MultiContext Approach for Parkinson Disease Pilot (MC4PD Pilot)

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Principal Investigator: Erin R. Foster

Grant Title: Strategy-based cognitive intervention for Parkinson disease: A pilot randomized controlled trial

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CONFIDENTIALITY STATEMENT

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 08/15/2019

Name: Erin Foster

Title: Assistant Professor in Occupational Therapy, Neurology & Psychiatry

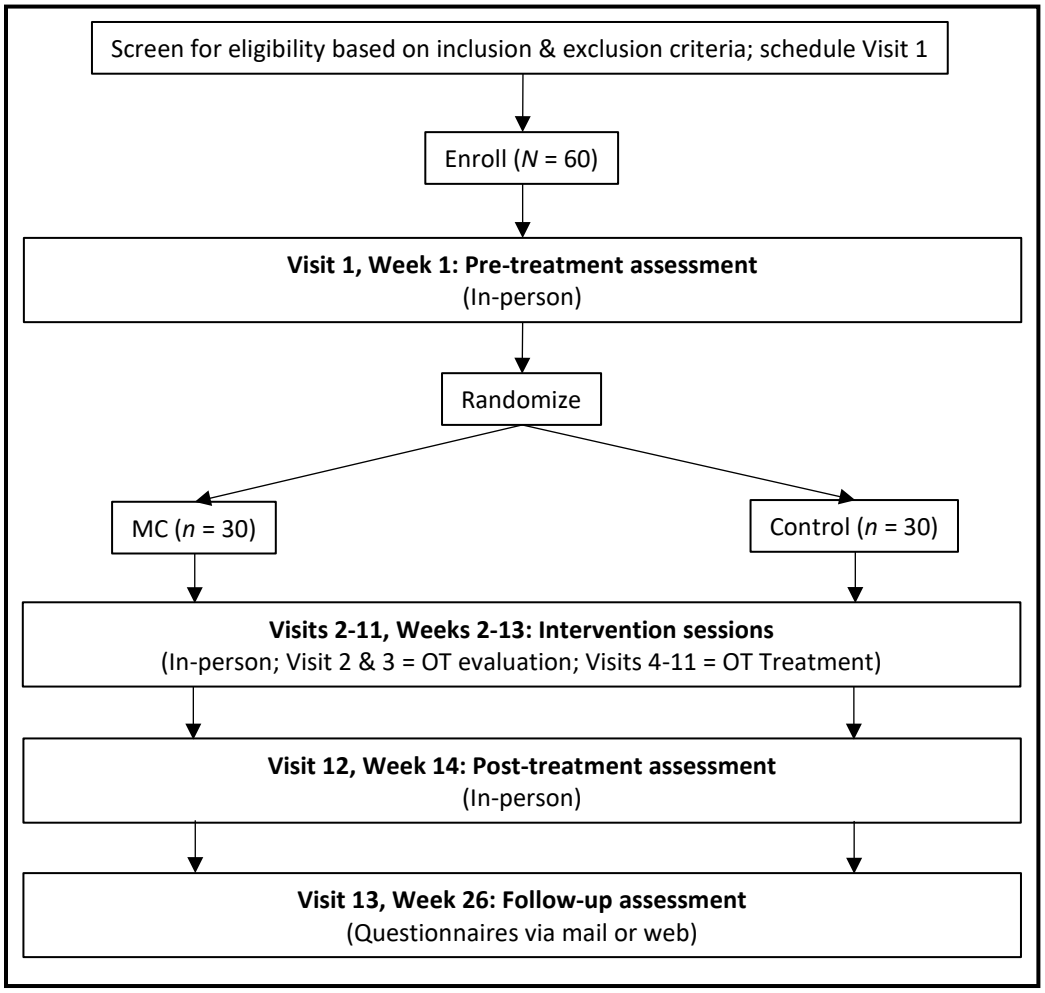
Investigator Contact Information
Affiliation: Washington University School of Medicine
Address: MSC 8505-66-01|4444 Forest Park Avenue| St. Louis, MO 63108
Telephone: (314) 286-1638
Email: *erfoster@wustl.edu*

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Strategy-based cognitive intervention for Parkinson Disease: A pilot randomized controlled trial. Aka: MultiContext Approach for Parkinson Disease (MC4PD) Pilot
Grant Number:	R21 AG063974
Study Description:	We have developed a strategy-based cognitive intervention, based on the MultiContext (MC) approach, to enable people with PD to apply strategies in their everyday lives to cope with cognitive decline and improve or maintain daily function. We hypothesize that this intervention will produce better functional outcomes compared to cognitive process training. This project will assess feasibility and treatment fidelity and generate data in preparation for a definitive clinical trial by conducting a single-blind pilot randomized controlled trial comparing the MC approach to a standard-of-care treatment (Control). Participants with PD without dementia (N = 60) will complete pre-treatment testing, randomization to treatment group, 10 treatment sessions, and immediate and 3 months post-treatment testing.
Objectives:	Aim 1: Examine the feasibility of the MC approach for people with PD within an RCT. Aim 2: Demonstrate adequate treatment fidelity to the MC approach. Aim 3: Obtain preliminary estimates of the MC approach's effect on patient-reported functional cognition.
Endpoints:	Aim 1 Endpoints: Recruitment rate (#/month); retention rate; % of participants completing the intervention in 12 weeks Aim 2 Endpoints: Therapist adherence and competence scores; Client Satisfaction Questionnaire; Pittsburgh Rehabilitation Participation Scale Aim 3: Bangor Goal Setting Interview
Study Population:	60 males and females over age 40 who meet criteria for typical idiopathic PD, are stage I-III, and do not have dementia.
Phase or Stage:	Stage I (generation, refinement, modification, adaptation, pilot testing)
Sites/Facilities Enrolling Participants:	Washington University School of Medicine in St. Louis
Description of Study Intervention/Experimental Manipulation:	Both the MC and Control intervention will consist of 10 1-1.5 hour sessions over 12 weeks delivered in an individual, face-to-face format by trained licensed occupational therapists. Both interventions involve collaborative client-centered goal setting, practice of cognitively challenging functional activities, and home practice assignments. The MC intervention additionally incorporates strategy training, a metacognitive framework, therapist mediation, and action planning.
Study Duration:	24 months
Participant Duration:	14 weeks of in-person participation with a 3 month follow-up; 26 weeks in total

1.2 SCHEMA



The following target interval limits will be used, expressed as "target (window)":

- Pre assessment will occur ≤ 14 days of screening for eligibility. If more than 14 days have passed, participants will be re-screened before enrollment.
- Treatment Session 1 will occur 7 (5-14) days after the Pre assessment.
- Each subsequent treatment session will occur 7 (5-9) days after the prior treatment session.
- Post assessment will occur 7 (5-14) days after Treatment Session 10.
- Follow-up assessment will occur 3 months (-7 days/+14 days) after Treatment Session 10.

Keep in mind that these are targets, and this study aims to determine whether these targets are feasible and/or how we can improve our processes to meet them in the future. Although we aim for participants to have a treatment session each calendar week, the stated goal of completing the intervention within 12 weeks allows for up to 2 missed weeks due to practical circumstances (that would be present in real-world clinical practice) such as participant or therapist illness, travel, inclement weather, holidays, etc.

1.3 SCHEDULE OF ACTIVITIES

		Pre-screening (Pre-consent)	Visit 1: Pre-treatment assessment	Intervention Sessions		Visit 12: Post-Treatment Assessment	Visit 13: Follow-up Assessment
				Visit 2-3: OT Eval	Visits 4-11: OT Treatment		
Inclusion/Exclusion criteria		X	X				
Informed Consent			X				
Baseline Characteristics							
	Demographics		X				
	Clinical characteristics		X				
	UPDRS III		X				
	NIH Toolbox Cognitive Battery		X				
	MoCA	X+	X				
Web or mailed questionnaires	MDS-UPDRS II		X				
	Beck Depression Inventory-II		X				
	Parkinson Anxiety Scale		X				
	Apathy Scale		X				
	Parkinson Fatigue Scale		X				
Randomization			X				
Primary Outcomes							
2a. Therapist Adherence & Proficiency*				X (random 30% of sessions rated)			
2b. Client Satisfaction Questionnaire						X#	
2b. Pittsburgh Rehabilitation Participation Scale*					X (3 sessions/pt)		
2b. Homework adherence*					X		
3. Bangor Goal Setting Interview^				X		X#	X#
Secondary/Exploratory Outcomes							
Weekly Calendar Planning Activity				X		X	
Self-Regulation Skills Inventory				X		X	
NeuroQOL Cognitive Function			X			X	X#
NeuroQOL Participation (Ability)			X			X	X#
Web or mailed questionnaires	Global Rating of Change					X	X
	PD-Cognitive Functional Rating Scale^		X			X	X
	Cognitive Self-Efficacy Scale		X			X	X
	General Self-Efficacy Scale		X			X	X
Credibility & Expectancy Questionnaire				X	X (in 4 and 7)	X#	
Adverse Events Reporting				X	X	X	

*Notes: * Completed by blind raters based on audiotape data (therapist adherence & competence; rehab participation) or homework worksheet. ^ Informants also complete these measures. # Collected by web or mailed questionnaires. + Phone/blind version.*

2 INTRODUCTION

2.1 STUDY RATIONALE

Parkinson disease (PD) affects over 1 million Americans and causes considerable personal and socioeconomic costs (>$34 billion/year in the US) that are expected to rise as the population ages[1]. Cognitive impairment produces disability and reduced quality of life among non-demented people with PD[2-4]. Surgical and pharmacologic treatments for PD do not prevent or treat cognitive impairment and may even exacerbate the problem[5-8]. As such, cognitive rehabilitation treatments that mitigate its negative functional consequences are a top research priority[8-13]. Unfortunately, existing cognitive rehabilitative programs for PD, which focus on restoring deficient cognitive processes through **process training** (repetitive practice of tasks that challenge specific cognitive processes), have had limited effect on daily function[10]. To overcome this limitation, we take a **strategy training** approach. We teach people targeted strategies to use in everyday life to circumvent cognitive deficits and accomplish meaningful daily activities. Contemporary cognitive rehabilitation evidence supports this approach for people with chronic neurocognitive dysfunction from stroke and brain injury[14-16]; however, it has not been studied in PD. By teaching strategies for everyday cognition and using training techniques to support transfer of learning beyond the training context, we hypothesize that our strategy training interventions will produce better functional outcomes for people with PD compared to process training.

We adapted the MultiContext (MC) Approach to enable people with PD to apply strategies in their everyday lives to cope with cognitive decline and improve or maintain daily function). The MC Approach is an individualized, community-based intervention that focuses on the attainment of personally meaningful functional goals using training techniques known to enhance strategy learning and transfer.

We hypothesize that the MC Approach can enable people with PD to manage everyday cognitive challenges so they can perform and participate in desired activities and roles. Such an intervention could improve function and quality of life, reduce caregiver burden, and enhance clinical care for this population. This specific study is part of a rigorous developmental process designed to optimize the MC Approach for clinical trials and eventual translation into clinical practice. It is **significant** because it will provide us with feasibility data, fidelity enhancements, clinical trials infrastructure, experience training and monitoring therapists, and an estimate of treatment effect—all essential elements for efficiency, rigor, reproducibility, and payoff in future clinical trials as well as for implementation and sustainability in real-world clinical practice.

2.2 BACKGROUND

We need effective cognitive interventions for people with PD. About one third of people in the earliest stages of PD demonstrate mild cognitive deficits—typically in memory and executive control functions—which are attributed to frontrostriatal circuitry dysfunction due to dopamine depletion in the basal ganglia and prefrontal cortex[5,17,18]. These deficits produce disability, reduced quality of life, and restricted participation early in the course of PD, potentially to a larger extent than motor impairment[2-4,19,20]. Due

to its negative impact on daily function and the fact that it does not respond to existing medical treatments, cognitive impairment is considered a major unmet need and important target for treatment by patients, families, practitioners, and scientists in the PD community[8,9].

Cognitive process training interventions do not improve daily function in PD. Almost all cognitive interventions for PD to date have taken a restorative process training approach, attempting to enhance underlying neural physiology and improve specific cognitive processes through practice[10,21-25]. Although this approach has produced small, specific, and short-term improvements on cognitive tests, these benefits do not translate to daily function[10]. The goal of cognitive rehabilitation is to enable people with cognitive dysfunction to perform and participate in meaningful everyday activities and roles[15,26]. Clearly, cognitive process training falls short of this goal for people with PD, so we should pursue a different approach.

Strategy training interventions may improve daily function in PD. A strategy training approach to cognitive intervention provides ways to maintain task performance despite the presence of cognitive deficits. It involves teaching people to use metacognitive, compensatory or adaptive techniques to bypass cognitive processing limitations and achieve task-related goals[27]. Strategy training is recommended for those with mild (vs. more severe) cognitive decline because it requires learning, capitalizes on existing cognitive resources, and aims to prevent or delay functional decline[27,28]. Although strategy training does not specifically target neurodegeneration or aim to improve cognition per se (which may be unrealistic in the context of neurodegeneration[29]), it can facilitate metacognitive control and continued activity engagement which may promote neuroplasticity, maintain cognition, or slow cognitive decline[30-32]. Strategy training is a Practice Standard for rehabilitation of mild memory and executive function deficits after stroke or brain injury[14], and it has a larger impact on daily function than process training in older adults with MCI[29,33]. Because people with PD-MCI have similar cognitive problems and cognitive rehabilitation goals as these populations, strategy training may also be beneficial for them[34,35]; however, its application in PD is very limited to date[10,13]. **Our prior work** in prospective memory supports the value of strategy training for non-demented people with PD for improving objective laboratory performance[36] and maintaining reported everyday performance[37].

We adapted the MultiContext (MC) Approach to teach non-demented people with PD strategies in a way that promotes generalization to daily function. In contrast to process training, which can produce skills that are tightly tied to the training context, strategy training can produce flexible skills that people can apply across situations **if** it uses training techniques that foster transfer of learned strategies to real-world activities and goals[38,39]. The MC Approach includes such techniques. First, it is client-directed in that the person identifies his or her own treatment priorities (goals), selects the treatment session focus, develops strategies to test, and is considered the expert in his or her own situation. Second, it uses a metacognitive framework to promote awareness of deficits and teach people to use structured and explicit methods to solve performance problems by anticipating challenges, generating and testing strategies or solutions, monitoring and evaluating their effectiveness during performance, and making connections between activity experiences and contexts (which facilitates generalization[39-42]). The therapist role within this client-directed metacognitive approach is to guide the process of self-awareness, strategy generation, and generalization. The therapist does not "tell" the person what to do, but instead

uses mediation (e.g. systematic questioning, prompts) to facilitate reflection and discovery. The above techniques are rooted in constructivism theories that suggest learning and transfer are enhanced when the learner actively engages in the process of discovering, testing, and evaluating solutions to challenging experiences[43-46]. Emerging evidence in older adults[27,47,48] and neurological conditions[16,49,50] increasingly supports the superiority of this type of approach over more directed training approaches. Finally, the MC Approach uses homework with action plans, which are effective tools in promoting behavior change, self-efficacy and daily function[51,52], to support strategy application in everyday life[38]. **Our preliminary study[53]** found that the MC Approach is acceptable, engaging, and may address the functional cognitive problems of people with PD.

Treatment fidelity is critical to complex behavioral interventions. Treatment fidelity—methods used to ensure interventions are implemented as intended—is increasingly recognized as essential to behavioral intervention development[54,55]. High treatment fidelity increases the ability to attribute change (or lack thereof) in outcomes to the intervention per se (rather than, e.g., implementation failure), facilitates theory testing, improves retention, is associated with better treatment outcomes, and enhances reproducibility and translation of interventions from research to real-world settings[56]. Therefore, in accordance with the NIH Behavioral Change Consortium Treatment Fidelity Workgroup guidelines[54,57] we developed processes to enhance and monitor treatment fidelity, and we will assess and optimize their effectiveness in this study **(Aim 2)**.

2.3 RISK/BENEFIT ASSESSMENT

See the Data & Safety Monitoring Plan

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Aim 1. Examine the feasibility of the MC Approach for people with PD within an RCT.	Recruitment, Retention, Intervention duration	Understanding and optimizing the procedures of an RCT of a complex behavioral intervention is necessary before evaluating outcomes[58-60]. We will track recruitment, retention, and intervention duration to ensure we can maintain a productive flow of participants and complete treatment in a reasonable timeframe. We will record reasons for attrition and examine characteristics of those who drop out to inform retention-enhancing strategies for the definitive RCT.
Aim 2. Demonstrate adequate treatment fidelity to the MC Approach.	Therapist Adherence & Proficiency; Participant Acceptance,	Appropriate delivery (Adherence & Proficiency) is the foundation of treatment fidelity[55,61]. To achieve the desired outcomes of any behavioral intervention, participants also must "buy into" its principles and practices (Acceptance), actively

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	Receipt, & Enactment	engage with the content during treatment (Receipt), and apply the learned skills in relevant real-life settings (Enactment)[54,55].
Aim 3. Obtain preliminary estimates of effect on patient-reported functional cognition.	Bangor Goal Setting Interview	Functional cognition—how cognitive abilities enable/disable function in daily activities—is the primary target of cognitive rehabilitation and is now recognized as an important outcome in PD cognitive research[62,63]. Patient-reported outcomes are increasingly used to measure this type of construct since it is not directly observable in research or clinical settings and because the patient's experience is a key determinant of treatment value[64]. In best practice cognitive rehabilitation, the therapist and client collaborate to identify problems with functional cognition and set related treatment goals[15,28], and progress on those problems/goals determines treatment success. To be consistent with real-world practice and, therefore, to facilitate future clinical implementation, we will use this same process to determine treatment effect.
Secondary		
To obtain preliminary estimates of effect on other measures of functional cognition.	Weekly Calendar Planning Task, Self-regulation Skills Inventory, NeuroQOL Cognitive Function, PD-Cognitive Functional Rating Scale	
To obtain preliminary estimates of effect on self-efficacy.	Cognitive Self-efficacy Scale, General Self-efficacy Scale	
Tertiary/Exploratory		
To obtain preliminary estimates of effect on participation.	NeuroQOL Ability to Participate in Social Roles and Activities	

The following criteria will be used to declare failure:
Aim 1: Feasibility

- ≤ 60% retention in the study intervention

- ≤ 75% retention in the study (80-85% is typically considered good in behavioral trials; e.g., Abshire et al., 2017; Coday et al., 2005)
- Note: Participants excluded post-Randomization count as failures in the above retention endpoints.

Aim 2: Fidelity

- Therapist adherence to protocol: Average ≤ 75%
- Therapist competence in administration: Average < 2
- Participant satisfaction: Average Client Satisfaction Questionnaire score ≤ 16
- Participant engagement: Average Rehabilitation Participation Scale score ≤ 3

Aim 3: Effect

- Average Bangor Goal Setting Interview Goal Attainment change of ≤ 1 with lower 95% CB below 0.

4 STUDY DESIGN

4.1 OVERALL DESIGN

We will conduct a single-site, single-blind pilot RCT. Participants will complete pre-treatment assessment and then will be randomized to treatment arm (stratified by sex and MoCA score [25/26][65]). Both arms will consist of 10 individualized treatment sessions within a 12-week period. In-person post-treatment assessment will be 1 week after intervention completion, and questionnaire follow-up will be 3 months after.

See also Sections 1.1, 1.2, 2.1, 2.2, 3

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This project will build on our prior work to assess and optimize the feasibility of the MC Approach for people with PD in a pilot RCT and to generate data to power a definitive RCT. This Stage I study is part of a rigorous developmental process designed to optimize the intervention for future efficacy or effectiveness trials and eventual translation into clinical practice. It will provide us with feasibility data, fidelity enhancements, clinical trials infrastructure, experience training and monitoring therapists, and an estimate of treatment effect—all essential elements for efficiency, rigor, reproducibility, and payoff in future clinical trials as well as for implementation and sustainability in real-world clinical practice.

See also Sections 1.1, 1.2, 2.1, 2.2, 3

4.3 JUSTIFICATION FOR INTERVENTION

Both treatments consist of 10 ~1-1.5 hour sessions over 12 weeks delivered in an individual, face-to-face format in participants' homes and/or communities by trained licensed occupational therapists (OTs). Both are realistic and reimbursable services within our current healthcare system.

See also Sections 2.1, 2.2, 3, 6

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the intervention if he or she has completed the baseline assessment and 10 intervention sessions.

Completion of the study is defined as completion of the 3-month follow-up assessment.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Males and females over age 40 who meet criteria for typical idiopathic PD[66], are stage I-III[67], have subjective cognitive decline (SCD)[68] (as defined by a positive answer to either question: Do you feel like your thinking skills or memory are becoming worse? Do you have problems with your thinking skills or memory?), and can list ≥ 1 daily cognitive challenge they wish to address. Medications should be stable for 4 weeks prior with no changes planned during the study.

Rationale for cognitive criteria for entry: We will include people with SCD regardless of whether they meet diagnostic criteria for PD-MCI. There is no gold standard assessment of SCD, so we are using a common method of ascertainment based on research criteria for SCD[68,69]. People with SCD are an important target for cognitive treatment because SCD may be a more sensitive measure of cognitive decline than cognitive tests in high functioning or at-risk individuals[68] and, in the absence of objective deficits, SCD predicts future development of PD-MCI[70,71]. Because the MC approach is client-centered, we hypothesize that it can meet the needs of people with SCD with or without objective cognitive deficits. Our preliminary study[53] supports this notion, as both kinds of participants (using MoCA cutoff 25/26)[65] reported improved functional cognition from the MC approach. To begin to explore this issue more thoroughly in the current study, we will recruit people with SCD and then use neuropsychological testing to characterize cognitive status (± PD-MCI) and assess it as a potential effect modifier. This study is not powered to detect significant effects of this factor, but our findings will guide sampling, inform hypotheses, and provide preliminary data for future trials.

5.2 EXCLUSION CRITERIA

Dementia according to MDS criteria[72] or MoCA score < 21[65], other neurological disorders (e.g., stroke), brain surgery (e.g., STN DBS), history of psychotic disorder or any significant current psychiatric disorder, or any condition that would interfere with participation (e.g. non-English speaking).

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to:

- Refrain from engaging in OT or other cognitive interventions.

5.4 SCREEN FAILURES

Screen failures are defined as participants who do not meet eligibility criteria upon record or phone screen and are not enrolled in the study.

Individuals who are ineligible to participate in the study because of not meeting criteria that could change over time may be rescreened. Examples include the development of SCD or emergence of functional cognitive goals.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

See Recruitment & Retention and Inclusion of Women & Minorities.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

MultiContext Approach (MC):

This treatment focuses on improving functional performance by enhancing the generation and use of strategies—which can be internal (e.g., self-talk, planning) or external (e.g., checklist, alarm)—to circumvent cognitive processing limitations caused by PD. It uses a standardized approach across and within sessions for all clients while being tailored to each client's cognitive problems and goals. The first two session are OT evaluation sessions designed to (1) provide the OT with a comprehensive understanding of the client's functional cognition, occupational performance and participation, (2) begin building the client's awareness of cognitive strengths and limitations and how they may relate to daily function, and (3) inform individualized goal setting and treatment planning. They involve an explanation of MC's purpose and process, OT functional cognitive "diagnostic" assessments (the WCPA, SRSI, structured treatment activity), review of pre-treatment assessments, collaborative goal setting (BGSI), and assignment and review of the cognitive log homework (record and reflect on daily cognitive lapses). All subsequent treatment sessions consist of a review of prior sessions and learning, homework review, treatment activities, homework provision, and session recap. Each session's treatment activities are selected collaboratively based on the client's goals and preferences and the OT's assessment of the client's cognitive and functional status. They involve the performance of simulated functional activities with OT mediation and a metacognitive framework to help the client anticipate performance problems, generate and use strategies to support performance, evaluate and modify performance and strategy use, and transfer these principles to other activities. The OT's expertise in functional cognition, task and performance analysis, and task manipulation and grading guides this process. Treatment activities also involve in-depth discussion of these issues, including making explicit connections between the simulated functional activities, strategies, and the client's real-life experiences, to promote generalization of learning[40,41]. Homework consists of action plans for using the strategies generated and practiced during the treatment session in specific everyday life situations. Clients record instances of strategy use (or

missed opportunities) along with their evaluation of strategy effectiveness and potential modifications on a structured worksheet, which is reviewed collaboratively in the next session. In this way, homework not only supports real-life strategy application and practice, but it also reinforces self-monitoring, self-evaluation, problem solving, strategy self-generation, and strategy optimization. Treatment progresses through three general phases (1: Understand and define problems and goals, 2: Generate, execute, and evaluate strategies, 3: Generalize and reinforce strategy use) and increases in difficulty, but progression is flexible depending on the client's goals and abilities.

Control:

This treatment parallels the cognitive process training used in PD to-date but with simulated functional tasks (vs. computer or paper & pencil tasks). It has the same basic protocol as MC, but it is therapist-directed, and the OT does not address strategies, metacognition, generalization, or use mediation or action plans. Therefore, this is a standard-of-care approach that includes all but the proposed critical elements of MC. The OT reviews pre-treatment cognitive test scores with the client but without discussion to build awareness. The OT selects treatment activities based on the client's cognitive profile and goals from a published set of activities designed for use in cognitive interventions[73]. Graded task practice with OT feedback on performance accuracy is used to produce neurocognitive improvement (or possibly independent strategy development). The OT assigns practice of specific cognitively challenging everyday life activities for homework (but without action plans).

6.1.2 ADMINISTRATION AND/OR DOSING

Both interventions consist of 10 1-1.5 hour sessions over 12 weeks delivered in an individual, face-to-face format in participants' homes and/or communities by trained licensed occupational therapists (OTs). Care partners are also invited to participate.

A complete intervention is defined as completion of 10 OT sessions.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Training: MC training will consist of a 2-day PI and Co-I led workshop and regular meetings. Control training will consist of a 1-day PI led workshop and regular meetings. Both will involve reading, didactic instruction, interactive discussions and activities, role-playing, and videotaped examples. Each therapist will observe the PI conduct treatment with 1 participant and then will conduct treatment with 1-2 participants under PI supervision. The Co-I has extensive experience training and supervising OTs in the MC Approach[49,74,75], and the PI has extensive experience administering it. The study OTs will have requisite knowledge in metacognitive strategy training and task-oriented training and clinical experience with PD.

Supervision: We will audiotape all treatment sessions, and the PI and Co-I will review the tapes and meet with the therapists to reinforce training, correct problems, and discuss issues. Initially, 50% of the tapes

will be reviewed, and the teams will have weekly meetings; this will reduce to 20% review and fewer meetings when appropriate[56].

Assessment: Interventionist fidelity is a primary outcome of this study (Aim 2a) and thus will be formally assessed. ***See section 8.1.***

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Participants will be randomized to treatment arm (MC, Control)* stratified by sex and MoCA score [25/26][65]. The study statistician created a randomization process that is implemented through REDCap by an independent person (Meghan Campbell, PhD). Immediately after a participant completes Pre assessment, the tester informs Dr. Campbell, via email, of their study ID, sex, and MoCA score (stratification variables). Within 2 days of being informed, Dr. Campbell will use the REDCap randomizer to assign treatment group and will inform the corresponding therapists, via email, that a participant has been assigned to their group. Only Dr. Campbell and the statistician can view the randomizer and its results. To maintain PI blinding during therapist supervision, the participants or treatment sessions under discussion will not be identified by study ID.

Personnel collecting Pre, Post and Follow-up data, which includes the study coordinator, will remain blind to treatment arm throughout the entirety of the study. They will not know which therapists are administering which intervention. Inadvertent unblinding of testers will be documented (yes/no, notes). Most of the outcomes, including the primary efficacy outcome (BGSI, Aim 3), are collected via computer, so inadvertent unblinding should not bias the data.

Personnel responsible for rating the audio files for fidelity (Aim 2) will be blind to study purpose. Due to the nature of their work, they will likely come to understand that there are two general intervention approaches being delivered and which therapists are delivering which approach; however, having no knowledge of the study aims and hypotheses and clear criteria for rating should reduce any associated biases in their ratings.

Participants will be aware that they have been randomly assigned to one of two interventions, but they will be given no information on what the other intervention entails, nor will they be informed which is the hypothesized “active” (MC) or Control intervention. In the Follow-up assessment, participants will be asked if they think they received the active or control intervention (yes/no/I don’t know with an option to provide an open-ended response describing why).

*Randomization ratios over the course of the study due to therapist availability:

- November 2019-December 2020 = 2:1, MC:Control
- January 2021- ~2021 = 1:2, MC:Control
- ~July 2021- = 1:1, MC:Control

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Participant engagement in and adherence to the intervention are primary outcomes of this study (Aim 2b) and thus will be formally assessed.

See section 8.1

6.5 CONCOMITANT THERAPY

There are no medication exclusions for this protocol. Medication information will be obtained from electronic medical records and confirmed with the participant at the Pre-treatment assessment. Medical records will be reviewed after participation to determine whether there were any changes over the course of the study. If so, they will be documented and potentially accounted for in analyses (exploratory).

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Participants may discontinue the study intervention before receiving 10 treatment sessions for a variety of reasons (e.g., adverse events, no longer interested, other obligations taking precedence). Temporary discontinuation of the study intervention can also be considered; however, this should not last longer than 3 weeks unless absolutely necessary (i.e., the COVID-19 situation). When a participant permanently discontinues from the study intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol (i.e, Post-treatment assessment within 2 weeks after last treatment session, and Follow-up assessment 3 months after that). The reason(s) for discontinuing the participant from the intervention will be documented on the Participant Tracking sheet.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants may withdraw voluntarily from the study or the study intervention at any time, but investigators will seek to minimize participant discontinuation/withdrawal from the study except for safety reasons. An investigator may discontinue a participant from the study for the following reasons:

- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be documented on the Master File. Because an aim of this study is to track retention and determine attrition rates to power a future full-scale trial, participants who discontinue/withdraw from the study will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they complete at least one study visit and subsequently miss two consecutive study visits and are unresponsive to study contact (after at least 3 attempts).

If a participant misses a scheduled study visit:

- The OT or study coordinator will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant. These contact attempts will be documented in the Master File.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

A trained tester blind to treatment group will conduct Pre and Post testing while participants are on their regular medication (to prevent motor interference[63] and best represent their function in daily life). Testing will occur at the same time of day to control for potential effects of dosage timing or wearing off. Follow-up assessment will occur via web-based or mailed survey.

Primary outcomes:

Aim 2

- Therapist fidelity: Trained raters who are blind to study purpose and treatment group will use the *MC Fidelity Tool* to perform the following ratings. *Adherence:* Proportion of protocol steps that occurred within the session will be rated as present or absent. *Proficiency:* Quality of delivery of each of MC's critical treatment components will be rated on a 4-point scale (0=Did not occur, 1=Little Evidence/Inadequate, 2=Emerging/Adequate, 3=Proficient; averaged for a competence score) with detailed guidelines for each component and anchor. The raters will rate a random sample (30%, n = 180) of MC and Control session audiofiles (evenly distributed across condition, OT, treatment session number, and study month).
- Acceptance: We will administer the *Client Satisfaction Questionnaire* (CSQ-8)[76,77] at post-treatment via mailed or web-based survey. Items have 4-point response scales (3-4: positive, 2: neutral, 1: negative) and are summed for a total score; higher scores indicate higher acceptance.
- Receipt: The raters will rate participants' engagement in treatment sessions with the *Pittsburgh Rehabilitation Participation Scale* (PRPS)[78] from the audiofiles (3 sessions per participant). The PRPS is a 6-point scale (1=None, 6=Excellent) with full descriptions of each anchor. Session scores are averaged for a single score, which is reliable and predictive of rehabilitation outcomes[78,79].
- Enactment (i.e, Adherence): The raters will code homework completion for each session (0=Did not do, 0.5=Partial, 1=Complete). We will sum these scores and divide by the total number of homework assignments (10) to yield a homework completion rate for each participant.

Aim 3

- Functional cognition: The *Bangor Goal-Setting Interview (BGSI)*[80,81] offers a standardized means of eliciting individual goals and rating goal attainment over time and has been successfully used in cognitive rehabilitation RCTs with older adults, including those with mild to moderate dementia[81-83]. During the first intervention session, the OT will conduct a semi-structured interview to gain an understanding the participant's functional cognitive performance and potential problem areas and goals. Part of the participant's first homework assignment will be to think further about problem areas and functional cognitive goals, and they will be provided with a handout and Activity Checklist to guide and document the process. At the second session, the OT and participant will review what was discussed in the first session and anything the participant wishes to add or modify. Then they will identify and set goals for 3-5 real-life functional cognitive problems. They and their informants will rate each of their goals for Attainment, Importance, and Readiness to Change on 10-point scales (e.g., Attainment: 1=Cannot do or am not doing successfully, 10=Can do and am doing very successfully) in the second session (Pre) and then again at Post and Follow-up. Goal attainment ratings are averaged to yield mean attainment scores[81].

Additional Measures:

In addition to the primary measures above, we will collect other data to characterize participants, as covariates, or as exploratory/secondary outcome measures of treatment effect (see Table below). Some objective and informant-report measures of functional cognition will be administered as exploratory outcomes in this trial to assess their potential to be co-primary outcomes for the future RCT, thus mitigating potential limitations associated with self-report. The rater will retrieve clinical characteristics from electronic medical records and confirm with the participant in the Pre assessment.

Purpose/Domain	Measure/Description
Baseline characteristics:	
Demographics	e.g., age, sex, education, ethnicity/race, living/work status, comorbidities
Clinical characteristics	e.g., disease duration, side/type of onset, medications, Hoehn & Yahr stage
Motor dysfunction	Unified Parkinson Disease Rating Scale (UPDRS) Parts II & III
Non-motor dysfunction	Beck Depression Inventory-II; Parkinson Anxiety Scale; Apathy Scale; Fatigue Severity Scale
Cognition	Montreal Cognitive Assessment (MoCA), NIH Toolbox Cognitive Battery
Exploratory/secondary outcomes:	
Functional cognition (proximal)	Objective performance: Weekly Calendar Planning Activity[84]
Functional cognition (proximal)	Patient-reported: NeuroQOL Cognitive Function; PD-Cognitive Functional Rating Scale (PD-CFRS)[85] (self & informant); Global Rating of Change[86]; SRSI
Self-efficacy (proximal)	Patient-reported: Cognitive Self-efficacy Scale; General Self-efficacy Scale[87]
Participation (distal)	Patient-reported: NeuroQOL Ability to Participate in Social
Process measure:	Credibility and Expectancy Questionnaire[88]

See also Sections 1.3, 3

8.2 SAFETY ASSESSMENTS

See the Data & Safety Monitoring Plan.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

See the Data & Safety Monitoring Plan.

8.4 UNANTICIPATED PROBLEMS

See the Data & Safety Monitoring Plan.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1: Examine the feasibility of the MC approach within an RCT.

- H1: Study recruitment will be 4 participants/month, retention in both treatment groups will be ≥ 85%, and ≥ 85% of participants in both groups will complete the intervention in 12 weeks.

Aim 2: Demonstrate adequate treatment fidelity to the MC approach.

- H2a: Therapists will deliver MC with good adherence (≥ 80%) and proficiency (scores ≥ 2/3, indicating Adequate).
- H2b: MC participants will have good acceptance (CSQ-8 ≥ 24/32, indicating all positive responses), receipt (PRPS ≥ 4/6, indicating at least "Good") and enactment (homework completion ≥ 80%).

Aim 3: Obtain preliminary estimates of the MC approach's effect on patient-reported functional cognition.

- H3 (exploratory): MC participants will report greater improvement in functional cognition than Control participants immediately and 3 months after treatment.

9.2 SAMPLE SIZE DETERMINATION

We will enroll 30 participants per group (N = 60). Although not required for an R21 proposal, we provide power analyses for our feasibility and fidelity hypotheses (Aims 1 & 2) assuming 15% attrition (see Table). We also estimate power for our (exploratory) pre-post comparisons of treatment effect (Aim 3). Based on our preliminary data (Goal Attainment Δ M = 2.4, SD = 0.97), with n = 30 per group we will be able to detect mean differences in change of 0.85 in Attainment (2-tailed, α = 0.05, 90% power). However, we want to reiterate that our reason for measuring treatment effect in this study is not to demonstrate efficacy but to obtain effect size estimates to power an efficacy trial. Our proposed sample size will provide enough information to achieve our aims and is feasible to accomplish in the timeframe of an R21.

Confidence bounds around target thresholds assuming 15% attrition (for Aim 2) and 95% confidence level.		
Aim	**Outcome** (with preliminary data source reference)	**Target (Lower, upper)**
1	Recruitment and retention	85% (73 – 93)
2a	Adherence (n=153 observations)[61]	80% (78 - 82)

2a	Proficiency (n=153 observations)[61]	3 (2.9 – 3.1)
2b	Acceptance: CSQ[53]	24 (23.8 – 24.2)
2b	Receipt: PRPS[78]	4 (3.8 – 4.2)
2b	Enactment: Homework completion[53]	80% (75 – 85)

9.3 POPULATIONS FOR ANALYSES

Our primary population for analysis of treatment effect (Aim 3) will be the Intention-to-Treat (ITT) Analysis Population (i.e., all randomized participants). We will also conduct Per-Protocol analyses on the subset considered to have completed the intervention (at least 4 treatment sessions).

9.4 STATISTICAL ANALYSES

Aim 1: Examine the feasibility of the MC approach within an RCT.

- H1: Study recruitment will be 4 participants/month, retention in both treatment groups will be ≥ 85%, and ≥ 85% of participants in both groups will complete the intervention in 12 weeks.

We will track and report recruitment, retention, intervention duration, and reasons for non-enrollment or attrition throughout the study period. Based on our preliminary study, we anticipate no problems in meeting our hypothesized thresholds. We enrolled 3 participants/month (with only 1 treating therapist and without an existing cohort from which to recruit), had 87.5% retention, and 85.7% of participants completed the intervention in the allotted timeframe[53]. With N=60, if we meet our retention and completion goals (85%), we can be 95% certain of true rates of at least 73% (see Table in Section 9.2).

Aim 2: Demonstrate adequate treatment fidelity to the MC approach.

- H2a: Therapists will deliver MC with good adherence (≥ 80%) and proficiency (scores ≥ 2/3).

Blinded raters will rate therapist adherence and proficiency for a random sample (30%, n=180) of MC and Control treatment sessions. We will calculate adherence and proficiency (to MC) for each therapist; adherence ≥ 80% and proficiency ≥ 2 (out of 3, indicating at least "Adequate") will be benchmarks for good treatment integrity.

- H2b: MC participants will have good acceptance (CSQ-8 ≥ 24/32, indicating all positive responses), receipt (PRPS ≥ 4/6, indicating at least "Good") and enactment (homework completion ≥ 80%).

MC participants will complete the Client Satisfaction Questionnaire (CSQ-8) at post-treatment, and blinded raters will rate participants' session participation (Pittsburgh Rehabilitation Participation Scale; PRPS) and homework completion. CSQ-8 scores ≥ 24, PRPS scores ≥ 4, and homework completion rates ≥ 80% will be benchmarks for good acceptance, receipt, and enactment, respectively.

For the Aim 2 outcomes, we will calculate mean scores ± 95% confidence bounds (CBs) and compare them to our stated thresholds. To assess treatment differentiation, we will compare Proficiency scores for the MC and Control sessions using *t*-tests. We can also categorize participants using cutoffs (e.g., homework: <50%=Poor, 50-79%=Fair, ≥80%= Good) for descriptive purposes and compare the MC and Control groups' scores on outcomes using appropriate non-parametric tests.

Aim 3: Obtain preliminary estimates of the MC approach's effect on patient-reported functional cognition.

- H3 (exploratory): MC participants will report greater improvement in functional cognition than Control participants immediately and 3 months after treatment.

We will compare treatment effects (Goal Attainment) using mixed model repeated measures ANOVA (2: group X 3: time point). We chose this model because we want to use statistical contrasts to compare pre-post and pre-follow up changes across group. We will evaluate the pattern of correlations within subjects and test various correlation structures as appropriate using Akaike's information criteria and the Schwarz Bayesian criteria. However, our purpose is not to demonstrate efficacy, but rather to obtain effect size data to inform sample size calculations for a definitive RCT. To this end, we will generate mean change between the time points with 95% CBs. We will compare these data to the suggested minimally clinically important difference (≥ 2 points improvement)[89] to help determine the appropriate sample size to test the hypothesis that, in addition to being superior to the Control treatment, MC produces a clinically significant effect[90]. We will also create a sample size table for various effect size values due to uncertainty of pilot estimates[91].

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

See Informed Consent document

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

See the Data & Safety Monitoring Plan

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to determination of unexpected, significant, or unacceptable risk to participants, significant protocol violations, or determination of futility.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).]

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety monitor, and funding agency and will be maintained in accordance with applicable state and federal laws. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the IRB.

All research activities will be conducted in as private a setting as possible. The study participants' contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, institutional policies, or sponsor/funding agency requirements.

Participant data will be coded numerically to protect individual identity. No identifiers will be used in presentations or publications. All data will be stored in locked cabinets or on computers within a private security network protected by a Cisco PIX firewall with remote access only permitted through VPN connections, as per HIPAA guidelines. All key personnel involved in the design or conduct of research involving the human subjects will receive the required education on the protection of human research participants.

Participants are asked the following question at Follow-up assessment to monitor for perceived confidentiality breach:

"Do you feel that the study team has protected your privacy over the course of the study? Yes/No"

See also the Data Sharing Plan

10.1.4 SAFETY OVERSIGHT

See the Data & Safety Monitoring Plan

10.1.5 DATA HANDLING AND RECORD KEEPING

10.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Appropriate records will be maintained for this trial, in compliance with ICH GCP and regulatory and institutional requirements for the protection of confidentiality of participants. As part of participating in a NIH-sponsored study, the site will permit authorized representatives of the NIH, sponsor, and regulatory agencies to examine (and when permitted by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Both paper and electronic data capture will be used for this study, and all quantitative data will ultimately be entered into the study's REDCap database. Data not collected directly by REDCap (e.g., those administered via REDCap Survey Mode) or imported from another electronic source directly into REDCap (e.g., NIH Toolbox Cognitive Battery and NeuroQOL data) will be entered by trained research personnel using a double scoring/entry and automated discrepancy flagging protocol to minimize errors.

Paper sources of data include some of the Pre and Post assessments, questionnaires for participants who opt for hard copy completion, all of the record forms and worksheets completed during the treatment sessions, and the treatment fidelity assessments. Electronic sources of data include electronic medical records (e.g., PD-related clinical characteristics), NIH Toolbox Cognitive Battery, NeuroQOL questionnaires, REDCap Survey Mode (web-based questionnaire delivery), and audio recordings of treatment sessions.

Data collection will be the responsibility of the testers and therapists under supervision of the study coordinator and PI. The coordinator and PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported as well as storage and management of source data. Hardcopies of the study visit worksheets will be maintained for future reference but will also be scanned and stored in a secure, web-based location for access by research personnel.

10.1.5.2 STUDY RECORDS RETENTION

Data collected under this protocol will be kept for a minimum of 7 years after the study is complete, as per IRB policy.

10.1.6 PUBLICATION AND DATA SHARING POLICY

See Data Sharing Plan and Dissemination Plan

10.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The university has established policies and procedures for disclosing all conflicts of interest and established mechanisms for the management of all reported dualities of interest.

10.2 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale
2	May 2020	Changed randomization process and related communication among team members	To remove PI from randomization process and blind her to study group; minimize bias
2	May 2020	All participants will undergo 10 treatment sessions	To ensure treatment groups are balanced on dose of intervention
2	May 2020	Changed definition of screen failure from what was initially provided by this template	Study monitor request
2	May 2020	Added criteria used to declare failure for each aim to Objectives and Endpoints section	To enhance rigor and inform decision-making for next steps
2	May 2020	Specified target interval limits for timing of assessment and treatment sessions (see Schema)	To enhance rigor
2	May 2020	Added question to AE report form to monitor for psychological risks	A stated risk of the study, needed to capture it
2	May 2020	Added a question to the Follow-up assessment to monitor for perceived confidentiality breach	A stated risk of the study, needed to capture it
3	Nov 2020	Fixed Schedule of Activities table to indicate that inclusion/exclusion criteria are assessed in Visit 1 (via MoCA); consent form will also be modified to include this information	To fix a prior inconsistency pointed out by study monitor
4	Dec 2020	Added phone/blind MoCA to screening phone call	To reduce risk of enrolling people who do not meet cognitive criteria for entry
4	Dec 2020	Specified randomization ratio changes over course of study	To enhance transparency
5	May 2021	Added note that participants excluded post-randomization count as failures in retention endpoints	To enhance rigor and transparency

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