004), rivastigmine was found to significantly improved cognitive function in persons with PD using the ADAS-Cog. Subsequent studies revealed that cognitive function improved across several domains including memory and executive function (Schmitt, Aarsland et al., 2010; Schmitt, Farlow et al., 2010) in a pattern indistinguishable from the response in AD.

2.5 What is Known about Factors that May Predict Cognitive Decline

2.5.1 Many Factors Examined With Inconsistent Results

Although there is limited information regarding factors that contribute to cognitive decline in PD, much effort has been devoted to elucidating factors that might predict cognitive decline and progression to AD in older adults. The vast majority of this research is derived from observational epidemiological studies. Several potentially modifiable lifestyle factors including dietary factors, cognitive engagement, and physical activity have been found to be associated with decreased risk of cognitive decline or AD (Plassman et al., 2010; Daviglus et al., 2011; Shih et al., 2007). Studies examining the benefits of interventions in reducing cognitive decline or AD through modifying these factors are much more limited. Several studies examining the benefits of nutritional factors found no associations or inconsistent associations (Plassman et al., 2010). On the other hand, a high quality RCT examining the efficacy of physical activity revealed a significant delay in cognitive decline in persons at risk for AD – suggesting the potential benefits of this approach in PD (Lautenschlager et al., 2008).

2.5.2 Evidence that Physical Activity Affects Cognitive Decline

A relatively substantial literature of observational epidemiological studies exists that explored the association between physical activity and AD. In this context, most prospective epidemiological studies of physical activity and subsequent AD have found a decreased risk of AD with higher levels of physical activity (Scarmeas et al., 2009;Yoshitake et al., 1995; Andel et al., 2008; Abbott et al., 2004; Larson et al., 2006; Laurin et al., 2001; Rovio et al., 2005; Podewils et al., 2005), although a few studies failed to find an association (Akbaraly et al., 2009; Ravaglia et al., 2008; Verghese et al., 2003). These studies all started with non-demented populations at baseline and followed participants for development of AD over a period of years, ranging from less than 4 to 31. A meta-analysis of nine of the cohort studies of physical activity and AD yielded a summary hazard ratio for AD with higher physical activity of 0.72 (95% CI, 0.53 to 0.98) (Daviglus et al., 2011). All of the studies used self-report of physical activity which lacks precision and, in turn, may underestimate the impact of exercise on cognitive decline. In support of this hypothesis, in a recent study (Buchman et al., 2012) using actigraphy to objectively measure physical activity in older adults, results revealed a significant hazard ratio of 0.477 (95% CI, 0.27 to 0.83) between daily physical activity and incident AD that exceeded the summary hazard ratio of 0.72 reported in the meta-analysis alluded to above (Daviglus et al., 2011).

Prospective epidemiological studies that have focused on cognitive decline as the outcome have tended to show less cognitive decline among those with higher levels of physical activity. Six of seven studies that considered a dichotomous outcome based on scoring below a given test threshold found reduced risks of cognitive decline with higher physical activity (Laurin et al., 2001; Lytle et al., 2004; Schuit et al., 2001; Verghese et al., 2006; Yaffe et al., 2001; Yaffe et al., 2009). The remaining study also found this association, but only among women (Ho et al., 2001). Not all of the studies arrived at results that reached statistical significance but they all trended in the expected direction, usually with a reasonable dose-response relation. Four other prospective studies examined the association between physical activity and a continuous measure of cognitive function. Two of these were based on the Nurses' Health Study and each found decreased cognitive decline – as measured by several cognitive tests – with higher physical activity (Weuve et al., 2004; Devore et al., 2009), with one of them focused on women with diabetes (Devore et al., 2009). Two other studies had less robust findings. Bosma et al. (Bosma et al., 2002) found physical activity to be associated with less cognitive decline on only one of several cognitive tests, while Yu et al. (Yu et al., 2009) found no association between physical activity and cognitive decline. All of these studies also assessed physical activity using self-reported questionnaires. Overall, the observational studies of physical activity and AD or cognitive decline have suggested that greater physical activity is associated with less cognitive decline and this was the conclusion reached by a recent review paper (Plassman et al., 2010).

The above systematic review by Plassman et al. (2010) identified one high quality RCT relevant to the proposed investigation. This study examined the effect of physical activity on improving and maintaining long-term cognitive performance (Lautenschlager et al., 2008). Subjects included in this trial (n=170) were 50 years of age or older and responded affirmatively to the question "Do you have any difficulty with your memory?"

Subjects in the intervention group were asked to engage in 150 minutes of moderate physical activity per week, to be completed in three 50-minute sessions over a period of 6 months. Although subjects were allowed to choose from a variety of forms of exercise, almost all chose walking. Subjects in the usual care control group received educational material about managing memory loss, stress management, healthful diet, alcohol consumption, and smoking. The study revealed a significant positive effect of physical activity on a comprehensive cognitive measure (ADAS-Cog) and a delayed recall task. A limitation of this study was the inability to adequately monitor the progression of physical activity and encourage adherence by telephone as originally planned.

In summary, these studies indicate positive effects of physical activity on cognitive impairment in older adults at risk for AD. Several studies in animal models of PD and humans also support the beneficial effects of exercise in improving cognitive function in PD (Petzinger et al., 2013). Importantly, exercise studies in animal models of PD provide some insight into the underlying molecular mechanisms by which exercise may induce neuroplasticity in the human brain of patients with PD – thereby leading to improvements in motor and cognitive function (Petzinger et al., 2013). Forced exercise in animal models of PD have revealed preservation of dopamine neurons attributed mainly to exercise-induced increase in neurotrophic factors such as BDNF or GDNF (Cohen et al., 2003; Real et al., 2013; Wu et al., 2011). A down-regulation of dopamine transporter has also been observed leading to greater levels of dopamine available to the striatum (Petzinger et al., 2007; O'Dell et al., 2007). In addition, intensive treadmill exercise in the PD mouse model has been shown to reverse the reduction of dopamine D2 receptors in the dorsal striatum allowing for greater binding of dopamine and improved behavior outcomes including learning capacity and motor function (Fisher et al., 2004). These studies reveal targeted effects of exercise on specific basal ganglia circuitry. There are also known benefits of exercise on global brain health that also may contribute to improved cognitive function in persons with PD. Exercise has been shown to improve blood flow through vascularization and angiogenesis as well as activation of the immune system (Petzinger et al., 2013). Collectively, these data provide compelling evidence of the benefits of exercise in PD animal models – at both the molecular and behavior levels – suggesting a potential mechanism for improving cognition in humans with PD.

Data from functional MRI studies in normal aging and AD suggest that aerobic exercise improves the efficiency of neuronal activity in areas within the prefrontal cortex similarly affected in PD (Colcombe et al., 2004; Angevaren et al., 2008). Impairments in cognition in PD are associated with dysfunction of the basal ganglia circuitry and the frontal-cortical regions. The disruption of the nigro-striatal-thalamic-cortical circuitry that connects the striatum to the prefrontal cortex accounts for the impairments in executive function characteristic of PD (Dujardin et al., 2003). Recent studies provide preliminary evidence of the effectiveness of aerobic exercise in improving frontal lobe function. For example, a controlled study investigating the efficacy of aerobic exercise training in persons with PD revealed selective benefits in frontal lobe-mediated executive function (i.e., letter fluency test) (Cruise et al., 2011). Similarly, a non-randomized controlled trial investigating the effects of a 6-month aerobic exercise program in persons with PD revealed significant improvements in executive function in the intervention relative to control group (Tanaka et al., 2009). More research is needed to evaluate the benefits of exercise in improving cognition in PD.

Significance

Progressive cognitive impairment leading to dementia is an important component of PD, contributing to significant levels of disability. The number of veterans who will develop PD and, in turn, the number of veterans with PD who are likely to develop dementia is likely to increase substantially (Dorsey et al., 2007). Given the profound negative health and social consequences associated with the development of dementia, it is critical to identify interventions that effectively slow the decline of cognitive function to prolong the time to onset of dementia.

Based on results of prior studies, physical activity is one of the few nonpharmacological interventions that holds promise in slowing cognitive decline. The benefits of a physical activity intervention for persons with PD may rival or exceed the benefits of pharmacologic interventions without the unwanted adverse effects. In addition, unlike medication, physical activity has broad benefits that are not confined to cognitive function. Studies in PD, for example, have revealed improvements in motor impairments, physical function, and QOL following exercise in the form of walking (Herman et al., 2007).

The proposed study uses rigorous methodology and builds on previous work in which a relationship between greater physical activity levels and less cognitive decline has been confirmed. Objective,

physiologically-based measures of physical activity will allow accurate representation of the duration and intensity of physical activity among subjects. Furthermore, these objective measures will be the basis for the progression and optimization of physical activity throughout the course of the trial. The incorporation of cognitive and behavioral strategies will promote increased adherence to exercise over the long term (Ellis et al., 2011). Information derived from this study could be easily translated into clinical practice guidelines and disseminated widely at relatively low cost within the VA Healthcare System and beyond.

The current proposal directly addresses a specific area of RR&D interest in that we have developed a computer-assisted rehabilitation strategy – specifically technology for remote real-time delivery of a physical activity program, primarily walking.

3. PRELIMINARY STUDIES

3.1 TLC-WALK

We have developed a novel automated telecommunications system for coaching and monitoring physical activity in real time which we are currently using in an HSR&D project with the aim of reducing sleep apnea severity. The system, the Telephone-Linked Computer-based system for Walking (TLC-WALK), provides a highly structured walking regimen with heart rate (HR) monitoring and real-time feedback. HR is collected from a chest strap and transmitted wirelessly to a smartphone and audio feedback is provided via a headset.

Each exercise session consists of three parts, a 5-minute warm-up phase, a walking or endurance phase, and a 5-minute cool-down phase. For the walking or endurance phase, TLC-WALK sets a target HR range for the participant to maintain for a minimum time while walking, which is set at 10 minutes in the beginning of the program. Each week, there is a minimum goal of completing three sessions. The entire length of the session and the total number of sessions required are both dependent on the ability of the participant to maintain the target HR. However, the session duration never exceeds 60 minutes (50 minutes of exercise plus 10 minutes of warm-up and cool-down stretches). The target HR range and/or the target minimum duration is increased at the end of each week as long as a participant is able to meet the target HR and duration goals for at least two sessions during the week. If a participant does not meet the target HR and duration goals during a given session, the system interactively compensates by increasing the duration of the walking phase and encouraging the participant to add more sessions to the weekly schedule.

We have incorporated multiple counseling modules into TLC-WALK which are delivered during the cool-down phases as well as a relapse-prevention module which is delivered at the beginning of selected walking sessions. The strategies employed by TLC-WALK have a strong behavioral theoretical underpinning in social cognitive theory (Bandura, 1986) and the stages of change model, which is used to guide interventions for a number of health behaviors (e.g., smoking cessation, physical activity) in various settings (e.g., in communities and physicians' offices). These theories make use of several constructs aimed at changing ways of thinking (cognitive strategies) and increasing specific behaviors (behavioral strategies). We have also incorporated a cognitive training module which is delivered via the smartphone before the warm-up phase of the session.

4. RESEARCH DESIGN AND METHODS

4.1 Study Design and Overview

Based on the RCT of Lautenschlager et al. (2008) using walking as the primary mode of physical activity training, the proposed study will build on this intervention using our TLC-WALK protocol. We will conduct an RCT of our home-based TLC-WALK program among patients with PD-MCI. One hundred and sixty subjects will be randomized to either the TLC-WALK intervention or a health education control intervention. Both of the interventions will last 18 months. The impact of the TLC-WALK intervention will be evaluated by comparing the intervention and control groups.

4.2 Research Assistant Training and Field Testing of Procedures and Equipment

Before the RCT is started, the procedures and equipment (including the TLC-WALK and health education control systems) will be refined and undergo final testing. This setup phase will include developing a detailed manual of operations, training study staff, interviewing subjects, implementing measurement techniques, and

collecting data. The study coordinator will organize, schedule, and oversee the completion of all training sessions. The importance of strict adherence to the manual of operations will be emphasized repeatedly during training sessions. An initial session will include the appropriate expert members of the study team to ensure that appropriate techniques are demonstrated to all research staff. Data collected during the staff training will be analyzed for quality purposes by the appropriate study team members. Minor refinements to the two intervention systems will also be made during this period.

4.3 Participants for the Randomized, Controlled Trial

We will recruit 160 patients with PD-MCI into our study. We will identify eligible patients with PD through review of electronic medical records. Specifically, this approach will involve identifying patients in VISN 1 with the following inclusion criteria: 40 years of age or older, an ICD-9 code for PD, at least 2 of the 3 cardinal signs of PD (resting tremor, rigidity, bradykinesia), response to dopaminergic medication, and MCI based on Movement Disorder Society Task Force criteria for MCI in PD (Petersen, 2004). Patients who have angina pectoris (unless symptomatically resolved post-revascularization), a history of myocardial infarction (MI) within 6 months, or a history of ventricular dysrhythmia requiring current therapy will be excluded from consideration.

To access electronic medical records we will use the CAPRI system which provides one interface into the Vista systems within VISN 1. We will review these data to confirm specific eligibility criteria. 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. Also, Primary Care provider notes and any hospital discharge summaries from the previous year will be reviewed for evidence of exclusionary conditions.

4.3.1 Randomization

All subjects are recruited with the understanding that they will be randomized to one of two groups: one group will be assigned to use the TLC-WALK system (see Section 4.4.1) and the other group will use the health education control TLC system (see Section 4.4.2). A staff member will be in charge of the randomization and all the tasks related to group assignment. At the conclusion of the baseline visit, half of the 160 subjects will be randomized to each experimental arm with a computer-based algorithm for group assignment, which cannot be modified once the inclusion parameters are specified for a given subject.

4.4 The Study Interventions

The study interventions represent a modification of the walking exercise and control interventions of Lautenschlager et al. (2008) (see Section 2.5.2 above). Our interventions will be remotely delivered via smartphone and will take place during an 18-month period of follow-up. Subjects who are randomized will have the appropriate remote connection system made available to them and will be instructed on how to use the system. All equipment and instruction manuals will be given to the subjects at the conclusion of the baseline visit.

4.4.1 TLC-WALK Intervention

Subjects assigned to receive TLC-WALK will be instructed in the specific components of the home-based exercise program, including proper warm-up before exercise, effective walking technique as well as appropriate shoes and foot care, and issues of safety during exercise (Section 3.1). This will include a hands-on training session during which the subject will actually use the TLC-WALK system for his/her initial walking session under the guidance of a trained staff member. We will individualize guidance regarding the walking program to reduce patient-identified barriers to walking within each subject's specific community. This discussion will focus on opportunities to engage in walking in safe outdoor locations (minimal traffic, adequate crosswalks), at senior or community centers, local exercise facilities such as the YMCA, or large climate-controlled spaces such as malls. The staff member assigned to randomization and subject orientation will carry out the subject training.

Adherence to this intervention will be encouraged by intermittent newsletters, birthday cards, holiday

greeting cards, and certificates of study participation. Another method to promote adherence will be through the use of incentives (Robinson et al., 2007). We will provide participants with an incentive program to reward adherence to the training program. Participants will earn points toward prizes (e.g., key chains, mugs, hats, t-shirts, movie passes, gift cards) for completion of each session with bonus points awarded at the end of each week if no sessions were missed for that week. Participants will be given a list of all available prizes with their point value. Points can be cashed in at any time to claim a prize.

4.4.2 Health Education Control

Subjects randomized to the health education control group will participate in interactive health education sessions via smartphone. This health education control system provides general information about a variety of health topics including topics on stretching and aerobic conditioning exercise. Control subjects will be asked to complete a health education session three times a week with the initial session being done with a research assistant at the conclusion of the baseline examination. The delivery of this content makes use of both the audio and video capabilities of the smartphone technology. Voice content is overlaid on background music and supplemented by still and video images to enhance the educational value of the presentation. There are opportunities for subject interaction, e.g., the ability to request additional information within the content area.

During the first three weeks of the intervention, instructions for exercise based on the Fitness Counts program developed by the National Parkinson Foundation (Cianci, 2006) are sequentially presented to the participant. There are a total of six topics (three related to stretching and three related to aerobic conditioning exercise) in this content area. 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. These PD-specific tips include 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 patients will also receive an illustrated booklet demonstrating these strategies and tips.

The health information dialogues were developed to allow users to identify subtopics about which they desire more information while skipping others of less interest. The dialogues avoid long stretches of uninterrupted talking by the system. Topics already viewed will be removed from the list at subsequent calls (although they can be located by choosing “previously viewed topics”) except for the six topics based on the Fitness Counts program. These six topics will remain on the list.

Health education sessions will be scheduled in advance. At enrollment, subjects will indicate their weekly preferred days and times to complete the sessions. This information will be used in a similar fashion to the TLC-WALK application to determine the next scheduled session and to initiate each session at the scheduled time if not already completed.

A similar approach as described above (see Section 4.4.1) will be used in the control group to encourage and maintain study participation including an incentive program that gives subjects points for completing sessions which can be used towards prizes.

4.5 Outcome Data Collection

We will assess the ADAS-Cog (Rosen et al., 1984) at baseline, 6 months, 12 months, and 18 months at the Jamaica Plain campus of the VA Boston Healthcare System. This will be collected by a trained staff member who will be blinded to group assignment. The ADAS-Cog also was assessed as part of the physical activity intervention study of Lautenschlager et al. (2008). The scale consists of eleven items assessing memory, orientation, language, and praxis, with scores ranging from 0 (least impaired) to 70 (most impaired).

4.6 Data Management and Security

For the purposes of this study, each subject 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 subject 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. 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. Access permissions will be removed and passwords will be changed whenever study personnel are no longer part of the research team. 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. Records will be destroyed, when allowed, in the following manner: paper records will be shredded and electronic records will be destroyed in a manner in which they cannot be retrieved. All suspected or identified information security incidents (e.g. theft or loss of data, theft or loss of smartphones, unauthorized access) will be reported to the PI, ISO, and PO immediately upon suspicion by study staff.

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. In addition, the data manager will perform a careful quality assessment of all measures through logic and consistency checks and distributional assessment of overall distributions of responses. Data at follow-up exams will be compared to previous data for longitudinal consistency. Any patterns in missing or erroneous data will be discussed with the staff members collecting the data to determine the cause of the problem and what corrective measures will be taken. Databases will be carefully versioned so that all analyses can be clearly audited.

4.7 Data Analyses

The intervention and control groups will be compared on the ADAS-Cog scale with the use of PROC MIXED (SAS) to estimate regression parameters based on a mixed-effects longitudinal model (Diggle et al., 1994). Initially, the regression parameter representing the differential change in ADAS-Cog for TLC-WALK vs. control between 6 months and baseline will be assessed. In addition, we will compare the intervention and control groups at 12 months and 18 months of follow-up using the appropriate regression parameters from the model.

4.8 Power Considerations

In Lautenschlager et al. (2008), among subjects with MCI, the walking group improved more than the control group in ADAS-Cog at 6 months (Table 2) with a mean difference of 2.16 between groups. This results in an effect size of 0.580 standard deviations between groups. A total of 128 participants (64 per group) will be required to provide 90% power to detect as significant, at the 5% level, an effect size of 0.580 for TLC-WALK subjects compared with control subjects.

Table 2

ADAS-Cog score	Exercise Group (n=48)	Control Group (n=52)
6 months	-0.87 (-1.83 to 0.08)	1.29 (0.20 to 2.39)

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