Study Protocol

Official Title: Facilitating Optimal Routines in Aging

ClinicalTrials.gov ID (NCT number): NCT03913637

Protocol Date: November 24, 2025

Scientific Background

We randomized 30 participants to Strategy Training or EUC in our preliminary study. Mean scores on the disability measure (Performance Assessment of Self-Care Skills) differed between groups at 6 months, and although this difference was not statistically significant after controlling for baseline scores, it was associated with a moderate effect size (Cohen's d = 0.54). Furthermore, for individuals in the Strategy Training group, a within group effect from preintervention to 6 months was found in disability, $t(7) = 5.16$, $p < 0.01$. These data are compelling. The outcome measure counts the number of prompts for assistance participants required on eight daily activities; at six-months, the participants in the Strategy Training group required approximately one prompt per task, which suggests that they were, at least, maintaining performance of daily activities. Finally, no between groups differences were found at baseline on demographic characteristics that would suggest a confounder influenced these findings. While promising, these data should be interpreted with caution. The small sample size limits the ability to present a robust statistical model, and aspects of the protocol were being operationalized during the trial. These findings suggest that Strategy Training may be one effective platform to slow decline to disability among individuals with MCI. An effective intervention, such as Strategy Training, that is designed to slow onset of disability for at risk individuals is critical for older adults to maintain living independently.

Achieved participant satisfaction. The participants' satisfaction (n=15) with the intervention was high. Upon completion of the intervention, participants randomized to Strategy Training had the opportunity to complete the Client Satisfaction Questionnaire-8[33] to measure their satisfaction with the Strategy Training intervention (scores could range from 8-32 where higher scores indicate greater satisfaction with the intervention). Questions asked about the quality of services, whether the services met their needs, and if they were satisfied. An average of 30.4 (SD = 1.3) was found, indicating that participants were mostly to very satisfied. No participants reported that they were dissatisfied or indifferent to the intervention.

In addition to the self-report of satisfaction, participants informally provided feedback on their experience in the Strategy Training intervention. One participant indicated satisfaction with the intervention by talking about his new strategies for engaging in daily activities by saying, "When I have a problem, I think about the fact that I have a plan." After talking about executing a plan, the participant said, "You feel a sense of accomplishment, and that was the thing with our projects." Another participant, who frequently participates in research indicated, "This was the first [study] so far that made an impact on me... This [study] is the one that gave something back to me." Ultimately, the participants discussed how the participation in daily activities made them feel better and enhanced their engagement in daily activities. One participant summarized this by saying, "[It is] like a booster, a cheerleader, encouragement [to do] the things that I know are good for me."

For the estimated 11 to 16 million older adults expected to have Alzheimer's by the year 2050,[1] disability associated with the disease is certain. This disability is insidious and devastating. In the early stages of cognitive decline, individuals experience subtle changes in complex daily activities, such as

managing medications and finances.[2] In the most severe stages, affected individuals completely depend on others for basic daily activities, such as eating and dressing. Mild Cognitive Impairment (MCI) is an early stage of decline and provides a window of opportunity to delay decline to disability and enhance our understanding of how biological and neurocognitive hallmarks of Alzheimer's disease are associated with disability. Research has primarily focused on underlying pathology associated with the disease. This research has taught us that Aβ deposition is often associated with neurocognitive decline. Among interventions designed to treat Aβ deposition or neurocognitive decline, few interventions - pharmaceutical or non-pharmacological - have effectively altered the underlying pathology or neurocognitive impairments.[3–9] We published a review of 32 non-pharmacological interventions for older adults with MCI. Interventions focused on cognitive training, physical exercise, and psychotherapeutic interventions; they demonstrated mixed results for selected areas of cognition and only modest changes in disability.[10] These modest improvements may be due to several reasons, including the interventions' limited focus on how mild cognitive impairments influence performance of daily activities; they do not address the barriers to performance of daily activities, problem-solving solutions, or daily activities that are meaningful to older adults. Interventions that optimize performance of meaningful daily activities may be an effective platform to slow onset of disability associated with cognitive impairments because these types of interventions promote positive environmental reinforcements and reduce negative influences in the existing daily lives of the older adults.[10,11] Alterations in the trajectory of decline to disability may be significant for older adults because the loss of cognitive abilities leaves older adults disabled. A slowing of this decline may help older adults remain absent of disability for as long as possible.

Strategy Training is one promising treatment model that optimizes engagement in daily activities.[12,13] We propose a phase II, efficacy trial of Strategy Training that includes assessing presence of Aβ deposition and executive function as effect modifiers.

What is Strategy Training? Strategy Training is a behavioral approach to help older adults who are beginning to have challenges with daily activities to develop solutions and skills to preserve their ability. Behavioral activation provides the theoretical basis for Strategy Training. Behavioral activation focuses the participant to engage in activities that he or she can do, instead of focusing on thoughts, feelings and physical symptoms.[12,14] Strategy Training optimizes engagement in meaningful daily activities through four integrated components: (i) generating self-selected goals that address activities,[15] (ii) monitoring daily activities to provide information on baseline level of activities and demonstrating the value of participating in activities, (iii) scheduling activities to increase contact with other individuals and participating in activities, and (iv) problem-solving solutions to barriers experienced when engaging in activities (Figure 1)[10,13,16–18] The hallmark of Strategy Training is its focus on daily activities. Therapists facilitate the participants' engagement in daily activities through prompts, questions, and problem solving. The participants derive their own goals and develop their own strategies to improve their ability to perform daily activities. Behavioral activation suggests that behavior changes derived through this method are sustainable because the participants focus on what they what to do and how they want to do it.[14] Due to its theoretical and scientific background,

Strategy Training is promising in its ability to slow decline to disability for older adults with MCI[10,15,16,19] because older adults with MCI maintain the ability to develop strategies for engagement in daily activities.[20,21]

Why investigate the extent to which CNS amyloid-beta deposition is an effect modifier on change in disability? Presence of Aβ and neurocognitive dysfunction are two hallmarks of Alzheimer's disease. Definitive diagnosis of Alzheimer's disease relies on the demonstration of amyloid plaques and neurofibrillary tangles at autopsy.[22] In vivo identification of amyloid deposition has important implications for early identification of individuals at high risk of decline to disability associated with Alzheimer's disease. The development of the PET tracer, Pittsburgh Compound B (PiB), has made it possible to image amyloid in vivo.[23]. With the PiB tracer, studies are examining how presence of Aβ is associated with neurocognitive function and decline. For example, the longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) showed that nearly 50% of individuals who had Aβ at baseline declined on neuropsychological examinations, while those who started with normal Aβ tended to maintain their cognitive performance over the following years.[24] As such, Aβ conspires to be a critical biological factor in an individual's decline to Alzheimer's disease. To better understand Aβ's influence, this project proposes to examine how presence of significant Aβ modifies the relationship between intervention groups and change in disability.

Why investigate the extent to which neurocognitive function is an effect modifier on change in disability? While Aβ deposition is one hallmark factor, it is not conclusive of neurocognitive disorder. Some individuals remain without disability or cognitive decline with significant brain amyloid load while others do not. Thus, examining neurocognitive function, in addition to CNS amyloid-beta deposition, is critical. Beyond memory, presence of intact executive function is essential for remaining disability free.[25–27] Executive function guides planning, solving problems, organizing and directing the body to carry out daily activities.[28–30] Thus, neurocognitive decline and progression to overt disability is often associated with declines in executive function.[28,30] Due to the role executive function plays in disability, executive function warrants careful examination. Information gleaned will determine whether executive function is an effect modifier and, ultimately, will inform for whom are interventions, such as Strategy Training, are most effective. The relationship between Aβ deposition, executive function, disability, and a promising non-pharmacological intervention remains unclear. The proposed study provides the opportunity to assess if Aβ or executive function modify the relationship between intervention groups and change in disability. This information can be used to inform the design and conduct of future clinical trials.

Study Objectives

A randomized controlled trial to test the efficacy of Strategy Training over Enhanced-Usual Care (EUC) on disability and whether Aβ status or neurocognitive function influences intervention outcomes in 150 older adults with MCI.

Aim 1: Test the effect of ST compared to EUC on change in disability among older adults with MCI. Hypothesis: Older adults in ST will demonstrate lower rates of decline to disability (measured with a performance-based measure of daily activities called the Performance Assessment of Self-Care Skills) than those who receive EUC. Rationale: We have a refined intervention; examining the intervention's efficacy is the next scientific step. The outcome observes performance of daily activities in the real-world. Subtle changes in disability are detected through performance not through self-report or informant-report.

Aim 2: Assess the extent to which CNS amyloid-beta deposition and neurocognitive function modify the relationship between ST and EUC on change in disability. Rationale: Findings will identify for whom the intervention is most effective. This information will inform the design and conduct of future clinical trials to delay decline to disability among older adults with MCI.

Study Design & Methods

Total number of subjects to be enrolled at this site (enter -1 for chart reviews, banking, registries): 600

Describe and explain the study design: Randomized-controlled trial, following participants for 12 months.

Describe the primary and secondary study endpoints: The study will assess improvements in instrumental activities of daily living. CNS amyloid-beta deposition (assessed using PET with [C-11]PiB) and executive function will be evaluated as effect modifiers.

Provide a description of the following study timelines: Duration of an individual subject's active participation: about 12 months. Duration anticipated to enroll all subjects: 4 years

Screening: Phone screen: A fifteen minute phone screen will be completed. It will include questions about performance on activities of daily living (ADL). The ADL screen will ask about difficulty with daily activities and history of medical conditions. The ADL Screen will be used to confirm that the participant notices a difference in the conduct of their daily activities. They may report any modification that they have made, taking more time, altering the task, obtaining support, or other modifications. If yes, we will ask if a physician has told them they have a central nervous system disorder other than mild cognitive changes, substance use disorder in the last 5 years, bipolar disorder, schizophrenia, Parkinson's disease, a stroke, multiple sclerosis, or a seizure disorder? We will not ask for any specifics about the diagnoses. The interested potential participants will be scheduled for an appointment to sign consent, Release of Information (ROI) form to review their medical records and complete the screening. All screening measures will be completed prior to the MRI/PET scan.

Screening after consent to determine eligibility: This screening battery is essential to determine whether someone is experiencing abnormal cognitive changes. We will use this screen to rule-out individuals who demonstrate dementia, and move forward if people qualify. A screening battery comprised of the modified Telephone Interview for Cognitive Status (TICS), Hayling Sentence

Completion Test and 3MS (Teng & Chui, 1987). These assessments were specifically selected due to their validity in a remote testing environment. If participant's scores reflect likely dementia (>1 SD below normed means) they will exit the study. Participants who score between 1 SD below normed means and the mean will be asked to undergo additional screening. These criteria will be followed at the PIs discretion.

The WRAT-5 will measure reading achievement to help interpret neuropsychological testing information (Appendix G of IRB).

Neuropsychological evaluation (RBANS (Randolph, et al. 1998) and DKEFS (Delis, et al. 2001) Trail Making and Color-Word Test; lasting about 50 mins.) Controlled Oral Word Fluency Association Test (COWA), Wechsler Adult Intelligence Scale, Fourth Edition (WAIS_IV Digit Span), Boston Naming Test (BNT), and Clock drawing.

ECOG with a caregiver to determine whether current functioning represents a decline.

OARS (Older American Resource and Services) to sample function in daily activities. Information from the OARS addresses performance in daily activities, which will be used in the cognitive diagnostic process.

Cumulative Illness Rating Scale (CIRS-G) - The CIRS-G is a standardized rating scale used extensively in medical rehabilitation to assess medical burden based on informant report.

GAD-7: The Generalized Anxiety Disorder-7 is an outcome measure for feelings of anxiety over the previous 2 weeks. The 7 items are rated on a four-point scale.

CDR: The Clinical Dementia Rating Scale is a 5-point scaled used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgement & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g. family member).

Demographic and Medical History: We will collect demographic (age, gender, race, ethnicity, education, vocation), and medical (MCI etiology and onset, co-morbidities, medications) from the participant interview. In addition, we will request them to verbally describe their medical history.

Mood will be measured with the Patient Health Questionnaire (9-item version). The PHQ-9 is a valid and reliable tool assessing nine symptoms of major depressive disorder. Severity of symptoms rated on a 4-point scale.

Mood disorders will be measured with the PRIME-MD mood. The PRIME-MD is a valid and reliable tool assessing mood disorders.

If the participants are coming to our center with a diagnosis of MCI from the ADRC and other centers, we will randomize them into the study, and continue on with all measures after the screening procedures. All data will be reviewed at the bi-weekly Diagnostic Adjudication Conference by a

neuropsychologist and a neurologist at baseline, 6 and 12 months. We will apply Pittsburgh ADRC procedures (Lopez, et al. 2000) and use NINCDS-ADRDA criteria (McKhann, et al. 1984) to diagnose dementia. Participants with likely dementia detected through either screening or adjudication will be referred to the ADRC for further evaluation and/or follow-up. We will use the National Alzheimer's Coordinating Center comprehensive criteria to diagnose MCI. The screening assessments require a duration of 4 hours to complete. Potential participants will continue based on these criteria and the PIs discretion.

Study Procedures:

General procedures: Informed Consent will be obtained by trained staff. Procedures will be conducted via video conferencing in a location of the participant's choice, including their home, community based location, or Pitt/UPMC research spaces. Community-based locations include community centers or community location where a private space is available. Privacy will be maintained in these locations by using a private setting or room. Randomization will occur after baseline testing (and imaging, if participant is eligible and chooses to undergo PET/MRI scan) has been completed. Imaging will only be conducted at baseline and if the participant elects to complete the PET/MRI scan portion of the study.

Assessments: Participants will be assessed at baseline and post intervention at 6 and 12 months. Participant time will be approximately 2 hours for baseline visit and up to 5 hours for 6 and 12 month visit to complete the measures below. All assessments will be performed by trained members of the study staff and supervised by the Principal Investigator.

The Performance Assessment of Self-Care Skills (PASS) is a valid and reliable tool that evaluates ADL critical to independent living in the community. The PASS includes instrumental activities of daily living. Activities are scored on a 4-point scale from 0 (dependent) to 3 (independent). We will use 8 cognitively-focused instrumental activities of daily living. Participants will be asked to solve problems given practical tasks such as medication management, financial management, and shopping.

The Apathy Evaluation Scale (AES) is a valid and reliable tool that measures motivation. This tool was developed at the University of Pittsburgh and is free of charge and easy to score. Each item receives a score of 1-4.

The Ways of Coping (WOC) is a self-report questionnaire that assesses how people cope with adversity. The individuals are asked to rate their ability to cope with daily life. We will use the measure to better understand how people cope in daily life.

Worry Questionnaire (PSWQ): The Penn State Worry Questionnaire asks participants how much they worry in their daily lives. We will use this information to better understand the worry that individuals at-risk for disability may have.

The Appraisal of Self-Care Agency Scale (ASAS-R): asks individuals about their self-efficacy in their ability to adapt to their daily lives. We will use this information to better understand how participants adapt to their daily activities.

PSQI: The Pittsburgh Sleep Quality Index is an outcomes measure for sleep quality over a 1-month period. Item is scored on a four-point scale.

ISEL12: The Interpersonal Support Evaluation List is an outcome measure for perceived availability of four separate functions of social support (tangible, belonging, self-esteem, and appraisal). The 12 items are rated on a four-point scale.

PASE: The Physical Activity Scale for Elderly is an outcome measure for the level of physical activity. It is comprised of self-reported occupational, household and leisure items over a one-week period. The PASE scoring is derived from counts from self-assessed activity levels.

PHQ-9: The Patient Health Questionnaire (9-item version) is a valid and reliable tool that measures mood by assessing nine symptoms of major depressive disorder. Severity of symptoms rated on a 4-point scale.

GAD-7: The Generalized Anxiety Disorder-7 is an outcome measure for feelings of anxiety over the previous 2 weeks. The 7 items are rated on a four-point scale.

LLFDI: The Late-Life Function & Disability Instrument is a self-report of activity and participation restrictions for older adults. The items are rated on a 5-point scale.

PROMIS: Patient Reported Outcomes Measurement Information System, which is a system of highly reliable, precise measures of patient–reported health status for physical, mental, and social well–being. PROMIS tools measure what patients are able to do and how they feel by asking questions. PROMIS' measures can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment, and PROMIS tools can be used across a wide variety of chronic diseases and conditions and in the general population. PROMIS is a computerized instrument that complements the structured assessment done at study entry to assess a variety of physical and mental health domains including emotional distress, sleep, pain, fatigue, social participation, and cognitive function. The PROMIS is not a diagnostic instrument, but rather assesses symptom severity in physical and mental health domains. The PROMIS measures are necessary to capture influence of symptoms on daily life, including social participation.

Adapted CHAOS Measure collects self-report information on participants daily routine and home environment. This is measured on a 5-point scale.

Unmet Needs Questionnaires asks questions regarding a person's available assistance with select self-care and household activities. The total score on this questionnaire is the sum of unmet needs.

For participants who previously participated in the IRB approved research protocols (PRO10110251, PRO10100591, PRO13100338, PRO14070341, PRO17030527, PRO16040102, PRO17060298, PRO15090555, PRO10110050) who sign a consent form for the current study, we will observe the following procedures. Information previously collected as part of the above listed IRB protocol may be collected, including demographic information, as well as information assessing cognition, behavior,

emotion, and disability. As stated in the consent form, research records and information may be shared with other investigators conducting studies in which the subject is currently enrolled.

Participants may elect to complete a PET/MRI scan, if eligible, on the mMR scanner. If the scanner is unavailable, PET with transmission scans and a separate MRI scan will be used as the backup imaging method.

For participants having PET/MRI scan we will utilize the PET Research Center/PET Radiochemistry Laboratory on the 9th floor of UPMC Presbyterian Hospital and the mMR scanner on the 8th floor of UPMC Presbyterian Hospital to simultaneous acquire MR and PET imaging.

In the backup imaging method, participants will undergo an MRI procedure for anatomical localization of regions-of-interest (ROI). Participants with a questionable history of metallic fragments will not be included in the imaging portion of the study. A single MRI study will be performed prior to the PET. The MRI examinations will be conducted on the 8th floor in the UPMC MRRC, which is located directly below the PET Facility, using a 3T scanner. A volumetric T1-weighted MRI will provide the anatomical framework for ROI analysis. This sequence maximizes contrast among gray matter, white matter, and cerebral spinal fluid and provides high-resolution delineation of cortical and subcortical structures. Imaging time for this pulse sequence is less than 8 minutes, with total time for the MRI scan estimated at 30 minutes. MRI data will be transferred to the PET Facility over the electronic network and co-registered with the PET data on a SUN Workstation using software routinely used for this purpose. The registered MRI will be used as an individualized anatomic map for the selection of ROIs used in the analysis of the PET data.

[C-11]PiB Imaging: Participants who have not had a previous PiB PET scan under a parent study within the past 18 months and live within 50 miles of scanning center, will be asked if they are willing to undergo a one-time Baseline PET scan with [C-11 PiB]. This is the only time the scan will be conducted at baseline. A separate consent for the PiB PET scan will be obtained by a physician. We anticipate needing to obtain a PET scan on approximately 50 of our participants. We will review participant images from a parent study if the PET scan was done within the past 18 months. Subjects who had a positive amyloid-beta PET scan completed greater than 18 months will only have images reviewed and will not have to undergo a separate PET scan.

PET/MRI scans will take place on the mMR scanner on the 8th floor of the B-Wing of UPMC Presbyterian Hospital in the MMRC. For the backup imaging method, PET scans will be acquired on the 9th floor of the B-Wing of UPMC Presbyterian Hospital in the UPMC PET Facility. The entire process at the PET facility will take approximately 2 hours. Participant preparation for the PiB PET scan will include intravenous catheterization and immobilization of the head for all participants.

[C-11] PiB will be manufactured by the University of Pittsburgh PET Facility in accordance with a respective Drug Master File approved by the University of Pittsburgh Radioactive Drug Research Committee. Injection of high specific activity PiB 15 mCi at t=0 min. The subject is then allowed to relax quietly in a chair for approximately 25 min, after which they are placed on the scanner bed. The backup

imaging method will have a transmission scan using rotating Ge-68/Ga-68 rods. Following the transmission scan, a 20±5 min PiB PET study will be acquired beginning ~ 50 min after injection.

After the completion of baseline assessments and imaging (if elected by participant) participants will be randomized to Enhanced Usual Care or Strategy Training. Randomization will be managed by the statistician on the study. Assessors will be made blinded to decisions made with regards to assessment/treatment of subjects, as well as the arm the subject is participating in. The group making the decisions about participation will be blinded to the participant's study arm.

Enhanced Usual Care Usually, older adults with MCI may interact with services and supports as they see fit. Enhanced usual care will allow older adults to interact with services and support. We will ask document and monitor all mental health treatment (e.g., medications that you may be taking) and psychotherapy (e.g. counseling or social services). We will notify appropriate physicians when required (e.g., participant meets criteria for depression). Furthermore, all participants assigned to EUC will receive the same assessments as other participants. The close monitoring will track potential changes in symptoms (e.g., depressive symptoms), and we'll refer them to services as appropriate.

Strategy Training + Enhanced Usual Care In addition to receiving everything in Enhanced Usual Care, participants will engage in 10 sessions over 5 weeks with a trained research interventionist. Participants will describe activities they do, no longer do, or have never done using the cards from the Activity Card Sort as a guide. The Activity Card Sort provides 100 photographs of older adults performing activities in the community. Based on the activities from the Activity Card Sort selected, the participants will be invited to prioritize these activities identifying activities that are most important to them. The therapist will ask the participants to use this information to identify and prioritize activity-based goals to address in the remaining sessions. These sessions will take place virtually with the participant in their homes or in a location of the participant's choice and will last approximately 1 hour. All Strategy Training sessions will be video recorded. Video recording will provide an opportunity to do ongoing fidelity assessment of the treating therapists to the intervention protocol.

Strategy Training Intervention Packet The packet given to the participants during the Strategy Training will assist the participants in brainstorming goals and evaluating how they are addressing them using the goal, plan, do, check method. Participants will complete the strategy review worksheet during each session to assess what was done each time. A daily routine calendar is included for participants to help create a plan to achieve their designated goals. The participants will also rate how confident they are in meeting the goals they come up with and at the end they rate how satisfied they are with the how they completed the goal.

Follow-up: All of the full screen and baseline measures will be administered at 6 and 12 months, except the WRAT-5, due to only being required at the full screen. The 3MS will also be administered at 6 and 12 months for adjudication purposes. The Unmet Needs Questionnaire will only be administered at baseline.

At post-intervention, which will occur 8 weeks after randomization, only the baseline measures will be administered, not the health and neuropsychological tests.

Eligibility Criteria

Inclusion Criteria

Participants must be 60 years of age or greater; have Mild Cognitive Impairment; acknowledge difficulty with a daily activity, and be community dwelling.

Exclusion Criteria

There must be no pregnancy, central nervous system disorder (other than MCI); substance use disorder in past 5 years; lifetime history of bipolar disorder, schizophrenia, Parkinson's disease, a stroke, multiple sclerosis, a seizure disorder, or deemed unsafe to proceed in the study (e.g., untreated Major Depression); or must not have a severe medical condition that limits engagement in daily activities. We will confirm early-stage cognitive decline status for entry into the study. If we note declines in daily activities or other health concerns (e.g., untreated Major Depression), we will make referrals for appropriate treatment.

Statistical Considerations

Given the repeated measures design and the expected attrition rate (less than 20%), the resultant sample size of subjects randomized will be 150 participants, or 75 per group. To achieve the sample size of 150 participants randomized we estimate we will need to enroll 600 participants. Our sample size estimates provide sufficient statistical power to test aims 1 and 2 in this study. Recruitment will take place over 42 months. Using a simulation program for repeated measures mixed models, it was determined that a sample size of 150 (75per group) has 90% power to detect a minimal detectable between-group difference of one and over 95% power to detect a minimal detectable difference of one for within-group and between-within interaction effects when alpha is set to .05. This sample size is conservative; we have had less than 20% dropout in our preliminary development study. It is anticipated that up to 50 of the subjects who qualify to undergo the research procedures will not have undergone a PET scan using [C-11]PiB within the prior 18 months.

Data management and analysis: The University of Pittsburgh's Health Services Research Data Center will manage, and store data collected. We will use three customized databases for the study, being the following: one for participant tracking, one for assessment data, and one for intervention data. Data will be monitored weekly during laboratory meetings. Prior to data analysis, data will be verified and checked for accuracy through double data entry procedures. Data analysis will be led by the study's biostatistician. The study's biostatistician's expertise lies in the design and conduct of statistical analyses for research projects, specifically clinical trials. The study's biostatistician is an associate professor and has over 55 peer-reviewed publications in rehabilitation, aging, and nursing.

Data analyses: This proposal will examine the efficacy of Strategy Training and the intervention's mechanism of action. To enhance rigor and report unbiased results we will use intention to treat protocols. We will use a two-part process for these analyses, consisting of a preliminary screening and specific tests for each aim.

Preliminary analyses: The results of the preliminary analysis will be used to: 1) screen univariate and bivariate distributions for normality and influential outliers; 2) identify potential differences in treatment groups; 3) determine the amounts and patterns of missing data; and 4) assess statistical assumptions for hypothesis testing. Descriptive statistics will be presented for all demographic variables at baseline and effect modifiers at baseline and follow-up. To ensure that observed differences between Strategy Training and EUC groups are not attributable to measurement error, the internal consistency reliability of the PASS items will be computed using Cronbach's alpha.[62] We will examine the relationship between our stratification variable (presence of amyloid β) and our outcome. If a relationship is detected, the stratification variable will be entered as a covariate in the efficacy analysis. We will also examine reasons for missing data and assessor blinding and their association with participants' baseline characteristics, visually inspect the distributions of timing and reasons for missing data (both attrition-related and intermittently missing data), and complete sensitivity analyses (e.g., fitting mixed effects models without informative missing data and comparing to models that adjust for informative missing data such as pattern mixture and shared parameter models).[63,64] If needed, multiple imputation will be used to impute missing values on predictor variables or covariates. Finally, we will screen for potential covariates that are correlated with the dependent variables (PASS). Critical covariates will be included in the efficacy model. This information will guide statistical analyses in this trial that require assessment of specific statistical assumptions for hypothesis testing.

Aim 1: Test the effect of ST compared to EUC on change in disability among older adults with MCI.

Aim 1 analyses: An intent-to-treat (ITT) approach will be implemented as an initial analysis of the efficacy of Strategy Training compared to EUC. Information on adherence to protocol and retention will be used to explore sensitivity of the results using the ITT approach. Repeated-measures linear mixed models will be used to investigate the efficacy of Strategy Training over time. Linear mixed models provide a flexible approach to account for unequally spaced measurements, modeling the covariance among the longitudinal responses, time-varying and time-invariant covariates, and missing outcome data.[65] Treatment group and time will be included as the independent variables, while the PASS will be the primary outcome. First, we will inspect the structure of the estimated covariance matrix for repeated measures to ascertain the appropriate covariance structure using model fit indices. F-tests will be used to test the treatment group X time interaction as well as the main effects of the model. Time-varying or time-invariant covariates may be included in the mixed model based on the results of the data screening to adjust for group imbalances or variables related to the dependent variable. Residual analyses will be conducted for each model to determine sources of model misspecification or influential outliers. Sensitivity analyses will be conducted to assess the effect of influential observations on results. The outcome is assumed to have a normal error distribution. If this assumption is not met, we will switch to a generalized mixed model, which can be used with other

distributions of the errors (e.g., Poisson, binomial).[66] Identified parameter estimates with their standard errors and confidence intervals will be used to inform larger, confirmatory studies of Strategy Training.

Aim 2: Assess the extent to which brain imaging and neurocognitive function modify the relationship between ST and EUC on change in disability.

Aim 2 analyses: The same repeated-measures linear mixed model approach will be used to test whether Aβ status or executive function moderate the relationship between group assignment and rates of decline to disability. Executive function will be dichotomized prior to model entry as >1 SD below the normative reference. Each effect modifier will be assessed independently with the same methods. Moderation will be tested with a series of regression models.[67] Each independent variable is tested separately (group assignment and time) in the modeling process, with presence of Aβ deposition or executive function as the moderator, and disability as the outcome. First, an additive model is created using one independent variable and presence of Aβ deposition or executive function. Next, the model is constructed using the independent variable and presence of Aβ deposition or executive function by moderator interaction term. We will determine if the difference between the additive and moderator models is significant by examining: 1) the change in R-squared; 2) the interaction regression coefficient; and 3) the partial correlation of the interaction and disability when controlling for the independent variable (group assignment) and the moderator (presence of Aβ deposition or executive function). Next, we will create plots of the predicted regression lines using specific values of presence of Aβ deposition or executive function (e.g. mean, one standard deviation above the mean, one standard deviation below the mean) to examine the moderating effect. Confounders associated with both independent and dependent variables, will be added secondarily and tested in separate models to explore how each individual confounder affects the results.

Potential limitations and plans to minimize limitations: If the study hypotheses related to intervention efficacy are not supported, this proposed study has the potential to answer scientifically interesting questions. We will be able to describe patterns of observed performance of daily activities among a cohort of individuals anticipated to experience changes in daily activities. Furthermore, we can leverage the existing data collected in the Heart SCORE study to examine mid-life biological markers, cardiovascular and brain related markers, and examine their association with performance of daily activities. These opportunities will facilitate the generation of additional hypotheses.

We anticipate a few challenges in implementing the proposed study. Challenges may include coordination and communication with participants, unblinding of blinded team members, untoward adverse events, and intervention protocol drift.

We will negotiate coordination of services and communication with participants by providing open and direct communication with participants; we will stay in regular contact with participants and keep a consistent intervention schedule.

It is possible that members of the clinical and research teams may become unblinded. We have addressed this potential challenge through a series of design decisions. All blinded personnel have their workspace separate from unblinded personnel. Furthermore, we will ask assessors to predict participant randomization arm. If bias is detected, this information will be assessed and controlled for through statistical analyses.

Participants may experience adverse events. Thus, we will carefully examine and monitor adverse events throughout this Phase II trial. This monitoring is critical for the safety of participants and understanding other factors that may influence outcomes.

Therapists may shift the delivery of the standardized intervention protocol. We will ensure that therapists demonstrate adequate treatment integrity prior to initiation of treatment on the proposed randomized controlled trial. Once trained, therapists will have all sessions videotaped for continuous treatment fidelity checking. We will review a random sample of 20% of the Strategy Training intervention sessions for fidelity using our validated treatment fidelity scale. An external monitor will observe and rate these sessions.

Participants included in the primary analyses were intention-to-treat, which included participants missing any follow-up PASS assessments. We used SAS (v 9.4) PROC GLIMMIX to construct generalized linear mixed effects models to test hypotheses and account for repeated measures. We regressed PASS total number of cues on time, group, and group by time controlling for age, education, and sex, with random effects for subjects. In the models, we used a negative binomial distribution with log link to account for the skewed distribution of the outcome, an autoregressive covariance matrix to account for correlated time points, and the Kenward-Roger method to estimate degrees of freedom for fixed effects. Post hoc testing was performed using the Tukey adjustment for multiple testing.