Cover Page

Cognitive Rehabilitation for Veterans with Parkinson's Disease

NCT03836963

Protocol with Statistical Analysis Plan

version 3 (approved 02/24/2022)

Protocol Title	Cognitive Rehabilitation for Veterans with Parkinson's Disease
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1.0 Study Design and Methods

Study Design
To address the study objectives, a pilot randomized controlled trial will be conducted.

Study population:

Group 1: Veterans
A convenience sample of Veterans , who are screened and diagnosed with Parkinson's disease (PD) and mild cognitive impairment in the executive function domain will be enrolled. Targeted enrollment for the intervention is 45; they will be randomized to one of three groups: CCT+PRIIS (n=15), CCT+PRIIS control (n=15) or CCT control +PRIIS control (n=15).

Group 2: Knowledgeable Informants
We will also enroll knowledgeable informants/caregivers of the enrolled Veterans. Thus, we will be enrolling civilians (however it is possible that caregiver could be a Veteran and this is acceptable). The purpose for enrolling a caregiver is to obtain their perspective on functional changes related to cognitive impairment in the Veteran living with PD. To obtained their perspective, they will complete the PD-Cognitive Functional Rating Scale (PD-CFRS) at three different time points during the study. The planned activities for the caregiver are the following: consent, demographic form, PD-CFRS at three different time points. The consent form, demographic form and PD-CFRS will be completed at their first visit. We will mail them the form when their Veteran completes the RCT, we will mail them the form again one month later. A knowledgeable informant/caregiver is not required in order for the Veterans to enroll. Targeted enrollment is 45, however we anticipate having to enroll 60 civilians due to Veterans being withdrawn – and thus the associated civilian will need to be withdrawn.

Below we list the inclusion and exclusion criteria for both Veterans and Knowledgeable Informants.

Group 1: Veterans

In general, eligibility criteria target Veterans with idiopathic PD and not other forms of parkinsonism. Thus, only Veterans older than 50 with PD diagnosed according to UK Parkinson's Disease Society Brain Bank

Diagnostic Criteria will be eligible. PD medication can influence cognitive function, thus, only participants receiving stable medication (i.e., no changes in medication or dose for the past month) and who are expected to remain on stable medication for the duration of the RCT will be eligible.

Inclusion criteria for Veterans:

- Diagnosis of PD as determined by the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria[46]
- age 50 and older
- receiving stable medication for at least 4 months (i.e., no changes in medication and medication dose in the past month) and who are expected to remain on stable medication for the duration of the study
- Mild cognitive impairment as determined by the MDS Level 2 criteria.
- Speak and read English

Exclusion criteria for Veterans:

- Dementia
- Failure to demonstrate decision making capacity
- cholinesterase inhibitor medication
- History of deep brain stimulation surgery
- severe depression
- severe anxiety
- severe apathy

Group 2: Knowledgeable Informants

Inclusion criteria for Knowledgeable Informants:

- age 18 or older
- Speak and read English
- Interacts with the Veteran on a weekly basis

Exclusion criteria for Knowledgeable Informants:

- Pregnant

Women and minorities will be included in the study as long as they meet the inclusion/exclusion criteria. Participants will not be excluded from the study based on their gender or ethnic background.

Study Phases

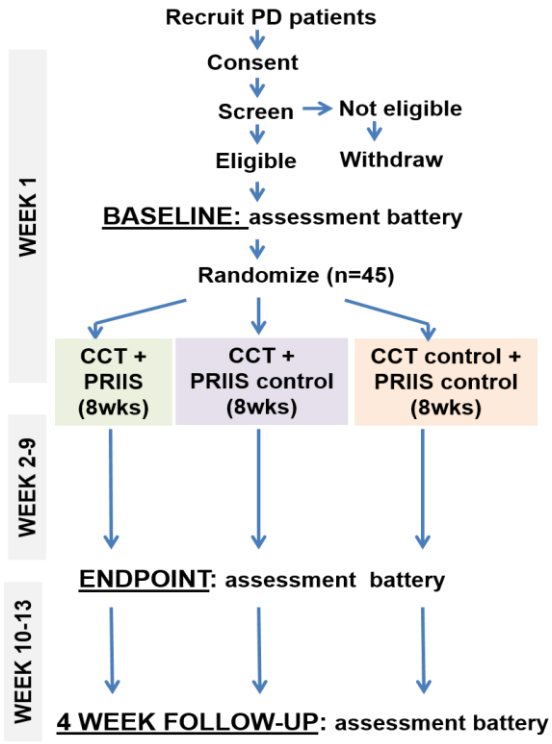
Phase 1: Initial Screening and Recruitment

Veterans will be recruited from the Hines VA Hospital (VAH). Based on the VA Administrative data bases, from 2012 -2016, 1,022 Veterans with PD were seen for a clinical visit at Hines VAH. At least 25% of them are expected to be PD-MCI All research procedures will be carried out under IRB and RR&D approved protocols at Hines VAH.

In order to gain access to Veterans being treated at Hines VA, study personnel will obtain appropriate data access approvals including partial HIPAA waiver. Once approvals are secured, we will identify research candidates using the national inpatient and outpatient files available at VA Informatics and Computing Infrastructure (VINCI). We will request access to data files on the Corporate Data Warehouse (CDW) (CDW Production Domains and Vital Status Files (including BIRLS), and CAPRI/VistAWeb, with real SSN identifiers located in VINCI using the Data Access Request Tracker (DART) system. Once this access is approved, we will

then search the database for the past 10 years (FY09-FY18) for Veterans who have had at least 2 diagnoses of PD and who have had a clinical visit at Hines. Initial screening will occur by reviewing electronic medical records. Patients will be excluded if they have a PD-D diagnosis, severe depression, anxiety or apathy, Deep Brain Stimulation (DBS)or are taking cholinesterase inhibitor medication. Those deemed eligible will be recruited for study participation. We will send these likely eligible Veterans a recruitment letter in the mail that briefly describes the study as well as notifies them that the research team will be calling to ask if they would like to participate in the study. At least 2 weeks after potential participants were mailed an informational letter, they will be contacted via phone to determine interest and complete a phone screening. In the initial attempt to contact the Veteran, we will leave only three messages, with a minimum of 24 hours between messages, and preferably at different times of the day.

Figure 1: Study Phases



The telephone conversation includes:

1. a description of the study and the time commitment required to complete the study (i.e., participation will last for approximately 2 months, this includes 4 study site visits.).

2. A list of prescribed and over-the counter medications and the length of time the participant has been on each medication will also be collected.

3. Identification of a potential knowledgeable informant/caregiver will be discussed. We would ask the Veteran to identify a person and give them our research contact number.

If the Veteran appears to be eligible after the phone screen, we would mail a letter to the Veteran along with the consent forms and HIPAA for themselves and a knowledgeable informant to review.

Once eligibility is determined for the Veteran, based on the phone screen, then the research team will call the Veteran to let them know if they are eligible or not. If they are eligible, we would schedule a time for them to continue talking on the phone to answer questions and schedule an appointment to review the consent forms and then discuss questions or concerns.

When the potential knowledgeable informant calls the research team, we will provide a description of the study and the time commitment required to complete the study. We will review eligibility criteria. If the person is eligible, we will mail them a letter with the knowledgeable informant consent form and HIPAA for them to review.

As a second method of recruitment, the research team will work with the clinical managers at the Hines Neurology Clinic to determine Veterans with an upcoming neurology clinical appointment. We will access their VA medical records (i.e., chart reviews) to screen for eligibility. If eligible, these Veterans will also be sent the same recruitment letter and receive the same phone call as described above. We will also work with agreeing Neurologists at Hines VAH on a third method of recruitment. In this case, the doctors will inform their patients of the study and give them a recruitment flier following their routine clinical visit. As a fourth method, we will

screen medical records of Veterans in relevant clinics, such as Neurology, Geriatric clinic and rehab clinic, which will be accessed through CPRS.

Phase 2. Informed Consent and Screening Procedures

Informed Consent: Authorized clinical researchers will meet with the eligible Veteran in a private room to review the consent form and all research procedures, risks, confidentiality measures and study contact information. All participants will be able to make their own decisions regarding research participation. They will be encouraged to have a family member or friend in the room during the discussion of the study. The participant will not be openly encouraged to participate in the research or told that there is any expected benefit from the experimental interventions during participation. Potential research participants will have access to research staff to assist with any questions or concerns until understanding is achieved to the judgement of the individual asking the question – this mean that discussion of the study can continue with additional phone conversations or additional visits. If a participant refuses participation, no further contact will be made.

Before the consent is signed, the decision-making capacity tool will be administered. This tool asks the Veteran to explain, in general, what the purpose of the study is and what is expected, in general from the participant. If the Veteran fails to demonstrate an understanding, they will not be eligible for the study.

When the signed informed consent forms are completed, a note will be made in the Hines VA EMR, and the original consent will be kept in a locked cabinet in a locked research office behind swipe-access doors in Bldg 1, Room B335 of Hines VA. Additionally, a copy will be provided to the participant.

During the same visit for informed consent, participants will be asked to complete additional screening and neuropsychological testing. Table 1 lists all standardized tests. Completion of consenting and screening is expected to take approximately 3 hours.

Phase 1 In Person-Screening

Screening for Depression: Participants will be screened with the Beck Depression Index-II. Those scoring between 29- 63 will be withdrawn from the study as this indicates severe depression.

Screening for Anxiety: Participants will be screened with the Beck Anxiety Scale. Those scoring 12 or greater will be withdrawn from the study as this indicates severe anxiety.

Screening for Apathy: Participants will be screened with the Starkstein Apathy Scale. Those scoring 14 or greater will be withdrawn from the study as this indicates severe apathy.

Screening for global cognitive function: First, participants will be screened with the MoCA (e.g., level 1 screening). Those scoring below 21 will be withdrawn from the study as this indicated dementia.

Phase 2 In-Person Screening

Screening for PD-MCI: The following tests for 5 cognitive domains will be used. Executive function: Trail making test, Action Fluency test, Wisconsin Card Sorting Test. Memory: Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised. Visuospatial: Judgment of Line Orientation, Hooper Visual Organization Test. Language: Similarities, Boston Naming Test. Attention/working memory: Letter number sequencing, Stroop color word test

Additional tests and questionnaires: Theories of Cognitive Abilities, Need for Cognition Scale, Memory for

Intentions Test and Modified Fatigue impact Scale . A questionnaire will also be administered to obtain demographic information (age, gender, ethnicity, race, and education level), service-related information (active duty or reserves and period of service time, and Parkinson's disease-related history (year of diagnosis, number of years on Parkinson's medication and side of motor symptom onset), and current general computer use and use of commercially available cognitive training tools.

Table 1: Standardized Assessment Tools for In-Person Screening Visit

Assessment Name	Construct measure	Time to complete (min)
Phase One of In-Person Screening		
Beck Depression Inventory-II	Depression	10
Montreal Cognitive Assessment	Global cognitive function	10
Beck Anxiety Inventory	Anxiety	10
Starkstein Apathy Scale	Apathy	5
Total time: 35 minutes		
Phase Two of In-Person Screening		
Letter number sequencing	Attention/working memory	5
Stroop color word test		10
Wisconsin Card Sorting Test	Executive function	15
Trail making test		5
Action Fluency Test		1
Hopkins Verbal Learning Test-Revised	Memory	10
Brief Visuospatial Memory Test-Revised		10
Judgment of Line Orientation short version	Visuospatial	10
Hooper Visual Organization Test		15
Similarities test	Language	10
Boston Naming Test Short form		5
Theories of Cognitive Abilities	Expectation of cognitive change	3
Need for Cognition Scale	Enjoyment of cognitively challenging tasks	5
The Memory for Intentions Test	Prospective memory	15
Modified Fatigue Impact Scale	Fatigue	5
Total Time: 124 minutes		

Table 2. Guidelines from the Movement Disorder Society Task Force on Defining & Assessing MCI[10]

Assessment:	
Level 1	Allows for diagnosis of possible PD-MCI using either a test to assess global cognitive function (i.e., the MoCA) or a limited battery of neuropsychological tests. Based on M0CA total scores, 26 or higher indicates PD-N, 21-25 indicates PD-MCI and less than 21 indicates PD-D[41,42].
Level 2	Allows for diagnosis and subtyping of PD-MCI using a full battery of neuropsychological tests which should include at least two tests in each of the five domains most affected in PD.
Definition of impairment: Using neuropsychological tests and appropriate normative data; impairment is defined as 1 standard deviation below normative mean in 2 tests in the same domain or any two tests in different domains.	

Phase 3: Baseline data collection

Repeated measures/study outcomes are included in a standardized battery of test that will be repeated at baseline, endpoint and follow-up. The battery is expected to take approximately 130 minutes to complete.

Tests administered during screening (e.g., the BDI-II, MoCA, BAI, and HVLT, Memory for Intentions Test, and Modified Fatigue Impact Scale) will not be replicated at baseline, but are included in Table 3 below to indicate it is a repeated measure.

Table 3: Repeated Measures Assessment Tools used in the RCT

Assessment Name (Abbreviation)	Outcome	Construct measure	Time to complete (min)
NIH-EXAMINER components:	1º (composite score of 7 tests listed below)	Executive function	29 total
Dot counting	2º	Working Memory	7
1-back			5
2-back			5
Flanker	2º	Cognitive Control	5
Set Shifting			5
Letter	2º	Verbal Fluency	1
Category			1
Hopkins Verbal Learning Test-Revised (**HVLT**)	2º	Memory	10
Symbol Digit Modalities Test (**SDMT**)	2º	Processing speed	5
The Memory for Intentions Test (MIST)	2º	Prospective memory	15
Monetary-Choice Questionnaire	2º	impulsivity	10
Parkinson's Disease-Cognitive Functional Rating Scale (**PD-CFRS**)	2º	Real-life function	5
The Activity Measure for Post-Acute Care™ (AM-PAC™) –Applied Cognition questionnaire	2º	Real-life function	10
Timed instrumental activities of daily living (iADL)	2º	Real-life function	15
Beck Depression Inventory-II	2º	Depression	10
Beck Anxiety Inventory	2º	Anxiety	10
Starkstein Apathy Scale	2º	Apathy	5
Montreal Cognitive Assessment	2º	Global Cognition	10
Epworth Sleepiness Scale	2º	Sleepiness	5
Modified Fatigue Impact Scale	2º	Fatigue	5
			Total Time: 144 minutes

Phase 4: Intervention

Participants will be randomized to one of three groups: CCT+PRIIS (n=15), CCT+PRIIS control (n=15) or CCT control +PRIIS control (n=15) and issued a VA iPad to take home and complete the study intervention. Participants and researchers who are administering and scoring outcome measures will be blinded to group assignment. Effectiveness of blinding will be evaluated by using data collected from mid-point and endpoint questionnaires that assess perception of training intervention[69]. The PI will oversee the RCT and coordinate research procedures and thus will not be blinded to treatment assignments. Dr. Fran Weaver, who will be blinded to group assignments, will coordinate sensitive aspects of the study that require blinding.

CCT training games are developed by Posit Science Corporation, San Francisco, CA, and are designed to train components of EF specifically affected in PD (Table 5). Participants will be asked to complete, at home, 4 sessions/week for 8 weeks. Each session will take 30min; totaling 16hr of CCT training. No dose effect is established for CCT, thus we looked to the literature[24,28] and expertise of consultants at Posit Science for guidance on the dose, and determined that 16 hours may be sufficient to detect effects of training on cognition. Progress of the training will not be fixed; training modules will be continuously adaptive, following "staircase" procedures[70], assuring that success in training on ~75% of exercise trials. While this leads to a

different progression of training across participants, it provides a customized, challenging and internally rewarding training experience that should increase performance motivation and optimize learning[71]. CCT active control will include 9 entertaining online games that are played on the same platform as the CCT games (Fig 2). Veterans will be asked to complete, at home, 4 sessions/week for 8wk.

For PRIIS, participants will work with a study team member to determine patient-centered prospective memory tasks. Participants will collaboratively agree on problem areas/areas that they would like to manage better (i.e., remember when to take my medicine) formulated in the form of up to three personal rehabilitation goals using the Bangor Goal-Setting Interview (BGSI)[72]. They will rate their own performance on these goals at initial and follow-up assessments. Participants will be taught to form a 'When X, I will do Y', recite the statement aloud three times, and imaging themselves performing the task during the situation in accordance with the statement for 30 s. In addition to the three patient-centered goals, a common goal for all participants in each group will be completing weekly CCT/CCT active control assignments (e.g., on Monday, Wednesday, and Friday, when I eat lunch, I will complete my cognitive training games).

PRIIS active control will include verbal rehearsal. These participants will be instructed to recite their prospective memory task (complete weekly intervention assignments) at least three times a day and study them for 30 s. Everyone will be given a handout with strategy instructions as reference. Weekly calls will be made to participants to assess their progress with the prospective memory task of completing weekly intervention assignments. Barriers, facilitators, and resources will be noted and discussed.
The study team member designated as the cognitive coach will make weekly phone calls to the participant to assess compliance and help troubleshoot any difficulties with the assigned programs. During the call, the cognitive coach will help the participant assess their progress with the prospective memory task of completing weekly intervention assignments (and for PRIIS the other goals). Barriers, facilitators, and resources will be discussed.

At midpoint and endpoint (weeks 4 and 8 of the intervention), participant's perception of the training will be assessed, over the phone and by a study team member, with a short questionnaire that will include questions such as: Are the games enjoyable? Are the games challenging? Do you look forward to playing the games? Are you motivated to play the games? Do you think your cognition is improving because of the games? Answers will be rated on a Likert scale. All participants will be reassessed with the neuropsychological battery at endpoint and one month after endpoint. During the one month after endpoint, participants will not be contacted during the one month except to remind them of their appointment for the follow-up assessment.

Specific to the CCT intervention, several factors may contribute to non-compliance with program use. Several elements of flexibility will be incorporated in the treatment schedule to accommodate the challenges that Veterans with PD may encounter. First, the participant may require extra time to complete the program. Participants will be asked to engage in four 30-minute sessions per week for 8 weeks, which is 16 hours in total.

Training progress and compliance will be automatically uploaded to a secure HIPAA-compliant server at Posit Science, and will be monitored weekly by the study staff. If participants have completed less than 12 of the 16 hours of total training, then they will be allowed up to 4 additional weeks to complete the intervention. To ensure a time-bounded study commitment, after a total of 12 weeks such participants will perform their post-assessment (completion) visit regardless of the number of sessions completed. Second, we expect that not all participants will complete four sessions every week. To accommodate this, during the weekly phone calls to participants, the study team will work with them to generate a feasible training schedule if they are finding it difficult to meet requirements. Third, there may be some cases in which a participant may wish to stop or minimize the use of the program going forward, while remaining in the study. Potential reasons for this

decision might be a change in health issues, family/personal issues or lack of interest in the intervention. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after a study team discussion with co-investigators, the participant will be permitted to cease using the program and be scheduled for a post-assessment (endpoint) visit at the appropriate time relative to the baseline assessment. If the participant completed at least 12 hours of training within 12 weeks, then a 1-month follow-up assessment will be scheduled. Fourth, some Veterans may not be able to complete the proposed training regimen in one sitting (i.e., 30 minutes) due to fatigue. To accommodate this issue, participants may choose to break the time into shorter segments, which are more easily manageable.

We will define "completers" of the intervention as those who completed at least 80% of the sessions.

Phase 5: Endpoint

Endpoint Behavioral Assessments:
All participants will complete the assessments listed in Table 3 in a private room with trained research staff at Hines. A semi-structured interview will also be conducted by trained research staff. This interview will take approximately 30 minutes and discussion will focus around feasibility of participating in the study, perception of training for the 2 interventions, usefulness of the weekly cognitive coach calls, and guess at treatment group allocation. We will audiotape this part of the session. The option to consent to audiotaping is included in the veterans's consent form

Phase 6: Follow-up

Follow-up Behavioral Assessments:

One month after the last intervention session, all participants will complete the assessments listed in Table 3 in a private room with trained research staff at Hines.

Unblinding:
Participants will be unblinded after the last participant completes the study. A letter will be mailed to the Veterans.

Knowledgeable informants/caregivers
Knowledgeable informants/caregivers enrolled in the study will be administered the PD-CFRS. Data from the informant will be collected at baseline in person and, to reduce burden of data collection, end-point and follow-up surveys will be mailed to informants for completion. Filling out this form three times (along with an initial demographic form) are the only research procedures performed by the knowledgeable informants/caregivers.

COMPENSATION FOR PARTICIPATION IN RESEARCH ACTIVITIES
Veteran participants will be compensated $120 for completing all research procedures in this study. Participants will receive $30 after completing the 2-3 hour long diagnostic confirmation screen. Participants will receive $30 after completing baseline neuropsychological assessments, $30 after completing endpoint neuropsychological assessments and $30 after completing follow-up neuropsychological assessments.

Payment Procedures if screening and/or assessments are completed Hines VA: they will be reimbursed $30 direct deposit via electronic funds transfer (EFT).

Knowledgeable informants/caregivers will not receive compensation.

2.0 Risks

We anticipate that this will be a study with minimal risk and low probability of adverse events. There may be some risk of emotional distress when subjects are completing self-report assessments; poor performance on neuropsychological tests may also cause distress. However, in the event that extreme distress is indicated by the study participant, that is, the study participant indicates that they wish to harm themselves or others, research staff will escort the participant to mental health intake. In the event of an adverse event it will be documented in the subject hard copy file and reported to the IRB within the time requirements set for by the local IRB and Office of Research Oversight.

Cognition and other Mental Health Behavioral Assessments:

Participant may experience some distress when completing self-report assessments or if they perform poorly on tests. Participants will be told they can decline to answer any question. They will also be told that some questions are meant to be hard and some are meant to be easy and we ask that they try their best. Screening assessments will take approximately 2-3 hours. At baseline, neuropsychological assessments will take approximately 90 minutes. For the end-point and follow-up, the battery will take approximately three hours to complete. Therefore, participants may experience fatigue. To address this burden, breaks will be encouraged and scheduled within the session. If a participant appears to be under undue strain, test sessions will be discontinued. The participants will be informed that at any point they can let the assessor know a break is requested.

Computer cognitive training intervention

Specific to intervention, several factors may contribute to non-compliance with program use. Several elements of flexibility will be incorporated in the treatment schedule to accommodate the challenges that Veterans with PD may encounter. First, the participant may require extra time to complete the program. Participants will be asked to engage in four 30-minute sessions per week for 8 weeks, which is 16 hours in total. Training progress and compliance will be automatically uploaded to a secure HIPAA-compliant server at Posit Science, and will be monitored weekly by the study staff. Note that participants will login to a web-based cognitive training program or gaming site using a number assigned to their loaned wireless equipped iPad, thus there is no PHI on this Posit Science server. If participants have completed less than 12 of the 16 hours of total training, then they will be allowed up to 4 additional weeks to complete the intervention. To ensure a time-bounded study commitment, after a total of 12 weeks such participants will perform their post-assessment (completion) visit regardless of the number of sessions completed. Second, we expect that not all participants will complete four sessions every week. To accommodate this, during the weekly phone calls to participants, the study team will work with them to generate a feasible training schedule if they are finding it difficult to meet requirements. Third, there may be some cases in which a participant may wish to stop or minimize the use of the program going forward, while remaining in the study. Potential reasons for this decision might be a change in health issues, family/personal issues or lack of interest in the intervention. However, the participant may want to meet their personal commitment to the basic scientific research of the study. In such cases, after a study team discussion with co-investigators, the participant will be permitted to cease using the program and be scheduled for a post-assessment (endpoint) visit at the appropriate time relative to the baseline assessment. If the participant completed at least 12 hours of training within 12 weeks, then a 1-month follow-up assessment will be scheduled. Fourth, some Veterans may not be able to complete the proposed training regimen in one sitting (i.e., 30 minutes) due to fatigue. To accommodate this issue, participants may choose to break the time into shorter segments, which are more easily manageable.

Confidentiality:

Loss of confidentiality is a potential risk. This research study involves collection of questionnaires. To protect from breach of confidentiality, each participant will be assigned a unique identification number by the study personnel and the only place where this participant identification number will be linked to identifying information (e.g., name, address, phone number, date of birth, social security number) will be on a cross-walk

file within secure Hines VA servers. Sandra Kletzel will provide limited access to the data. Hard copies of questionnaires response forms will be kept in a lockable file cabinet in a lockable office of Dr. Sandra Kletzel at Hines VAH. Any breach in security will be reported to ACOS/Research, Facility Information Security Officer (ISO) and facility Privacy Officer within one hour. All Hines data will remain at Hines and will not be taken off station. No data will be stored on hard drives.

Unknown cognitive training Risks:
There may be other unforeseeable and/or unanticipated side effects that could occur. An adverse events (AE) log and weekly study monitor log will be used to monitor the occurrence of any AE including unanticipated events. A response plan to unanticipated AE will be developed should this occur.

3.0 Benefits of participation in the study

Individuals that participate may benefit from CCT. The Aims are designed to examine the impact of CCT with or with *PRIIS* to improve cognitive function as well as ADL. Cognitive training programs has been shown efficacious for PD patients as well as patients with other pathologies including TBI and stroke cholinesterase inhibitor medication[23]. The information gained in this project will be utilized for further treatment development for cognitive function in Veterans with PD. These pilot data will be used as preliminary data for a larger-scale Merit grant proposal submitted to the VA RR&D service.

4.0 Alternatives to participation

The alternative to participation is to not participate in the study. Participation is entirely voluntary and the participant may withdraw at any time for any reason

5.0 Data Analysis

All test administrators will undergo the same training. Data will be cleaned and tested for normality (if normality tests fail, appropriate transformations will be made), and proper missing data imputation techniques will be used. Test for multicollinearity will be made. The 3 treatment groups will be characterized using descriptive statistics for demographic factors, disease-related variables, and medication use. Groups will be examined for comparability according to the descriptive variables using ANCOVA and mixed-effects model with random subject effects. For ANCOVA, type I error rate (α=0.05) will be adjusted for multiple comparisons using Bonferroni corrections.

Neuropsychological Data Analytical Approaches. For Aims 2 and 3, data will be analyzed using a two-level longitudinal mixed effects model with random subject effects to incorporate correlation of measurements nested within the same subject. Covariates will include medication dose, anxiety, apathy, and depression level. Parameters will be estimated using measurements from baseline, endpoint, and follow-up. The group by time interaction parameter will be used to examine the difference of the trends between the three groups. Significance of this parameter will indicate that treatment is efficacious in terms of EF over time when adjusted by covariates. To assess immediate effects of CCT, an experiment group contrast will be formed using test score means at baseline and endpoint and a control group contrast will be made with those same types of means. To assess sustainability of CCT effects, contrasts using means of test scores at endpoint and follow-up will be made for each group. Estimates of variance components from mixed-model analysis will be used to calculate test statistics. Data analysis will be performed using SAS 9.3 Proc Mixed. This modeling process will be reported for each outcome of interest in Aims 2 and 3. Potential moderators of the effects of the CCT will be explored through Pearson correlations and regression analyses. Factors include, age, age at PD onset, disease duration, MoCA score, depression, anxiety, apathy, L-dopa equivalent dose, PD-MCI subtype diagnosis,

scores on training perception, prior computer use and cognitive training. Co-morbidities and medications will be considered as confounders.

MCID for the NIH-EXAMINER executive composite score will be computed using two anchor-based MCID approaches. First, a within patient score change approach will be used, which defines MCID as the mean change between the outcome scores (NIH EXAMINER Executive composite score) of a group of patients selected per their answers. Second, a sensitivity- and specificity-based approach will be used. This anchor-based approach is useful to calculate the threshold that allows for the best discrimination between groups of patients. The outcome score that produces the greatest and most balanced sensitivity and specificity for discriminating patients with minimal change from patients without any change will be considered as the MCID. Used in con-junction with MCID estimations, sensitivity is the proportion of the patients having change on the external criterion (PD-CFRS) and whose outcome score (NIH EXAMINER Executive composite score) change exceeds the threshold MCID value. Similarly, specificity is the proportion of subjects without any changes on the external criterion (PD-CFRS) and whose outcome changes are below the threshold MCID value. Full, partial and non-responders will be defined using the MCID in both the sham and active rTMS groups (i.e., full = > 1 MCID, partial= 1 MCID, non= < 1MCID).

The psychometric properties of the PD-CFRS (both self-report and informant report assessed separately) will be assessed using the Rasch model (i.e., construct validity) and concurrent validity will be examined using traditional correlational methods (i.e., concurrent validity with NIH-EXAMINER). For the PD-CFRS, the interrater agreement between self- and informant ratings will be calculated using the Corrected Discrepancy score, which is a rigorous measure correcting for between-subject differences in actual level of scoring.